Testing the nature of the alcohol-related attentional bias in binge drinking and severe alcohol use disorder

An eye-tracking approach

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Zoé BOLLEN

Promoteur

Pierre MAURAGE (UCLouvain)

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Comité d'accompagnement et jury

Alexandre HEEREN (UCLouvain, président de jury)
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Résumé

La consommation répétée et excessive d'alcool a des effets néfastes sur le cerveau, provoquant notamment la suractivation du système de récompense. Cette suractivation engendrerait l'apparition d'un biais attentionnel, se définissant comme l'orientation préférentielle des ressources attentionnelles envers les stimuli liés à l'alcool. Ce biais jouerait un rôle clé dans le développement et le maintien des troubles d'usage d'alcool. De nombreux postulats théoriques ont ainsi été formulés et communément admis par la communauté scientifique concernant la nature de ce biais. L'objectif de cette thèse était de tester leur validation expérimentale en investiguant la nature du biais grâce à une technique d'oculométrie auprès d'une jeune population de buveurs excessifs et de patients souffrant d'un trouble sévère d'usage d'alcool. Nos résultats mettent sévèrement en doute la majorité des postulats théoriques sur le biais, en démontrant notamment que celui-ci est davantage influencé par l'état motivationnel que par la sévérité de la consommation et qu'il se définit par un évitement de l'alcool chez la plupart des patients en période de sevrage.

Abstract

Excessive and repeated alcohol use leads to deleterious effects on the brain, notably by causing the over-sensitization of the reward system. This overactivation would generate the apparition of an attentional bias, defined as the preferential allocation of attentional resources towards alcohol-related stimuli. This attentional bias would play a key role in the development and maintenance of alcohol use disorders. Various theoretical assumptions have been formulated and commonly accepted by researchers concerning the nature of this bias. The aim of this thesis was to test their experimental validation in a population of binge drinking students and patients with severe alcohol use disorder by investigating the nature of the attentional bias using an eye-tracking technique. Our results severely challenge most theoretical assumptions about alcohol-related attentional bias, notably by demonstrating that the bias is more affected by motivational states than by severity of alcohol use, and is characterized by the avoidance of alcohol-related stimuli in most detoxified patients with severe alcohol use disorder.

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List of abbreviations

This list inventories the most common abbreviations used in this thesis.

AB	Attentional bias
SAUD	Severe alcohol use disorder
BD	Binge drinkers
CTL	Control participants
LD	Light drinkers
MD	Moderate drinkers
ABM	Attentional bias modification
CBM	Cognitive bias modification
RT	Reaction time
AOI	Saccadic reaction time
VPT	Area of interest
SRT	Visual probe task
VAS	Visual analogue scale
AUDIT	Alcohol use disorder identification test
DSM	Diagnostic and Statistical Manual of Mental Disorders
PANAS	Positive and negative affect scale
EEG	Electroencephalogram
fMRI	functional magnetic resonance imaging
MIP	Mood induction procedure

Foreword

In our daily life, we are constantly exposed to a multitude of sensory stimuli. However, our cognitive resources are limited. We have to select and focus on specific stimuli present in our surrounding physical world, while simultaneously filtering out distracting or irrelevant stimulations. By performing such initial sorting of the stimuli available in our environment, attention will crucially select information which is then further processed by all the subsequent mechanisms involved in human cognition (e.g., decision making, memory, approach behaviour). This allocation of attentional resources towards specific stimuli can be driven by top-down processes, referring to internal guidance of attention based on prior knowledge and goal relevance, or by bottom-up processes, referring to attentional guidance purely driven by external factors such as the salience of stimuli (Katsuki & Constantinidis, 2014).

Although this attentional selectivity is generally adaptive as it allows us to better apprehend the physical world and optimize our behaviours by adjusting cognitive processes to current goals, in some cases, it can become dysfunctional and overkill. Indeed, a core assumption espoused by many researchers in clinical psychology is that individuals suffering from psychopathological states would process the information present in their environment differently than healthy individuals, and that such biased attentive processing would play a key role in the development and maintenance of the disorder. This attentional bias (AB) is defined as the tendency to preferentially allocate one's attentional resources toward a certain type of stimuli when such stimuli are presented in the environment. It usually refers to automatically grabbing attention even when such stimuli are not relevant for the current task or contradict current individual goals. This AB would be directed towards threat in anxiety (Armstrong & Olantunji, 2012; Mogg & Bradley, 2016), negative emotional stimuli in depression (Mennen et al., 2019; Mogg & Bradley, 2005), food-related stimuli in obesity (Field et al., 2016; Hendrikse et al., 2015) and substance-related stimuli in substance use disorders (Field et al., 2014; 2016). Together with other cognitive biases such as approach bias (i.e., action tendency to automatically approach a certain type of stimuli) or memory bias (i.e., tendency to selectively recall memories congruent with emotional or motivational states), AB is known to strongly affect cognitive processing, and hence decision making, in everyday life.

Many researchers claimed that AB would be a core feature of substance use disorders by being part of a vicious cycle, in which excessive and chronic substance use leads to greater attraction towards substance-related cues, enhancing the desire to use drug (i.e., craving) and ending up in increased use (Field & Cox, 2008; Field et al., 2009). In particular, AB towards alcohol-related stimuli in alcohol use disorders is of particular interest given the excessive exposure to alcohol in the visual environment of Western countries. Indeed, being continuously confronted to the alcohol-related cues overly present in our everyday life might constantly mobilize the attentional resources of individuals suffering from alcohol use disorders, facilitating the processing of these stimuli, increasing craving and thus undermining their cognitive efforts to overcome their compulsions to drink.

Alcohol-related AB has therefore been considered by many researchers as a core determinant of the onset and persistence of alcohol use disorders and has recently led to the development of rehabilitation programs aimed at modifying AB. Nevertheless, its wide implementation in clinical settings might have been premature, as the clinical relevance of AB is still currently debated. Moreover, many theoretical and empirical questions remain regarding the nature of AB and its underlying processes. Indeed, most theoretical models assume that alcohol-related AB (1) is directly related to the severity of alcohol use, (2) is based on early and automatic processes, (3) is a long-lasting and stable feature of alcohol use disorders, (4) is effortless and not influenced by higher-level reflective processes, and (5) is specific to alcohol-related stimuli. However, the appraisal of the empirical validity of those assumptions urgently needs to be addressed by reliable AB measures in order to get a better understanding of alcohol use disorders, improve its clinical care and reduce the risk of subsequent relapse.

The present thesis aims to offer a better understanding of the nature of AB in (sub-)clinical populations of alcohol use disorders. To this end, the first part of the thesis will provide a state of the art regarding the theoretical conceptualizations of AB, the empirical evidence of its occurrence in previous studies, and the remaining questions regarding its nature and functioning in alcohol use disorders. The second part will present the six experimental studies carried out within the framework of this thesis to test the theoretical assumptions made about AB, before discussing their implications at the theoretical, methodological and clinical levels, and highlighting the limits and recommendations to be considered by future research.

PART I: STATE OF THE ART

Chapter 1

Theoretical background

1. Introduction

This first chapter will introduce the theoretical background of the Ph.D. thesis. The first section will present the two patterns of alcohol use disorders on which our work has been focused, namely binge drinking and severe alcohol use disorder (SAUD), as well as their cognitive and cerebral impairments. The second section will describe dominant theoretical conceptualizations of alcohol use disorders. The third section will develop the main assumptions made by theoretical models about AB. The fourth section will describe the different methods of assessment of AB. Finally, the fifth section of this chapter will discuss the rehabilitation programs developed to retrain AB and their effectiveness.

2. Alcohol use disorders

Alcohol is ubiquitous in our society and its consumption is encouraged in multiple social and entertaining contexts. The societal valorisation of alcohol consumption, as well as the frequent positive evaluation of its excessive consumption (particularly in youth), make it the most prevalent substance in Western countries (WHO, 2018). Ironically, it is also thought to be the substance with the most deleterious consequences for the consumer and for others (Figure 1; Nutt et al., 2010). Indeed, besides the risks related to acute alcohol consumption, for example during isolated episodes of heavy drinking, repeated or chronic alcohol use highly contributes to a wide range of physical (e.g., liver disease, cardiovascular problems, neurological syndromes, injuries), interpersonal (e.g., domestic violence, family problems, divorce) and socioeconomic (e.g., unemployment, absenteeism, accidents) issues, as well as to considerable psychological distress (e.g., depression, anxiety; WHO, 2018). In addition to these health and social consequences for the drinkers themselves, the harmful use of alcohol also results in consequential damages for other people (e.g., family, employer, other road users) and the society at large. Excessive alcohol use therefore constitutes a major public health concern, being a key contributor to the burden of disease and mortality worldwide (Navarro et al., 2010; Rehm et al., 2017).

According to a recent Belgian health survey (Drieskens et al., 2018), 14% of the Belgian population over the age of 15 reported drinking 10 or more units of alcohol per week (one standard unit corresponding to 10g of pure ethanol in Belgium), thus exceeding the recommendations provided by the Belgian Higher Health Council (2018) for minimizing alcohol-related risk to physical and mental health. Importantly, this excessive alcohol use can take the form of different subclinical and clinical drinking patterns, from binge drinking to SAUD.

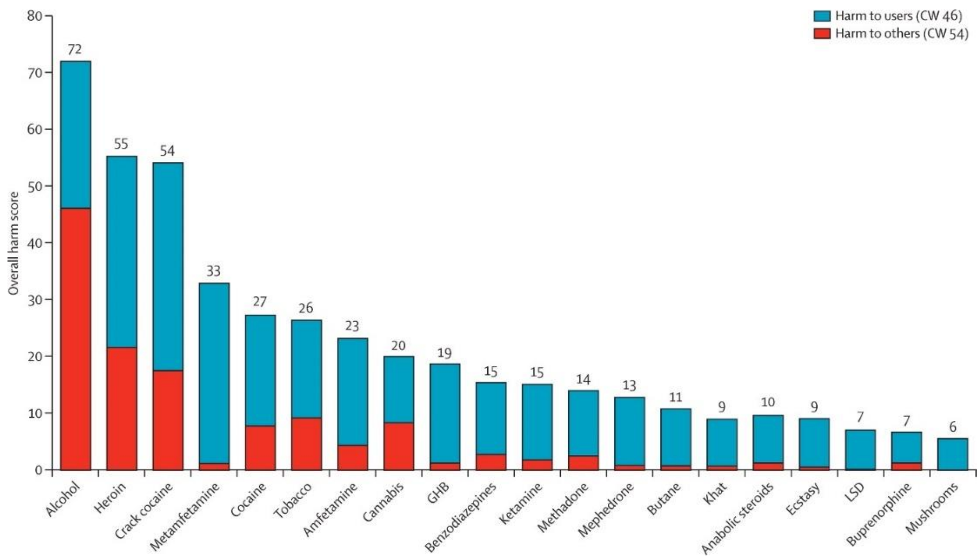

Figure 1. Substances ordered according to their overall scores of harms to the user and to others (Nutt et al., 2010).

2.1. Binge drinking

Binge drinking refers to an excessive but episodic pattern of alcohol consumption, characterized by recurring alternations between intense intoxication episodes and periods of abstinence (Rolland & Naassila, 2017). This particular drinking behaviour is the most prevalent alcohol-related habit among adolescents and young adults in Western countries (Dormal et al., 2019), 40% of them reporting at least one binge drinking episode per month during the last 6 months.

To date, the conceptualization of binge drinking is still a matter of debate and no consensus has been reached on its most precise definition (Lannoy et al., 2019a). Confusion remains regarding selection criteria and consumption thresholds, dampening the comparison across studies. Moreover, there is a lack of clarification regarding the distinction between binge drinking and related alcohol consumption patterns, such as « heavy drinking » (i.e., a binge-like drinking pattern with a frequency of 5 days or more in the past month; Substance Abuse and Mental Health Services Administration, 2003) « social drinking » (i.e., a low-risk drinking pattern with a frequency of maximum 3/4 doses per occasion and 7/14 doses per week for women/men; NIAAA, 2004) and « problem drinking » (i.e., high-risk drinking pattern due to high quantity and frequency of alcohol use, but without meeting the inclusion criteria for SAUD; Oei & Morawska, 2004).

Among the most consensual definition, the NIAAA (National Institute on Alcohol Abuse and Alcoholism, 2004) proposed defining binge drinking as an episode of drinking resulting in a blood alcohol concentration level of at least 0.08 grams/decilitre. For a normal adult individual, it equates to consume a minimum of 5 standard doses of alcohol for men, and a minimum of 4 standard doses for women, on a single occasion within a two-hour period (Wechsler et al., 1994).

Besides proposing criteria related to the presence of a chronic drinking pattern rather than a single and isolated binge drinking episode, the Alcohol Use Questionnaire (AUQ), developed by Mehrabian and Russell (1978), also offered a more behavioural approach to characterize binge drinking. It defined it in terms of various factors such as the speed of consumption, the frequency of drunkenness (drunkenness being defined by loss of coordination, nausea, memory blackouts and/or inability to express oneself clearly) or the percentage of drunkenness achieved during drinking episodes in the last 6 months (Townshend & Duka, 2005).

More recently, Maurage et al. (2020a) proposed an integrated conceptualization of binge drinking that combines quantitative and qualitative factors as well as threshold and continuum approaches. They operationalized the core features of binge drinking by six criteria, namely the presence of physiological and psychological binge drinking episodes, the ratio and frequency of those episodes, the consumption speed and the alternation between binge drinking episodes and soberness (Figure 2). They also suggested a list of biasing variables and exclusion criteria, notably to reliably distinguish binge drinking from other drinking patterns. We will use an adapted version of this most recent definition of binge drinking for the recruitment procedure of our experimental studies.

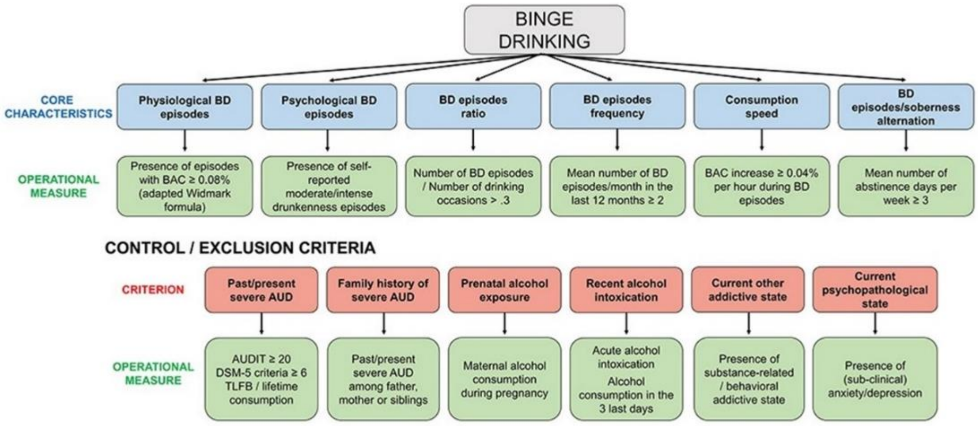

Figure 2. Binge drinking criteria, associated operational measures and exclusion/control variables from Maurage et al. (2020a).

2.2. SAUD

Excessive and uncontrolled alcohol consumption can lead to alcohol use disorder, recognized as a psychiatric disorder by the International Classification of Diseases (ICD-11) and Diagnostic and Statistical Manual of Mental Disorders (DSM-V; American Psychiatric Association, APA, 2013). Formerly labelled as “alcoholism” (DSM-III, APA, 1980) or “alcohol-dependence” (DSM-IV, APA, 1994), alcohol use disorder is described as a problematic pattern of alcohol use that result in clinically significant impairment or distress, as manifested by various psychosocial, behavioural, or physiological consequences. The fifth edition of the DSM switched from a categorical to a dimensional approach of alcohol use disorder, proposing three severity levels (mild, moderate, severe) according to the number of diagnostic criteria fulfilled by the individual within a 12-month period (respectively 2, 4 and 6 criteria for mild, moderate and severe alcohol use disorder, NIAAA, 2021).

These criteria fall into four broad categories, namely (1) the loss of control (having times when ending up drinking more or longer than intended); (2) the personal and social impact (continuing drinking despite causing trouble to relatives), (3) the dangerousness of use, in terms of risks taken (having gotten into situations where drinking increased the risk of injury) or physical/psychological effects (keeping on drinking even though it made the individual feel depressed or anxious, or created another health problem); and (4) the pharmacological indicators of tolerance (having to increase consumption to obtain the same effect, as a result of the body's habituation to the substance) and withdrawal (feeling the presence of physical and psychological symptoms when stopping to consume the substance; Campanella & Maurage, 2021).

SAUD is among the most prevalent psychiatric conditions (Rehm & Shield, 2019). In 2016, around 100 million people, aged between 18 and 64, suffered from SAUD worldwide (Vos et al., 2017). In Belgium, the issue of alcohol-related health is of great concern, with seven percent of the population revealing problematic alcohol consumption, suggesting a potential SAUD (Drieskens et al., 2018). The individual and societal burden of SAUD remains massive, notably because of the still limited efficiency presented by therapeutic settings: SAUD is associated with the widest treatment gap among psychiatric disorders, more than 92% of individuals with SAUD not receiving any clinical support in European countries (Kohn et al., 2004). Moreover, even when SAUD is treated, the relapse rate is still beyond 60% one year after detoxification treatment (Maisto et al., 2018). This high relapse risk questions the efficiency of the current rehabilitation programs and calls for a better understanding of the processes involved in alcohol use disorders, to offer more accessible and efficient prevention and treatment programs.

2.3. Cerebral and cognitive impairments

Besides the well-established physical consequences of excessive alcohol use (Nutt et al., 2010), the cognitive and cerebral correlates of SAUD have been extensively explored during the past decades. Chronic and excessive alcohol use has been linked to widespread volume reductions of white and grey matter brain tissue (Bühler & Mann, 2011). Certain regions appear to be more affected by the alcohol-related shrinkage of brain volumes (Bühler & Mann, 2011), notably the cerebellum, the limbic system and the frontal and prefrontal regions. The severe brain alternations in those latter regions led to the emergence of the frontal lobe hypothesis (Moselhy et al., 2001), suggesting that symptoms associated with SAUD, and in particular the inability to regulate drinking behaviour in spite of the negative consequences experienced, would centrally result from brain alterations in frontal regions.

Structural impairments are associated with major functional changes, notably the reduction of glucose metabolism and cerebral flow in prefrontal regions (Moselhy et al., 2001). Moreover, reduced connectivity has been found between crucial frontal areas, such as the orbitofrontal cortex, and other important pivotal motivational brain regions like the insula (Sullivan & Pfefferbaum, 2013). In contrast, functional neuroimaging studies also revealed an increased reactivity of the entire reward system and associated structures (i.e., anterior thalamus, ventral putamen, amygdala, hippocampus, striatum and insula) when confronted to alcohol-related stimuli. This modified functioning of the reward system is associated with relapse risk, thus suggesting a key role played by this system in SAUD persistence (Bühler & Mann, 2011). Moreover, these opposite activations between the frontal regions and the reward system led to the emergence of the dual-process models, as further described the following section.

The degradation of cerebral structures and connecting circuitry, in addition to the high vulnerability of prefrontal regions to the neurotoxic effects of alcohol, result in severe deficits in cognitive function among patients with SAUD (Sullivan & Pfefferbaum, 2005). The extent of these cognitive deficits is massive, as underlined by a meta-analysis showing that SAUD was associated with significant impairment across multiple cognitive functions, including attention, verbal and working memory, speed of processing, visuospatial abilities, executive functions and verbal fluency (Stavro et al., 2013). Moreover, a massive variation was found across cognitive functions regarding the pace of spontaneous recovery. For example, verbal abilities resolve more quickly than visuospatial ones, some abilities being already improved after less than a month of abstinence (Angerville et al., 2023; Bates et al., 2002). Conversely, some memory subcomponents can take months to recover, and some decision-making impairments, for example for problem-solving, can even persist for years. Those long-lasting deficits impeded the implementation of the strategies provided by therapeutic interventions during short-term detoxification treatment (Bates et al., 2013; Stavro et al., 2013). Hence, the rehabilitation of these deficits through cognitive remediation appears as a promising avenue for improving cognitive abilities in patients with SAUD and, therefore, treatment outcomes (Nardo et al., 2022; Rolland et al., 2019).

While the scientific literature has long focused on the harmful consequences of acute alcohol intoxication (Bjork & Gilman, 2014) and SAUD (Bühler & Mann, 2011), a growing body of interest has emerged regarding the deleterious impact of other drinking patterns (e.g., heavy, hazardous or binge drinking) on physical and mental health (Hermens et al., 2013; Jacobus & Tapert, 2013). Binge drinking habits appears as particularly deleterious to brain function and structure because of its multiple withdrawals periods resulting from the repeated alternations between intoxication and abstinence (López-Caneda et al., 2013). Moreover, many converging studies have recently demonstrated the rapid and long-lasting cognitive impairments caused by binge drinking pattern (Carbia et al., 2018; Lannoy et al., 2019b). They showed that binge drinking was mainly associated with memory weakness and deficits in executive functions, especially inhibitory control (e.g., Czapla et al., 2015; Parada et al., 2012; Salas-Gomez et al., 2016).

These results suggested that some deleterious consequences of alcohol arise before the emergence of SAUD, namely in subclinical drinking patterns like binge drinking. It even led to the continuum hypothesis, referring to the analogous qualitative impairments at cognitive and cerebral levels between binge drinking and SAUD and thus suggesting that these patterns constitute two successive steps of the same phenomenon (Enoch, 2006; Stephens & Duka, 2008). Accordingly, binge drinking could be described as the gateway to SAUD through the incremental aggravation of neurocognitive impairments that promote the maintenance of excessive alcohol consumption (Lannoy et al., 2019a).

3. Theoretical conceptualization of alcohol use disorders

Many models have attempted to offer insights on the underlying mechanisms of addictive state such as SAUD. The European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) & West (2013) proposed a classification of the main theoretical models regarding addiction (Figure 3).

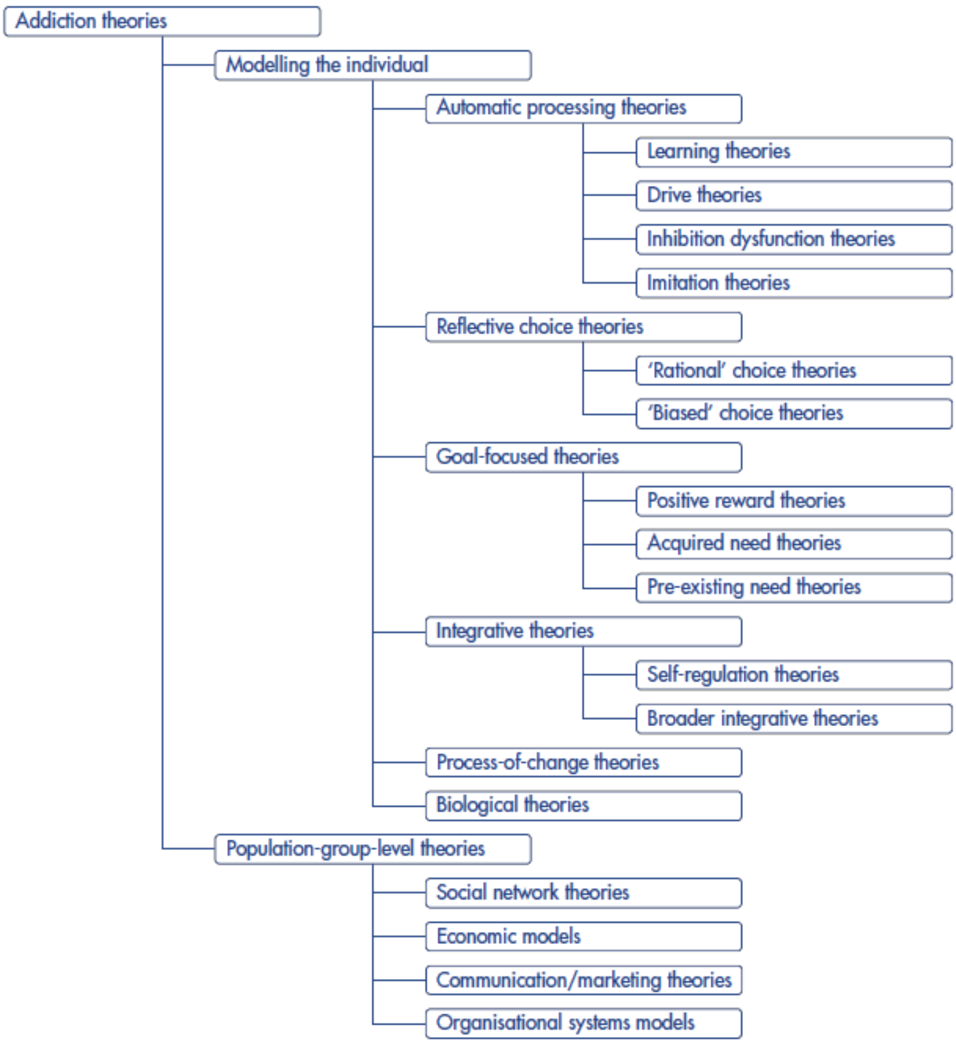

Figure 3. Classification of models of addiction offered by EMCDDA & West, 2013.

Individual-level theories were divided in six main approaches: (1) automatic processing theories, which define addiction based on "automatic processes" that do not involve self-conscious analysis or reflective thoughts; (2) reflective choice theories, which posit that addictive behaviours result from a self-conscious choice that is either rational or biased; (3) goal-focused theories, which describe the types of stimuli and events that drive the underlying processes of addiction (regardless of their automatic or reflective nature); (4) integrative theories, which integrate to varying degrees the components described in the previous theories; (5) biological theories, which consider addiction as a "brain disease" in which neural pathways of executive function are impaired while motivational processes are amplified notably because of drug ingestion; and (6) process-of-change theories, which focus on the different stages of the disease course and discuss the interventions related to each stage.

In the present thesis, we will focus on dominant models of addiction that combine different theoretical approaches and include the alcohol-related AB (defined as the tendency to preferentially allocate one's attentional resources toward alcohol-related stimuli) as a central feature in their conceptualization of addiction. First, the incentive-sensitization theory (Robinson & Berridge, 1993) and its variants combine learning associations theories (being part of automatic processing models) and neurobiological models to describe the development of addiction from "liking" to "wanting" behaviour. Second, dual-process models offer more integrative biological models by defining addiction as the interaction between disrupted brain systems specifically related to automatic and reflective processes. Importantly, both approaches highlight the reward brain system as a central mechanism in the emergence and persistence of SAUD, this system being notably involved in the occurrence of AB toward alcohol-related stimuli. We will describe their main theoretical proposals about SAUD in the present section, before spotlighting their specific assumptions about the nature and extent of alcohol-related AB.

3.1. The incentive-sensitization theory

Various neuroscientific theories of addictive states have underlined the key role played by the over-activation of the reflexive/reward system when confronted with substance-related stimuli. Among them, the well-known incentive-sensitization theory (Robinson & Berridge, 1993) postulated that the repetition of alcohol exposures sensitizes the dopaminergic response in brain reward areas, enhancing the incentive-motivational properties of alcohol-related cues through associative learning. Becoming more salient, these cues hijack consumer's attention (generating an alcohol-related AB), acquire an attractive and desirable value, and guide behaviour toward alcohol consumption. Particular emphasis on the incentive salience were also placed by more recent influential models of addiction (e.g., Everitt et al., 2008; Lewis, 2018; Volkow et al., 2016) which jointly underline the existence of an increased salience of addiction-related cues (related to an over-reactivity of the reward system), as well as the influence of such cue salience in the development of these disorders.

Importantly, the incentive-sensitization theory postulates that subjective craving (i.e., the intense and irrepressible desire to consume alcohol) and alcohol-related AB are positively associated with each other, both being considered as the emotional and cognitive outputs of the overactivation of the reflexive/reward system. Moreover, more recent extensions of the model (Franken, 2003; Ryan, 2002) further suggest that those two processes maintain a mutual excitatory relationship: when alcohol-related cues grab one's attention, subjective craving increases; this, in turn, increases the attention paid to the cues, and so on, until eventually leading to alcohol consumption (Field & Cox, 2008). In the same vein, the central tenet of the "elaborated intrusion" theory of desire (Kavanagh et al., 2005) is that craving would first be experienced as an intrusion, either caused by internal states (e.g., negative mood, withdrawal symptoms) or external cues (e.g., exposition to alcohol-related cues). Then, once aware of this subjective craving, the drinker elaborates on it, notably by directing and maintaining attentional resources on those triggering external cues, which in turn further increases craving.

3.2. Dual-process models

By suggesting that automatic/reflexive phenomena such as craving intrusion can then be relayed by more elaborative processes, the elaborated intrusion theory of desire announced the early days of more integrative theories such as dual-process models. These latter models share the key proposal that human behaviours result from interactions between conscious/deliberative and automatic/uncontrolled processes (Mukherjee, 2010). They postulate that decision-making is determined by the interaction between: (1) the "reflective/control system", responsible for the deliberative and controlled responses and relying on memory and executive functions, and (2) the "reflexive/reward system", involved in the appetitive evaluation of the stimulus and initiating the automatic and appetitive behaviours.

Among healthy individuals, the balance between these systems leads to adapted behavioural responses (e.g., efficient reflective control on appetitive impulses) when confronted with appetitive stimuli from their environment. The presence of two systems, as postulated by dual-process models, has received empirical support through neuroimaging explorations, indicating that the systems rely on separated brain networks, centrally the prefrontal network (orbitofrontal-dorsolateral cortices) for the reflective/control system (Hampton & O'Doherty, 2007) and the limbic network (striatum/amygdala) for the reflexive/reward system (Daw et al., 2005).

Over the last decades, this dual-process perspective has become dominant in the conceptualization of addictive disorders, and notably SAUD (Noël et al., 2010; Wiers et al., 2007). In this view, SAUD would emerge from altered interactions between these systems: (1) the "reflective/control system" is impaired by the neurotoxic effects of excessive alcohol consumption and under-activated; (2) the "reflexive/reward system" becomes sensitized and over-activated by the repeated reward emerging from alcohol-related cues exposure. Hence, this theoretical framework conceptualizes SAUD as relying on an under-activated reflective/control system, resulting in an inefficient control of drinking behaviours, coupled with an overactivated reflexive/reward system, leading to enhanced attraction towards alcohol-related cues.

The under-activation of the reflective/control system in SAUD was widely supported by experimental data: neuroscience results have confirmed the impaired anatomical integrity as well as functional efficiency of prefrontal areas (Bühler & Mann, 2011; Koob & Volkow, 2016), and many neuropsychological explorations have documented reduced executive or memory abilities among these patients (Bernardin et al., 2014; Stavro et al., 2013). Centrally, the predictive role of these deficits in the course of the pathology has also been confirmed, the extent of reflective/control system's impairments being correlated with increased relapse risk and disease maintenance (Rando et al., 2011; Rupp et al., 2016). The over-activation of the reflexive/reward system would in turn result in the occurrence of AB and approach biases (defined as the automatic action tendencies to approach alcohol-related stimuli; Wiers et al., 2013) towards alcohol when confronted with alcohol-related cues (Bechara, 2005). Yet, while this under-activation of the reflective/control system is now consensually accepted, the extent of the reflexive/reward system over-activation and its role in SAUD are far less established and need further exploration. More recently, an extension of the dual-process perspective has been proposed to integrate a third system related to internal bodily sensations (i.e., the triadic model; Noël et al., 2013). This interoceptive system would depend on the activity of the insular cortex and promote drinking behaviours by fostering the activity of the reflexive/reward system while undermining the effectiveness of the reflective/control one.

The dual-process perspective has also been proposed to get a better understanding of subclinical patterns of excessive alcohol use, and more especially binge drinking (Lannoy et al., 2014). Indeed, several authors have suggested an association between binge drinking and SAUD, either by demonstrating qualitatively similar impairments among those populations (Maurage et al., 2012) or by showing an increased risk to develop SAUD in adulthood when having binge drinking habits during adolescence (Bonomo et al., 2004). According to this continuum hypothesis (Enoch, 2006), binge drinking might also be characterized by an imbalance between reduced inhibitory control (resulting from an underactive reflective/control system) and enhanced attraction towards alcohol-related cues (caused by an overactive reflexive/reward system), which would facilitate the transition towards SAUD (Carbia et al., 2018). Although impairments in executive functioning have been extensively demonstrated in binge drinking in the past decades (Hartley et al., 2004; Parada et al., 2012; VanderVeen et al., 2013), the alterations of the reflexive/reward system and their interactions with deficits in the reflective/control system need to be further explored to determine the validity of the dual-process perspective in this subclinical population (Lannoy et al., 2020).

4. Theoretical assumptions regarding AB

A key prediction shared by dominant theoretical models is that the alcohol-related AB would subsequently contribute to higher craving, consumption behaviour and thus elevated relapse risk (Field & Cox, 2008). The most influential theoretical frameworks of alcohol addiction thus assume that AB, indexing the over-activation of the reflexive/reward system, is a central feature of SAUD onset and persistence.

Despite the massive lack of knowledge that remains about the processes underlying AB, these theoretical predictions led researchers to make strong inferences regarding the nature of AB. Namely, it is most often implicitly or explicitly considered that AB is (1) directly related to alcohol use severity, (2) automatic and offering a specific index of the overactivation of the reflexive/reward system when facing alcohol-related stimuli, (3) stable and potentially permanent, (4) independent of any influence of reflective abilities, and (5) specific to alcohol-related stimuli. Given the heterogeneity of experimental evidence and the massive lack of reliable data regarding the nature of alcohol-related AB in the current literature (see Chapter 2), these strong assumptions appear premature and will be challenged in the following sections.

4.1. AB increased with alcohol use severity

Most theoretical frameworks assume that AB would progressively emerge as a consequence of classical conditioning from previous experiences, during which the individual has been repeatedly confronted with the association between substance-related stimuli and beneficial outcomes such as social disinhibition or reduced negative emotions (i.e., “reward history” according to learning models; Anderson, 2013; Marchner and Preuschhof, 2018) and/or through repeated alcohol exposure reducing top-down control (according to dual-process models; Noël et al., 2010; Wiers et al., 2007). In this view, AB would then constitute a long-lasting characteristic of SAUD once the disorder is established. Therefore, a first shared prediction of dominant theoretical models is that alcohol AB should be observed in most excessive drinkers, and that its magnitude would be related to the frequency and severity of alcohol consumption. That is, individuals with SAUD would present a stronger alcohol-related AB than subclinical populations, themselves presenting a stronger bias than low drinkers or non-drinkers.

4.2. AB relies on early and automatic processes

Although AB is usually considered as an index of reflexive/reward system’s overactivation, giving rise to automatic and uncontrolled behaviours, its automatic nature has not been thoroughly tested in the literature. The definition of automaticity is still related to a lot of debates (Moors, 2016), but specific criteria have been proposed to determine the automatic nature of a psychological process, including unconsciousness, efficiency, unintentionality and uncontrollability (Moors & De Houwer, 2006). Moreover, in addition to the lack of consensus concerning the definition of automaticity, previous explorations were not designed to assert the automatic nature of AB, since the behavioural paradigms most commonly used to assess AB are not suited to dissociate early automatic processing stages from later more controlled ones. Indeed, they mostly relied on reaction time (RT) measures, which are only indexing the final output of all the successive stages involved in alcohol cues processing and thus cannot offer sufficient insight into AB time course.

As most thoroughly described in the following section, several studies have attempted to distinguish different levels of attentional processing through the manipulation of stimulus presentation's duration in AB tasks (Vollstädt-Klein et al., 2009; Noël et al., 2006). Nevertheless, there is no consensus in the literature regarding the time frame required to shift or disengage attention from a single cue, as it highly depends on stimuli complexity. This prevents from drawing any clear-cut conclusion based on RT results.

Furthermore, would AB indeed be automatic, its attentional specificity should also be questioned, as low-level perceptual features of stimuli influence attention allocation. AB might thus be modulated by early cognitive processes occurring before the attentional stages. For example, Harrison and McCann (2014) showed that some salient visual properties (e.g., color) of neutral cues reduce the magnitude of AB toward alcohol cues in social drinkers. AB could thus also partly rely on perceptual differences between stimuli rather than on purely attentional processes.

4.3. AB is stable

Another theoretical assumption directly resulting from theoretical models is that the neuroadaptations resulting in alcohol-related AB (e.g., dopaminergic sensitization; Robinson & Berridge, 1993) would be stable (i.e., constantly present once instantiated) in individuals with an history of excessive alcohol use. Without the support of experimental evidence, most traditional models assume that AB progressively develops through associative learning and/or reflexive/reward system over-sensitization, finally constituting an enduring and potentially permanent SAUD characteristic (Robinson & Berridge, 1993; Hardman et al., 2021). Hence, these models understated the sensitivity of AB to momentary motivational states compared to the influence of stable SAUD-related factors (e.g., duration, severity). The consistency of AB through contexts and time is thus supposed to be a core characteristic of SAUD. Moreover, it constitutes a prerequisite for the clinical implementation of attentional bias modification (ABM), since a highly unstable AB would hamper its valid measurement and thus lose the interest to re-train it. Nevertheless, narrative reviews (Christiansen et al., 2015a; Field et al., 2014) have raised doubts regarding AB stability. Indeed, they have underlined the presence of AB fluctuations, particularly according to current motivational states affected by environmental and internal factors (e.g., stress, subjective craving or alcohol cue exposure).

These findings led Field et al. (2016) to reconsider the predictions shared by most theoretical models regarding AB by underlining their overstatement of its stability. An alternative theoretical account thus emerged whereby AB is the expression of the momentary motivational evaluation of substance-related stimuli (Field et al., 2016). Specifically, AB would arise from momentary changes in evaluations of these stimuli that can be positive (when the incentive value of the substance is high), negative (when individuals have a goal to stop drinking), or both (when individuals experience motivational conflict). According to the valence [positive, negative or both (i.e., ambivalence)] of the evaluation of a substance-related cue, individuals may maintain their gaze on it or conversely ignore it, resulting in different AB patterns (Field et al., 2016).

4.3.1. Association between AB and craving

As previously described, theoretical models (Franken, 2003; Robinson & Berridge, 1983; Ryan, 2002) already suggested a positive (and mutual excitatory) relationship between AB and subjective craving, resulting in a vicious circle ultimately leading to alcohol consumption (Field & Cox, 2008). Therefore, a prediction shared by existing theories is that AB reflects an underlying appetitive motivational process, and is thus positively associated with subjective craving. Consequently, motivational state might influence the expression of AB (Robinson & Berridge, 1993). However, these models postulated that AB is constantly present in individuals with alcohol use disorder once the alcohol-related cues have acquired incentive salience. Hence, while they recognize that AB might slightly vary between or within individuals according to their motivational state, they assume that the attentional processing of these cues strongly differs from healthy subjects, regardless of the current motivational state.

4.3.2. AB is directed towards alcohol

Importantly, the involvement of appetitive motivational processes in AB does not exclude a potential influence of aversive motivational processes and motivational conflict (i.e., ambivalence between appetitive and aversive processes) in AB (Field et al., 2016). Specifically, people who want to reduce their alcohol consumption might experience aversion or ambivalence about alcohol-related cues, and thus evaluate them negatively. Consequently, those people may attempt to override their alcohol-related AB in order to regulate their emotional response or subjective craving. Patients with SAUD recently or currently involved in a detoxification process and hence attempting to remain abstinent might exhibit a pattern of AB that is qualitatively different (i.e., avoidance AB away from alcohol) from the one seen in heavy drinkers, who are not attempting to abstain or reduce their drinking habits and might thus present an AB toward alcohol.

Overall, these appetitive and/or aversive motivational states regarding alcohol-related stimuli might thus highly fluctuate between and particularly within individuals, questioning previous conceptualizations of alcohol AB as a relatively stable characteristic of alcohol use disorder once established (Robinson & Berridge, 1993; Wiers et al., 2007). AB stability is a key issue for the clinical implementation of rehabilitation programs, as it is supposed that AB measures give a reliable index of the presence and extent of AB in each individual (which notably determine the decision to rehabilitate these AB). Would AB be labile and strongly varying with short-term environmental or internal contingencies, the usefulness and reliability of its evaluation and training in clinical context would be strongly questioned.

4.4. AB is a pure index of the reflexive/reward system's overactivation

The presence of AB is the most frequently used behavioural index to characterize the modification of the reflexive/reward system, its occurrence in patients with SAUD being commonly considered as the behavioural result of the reflexive/reward system's overactivation. However, it remains unclear whether the reflective/control system might also play a role in the occurrence of AB. Indeed, dual-process models stated that situational factors such as cognitive load could selectively impair the reflective/control system, leading the reflexive/reward system to take the lead (therefore assuming a continuous interaction between systems). Nevertheless, they simultaneously stated that reflexive/reward processes operate in an effortless manner, independently from reflective processing and cognitive resources (Hofmann et al., 2008; Strack & Deutsch, 2004).

According to the biased competition model of selective attention (Kastner and Ungerleider, 2000), the attentional capture of salient cues (e.g., threat or alcohol-related stimuli) is determined by both bottom-up sensory mechanisms sensitive to stimuli salience and top-down control mechanisms prioritizing the processing of task relevant stimuli. Such interaction between automatic and controlled processes has also been suggested by Field and colleagues (2010). They postulated that response inhibition moderates the influence of AB on alcohol-seeking behaviour but that this moderating effect would be reduced when drinking alcohol, as alcohol exposure increases AB and impairs inhibitory abilities. Similarly, Goldstein and Volkow (2002) proposed the existence of the “impaired response inhibition and salience attribution” syndrome, leading to the proposal that inhibition deficit and increased salience toward drug-related cues would both be caused by frontal cortex disruption in drug addiction and would be involved in AB.

In the same line, previous research in anxiety has shown that AB toward salient stimuli are no longer observed when increasing the perceptual load of the task, suggesting the involvement of high-level and non-attentional cognitive functions to inhibit distractor processing and facilitate task-relevant ones (Pessoa et al., 2005). Moreover, previous studies in substance use disorders have shown that AB could at least partly vary following changes in higher-level cognitive abilities related to the reflective/control system, like executive control. For example, Liu et al. (2011) found that cocaine-dependent patients with poor inhibitory control showed stronger AB toward cocaine-related words, compared with control participants (CTL) or patients without inhibition deficits. Even the addiction Stroop task, commonly used to measure AB in SAUD, requires to inhibit a predominant response (i.e., reading the word) in favour of a largely less automated one (i.e., naming the color of the word). The possible implication of reflective functioning in the reported AB thus raises doubt on the validity of AB measures to specifically index the reflexive/reward system’s functioning.

4.5. AB is specific to alcohol-related stimuli

Previous studies have mostly investigated the presence of AB toward alcohol-related stimuli compared with non-alcohol-related and emotionally neutral stimuli. Thus, the generalization of the observed alcohol-related AB toward other rewarding stimuli cannot be excluded. Recent research among student drinkers have compared alcoholic stimuli with non-alcoholic appetitive stimuli (i.e., soft drink) and/or neutral stimuli, and have shown stronger AB for both appetitive cues (Pennington et al., 2019; Qureshi et al., 2019). However, what can be considered as a neutral or appetitive non-alcoholic stimulus remains unclear, since various studies used soft drinks or water pictures as neutral cues, whereas more recent ones used them as appetitive cues. Further work is needed to clarify the concept of appetence and the distinct appetitive value of alcohol compared with other stimuli reducing thirst or hunger before challenging AB specificity, as a generalized AB toward all appetitive cues without any preference for the alcohol-related ones would undermine the validity of the aforementioned assumptions regarding AB.

5. AB evaluation

Capitalizing on the theoretical proposal that AB constitutes a key factor in alcohol use disorders, numerous experimental paradigms have emerged to quantify this bias (Table 1). While most of them relied on behavioural measures (i.e., RT and accuracy), a recent surge of interest has emerged for the assessment of AB through the use of neuroscience tools, notably eye-tracking.

Table 1. Overview of experimental AB paradigms frequently used.

Paradigm	Description
Visual probe task (VPT)	The task requires participants to process a probe, following a cue, as quickly and correctly as possible. First, two pictures (cues), one representing an alcohol-related stimulus (e.g., alcoholic beverage bottle) and one a neutral stimulus (e.g., non-alcoholic beverage bottle), are displayed on the left and right side of a computer screen, respectively. Second, they are replaced by a probe appearing at the location previously occupied by one of the pictures. Participants have to process the probe (e.g., to determine the upwards or downwards direction of an arrow constituting the probe). Faster responses to

	probes appearing at the location previously occupied by the alcohol-related cue (compared with the neutral cue) reflect AB toward alcohol-related stimuli.
Alcohol Stroop task	The task requires participants to name as quickly as possible the color of alcohol-related and neutral matched words presented in different font colours. Slower responses to alcohol-related words compared with neutral ones index alcohol-related AB, assuming that the increased automatic allocation of attentional resources to the semantic processing of alcohol-related words slows down colour naming for these words.
Free viewing task	The task requires participants to freely explore the presented stimuli, either depicting a grid of pictures or complex scenes with alcoholic and non-alcoholic cues. This task is usually combined with eye-tracking measures to analyse eye movements during the exploration.
Flicker induced-blindness paradigm	The task requires participants to detect a brief change in sub-parts of complex stimuli, either depicting real world scenes or a grid of alcohol-related and neutral pictures. Alcohol AB are indexed by a faster or more frequent detection of changes concerning alcohol-related stimuli.
Gaze contingency paradigm	The task requires participants to stare a fixation target and refrain from producing a saccade towards the neutral or alcohol-related distractors appearing in other parts of the screen. The dependent measure is the comparison of “break frequency” rates (i.e., the number of times a participant erroneously looks at the peripheral stimulus) related to neutral and alcohol-related stimuli. The task specifically measures the ability to inhibit the orientation of attentional resources towards peripherally appearing alcohol-related stimuli.
Odd-One-Out task	The task requires participants to indicate whether images in a matrix are from the same category (i.e., alcoholic drinks, non-alcohol drinks or other objects) or whether there is an odd-one-out (i.e., target image). Engagement index is calculated by subtracting the mean RT for *the alcohol target in neutral distractors trials* from the mean RT for the *neutral target in neutral distractors trials*. Disengagement index is calculated by subtracting the mean RT for the *neutral target in neutral distractors trials* from the mean RT for the *neutral target in alcohol distractors trials*. Positive scores respectively reflect attentional engagement with alcohol-related cues and difficulty to disengage attention from alcohol-related cues.
Attentional blink paradigm	The task requires participants to report two targets presented in a rapid serial visual presentation stream, with a various time lag between them. The identification of the first target is supposed to temporarily reduce attentional resources, causing the attentional system to blink, such that subsequent stimuli cannot be fully encoded until attention recovers. This deficit in the identification of the second target generally appears at short lags (<500ms). The absence of this attentional blink for alcohol-related second target suggests an increased efficiency to process these cues at early levels, indexing the presence of an alcohol AB.

Cued VPT	The task is a cued version of the VPT with priming cues predicting the location of alcohol-related or neutral stimuli.
Rapid serial visual presentation task	The task requires participants to detect either an alcohol or a non-alcohol target in a stream of 9 rapidly presented objects, and ignore alcohol or non-alcohol distractors presented in task-irrelevant parafoveal locations. A detection sensitivity index is computed based on the proportion of hits and false alarms recorded for alcohol or non-alcohol targets, with the presence of alcohol or non-alcohol peripheral distractors.
Spatial cueing task	The task requires participants to direct their attention towards alcohol cues (approach-alcohol block) or non-alcohol cues (avoid-alcohol block), which are randomly presented to the left or right side of a fixation cross. On 25% of all trials, a probe (i.e., an abstract arrow pointing up or down) appears after the stimulus. The probe is located at the attended position on 80% of the trials (valid cue trials), and on the opposite side for the remaining 20% of trials (invalid cue trials). Participants have to indicate the orientation of the arrow. Faster responses to probes appearing at the location previously occupied by the alcohol-related cue (compared with the non-alcohol cue) in valid and invalid trials reflect AB toward alcohol-related stimuli.
Alcohol-change detection task	The task requires participants to detect whether a change has occurred in a grid comprising four images. Five type of trials are presented with equal frequency: alcohol-alcohol (i.e., all images originally alcohol-related, one changing into different alcohol-related image), alcohol-neutral (i.e., all images originally alcohol-related, one changing into a neutral image), neutral-alcohol (i.e., all images originally neutral, one changing into an alcohol-related image), neutral-neutral (i.e. all images originally neutral, one changing into a neutral image) and no-change (i.e., no change occurring) trials. Participants respond by clicking on the right-hand button when a change occurred, and on the left-hand button when no change is perceived. Sensitivity to change (indexing alcohol-related AB) is measured via a d-prime based on hit and miss rate.
Visual search task	The task requires participants to detect in a matrix a target image of the search category named before the beginning of the task. The matrix is composed of 15 images from the same category (alcoholic or non-alcoholic drinks) and one different image (target stimulus). AB index is calculated by subtracting the mean RT for *alcohol target trials* from the mean RT for *alcohol distractors trials*. Higher positive scores reflect stronger AB for alcohol.
Selective-attention/ action-tendency task	The task requires participants to identify a first probe and then keep or shift their attentional focus (selective-attention assessment trials) or hand (action-tendency assessment trials) on the location of the first probe to identify a second probe and report whether their orientation was matched. An alcoholic or non-alcoholic beverage image appears between the presentation of the two probes. AB is indexed by facilitated response times on trials requiring shifting towards the alcohol relative to non-alcohol stimuli (engagement trials), or by impaired response times on trials that require shifting away from the alcohol relative to non-alcohol stimuli (disengagement trials).

Visual conjunction search task	The task requires participants to detect whether a left-hanging alcoholic or non-alcoholic target is present or absent within arrays of alcoholic and non-alcoholic distractors. Participants respond by clicking on the target location with the computer mouse when the target is present, and clicking anywhere within the black background surrounding the array when the target is absent. The dependent variable is the RT for correct responses, with quicker RT for alcoholic targets indexing alcohol-related AB.
Dual task paradigm	The task requires participants to perform an odd/even decision task with a centrally presented number while also performing a peripherally presented lexical decision task with alcohol-related or neutral words. Participants are then asked to recall the words presented in the peripheral task.

5.1. Behavioural measures

An initial narrative review of behavioural studies exploring AB presented encouraging results (Field & Cox, 2008): in line with dominant models, the authors suggested that alcohol-related AB is developed through classical conditioning and presents relationships with key alcohol-related factors (e.g., craving, impaired executive functions, abstinence motivation). Meta-analyses further demonstrated a weak but significant relationship between substance-related AB and craving or impulsivity (Field et al., 2009; Leung et al., 2017). However, other narrative reviews highlighted serious methodological and statistical limitations in studies linking AB and alcohol use (Christiansen et al., 2015a; Field et al., 2014).

Indeed, the RT measures derived from those paradigms show poor internal reliability (Ataya et al., 2012). Moreover, inferring AB exclusively through RT measures raises concerns, as such measures relied on hand movements and could thus be biased by potential deficits in motor responses. More centrally, RT measures in the most frequently used visual probe task (VPT) only offer information about the location at which participants focused their attention at the specific time of probe onset, without indexing the global stream and successive steps of attentional processing involved in AB (Field & Cox, 2008). This concern has been further reinforced by studies showing that when manipulating stimulus presentation's duration, the results obtained for short durations (e.g., 50–200ms) largely differed from those obtained with long (e.g., 500–2000ms) ones (Field et al., 2013). For example, Vollstädt-Klein et al. (2009) showed that patients with SAUD and light social drinkers both presented approach AB toward alcohol-related cues presented for 50ms, but that the reverse pattern (i.e., avoidance AB for alcohol-related stimuli) was observed for cues presented during 500ms. These findings underline the need to distinguish early (i.e., initial attentional orienting) and late (i.e., attention maintenance) processes related to AB. Nevertheless, such exploration of AB time course remains impossible through the unique use of RT measures.

In the same vein, the interpretation of the direction of AB could be particularly ambiguous when using the addiction Stroop task, as attempts to avoid processing alcohol-related words might also result in Stroop interferences for such words (Klein, 2007). Here again, the mere RT measures previously used prevent from testing this alternative proposal. Thereby, although the crucial role of alcohol-related AB in the maintenance of SAUD is strongly suggested at clinical and theoretical levels, its evaluation is still facing important limits. Indeed, the behavioural measures do not allow distinguishing between different AB patterns (e.g., initial shifting, attentional engagement, attentional maintenance or disengagement, Stacy & Wiers, 2010). A recent paper (Pennington et al., 2021) listed these methodological shortcomings, including the use of unreliable tasks and inappropriately matched control stimuli, or the high variability in design and statistical analyses across studies. Some researchers therefore developed novel paradigms to enhance the reliability of AB measures and explore its underlying components (i.e., attentional engagement, shift or disengagement; Heitmann et al., 2020; 2021; Sharbanee et al., 2013). Such approach could help to determine whether AB is also characterized by a difficulty to disengage attention from alcohol-related stimuli, beyond the increased attentional engagement towards these stimuli (Soleymani et al., 2020). An enhanced understanding of AB, beyond unreliable behavioural measures, is therefore needed to refine theoretical models. Such refining would clarify the genuine role played by AB in alcohol use disorders and could promote new interventions to reduce AB.

5.2. Eye-tracking measures

An efficient way to determine the genuine potential of AB paradigms for applied research and clinical implementation is to disentangle the processes involved in AB through innovative measuring tools. To do so, one way is to go beyond traditional behavioural measures, not only by using alternative experimental paradigms (e.g., change detection paradigms) that offer a more accurate exploration of the processes underlying AB, but also by using eye-tracking measures.

This non-invasive technique measures the consecutive gaze positions throughout the task with a high temporal resolution, informing on the time course of eye movements (Popa et al., 2015). Various eye movements can be indexed, among which fixations (i.e., maintenance of the visual gaze on a specific location), saccades (i.e., coordinated movement of both eyes from one fixation point to another) and smooth pursuit (i.e., following a target moving in a predictable way) are particularly relevant in assessing cognitive processes (Leigh and Kennard, 2004; Lisberger, 2010). Visual acuity is heterogeneous across the visual field: the fovea presents the highest visual acuity and offers the sharpest vision. Saccadic eye movements allow bringing peripheral visual stimuli to the fovea for fine-grained visual analysis. Visuomotor and perceptive processes can thus be indexed by the amplitude, velocity or duration of these saccades (Leigh and Kennard, 2004), while shifts of visual attention are explored through saccade direction measures. Such attentional shifts can be goal-directed (voluntary) or stimulus-driven (involuntary), these systems interacting during perception while being sustained by partially segregated brain networks (Corbetta and Shulman, 2002). When visual objects are moving, smooth pursuit keep them on the fovea. Foveal fixations are considered as points of overt attention, the direction of the gaze being tightly linked to attentional focus (Deubel and Schneider, 1996).

Eye-tracking can also index attentional processes by measuring (1) the initial attentional capture occurring quickly and early during a trial, mostly through first saccadic latency (i.e., time between stimulus onset and the start of the first recorded saccade) and first area of interest (AOI) visited (i.e., first zone of the stimulus targeted by a fixation); (2) processes related to the controlled maintenance of attention, centrally through dwell time (i.e., overall fixation time on each AOI) and number of fixations (i.e., number of times a fixation is made on an area). Whereas traditional behavioural results only offer an indirect AB measure (i.e., the final processing output), the eye-tracking technique directly and precisely measures the consecutive steps involved in attentional processing, deepening the understanding of the core mechanisms and processes (Armstrong & Olatunji, 2012). The combination of eye-tracking with behavioural tasks thus clarifies the spatial and temporal dynamics of AB, from the initial orientation to the later stages of attentional processing. Moreover, while the eye-tracking methodology has been widely used to assess attention and visual perception, it can also explore higher-level cognitive processes like memory or executive functions (Eckstein et al., 2017; König et al., 2016).

To date, eye-tracking studies in alcohol use disorders are limited to nonclinical populations presenting low or heavy alcohol consumption (Maurage et al., 2020b for a recent systematic review). While the use of eye tracking in alcohol use disorders has been massively focused on the exploration of AB towards alcohol-related stimuli, three studies explored perceptive impairments, four measured the impact of alcohol use on the executive processes related to eye movements, and one measured emotional processes through pupillary dilatation. Regarding perceptive abilities, heavy drinkers present impaired smooth pursuit as well as saccadic latency/velocity during alcohol intoxication (King and Byars, 2004). The increased tolerance associated with drinking habits might lead to a partial reduction of these impairments (Roche and King, 2010), but heavy drinkers nevertheless present a reproducible pattern of eye movement deficits (for smooth pursuit gain and saccadic efficiency) during high alcohol intoxication (Roche et al., 2014). Concerning executive functions, alcohol intoxication impairs inhibitory control of saccades (Roberts et al., 2014) in social drinkers. Independently of alcohol intoxication, adolescents at high risk for substance use have a reduced inhibitory control on eye movements (Iacono et al., 2000). The use of alcohol-related stimuli reduces conditioned inhibition learning in frequent drinkers (Laude and Fillmore, 2015) but does not influence the impact of oculomotor inhibition training on alcohol consumption (Jones and Field, 2013). Regarding emotional processing, a globally increased pupillary reactivity has been shown in severe AUD, but this modification might disappear with long-term abstinence (Claisse et al., 2016).

With regard to AB, an AB towards alcohol-related cues has been identified among heavy drinkers during alcohol intoxication, but results are not coherent regarding the modulation of AB by drinking habits. It had initially been postulated (Schoenmakers et al., 2008) that AB would be absent during sobriety, while more recent works have argued that alcohol intoxication does not influence AB in heavy drinkers (Fernie et al., 2012; Miller and Fillmore, 2011) or even reduces it (Weafer and Fillmore, 2013). In the absence of alcohol intoxication, adolescent heavy drinkers do not present AB indexed by reaction time measures but have increased controlled attention (McAteer et al., 2015) and dwell time (McAteer et al., 2018) towards alcohol-related stimuli. Conversely, young adult drinkers present a robust AB (better indexed by eye tracking than behavioural measures) for simple (but not complex) alcohol pictures (Ceballos et al., 2009; Miller and Fillmore, 2010), which appears mostly related to modifications of the high-level attentional processes (Monem and Fillmore, 2017) and to reduced inhibitory control on saccadic movements (Wilcockson and Pothos, 2015). The evaluation of AB presents increased reliability when using eye tracking indexes (compared to behavioural performance measures) and personalized stimuli (Christiansen et al., 2015b), and AB is better evidenced by dynamic eye tracking measures (Roy-Charland et al., 2017). It might be increased by reward expectancy (Jones et al., 2012), craving (Hobson et al., 2013) and low alcohol ambivalence (Lee et al., 2014), but other studies have suggested that it is independent of craving, positive alcohol expectancies (Field et al., 2011), consumption intention (Wilcockson et al., 2019), as well as actual consumption and mental disabilities (Van Duijvenbode et al., 2017a). AB is absent in individuals with long term abstinence (Van Duijvenbode et al., 2012). It appears substance-specific, as it is absent in cocaine-dependent individuals (Marks et al., 2015), but it might be generalized to stimuli considered as appetitive for the participant (Qureshi et al., 2019). ABM training can reduce AB in problematic drinkers, this change being centrally related to an increase in controlled alcohol avoidance (Lee and Lee, 2015).

5.3. Other neuroscience measures

In a complementary way, neuroscience tools such as electroencephalography (EEG) and functional magnetic resonance imaging (fMRI) can be used to determine the neural activation underlying the different processes of alcohol AB. On one hand, the study of brain electrical activity through EEG allows to measure the neurofunctional brain response evoked by alcohol-related stimuli with high temporal resolution, thus providing major insights on the early brain processes involved when exposed to alcohol-related stimuli (Almeida-Antunes et al., 2022). Most studies using EEG to evaluate alcohol-related AB have focused on the P300 and Slow Potential components of event-related potential (ERP; Littel et al., 2012), two electrophysiological indices of cognitive processing consistently associated with the allocation of attentional resources. A meta-analysis on electrophysiological indices of cognitive biases for substance-related stimuli indicated enhanced electrophysiological processing of substance-related stimuli in substance users compared to CTL, as reflected by larger P300 and Slow Potential amplitudes in response to these stimuli (Littel et al., 2012). In the same vein, a narrative review conducted on the relevance of ERP in alcohol use disorders has suggested that a reduced P300 amplitude to alcohol cues might be a reliable biological predictor of abstinence in recently detoxified patients with SAUD, but these results remain to be confirmed (Campanella et al., 2019). On the other hand, the study of brain activation through fMRI allows to investigate the neural basis and brain correlates of alcohol-related AB. For example, a fMRI study conducted in patients with SAUD showed that AB scores on VPT were associated with cue-induced fMRI activation in response to alcohol-related stimuli in the anterior cingulate cortex and thalamus (usually implicated in attentional processing), areas of the cortico-striatal circuit (prefrontal areas, ventral and dorsal striatum) and the insula (usually involved in emotional processing; Vollstädt-Klein et al., 2012).

Nevertheless, these neuroscience tools are usually combined with cue-reactivity paradigms since they require the exposition to a single stimulus per trial in order to dissociate the neural activations specifically elicited by alcohol-related cues. Hence, although these specific EEG and fMRI indices of brain activation could be used as indirect measures of AB, they do not allow to investigate the specific processes involved in the preferential allocation of attentional resources towards alcohol-related stimuli when confronted with neutral ones, in contrast to eye-tracking measures.

6. ABM

An increased understanding of AB, going beyond unreliable behavioural measures, is needed to refine theoretical models by clarifying the genuine role played by AB in alcohol use disorders. This would eventually lead to the development of new interventions to reduce this bias, and hence relapse risk among patients. In this respect, a growing enthusiasm was observed for cognitive bias modification (CBM) over the last decade, these interventions aiming to directly manipulate reflexive/reward processes through task contingencies (MacLeod & Matthews, 2012). Those processes usually refer to alcohol-related AB and approach biases. Among the different ABM programs, a modified version of the VPT has been widely implemented in clinical settings to retrain AB (Heitmann et al., 2018). In this version, a contingency is created so that the probe mainly or always (depending on the ratio used) appears behind the non-alcohol stimuli, the rationale being that patients with SAUD would progressively and implicitly learn to shift their attention toward non-alcohol stimuli and away from alcohol stimuli, as this strategy would improve task performance (Heitmann et al., 2018).

Those CBM interventions have been considered particularly promising to potentially address the persistent lack of effective therapeutic settings in SAUD (Verdejo-Garcia et al., 2023), which contributes to the maintenance of its personal and societal burden. As previously described, SAUD is associated with the largest treatment gap in mental health disorders (Kohn et al., 2004), and is characterised by a massive relapse rate one year after detoxification (Maisto et al., 2018). This high relapse risk thus questions the efficiency of the rehabilitation programs currently offered. Understanding the key factors involved in the emergence and persistence of alcohol misuse is therefore urgent to improve the preventive and treatment strategies, and in fine efficiently reduce SAUD and subclinical excessive drinking patterns. However, these clinical promises are hampered by the scattered state of the current research on alcohol-related AB.

To date, existing reviews on the efficacy of ABM interventions on alcohol use disorders have provided mixed conclusions (Boffo et al., 2019; Christiansen et al., 2015a). A meta-analysis conducted by Cristea et al. (2016) strongly questioned the clinical relevance of CBM interventions in addiction by showing a small positive effect of these interventions on substance use outcomes that they attributed to the risk of bias. However, Wiers et al. (2018) argued that their conclusion was invalid because their analysis included both laboratory studies with student participants not motivated to change their alcohol consumption, and randomized controlled trials among patients with strong abstinence motivation. When focusing on the latter study type, they demonstrated small but robust effects of CBM on treatment outcomes when integrated into clinical treatment followed by patients with SAUD. Heitmann et al. (2018) further recommended to provide multiple ABM sessions to enhance the clinical effects of such interventions, although they argued that no clear conclusions could be drawn about their effectiveness on addiction symptoms. They also highlighted the surprising absence of association between those treatment outcomes and baseline AB or AB changes after intervention. For example, the largest study exploring ABM in patients with SAUD (Rinck et al., 2018) demonstrated its positive effect on success rate at one-year follow-up but surprisingly did not find any alcohol-related AB at baseline (most patients rather showing an avoidance bias for alcohol-related cues) or any reduction of AB following intervention sessions. These lively debates regarding the clinical relevance of ABM paradigms might be partly explained by the lack of understanding of the underlying mechanisms at stake, leading to inappropriate measures and interventions, ending up in inconsistent experimental findings regarding AB evaluation and modification.

7. Conclusion

In this chapter, we have introduced the two drinking patterns of interest in the present thesis, namely binge drinking and SAUD, and how they can be related to different levels of severity on the same continuum given their qualitatively similar but quantitively different cognitive and cerebral impairments. We further described them through the theoretical conceptualizations made by the dominant models in addiction. According to the incentive-sensitization theory, repeated alcohol exposures would result in the over-sensitization of the reflexive/reward brain system and subsequently lead to increased "attention-grabbing" properties of alcohol-related cues (i.e., alcohol-related AB). Dual-process models further postulated that alcohol use disorders would result from an imbalance between this over-activated reflexive/reward brain system and an under-activated reflective/control brain system. Those models led to the emergence of five main theoretical assumptions regarding AB, suggesting that AB is (1) positively related to alcohol use severity; (2) underpinned by automatic and attentional processes; (3) stable and unaffected by transient motivational states; (4) not influenced by the reflective/control system's activity; and (5) specific to alcohol-related stimuli. Following the importance given by theoretical models to this AB in the development and persistence of SAUD, various paradigms were developed. While its assessment was initially based on unreliable behavioural measures, the combination of these paradigms with eye-tracking and other neuroscience measures offer major insights on the underlying processes of AB. Importantly, a more appropriate evaluation of AB might help us to experimentally test the main theoretical assumptions made about AB and determine the clinical relevance of its modification.

Chapter 2

A systematic review of AB in alcohol use disorders

This chapter is adapted from:

Bollen, Z., Field, M., Billaux, P., & Maurage, P. (2022). Attentional bias in alcohol drinkers: A systematic review of its link with consumption variables. *Neuroscience & Biobehavioral Reviews*, *139*, 104703.

1. Introduction

This second chapter provides the first comprehensive and systematic review of studies conducted during the last two decades on alcohol drinkers to examine the association between alcohol-related AB and alcohol consumption in behavioural, eye-tracking and neuroscience measures. Following preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines, we compared studies investigating the impact of alcohol use on alcohol-related AB in subclinical populations and SAUD, and assessed their methodological quality. We addressed five main theoretical issues identified in Chapter 1: (1) the presence of alcohol-related AB in alcohol drinkers and its links with alcohol use intensity; (2) the automaticity of AB, its time course (from early to late processing stages) and its underlying attentional processes (attentional engagement, shift or disengagement); (3) AB stability according to momentary motivational states; (4) the specific relation between AB and the over-activation of the reflexive/reward system, independent of the reflective/control system (Bechara, 2005; Wiers et al., 2007); (5) the specificity of AB for alcohol-related stimuli. We selected studies exploring the relationship between alcohol-related AB and alcohol consumption (assumption 1). We reported their specific results on the temporal dynamics of AB (assumption 2) and also focused on the specific influence of variables related to motivational state (assumption 3) and executive functioning (assumption 4). In addition, we evaluated and discussed the methodology of the reviewed studies, including the use of (non-)appetitive stimuli as control stimuli (assumption 5), and the added usefulness of eye-tracking and neuroscience tools to enhance the reliability of AB measures. Finally, we reviewed the current evidence for the beneficial therapeutic impact of evaluating and retraining AB in clinical settings.

2. Methods

2.1. Articles selection

2.1.1. Eligibility criteria

We used the PICOS procedure (Population, Intervention/Exposure, Comparator, Outcome, Setting; Liberati et al., 2009) to determine the inclusion criteria. Regarding the Population, we only considered studies on human samples, which had to include (a) participants identified as presenting excessive alcohol consumption, determined through standardized diagnosis tools (e.g., DSM-5 criteria for alcohol use disorder) or through alcohol consumption measures with validated cut-offs [e.g., score higher than 7 at the Alcohol Use Identification Test (AUDIT, Saunders et al., 1993), indexing risky consumption], or (b) a valid measure of alcohol consumption [e.g., AUDIT; Timeline Followback (TLFB, Sobell and Sobell, 1992)] and the analysis of this measure as a main variable. We thus excluded animal studies and studies in which alcohol-related measures were only considered as control/secondary variables. For Intervention/Exposure, we selected studies that included validated measures of alcohol consumption (i.e., lifetime/recent alcohol exposure). Regarding the Comparator, studies were considered if they offered a direct comparison between an experimental group with alcohol exposure and a matched control group with no/limited alcohol consumption, or a main analysis including alcohol-related measures (e.g., a correlational analysis exploring the influence of alcohol consumption on dependent variables). Regarding the Outcome, we included studies if they proposed an alcohol-related AB measure as a dependent variable. In terms of Setting, only studies proposing between-group comparisons or experimental conditions (i.e., interventional, observational, cross-sectional) were considered, thus excluding single-case or case series studies, as well as studies without experimental data (i.e., review, meta-analysis, reply, commentary, erratum, conference proceedings, study protocol).

2.1.2. Literature search

We conducted this systematic review following the PRISMA guidelines. We conducted an electronic database search using three databases (PsycINFO, Pubmed, Scopus). The procedure focused on peer-reviewed articles published in English between January 1st 2000 and July 12th 2021. The search phrase combined AB words (i.e., "bias*" AND “attention*”) and a large range of alcohol-related terms (i.e., "alcoholism" OR "alcohol dependence" OR "alcohol use disorder" OR "binge drink*" OR "heavy drink*" OR "social drink*" OR "episodic drink*" OR "college drink*" OR "alcohol”). The initial search identified 1089 papers (299 in PsycINFO, 216 in Pubmed, 574 in Scopus).

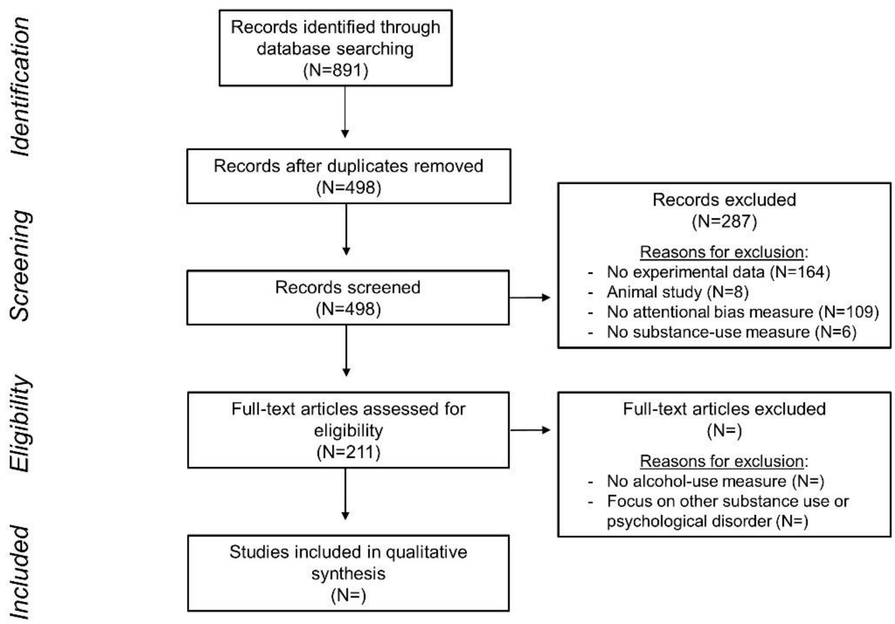

Figure 4. PRISMA flow diagram describing the selection and review process of the papers included.

We then selected the papers according to a 3-step procedure (Figure 4): First, duplicates were removed, leading to the identification of 619 unique papers. Second, title and abstracts were screened, and papers presenting at least one of the following exclusion criteria were removed: (1) no experimental data; (2) no human sample (i.e., animal study); (3) no AB measure; (4) no substance-use measure. When the title/abstract screening did not allow a clear-cut decision regarding the inclusion of the paper, it was included in the full-text reading phase. This step led to the exclusion of 363 papers. Third, we screened the 256 remaining papers through full-text reading. This led to the exclusion of 161 papers, because they (1) only considered alcohol consumption measures as control variables and/or were centrally focused on other substance abuse or psychiatric/neurological disorders and/or did not report alcohol-related results; or (2) did not include participants with diagnosed SAUD, or with a validly evaluated and clearly labelled excessive alcohol consumption pattern, or did not propose a valid measure of alcohol consumption habits; or (3) did not propose a valid measure of AB toward visual alcohol-related stimuli and/or did not report AB results before intervention. We excluded several studies that, while evaluating alcohol consumption through validated questionnaires, did not (1) report indices of drinking habits (e.g., AUDIT score, drinking frequency/quantity); (2) evaluate the influence of alcohol consumption variables on AB through correlation analyses or between-group comparisons (i.e., low versus high alcohol consumers). In the same vein, whereas many studies investigated the effect of acute intoxication on alcohol AB, our systematic review included solely those conducted on populations with chronic alcohol consumption. To increase the procedure reliability, two independent judges performed the literature search. This procedure ended up in the inclusion of 93 papers in the systematic review process.

2.2. Methodological quality assessment

We evaluated the methodological quality of each study using an adapted version (Maurage et al., 2020b) of the "Quality assessment tool for observational cohort and cross-sectional studies", developed by the National Heart, Lung and Blood Institute (NHLBI, 2014). This scale appeared as the most appropriate for the cross-sectional studies included. However, we performed several adaptations to address our specific needs. Firstly, we removed two items that were not pertinent (i.e., item 3: “Was the participation rate of eligible persons at least 50%?”; item 13: “Was loss to follow-up after baseline 20% or less?”). Secondly, we split some items including sub-questions (i.e., item 4 for participants’ selection, item 5 for statistical analyses, item 9 for exposure measures, item 11 for outcome measures and item 14 for confounding variables). The adapted version of the methodological assessment scale used here thus comprised 19 items with a binary answer (Yes/No, corresponding to scores of 1/0), leading to a maximum score of 19. The percentage of "Yes" items was computed, leading to a global quality rating (poor: <50%; fair: 50%-69%; good: 70%-79%; strong: 80% and beyond, adapted from Black et al., 2017). To increase the procedure reliability, two independent judges performed the quality assessment. Assessment discrepancies were then discussed with the last author to obtain a consensus.

2.3. Data extraction and synthesis

Firstly, the main results related to quality assessment are described. Secondly, a brief overview of the characteristics presented by the selected studies is reported. Finally, the main outcomes obtained in the included studies concerning alcohol AB are reviewed. For the sake of clarity, this latter part is organized in two sections according to the study population (subclinical populations, patients with SAUD), each divided in subsections either focusing on the most commonly used behavioural paradigms (i.e., VPT and alcohol Stroop task), alternative ones, eye-tracking and neuroscience data. Finally, each subsection successively presents the findings of studies investigating the main aims of the systematic review: (1) the relationship between alcohol-related AB and alcohol use; (2) the time course and components of AB; (3) the impact of current psychological state on the association between alcohol-related AB and alcohol use; and (4) the influence of the reflective/control system's activity on AB. Each subsection also presents the findings regarding the effect of medical or AB training interventions. We chose to emphasize between-group analyses in the result section and we thus only report correlations between AB and alcohol-use variables when studies did not perform between-group comparisons to explore the influence of chronic drinking habits on AB (note that all results are described in the Table provided by Bollen et al., 2022[1]). Moreover, findings regarding the influence of other variables (e.g., comorbidities, demographics, environmental contexts) on the relationship between AB and alcohol use are described in Appendix A.

We used a systematic data extraction procedure to individually determine the main characteristics of the included studies regarding five categories of variables, adapted from the PICOS protocol: (1) Population (sample size, age, gender ratio, exclusion criteria); (2) Exposures (psychiatric diagnosis or subclinical characteristics, alcohol consumption measure, psychopathological comorbidities); (3) Comparator [control group (presence and size), matching variables (pre-specified or not statistically differing between groups)]; (4) Experimental design (processes measured, tasks, questionnaires, stimuli used in the AB task, methodology, AB

[1] Because of the large size of the table, the synthesis of the information extracted from each study is not included in the thesis but available upon request in our systematic review published online (Bollen et al., 2022).

measurements); (5) Outcomes (results regarding alcohol AB, limitations reported, key conclusions regarding alcohol AB).

3. Results

3.1. Quality assessment (Table 2)

According to the criteria of the quality assessment tool, four studies presented strong quality, 22 good quality, 62 fair quality and five poor quality. All studies clearly defined their measures of alcohol consumption and alcohol AB, and analysed AB outcomes based on prior alcohol consumption. Most studies had clear research objectives and characterized participants' drinking pattern through standardized diagnostic tools (e.g., DSM-5 or ICD-10) or valid questionnaires (mostly AUDIT or TLFB). Moreover, the vast majority used established paradigms (mainly the VPT or alcohol Stroop task) with a controlled comparison between alcohol-related and neutral stimuli, and/or between lighter and heavier drinkers, and proposed at least two levels of alcohol consumption to investigate the relationship between alcohol use and alcohol AB. However, key limitations were frequent in the reviewed studies: several studies assessed chronic alcohol consumption using a short timeframe (i.e., less than 6 months), which could reduce the ability to detect the existence of an association between alcohol use and alcohol AB. Other studies did not sufficiently identify characteristics of the sample or confounding variables, as several recruited their participants in the general population, with very limited exclusion criteria and a weak control of comorbidities. Most studies also omitted sample size justification (most studies relying on small samples) and statistical power or effect size computation to estimate the strengths of their findings.

Table 2. Studies scoring using the adapted quality assessment tool for observational cohort and cross-sectional studies.

Studies	Score for each item																			%
	1	2	4a	4b	5a	5b	5c	5d	6	7	8	9a	9b	10	11a	11b	12	14a	14b	
Albery et al., 2015	Y	N	Y	N	Y	N	N	Y	Y	Y	Y	Y	Y	N	Y	Y	N	Y	Y	68
Baker et al., 2014	Y	Y	N	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	N	Y	Y	N	Y	Y	79
Beraha et al., 2018	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	N	Y	Y	Y	Y	Y	N	Y	Y	84
Brown et al., 2018	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	N	Y	Y	84
Brown et al., 2020	Y	Y	Y	N	N	N	N	N	Y	Y	Y	Y	Y	N	Y	Y	N	N	Y	58
Bruce & Jones, 2004	Y	Y	Y	Y	N	N	Y	Y	Y	N	Y	Y	Y	N	Y	Y	N	N	N	63
Ceballos et al., 2009	Y	Y	Y	N	Y	N	N	N	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	74
Carrigan et al., 2004	Y	Y	N	Y	Y	N	N	Y	Y	N	Y	Y	Y	N	Y	Y	N	Y	Y	68
Christiansen & Bloor, 2014	Y	Y	Y	Y	Y	N	N	N	Y	Y	Y	Y	Y	N	Y	Y	N	Y	N	68
Christiansen et al., 2015	Y	Y	Y	Y	Y	N	N	Y	Y	Y	Y	Y	Y	N	Y	Y	N	N	Y	74
Clarke et al., 2014	Y	Y	Y	Y	Y	N	N	N	Y	Y	Y	Y	Y	N	Y	Y	N	Y	Y	74
Cox et al., 2002	Y	N	Y	N	N	N	N	N	Y	Y	Y	Y	Y	Y	Y	Y	N	N	N	53
Cox et al., 2003	Y	N	Y	Y	Y	N	N	N	Y	Y	Y	Y	Y	N	Y	Y	N	Y	Y	68
den Uyl et al., 2018	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	N	Y	Y	N	Y	N	79
DePalma et al., 2017	Y	Y	Y	Y	N	N	N	Y	Y	Y	Y	Y	Y	N	Y	Y	N	Y	Y	74
Duka et al., 2002	N	Y	N	Y	N	N	N	N	Y	Y	Y	Y	Y	N	Y	Y	N	Y	N	53
Duka & Townshend, 2004	Y	Y	Y	Y	N	N	N	N	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	N	68
Elton et al., 2021	Y	Y	N	Y	Y	N	N	N	Y	Y	Y	Y	Y	N	Y	Y	N	Y	Y	68
Emery & Simons, 2015	Y	N	N	N	Y	N	N	Y	Y	N	Y	Y	Y	N	Y	Y	N	Y	Y	58
Fadardi & Cox, 2006	Y	Y	Y	Y	Y	N	N	Y	Y	Y	Y	Y	Y	N	Y	Y	N	Y	Y	79
Fadardi & Cox, 2008	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	N	Y	Y	89
Fadardi & Cox, 2009	Y	Y	N	Y	Y	N	N	Y	Y	Y	Y	Y	Y	N	Y	Y	N	Y	N	68
Fernie et al., 2012	Y	Y	N	Y	Y	N	N	N	Y	Y	N	Y	Y	Y	Y	Y	N	N	Y	63
Field et al., 2004	Y	Y	Y	Y	N	N	N	N	Y	Y	Y	Y	Y	N	Y	Y	N	Y	N	63

Field et al., 2005	Y	Y	Y	Y	N	N	N	N	Y	Y	Y	Y	Y	N	Y	Y	N	Y	Y	68
Field et al., 2007a	Y	Y	Y	Y	Y	N	N	N	Y	Y	Y	Y	Y	N	Y	Y	N	Y	Y	74
Field et al., 2011	Y	Y	Y	Y	Y	N	N	N	Y	Y	Y	Y	Y	N	Y	Y	N	N	Y	68
Field et al., 2013	Y	N	N	Y	Y	N	N	Y	Y	Y	Y	Y	N	N	Y	Y	N	N	Y	58
Fridici et al., 2013	Y	Y	N	Y	Y	N	N	N	Y	N	N	Y	Y	N	Y	Y	N	Y	Y	58
Fridici et al., 2014	Y	Y	N	Y	Y	N	N	N	Y	N	N	Y	Y	N	Y	Y	N	Y	Y	58
Garland, 2011	Y	N	Y	Y	Y	N	N	N	Y	Y	Y	Y	Y	N	Y	Y	N	Y	Y	68
Gladwin et al., 2013	Y	N	Y	Y	Y	N	N	N	Y	Y	Y	Y	Y	N	Y	Y	N	N	Y	63
Gladwin, 2017	Y	N	N	N	Y	N	N	N	Y	Y	Y	Y	Y	N	Y	Y	N	N	Y	53
Gladwin et al., 2020	Y	N	N	N	Y	N	N	Y	Y	Y	Y	Y	Y	N	Y	Y	N	Y	N	58
Groefsema et al., 2016	Y	N	N	Y	Y	N	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	74
Gunn et al., 2021	Y	N	Y	Y	Y	N	N	Y	Y	Y	Y	Y	Y	N	Y	Y	N	N	N	63
Hallgren & McCrady, 2013	Y	Y	Y	Y	Y	N	N	N	Y	N	Y	Y	Y	N	Y	Y	N	N	Y	63
Heitmann et al., 2020	Y	Y	Y	N	Y	Y	Y	N	Y	N	Y	Y	Y	N	Y	Y	N	Y	Y	74
Heitmann et al., 2021	Y	Y	Y	N	Y	Y	Y	Y	Y	N	N	Y	Y	N	Y	Y	N	N	Y	68
Heitmann & de Jong, 2021	Y	N	N	Y	Y	Y	Y	Y	Y	N	N	Y	Y	N	Y	Y	N	Y	Y	68
Hobson et al., 2013	Y	N	N	N	Y	N	N	Y	Y	N	Y	Y	Y	N	Y	Y	N	N	N	47
Janssen et al., 2015	Y	Y	Y	N	Y	N	N	N	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	N	68
Jones et al., 2002	Y	N	N	N	N	N	N	N	Y	N	Y	Y	Y	N	Y	Y	N	N	N	37
Jones et al., 2003	Y	N	N	N	N	N	N	N	Y	N	Y	Y	Y	N	Y	Y	N	N	N	37
Jones et al., 2006	Y	N	N	N	Y	N	N	Y	Y	N	Y	Y	N	N	Y	Y	N	N	N	42
Jones et al., 2012	Y	N	N	Y	Y	N	N	N	Y	Y	Y	Y	Y	N	Y	Y	N	N	Y	58
Jones et al., 2018	Y	Y	N	Y	Y	N	N	N	Y	N	Y	Y	Y	N	Y	Y	N	Y	N	58
Knight et al., 2018	Y	Y	Y	Y	Y	N	N	N	Y	Y	Y	Y	Y	N	Y	Y	N	N	Y	68
Langbridge et al., 2019	Y	Y	N	Y	N	Y	Y	Y	Y	Y	N	Y	Y	N	Y	Y	N	Y	Y	74
Luehring-Jones et al., 2017	Y	Y	N	Y	Y	N	N	Y	Y	Y	Y	Y	Y	N	Y	Y	N	Y	Y	74

Lusher et al., 2004	Y	Y	Y	N	Y	Y	Y	N	Y	Y	Y	Y	N	N	Y	Y	N	Y	N	68
McAteer et al., 2015	Y	Y	Y	N	N	N	N	N	Y	Y	Y	Y	Y	N	Y	Y	N	N	Y	58
McAteer et al., 2018	Y	N	N	N	N	N	N	N	Y	Y	Y	Y	Y	N	Y	Y	N	N	Y	47
McGivern et al., 2021	Y	Y	Y	N	N	N	N	N	Y	Y	Y	Y	Y	N	Y	Y	N	N	N	53
Miller & Fillmore, 2010	Y	N	N	Y	Y	N	N	N	Y	Y	Y	Y	Y	N	Y	Y	N	N	N	53
Monem & Fillmore, 2017	Y	N	N	Y	Y	N	N	N	Y	Y	Y	Y	Y	N	Y	Y	N	Y	N	58
Müller-Oehring et al., 2019	Y	N	N	Y	N	N	N	N	Y	Y	Y	Y	Y	N	Y	Y	N	Y	Y	58
Murphy & Garavan, 2011	Y	Y	Y	Y	Y	N	N	Y	Y	Y	N	Y	Y	N	Y	Y	N	Y	N	68
Nikolaou et al., 2013	Y	Y	Y	Y	N	N	N	Y	Y	Y	Y	Y	Y	N	Y	Y	N	Y	Y	74
Noel et al., 2006	Y	Y	N	Y	Y	N	N	N	Y	Y	Y	Y	Y	N	Y	Y	N	Y	Y	68
Pennington et al., 2020	Y	N	N	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	N	Y	Y	74
Pieters et al., 2011	Y	Y	Y	N	Y	N	N	N	Y	Y	Y	Y	Y	N	Y	Y	N	Y	Y	68
Pieters et al., 2014	Y	Y	Y	Y	Y	N	N	N	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	79
Qureshi et al., 2019	Y	Y	N	N	N	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	N	Y	Y	74
Ramirez et al., 2015a	Y	N	Y	Y	Y	N	N	N	Y	Y	Y	Y	Y	N	Y	Y	N	Y	Y	68
Ramirez et al., 2015b	Y	N	Y	Y	N	N	N	N	Y	Y	Y	Y	Y	N	Y	Y	N	Y	Y	63
Rettie et al., 2018	Y	N	Y	N	Y	Y	N	N	Y	N	Y	Y	Y	Y	Y	Y	N	Y	N	63
Roy-Charland et al., 2017	Y	N	Y	N	Y	N	N	Y	Y	Y	Y	Y	Y	N	Y	Y	N	N	Y	63
Ryan et al., 2002	Y	N	Y	Y	Y	N	N	N	Y	Y	Y	Y	Y	N	Y	Y	N	Y	Y	68
Sharbanee et al., 2013	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	N	Y	N	79
Sharma et al., 2001	Y	N	Y	N	N	N	N	N	Y	Y	Y	Y	Y	N	Y	Y	N	Y	Y	58
Sinclair et al., 2016	Y	N	Y	N	Y	N	N	Y	Y	Y	Y	Y	Y	N	Y	Y	N	Y	Y	68
Soleymani et al., 2020	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	89

Spanakis et al., 2018	Y	Y	N	Y	Y	N	N	Y	Y	Y	Y	Y	Y	N	Y	Y	N	Y	Y	74
Suffoletto et al., 2019	Y	N	Y	Y	Y	N	N	N	Y	Y	Y	Y	Y	Y	Y	N	N	N	Y	63
Tibboel et al., 2010	Y	N	Y	N	N	N	N	Y	Y	Y	Y	Y	Y	N	Y	Y	N	N	Y	58
Townshend & Duka, 2001	Y	Y	Y	N	N	N	N	N	Y	Y	Y	Y	N	N	Y	Y	N	Y	N	53
Townshend & Duka, 2007	Y	Y	N	Y	Y	N	N	N	Y	Y	Y	Y	Y	N	Y	Y	N	Y	N	63
Van Den Wildenberg et al., 2006	Y	Y	N	Y	Y	N	N	N	Y	Y	Y	Y	Y	N	Y	Y	N	Y	Y	68
Van Duijvenbode et al., 2012	Y	Y	Y	N	N	N	N	N	Y	N	Y	Y	Y	N	Y	Y	N	N	Y	53
Van Duijvenbode et al., 2016	Y	N	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	N	Y	Y	79
Van Duijvenbode et al., 2017a	Y	N	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	N	Y	Y	79
Van Duijvenbode et al., 2017b	Y	N	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	N	Y	Y	79
Van Hemel-Ruiter et al., 2015	Y	Y	Y	N	Y	N	N	N	Y	N	Y	Y	Y	N	Y	Y	N	Y	Y	63
Van Hemel-Ruiter et al., 2016	Y	Y	Y	Y	N	N	N	N	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	74
Vollstädt-Klein et al., 2009	Y	Y	N	Y	N	N	N	N	Y	Y	Y	Y	Y	N	Y	Y	N	Y	N	58
Waters & Green, 2003	Y	N	N	N	Y	N	N	N	Y	Y	Y	Y	Y	N	Y	Y	N	Y	Y	58
Weafer & Fillmore, 2012a	Y	N	N	Y	Y	N	N	Y	Y	N	Y	Y	Y	N	Y	Y	N	Y	Y	63
Weafer & Fillmore, 2013	Y	N	N	Y	N	N	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	68
Wiers et al., 2017	Y	Y	N	Y	N	N	N	N	Y	Y	Y	Y	N	N	Y	Y	N	Y	Y	58
Wilcockson & Pothos, 2015	Y	Y	Y	N	Y	N	N	N	Y	N	Y	Y	N	N	Y	Y	N	Y	Y	58
Wilcockson et al., 2019	Y	Y	Y	N	N	N	N	Y	Y	N	Y	Y	N	N	Y	Y	N	N	Y	53
Willem et al., 2013	Y	N	N	Y	Y	N	N	N	Y	N	Y	Y	Y	N	Y	Y	N	Y	Y	58

Legend: N, No; Y, Yes.

Note: Question related to each item:
(1) Was the research question or objective in this paper clearly stated?
(2) Was the study population clearly specified and defined (i.e., demographics, location)?
(4a) Were all the subjects selected or recruited from the same or similar populations?
(4b) Were inclusion and exclusion criteria for being in the study pre-specified and applied uniformly to all participants?
(5a) Was the sample size sufficiently large (higher than 20 participants per group)?
(5b) Was a sample size justification provided?
(5c) Was a power description provided?
(5d) Was a variance and effect estimates provided?
(6) For the analyses in this paper, were the exposure(s) of interest (i.e., measure of chronic alcohol-consumption) measured prior to the outcome(s) being measured?
(7) Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed (a minimum of 6 months)?
(8) For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?
(9a) Were the exposure measures (independent variables) clearly defined?
(9b) Were the exposure measures (independent variables) valid, reliable, and implemented consistently across all study participants?
(10) Was the exposure(s) assessed more than once over time?
(11a) Were the outcome measures (dependent variables, i.e., AB measures) clearly defined?
(11b) Were the outcome measures (dependent variables) valid, reliable, and implemented consistently across all study participants?
(12) Were the outcome assessors blinded to the exposure status of participants?
(14a) Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?
(14b) Were key potential confounding variables identified and discussed in the limitation section of the discussion?

3.2. Global overview

Studies explored the presence and nature of alcohol AB in populations with a vast range of drinking patterns. Sixty-nine studies recruited subclinical populations with excessive alcohol use patterns (e.g., heavy drinkers, binge drinkers, social drinkers), which had neither been diagnosed as presenting SAUD nor been involved in an alcohol-related treatment. The 'control group' will refer to healthy individuals with low alcohol consumption, when not stated otherwise. Twenty-four focused on clinical populations of patients under detoxification treatment diagnosed with SAUD (DSM-V criteria) or alcohol dependence (DSM-IV, DSM-IV-TR or ICD-10 criteria). For the sake of clarity, these patients will be described as patients with SAUD. Some studies focused solely on the relationship between alcohol AB and alcohol consumption, while others also investigated the influence of psychological variables (e.g., high-level cognitive processes, psychological states) on the association between alcohol AB and drinking habits. Sixty-six studies assessed the presence and magnitude of alcohol AB exclusively through behavioural measures. Among them, 55 used the two most classical tasks, namely the VPT (31 studies) and the alcohol Stroop task (28 studies). Seven studies combined behavioural paradigms with eye-tracking measures and 14 performed newly developed tasks focusing on eye-tracking indexes (e.g., free-viewing tasks). Finally, six studies measured the alcohol AB through neuroscience tools (e.g., EEG, fMRI).

3.3. Study findings

3.3.1. Subclinical populations

3.3.1.1. Classical behavioural paradigms

Relationship between alcohol AB and alcohol use. Nineteen studies explored the presence of AB in subclinical populations using classical behavioural paradigms. Elton et al. (2021) showed higher AB using a VPT in individuals reporting greater current binge drinking. Similar findings were found in Langbridge et al. (2019), who evaluated alcohol AB with a VPT in binge drinkers before intervention. Higher alcohol AB scores were found at baseline in binge drinkers compared to non-binge drinkers. The small sample size of non-binge drinkers calls for caution when interpreting their findings. Using a longitudinal design, Janssen et al. (2015) and Pieters et al. (2014)

investigated whether alcohol AB would be predicted by alcohol use and/or whether it would predict the development of adolescent alcohol use. In Pieters et al. (2014), alcohol-related AB in VPT did not predict changes in alcohol use. In Janssen et al. (2015), data regarding weekly alcohol use were collected at four time points (within a six-month interval) and alcohol AB was assessed at T1 and T4 through VPT and Stroop tasks. Results showed that: (1) alcohol AB at baseline was not correlated with alcohol use at any time point, (2) alcohol AB, measured by VPT, significantly predicted weekly alcohol use at each time point except T1. Alcohol AB thus did not predict early alcohol use but predicted later drinking intensity. In van Duijvenbode et al. (2012), light, moderate and heavy drinkers did not differ for RT in the VPT, showing no association between AB and drinking patterns. The composition of groups was however based on invalid AUDIT cut-off scores. Three other studies on problematic and light drinkers also found no alcohol AB among these groups (van Duijvenbode et al., 2016; 2017a; 2017b). Luehring-Jones et al. (2017) administered a VPT to young social drinkers before intervention but did not find any association between AB and alcohol use. Van Hemel-Ruiter et al. (2015) showed that alcohol AB did not correlate with adolescent alcohol use, and did not mediate the relationship between reward sensitivity and alcohol use. In Willem et al. (2013), alcohol consumption in the last 3 months did not correlate with alcohol AB in adolescents and young adults. Interestingly, three studies found an association between AB and alcohol consumption in specific populations: Emery and Simons (2015) showed a positive association between AB and alcohol use in men. Conversely, Groefsema et al. (2016) found that women presented higher AB. Finally, Pieters et al. (2011) showed an association between AB and (1) alcohol frequency/intensity only in early adolescents with an OPRM1 (i.e., polymorphism reflecting both liking and wanting processes) risk genotype; (2) problem drinking only in young adult men with DRD4 (i.e., polymorphism reflecting wanting processes) risk genotype.

Among the VPT studies, five investigated how stimuli properties might influence AB. Townshend and Duka (2001) administered a VPT using words or pictures in heavy and occasional social drinkers. Heavy drinkers showed greater AB than occasional drinkers only in the picture task. Miller and Fillmore (2010) compared AB toward simple (isolated alcohol-related cue) and complex (alcohol-related cue inserted in an elaborated scene) images in adult regular drinkers. AB was present only with simple stimuli and was associated with heavy drinking. Nevertheless, complex stimuli require the processing of non-alcohol-related features and increase the need for visual search and scan, which could lower the attentional capture by alcohol-related stimuli. The association between AB and alcohol consumption is however not consistent across studies. Groefsema et al. (2016) determined whether social drinkers show AB specific to social alcohol-related stimuli. Participants performed a VPT with alcohol-related and soft drink pictures depicting social or non-social contexts. AB was not correlated with weekly alcohol use and AUDIT. Moreover, participants presented longer RT for social pictures - independently of drink type -, suggesting stronger AB for social stimuli compared to alcohol-related stimuli in social drinkers. Christiansen et al. (2015b) showed that the reliability of the VPT and the intensity of RT-based AB was higher when using personalized stimuli among social drinkers. However, no correlation was observed between AB and alcohol consumption, thus indexing poor construct validity. Jones et al. (2018a) included personalized stimuli, repeated time measurements and different variations to improve the VPT. Results showed that: (1) AB did not change across time, (2) AB was not correlated with alcohol consumption, (3) alcohol AB toward personalized cues did not differ from AB to standardized cues. Altogether, these findings raise concerns regarding AB assessment using the VPT as its poor reliability was consistently evidenced across stimuli, analyses, and protocols.

More significant findings were observed in the eleven studies using the alcohol Stroop task. Fadardi and Cox (2008) showed that alcohol consumption was positively predicted by alcohol Stroop interference in social drinkers. Murphy and Garavan (2011) showed that AB could discriminate problem from non-problem drinkers. In Albery et al. (2015), alcohol Stroop interferences were found in heavy social drinkers (but absent in light social drinkers) - with groups based on only two AUDIT questions. In Fadardi and Cox (2009), higher alcohol Stroop interferences were found in harmful and hazardous drinkers compared to social drinkers before intervention. In a similar intervention study (Luehring-Jones et al., 2017), alcohol Stroop interference at baseline was correlated with the number of drinks per occasion in young social drinkers, but not with AUDIT score or the number of occasions per week. In Carrigan et al. (2004), alcohol Stroop interference was associated with alcohol dependence, but not with drinking frequency/quantity. Bruce and Jones (2004) explored AB through a pictorial Stroop task in light or heavy social drinkers - based on their alcohol consumption during the heaviest drinking day of the previous week. Despite the limited evaluation of chronic consumption and small sample size, the authors concluded for the presence of alcohol-related AB, indexed by higher alcohol Stroop interferences, in heavy social drinkers. In Christiansen and Bloor (2014), undergraduate social drinkers performed three versions of the task: control Stroop (containing soft drink-related words), general alcohol Stroop (containing alcohol-related words) and individualized alcohol Stroop (containing words related to participants' favourite alcohol beverages). Whereas RT did not differ across tasks, only the individualized alcohol Stroop task predicted variance in alcohol involvement, thus showing a higher predictive value for alcohol consumption when exposed to their favourite beverages. However, potential carry-over effects, due to blocked format of the tasks, might have exaggerated the AB in the individualized Stroop task.

Conversely, three of those studies did not observe such relationship between AB and alcohol consumption, even when investigating the psychometric properties of the alcohol Stroop task through ecological momentary assessment (EMA) settings (Spanakis et al., 2018; Suffoletto et al., 2019). In van den Wildenberg (2006), alcohol Stroop interference in male heavy drinkers was unrelated to alcohol use and problems. In Spanakis et al. (2018), social beer drinkers performed a general and an individualized alcohol Stroop task either on a computer in laboratory settings or on a smartphone at home (EMA settings). They showed slower responses to alcohol-related words compared to neutral words in the general Stroop task, but no difference regarding the type of images in the individualized Stroop task. AB in both tasks did not predict alcohol consumption, regardless of the settings. The alcohol Stroop task showed better psychometric reliability in ecological settings, but the absence of association between AB and alcohol consumption showed its poor predictive validity. Suffoletto et al. (2019) investigated AB through EMA over 14 weeks using smartphone apps. Young adult risky drinkers performed an alcohol Stroop task weekly and reported their alcohol consumption twice per week. AB did not correlate with baseline consumption and did not predict same day binge drinking. Ecological assessments of AB among risky drinkers are thus not robustly related with baseline or same-day consumption.

Time course of AB. Four studies investigated the temporal dynamics of AB in subclinical drinkers by adapting classical paradigms. Field et al. (2004) dissociated initial orienting from attention maintenance in AB, by manipulating stimuli duration in the VPT. Heavy drinkers had greater AB scores than light drinkers for stimuli with longer exposure durations (500-2000ms) but not for shorter ones (200ms). Despite a limited sample size, they concluded that heavy social drinkers presented an AB in the maintenance but not in the initial orienting of attention. The task was further manipulated by two online studies using a cued VPT (Gladwin, 2017; Gladwin et al., 2020). The former study (Gladwin, 2017) firstly investigated the variability of AB (i.e., short-time fluctuation in AB) among students by focusing on intra-individual variability rather than median/mean value of VPT measure. Their results showed that high AB variability was associated with riskier drinking. Secondly, they used a cued VPT with arbitrary cues signalling the location of subsequent alcohol or non-alcohol stimuli. Participants with risky drinking behaviour were slower for probes appearing at the location of cues predicting soft drinks stimuli, suggesting that predictive cues could capture the attention related to alcohol use. However, the effects from this cued version were weaker and required a longer training period. The latter study (Gladwin et al., 2020) tested the reliability of anticipatory alcohol AB assessed by the cued VPT, and determined whether its reliability might be attributed to various aspects of the predictive cues. To do so, participants performed several variations of the task, including the use of non-predictive cues. Only participants who performed predictive versions of the task showed an AB, but without association between AB and risky drinking. The alcohol Stroop task has also been modulated to dissociate the time course of AB in subclinical drinkers. Hallgren and McCrady (2013) investigated the association between AB and alcohol involvement in college students with recent binge drinking, by using an alcohol Stroop task with immediate (i.e., current-trial responding) and delayed (i.e., subsequent-trial responding) interference measure. Participants responded more slowly when two alcohol words (compared to two neutral words) were presented sequentially. They also analysed participants' performances based on their alcohol involvement. No RT difference was found regarding drinking frequency or problematic alcohol use but high-intensity drinkers showed a delayed interference effect of alcohol-related words.

Influence of the current state on the relationship between AB and alcohol use. Twelve studies explored the impact of motivational and/or temporary variables on AB among subclinical drinkers using classical paradigms. Baker et al. (2014) investigated the role of motivational orientations (approach/avoidance motivation for alcohol) on AB in heavy drinkers. Participants were randomly allocated in different groups of implicit priming: alcohol-appetitive, alcohol-aversive or neutral primes. They performed a VPT, each trial being subliminally preceded by a word prime. Results showed: (1) no effect of subliminal priming of alcohol-appetitive or alcohol-aversive motivational states on AB; (2) the presence of an avoidance AB for alcohol cues presented for 50ms and no AB when presented for 500ms; (3) a small but positive correlation between AUDIT and AB. However, the use of a response window, while maximizing masked priming effects, might have invalidated RT measures.

Three studies showed how in vivo alcohol cue exposure impacts AB in students. In Cox et al. (2003), participants performed an alcohol Stroop task immediately after being exposed to either an alcohol or non-alcohol beverage. Results showed that alcohol interference scores were predicted (1) solely by consumption (as calculated by annual absolute alcohol intake scores), (2) only in heavier consumers and (3) when previously exposed to an alcohol beverage. Nevertheless, the reliability of such results might be questioned since the task was administered through physical cards and RT were measured using a watch. Moreover, no information was provided regarding the experimental groups (e.g., sample size, matching variables). In Ramirez et al. (2015a), underage college student drinkers performed a VPT after being exposed to a beer or water cue-reactivity procedure in two separate sessions. Participants showed faster RT for alcohol-related stimuli only in alcohol-CR session, and the AUDIT was negatively correlated with AB only in water-CR session. In-vivo exposure to alcohol cues thus led to a stronger AB in student drinkers. The authors further examined whether momentary decreases in craving were associated with reduced AB by extending the duration of alcohol-cue exposure protocols (Ramirez et al., 2015b). AB at baseline did not correlate with craving nor consumption. Both brief and extended alcohol-cue exposure increased craving and AB, and craving changes predicted AB changes among women in the long exposure group.

Five studies measured subjective craving to explore its influence on AB. In Field et al. (2005), social drinkers were split into low/high craving groups. Results showed that: (1) higher cravers presented greater AB scores in the VPT; (2) AB positively correlated with craving but not with alcohol-seeking behaviour or alcohol consumption. These findings were however constrained by a small sample size. The positive association between AB and craving was also found in other studies. Field et al. (2004) found a positive correlation between craving and AB scores, when social drinkers performed the VPT with long stimulus duration. In Field et al. (2007a), adolescent heavy drinkers, but not light drinkers, were slower at naming alcohol-related words than neutral words, these interference scores being correlated with craving. However, alcohol-related AB did not correlate with craving in other previously described studies (Christiansen et al., 2015b; Jones et al., 2018a).

Finally, three studies investigated the effects of acute intoxication or hangover on AB. In Duka and Townshend (2004), social drinkers were randomly allocated in the placebo, 0.3g or 0.6g/kg alcohol pre-load conditions. Only the low alcohol dose group showed a significant AB in the VPT. A negative correlation was found in the high alcohol dose group between AB and consumption. When performing the alcohol Stroop task, results showed no difference on RT between conditions or stimuli. The high alcohol dose group, however, made more errors for the alcohol-related words. Findings from the VPT showed that the administration of low alcohol dose prime AB, whereas high alcohol dose might induce a state of satiation and, thus, decrease the salience of alcohol-related stimuli. However, besides the low sample size, findings from the VPT are inconsistent with the errors made in the alcohol Stroop task - which were increased only by the priming of high alcohol dose. In Fernie et al. (2012), both moderate and heavy drinkers were administered 0.4g/kg alcohol or placebo in a within-subject design and performed a VPT at both sessions. Results showed no difference in RT between moderate and heavy drinkers, or between alcohol or placebo condition. AB was therefore unaffected by drinking habits or intoxication. Participants were however not asked to abstain from alcohol in the previous days, which might have affected results regarding the alcohol or placebo condition. Gunn et al. (2021) examined the influence of hangover on cognitive processes. Student drinkers performed a VPT the day following consumption (hangover condition) and at least 24h after alcohol consumption (no-hangover condition). Hangover did not influence performance, and no AB was found, regardless of hangover (as AB scores did not differ from zero in either condition) or drinking habits (AUDIT scores).

Influence of reflective processes on the relationship between AB and alcohol use. Many studies investigated how cognitive processes, relying on bottom-up or top-down mechanisms, might impact alcohol-related AB in subclinical drinkers. Capitalizing on dual process models, a longitudinal study

(Pieters et al., 2014) examined the conditional effects of alcohol-related implicit processes (i.e., alcohol-related memory associations, AB and approach bias) and reflective processes (i.e., alcohol expectancies, working memory) on changes in alcohol use in a normative adolescent population. Results showed that alcohol AB, measured by a VPT, was however not correlated with any other cognitive variables and did not predict changes in alcohol use. In the same vein, three studies found a weak moderating or mediating role of executive functioning on the relationship between AB and alcohol consumption. First, van Duijvenbode et al. (2017b) investigated the moderating role of executive control and readiness to change in light and problematic drinkers with and without mild to borderline intellectual disability. They found no effect of IQ on alcohol AB. Second, van Hemel-Ruiter et al. (2015) explored the relationship between alcohol AB and executive control. They also investigated whether the association between reward sensitivity and adolescent alcohol use was partly mediated by alcohol AB. Adolescents completed a VPT as an index of alcohol AB. Alcohol AB did not correlate with reward and punishment sensitivity, executive control or alcohol use, and did not mediate the relationship between reward sensitivity and alcohol use. However, stronger alcohol AB, stronger reward sensitivity and weaker executive control predicted alcohol use. Alcohol AB was therefore only associated with alcohol use in adolescents with low executive control. Third, Willem et al. (2013) explored the moderating role of attentional control and inhibition on the association between cognitive biases and alcohol use in adolescents and young adults. Participants completed a VPT and an approach/avoidance stimulus-response compatibility task to assess alcohol AB and approach bias, respectively. Results showed that alcohol consumption in the last 3 months (as measured by the AUDIT) correlated with approach bias and attentional control but not with alcohol AB. Moreover, being a man and presenting stronger approach biases (but not AB) were the only predictors of AUDIT scores. Results further showed that lower alcohol use was associated with lower alcohol AB - only among adolescents with high attentional control. More significant findings emerged from Murphy and Garavan (2011), who investigated whether alcohol AB, impulsivity and inhibitory control could discriminate problem from non-problem drinkers. Results showed that: (1) alcohol AB was positively correlated with impaired inhibition and impulsivity; (2) alcohol AB could discriminate problem from non-problem drinkers. In Field et al. (2007a), alcohol AB in adolescent heavy drinkers was positively correlated with alcohol-related impulsive decision making (assessed through a delay discounting task).

Effect of training interventions on alcohol AB. Luehring-Jones and al. (2017) investigated the effectiveness of a single session of ABM in reducing craving and alcohol AB in young social drinkers. Participants were randomly assigned to active ABM training or sham training condition. Alcohol AB tasks (VPT and alcohol Stroop task), an implicit association task and a cue-induced craving task were administered at baseline and during the post-training assessment. At baseline, alcohol Stroop interference was correlated with the number of drinks per occasion. Active ABM training reduced alcohol AB scores and indirectly reduced craving through a decrease in Stroop interference scores. Alcohol AB was thus associated with alcohol consumption in social drinkers and was reduced by a single session of ABM training. Nevertheless, Langbridge et al. (2019) did not observe any beneficial effect of ABM in binge drinking. In their study, binge drinkers received either ABM, sense of control training, both interventions, or no intervention, and were compared with non-binge drinkers who did not receive any intervention. At baseline, binge drinkers showed higher alcohol AB scores than non-binge drinkers. After the intervention, the alcohol AB decreased over time in all participants, regardless of the intervention administered. Alcohol consumption in binge drinkers was reduced when receiving the combined interventions. While binge drinkers showed higher alcohol AB than non-binge drinkers at baseline, these findings showed the null effect of ABM on alcohol AB in binge drinking. The authors however underlined the insufficient power of their analyses to detect group differences, as well as the overrepresentation of young adults and students in the sample.

3.3.1.2. Alternative behavioural paradigms

Relationship between alcohol AB and alcohol use. As the most widely used tasks of AB repeatedly showed poor reliability (Ataya et al., 2012), eight studies developed new AB tasks. Three studies showed an association between AB and alcohol consumption in subclinical populations, using the flicker change induced-blindness paradigm. Jones et al. (2002) investigated alcohol AB in social drinkers using the flicker paradigm with a visual scene containing both an alcohol-related and a neutral change. Participants who detected the alcohol-related change showed higher consumption than those who detected the neutral change. In Jones et al. (2003), heaviest drinkers detected the alcohol-related change faster than lightest drinkers, and quicker than the neutral change. Moreover, lightest drinkers detected the neutral change faster than heaviest drinkers, and quicker than alcohol-related change. However, these two studies based their conclusions on a single trial and based their evaluation of chronic consumption solely on report of the heaviest drinking day in the last week, which hampers the generalization of these findings. In Hobson et al. (2013), students had to detect the change in complex stimuli either depicting real world scenes or a grid of alcohol-related and neutral pictures. They showed that heavier drinking patterns were associated with increased percentage of alcohol-related changes detections in real world scenes. Using a similar task, Knight et al. (2018) investigated AB in heavy and light social drinkers using an alcohol-change detection task. Heavy drinkers were more sensitive to alcohol changes in neutral-alcohol trials (i.e., all images originally neutral, one changing into an alcohol-related image) than light drinkers, indexing the presence of an AB. Pennington et al. (2020), who explored the psychometric properties of their newly developed visual conjunction search task in social drinkers, reported similar results. Participants showed, overall, faster RT for alcohol-related cues, indexing the presence of an alcohol AB predicted by AUDIT and alcohol consumption. Heitmann et al. (2020) also investigated the psychometric properties of newly developed alcohol AB measures using a visual search task. Its validity was tested by examining the association between AB index with alcohol use quantity/frequency or alcohol use problems. Their results showed however that AB presented a positive but weak association only with alcohol use frequency. Nikolaou et al. (2013) investigated AB in social drinkers using a concurrent flanker/alcohol AB task. The flanker effect difference score (i.e., flanker effect in the presence of alcohol minus neutral pictures) was associated with higher alcohol consumption. Finally, Brown et al. (2018) determined whether goal-driven mechanisms could account for involuntary AB toward task-irrelevant alcohol distractors in social drinkers. They conducted various versions of the rapid serial visual presentation paradigm to test the replicability of their effects. Overall, results showed that distractor interference was not correlated with consumption.

Time course and components of AB. Beyond the modulation of classical tasks, novel paradigms were also developed to investigate the temporal dynamics of AB. Three studies examined AB at encoding through an attentional blink paradigm (DePalma et al., 2017; Elton et al., 2021;

Tibboel et al., 2010). DePalma and colleagues (2017) administered word-based and pictorial-based versions of the task in binge drinkers. They explored whether AB was due to increased efficiency of attentional processing of alcohol cues at early encoding levels, thus reflecting more automatic processes. Binge drinkers did not show any attentional blink for alcohol cues, indexing an increased efficiency to process these cues at early levels. They, however, presented a delayed attentional blink for non-alcohol cues. Non-binge drinkers showed an early attentional blink, similar for alcohol and non-alcohol word cues, but reduced for alcohol compared to control images. Binge drinkers might therefore be more efficient in the processing of alcohol-related cues at early encoding levels than non-alcohol targets or non-binge drinkers, indexing the presence of an AB. Similar findings were reported in Tibboel et al. (2010), as heavy drinkers showed a smaller attentional blink effect for alcohol-related words compared to soft drink words, this effect being identical for both words in light drinkers. Under high cognitive load (i.e., at smaller lag), alcohol-related stimuli were processed more efficiently than soft drinks in heavy drinkers, reflecting an AB at encoding. Nevertheless, the low reliability of the task, the small sample size and the near-ceiling performance call for caution when interpreting these findings. Finally, Elton et al. (2021) showed that AB – indexed here by greater attentional blink following an alcohol distractor – was associated with greater binge patterns of drinking during adolescence.

Four studies investigated the engagement and disengagement processes of alcohol AB in subclinical drinkers. In Gladwin et al. (2013), social drinkers had to perform a spatial cueing task with approach-alcohol (i.e., instructions to direct attention towards alcohol and away from non-alcohol cues) and avoid-alcohol (i.e., opposite instructions) blocks to evoke conflict between automatic alcohol AB and task instructions. Their results showed that social drinkers were faster to shift their attention to an invalidly cue location following alcoholic versus non-alcoholic cues. Two other studies dissociated engagement/disengagement components of AB using the Odd-One-Out task (Heitmann et al., 2020, 2021). Firstly, they tested its validity by examining the association between AB indices with drinking quantity/frequency or alcohol use problems (Heitmann et al., 2020). The index of attentional disengagement showed a positive but weak association with drinking quantity/frequency, while the engagement index was associated with drinking frequency only in males. Alcohol AB processes related to attentional disengagement was thus associated with consumption in students. Secondly, they improved the low reliability of the task to provide a solid assessment of engagement/disengagement bias toward alcohol-related stimuli (Heitmann et al., 2021). The adapted Odd-One-Out task had more distinct contrast stimuli, more trials, practice trials and was administered in an alcohol-related context (i.e., a bar). High drinkers presented a greater engagement AB toward alcohol-related cues when performing the adapted task. Groups did not differ regarding disengagement AB index or when performing the original task. The internal consistency of the adapted task was increased but remained under acceptable threshold. Moreover, the study design did not distinguish contextual effects (bar/laboratory) from task modifications. The dissociation between engagement and disengagement processes was further explored through a selective-attention/action-tendency task (Sharbanee et al., 2013). Social drinkers were divided based on consumption regulation abilities. Results showed that: (1) dysregulated drinkers presented a greater AB in disengagement trials, while groups did not differ on alcohol AB in engagement trials; (2) disengagement AB scores predicted variance of drinking-group status. AB, indexed by a difficulty to disengage from alcohol cues, thus contributes to dysregulated drinking. To sum up, three studies showed an AB specifically observed at the disengagement level (Gladwin et al., 2013; Heitmann et al., 2020; Sharbanee et al., 2013) while another one located the AB at the engagement level (Heitmann et al., 2021).

Influence of the current state on the relationship between AB and alcohol use. Four studies explored the impact of craving on alcohol AB in subclinical drinkers. Hobson and colleagues (2013) showed that both higher consumption and higher craving were associated with increased percentage of alcohol-related changes detection in a flicker induced-blindness change paradigm. However, alcohol-related AB did not correlate with craving in some previously described studies (Heitmann et al., 2020; Pennington et al., 2020; Tibboel et al., 2010).

Influence of reflective processes on the relationship between AB and alcohol use. Two studies explored the influence of reflective processes on alcohol AB by manipulating cognitive load (Nikolaou et al., 2013; Tibboel et al., 2010). Nikolaou et al. (2013) investigated whether alcohol AB was modulated by cognitive control mechanisms using a dual task. Social drinkers performed a concurrent flanker/alcohol AB task with low (i.e., congruent flankers) and high (i.e., incongruent flankers) cognitive load in the presence of alcohol-related, neutral or plain grey background. In the congruent condition, social drinkers showed longer RT for neutral and alcohol-related images compared to grey background, and lower accuracy for alcohol-related images compared to neutral and grey background. In the incongruent condition, social drinkers showed longer RT for alcohol-related images compared to neutral and grey backgrounds while response accuracy did not show such difference. The number of drinks per week was positively associated with the flanker effect difference score (greater interference exerted by alcohol-related images under increased cognitive load). Alcohol AB thus attenuates cognitive control mechanisms, this interference effect being associated with higher alcohol consumption. As described earlier, Tibboel et al. (2010) examined alcohol AB using an attentional blink paradigm in heavy and light drinkers. They showed that alcohol-related stimuli were processed more efficiently than soft drink in heavy drinkers under high cognitive load (i.e., at smaller lag), reflecting an alcohol AB at the encoding level. Sharbanee et al. (2013) showed that working memory performance did not substantially contribute to the prediction of drinking patterns by AB scores.

Finally, Brown et al. (2018) determined whether goal-driven mechanisms could account for involuntary AB towards task-irrelevant alcohol distractors in social drinkers. In three experiments, they conducted various versions of the rapid serial visual presentation (RSVP) paradigm to test the replicability of their effects, while modifying task characteristics (presentation speed, non-alcohol stimulus category). In a fourth experiment, participants performed a modified version of the RSVP paradigm, in which they had to maintain alcohol or non-alcohol stimuli in their visual working memory, while searching for a non-alcohol target. Overall, results showed that distractor interference was: (1) only observed when distractors were goal-congruent, (2) larger for alcohol than non-alcohol goal-congruent distractors, (3) not observed when alcohol images were held in visual working memory and not related to search goals, (4) not correlated with alcohol consumption. Involuntary attentional capture by alcohol-related stimuli could therefore be induced by manipulating goal-driven mechanisms.

Effect of training interventions on alcohol AB. In Fadardi and Cox (2009), social, hazardous and harmful drinkers performed classical, alcohol and concern-related Stroop tasks at baseline. Hazardous and harmful drinkers were then trained to modify their alcohol AB with the Alcohol

Attention-Control Training Program for two and four sessions respectively. At baseline, harmful and hazardous drinkers showed higher alcohol Stroop interference than social drinkers. After ABM, both hazardous and harmful drinkers showed a decrease in classic and alcohol interference scores and an increase in motivation to change after AB training. Moreover, harmful drinkers reduced alcohol consumption after AB training. The authors did not include randomized control trials with a control group, thus preventing the evaluation of the training program.

3.3.1.3. Eye-tracking data

Relationship between alcohol AB and alcohol use. Six previously described studies used eye-tracking to enhance the reliability of AB measures. Miller and Fillmore (2010) explored the effect of stimuli properties on AB using a VPT with simple and complex images. AB indexed by dwell times was found only for simple images in regular drinkers. Nevertheless, eye-tracking measures constituted a more robust evaluation of alcohol AB than behavioural ones, the effect size of AB indexed by dwell times being twice larger. Christiansen et al. (2015b) showed that the joint use of eye-tracking measures (dwell times), and personalized stimuli increased task reliability up to .76. The validity of the task was however questioned, as no correlation was found between AB and alcohol use. In van Duijvenbode et al. (2012), participants with long term abstinence were grouped in light or heavy drinkers for eye-tracking analyses. Participants did not present AB, independently of their past consumption. Van Duijvenbode et al. (2017a) identified the presence of AB (based on eye-tracking measures) in a large sample of participants. However, AB intensity did not differ according to alcohol consumption. The increased reliability of the VPT by using eye-tracking measures was not found in Jones et al. (2018a): eye-tracking measures showed poor reliability and validity, which questions the use of the VPT to assess AB. More surprisingly, the global behavioural AB found in a flicker paradigm used by Hobson et al. (2013) was not observed among heavy drinkers when analysing eye-tracking measures. This could be partly explained by the instructions, which limited the maintenance of attention on the target stimulus.

Four studies investigated alcohol-related AB only through eye-tracking. In Weafer and Fillmore (2012a), beer drinkers performed a free viewing task. Higher drinkers showed longer dwell times toward alcohol-related scenes, thus showing that AB was related to alcohol consumption.

Time course and components of AB. Seven studies dissociated initial orienting and maintenance of attention using eye-tracking. Ceballos et al. (2009) used a free exploration paradigm when presenting images (alcohol-related stimuli, household objects, or both) among college drinkers. Positive correlations were found between consumption (quantity-frequency index) and eye-tracking. The authors suggested that consumption intensity among college students was simultaneously related to a higher automatic attraction toward alcohol and to a stronger tendency to focus voluntarily on alcohol-related stimuli. However, the imprecise alcohol consumption measure, combined with the low global consumption in this sample and the continuous approach chosen, raise questions regarding the role played by alcohol consumption in the results. Soleymani et al. (2020) investigated the psychometric value of a free-viewing eye-tracking task to assess AB. Students freely explored 4x4 matrices of alcohol and soft drink images. In the first session, longer dwell times and higher number of first fixations on alcohol-related cues, as well as shorter first fixation latency on soft drinks, were associated with stronger alcohol problems. Findings from the second session showed weaker evidence for criterion validity, with only first alcohol fixations being associated with AUDIT scores.

Three studies distinguished automatic and controlled processes of AB among adolescents (McAteer et al., 2015; 2018; McGivern et al., 2021). In McAteer et al. (2015), heavy, light and non-drinkers performed a free visual exploration task. None of them showed an automatic orienting to alcohol stimuli (location/speed of the initial fixation). Heavy drinkers showed a significant increase in dwell times for alcohol-related stimuli, particularly during the second part of stimuli presentation (1500-2500ms), indexing prolonged or fixed attention. The authors concluded that AB might be underpinned by controlled rather than automatic processes. They further explored AB on the free viewing task (McAteer et al., 2018) according to age (early adolescents, late adolescents, young adults) and drinking pattern (heavy, light and non-drinkers). Results replicated previous findings, as heavy drinkers showed longer dwell times for alcohol-related stimuli than light drinkers, independently of age. Moreover, an increased percentage of first fixation toward alcohol-related stimuli was observed in young adults when compared to late adolescents, independently of consumption. Heavy drinking thus appears associated with AB and underpinned by controlled processes. Age is related to a higher automatic capture of attention, indexing a progressive rise of the automatic attention hijack by alcohol-related stimuli with age. Here again, the absence of genuine AB and results going against the main conclusions (e.g., no age or alcohol consumption effect on early or late attentional processes) strongly reduced insights brought by this study. Using the same methodology, McGivern et al. (2021) explored the different components of alcohol AB in a small sample of adolescents. Heavy drinkers performed longer first fixations toward alcohol than abstainers, indicating the presence of a delayed disengagement bias. They also showed more fixations and longer dwell times for alcohol-related stimuli than abstainers, indexing a maintenance bias. Heavy and light drinkers did not differ from abstainers regarding the direction of their first fixations, suggesting the absence of a vigilance bias in adolescents. Finally, heavy drinkers showed longer alcohol dwell times than light drinkers and abstainers in the first half of stimuli presentation (indexing early attentional processes), while both heavy and light drinkers showed longer alcohol dwell times than abstainers in the second half (indexing late attentional processes).

Roy-Charland et al. (2017) proposed a more dynamic exploration of attention, by analysing the global pattern of saccadic eye movements produced by undergraduate students when freely exploring complex visual scenes (with/without alcohol cues). The first experiment did not show any AB or any correlation between eye-tracking indexes and consumption. The second one, where participants had to memorize a visual scene, demonstrated a positive correlation between consumption and the number of saccades toward and away from alcohol-related zones (measuring the tendency to draw back their attention to these zones). The number of saccades toward alcohol-related stimuli in complex scenes was associated with consumption only when instructions motivated the participants to attend to them. Monem and Fillmore (2017) explored alcohol AB in natural settings. Portable eye-tracking glasses were combined with video recording while participants freely explored, during two sessions, a recreational room containing objects, including alcohol beverages and matched soft drinks. Results showed (1) no AB during the first session, (2) a habituation effect during the second session for soft drinks (i.e., reduced dwell times) but not for alcohol stimuli, indicating an alcohol AB, (3) a correlation between AB and consumption intensity.

Influence of the current state on the relationship between AB and alcohol use. Five studies investigated the effect of craving on subclinical drinkers by using eye-tracking measures. Hobson et al. (2013) demonstrated that eye-tracking indices of AB were related to craving but not to consumption. Indeed, they did not find any global AB in heavy drinkers, but showed faster saccades toward alcohol-related stimuli in real world scenes among individuals with higher craving. In Soleymani et al. (2020), stronger craving was associated with longer dwell times, higher proportion of first fixations and shorter first fixation latencies on alcohol-related cues. These findings indexed a powerful correlation between craving and direct AB measures. Van Duijvenbode et al. (2017a) also found a positive (but weak) correlation between AB and craving. Wilcockson et al. (2019) measured, in a within-subject design, the influence of current consumption intention on AB using a free visual exploration. Heavy drinkers showed AB (indexed by dwell times), regardless of consumption intentions. This AB was positively correlated with consumption intensity/frequency, only when use was intended and with negative expectancies toward alcohol. Finally, Christiansen et al. (2015b) did not find any association between AB (indexed by dwell times) and craving.

Two studies explored the effect that alcohol expectancies might have on AB using a free exploration task (Field et al., 2011; Jones et al., 2012). In Field et al. (2011), alcohol expectancy was modulated at the beginning of each trial by a message indicating the probability (0/50/100%) of receiving a small amount of beer after the trial. The modulation of alcohol expectancy did not affect AB among heavy drinkers, showing higher dwell times for alcohol-related stimuli in all conditions. Conversely, light drinkers only presented higher alcohol dwell times when alcohol expectancies were high. AB thus appeared stable in heavy drinkers, while it depended on current expectancies in light drinkers. It should be noted that participants were administered non-alcohol beer, to prevent increased AB following intoxication. This might have resulted in reduced sensitivity to the expectancy manipulation. Jones et al. (2012) then explored whether the influence of alcohol expectancies was specific for alcohol-related cues or generalized toward other appetitive stimuli. Social drinkers performed a free exploration task with alcohol/neutral or chocolate/neutral pairs of images. Reward expectancy was also modulated by a message indicating the probability (0/100%) of receiving a small amount of beer or chocolate. For both stimuli, increased expectancy was associated with longer dwell times for appetitive cues, this effect being reward-independent. The expectancy to receive a reward thus globally increased the AB toward appetitive cues. Nevertheless, participants did not actually receive and consume the rewards, and their preference regarding one reward for another was not evaluated.

Two studies investigated whether acute intoxication influences AB in heavy and moderate drinkers through a VPT, followed by a bogus taste test (Fernie et al., 2012; Weafer & Fillmore, 2013). Participants received either 0.4g/kg doses of alcohol or placebo in a within-subject design in Fernie et al. (2012). Higher dwell times for alcohol-related stimuli were observed only after intoxication in moderate drinkers, and after both alcohol and placebo administration in heavy drinkers. AB therefore increased after alcohol administration in moderate drinkers, while heavy drinkers showed a stable AB. These findings were not replicated in Weafer and Fillmore (2013), who administered a placebo and 0.45g/kg and 0.65g/kg doses. Heavy drinkers displayed greater AB than moderate drinkers following placebo, this AB predicting the amount of ad libitum consumption. However, heavy drinkers displayed a dose-dependent decrease of AB following alcohol, whereas intoxication had no impact on AB in moderate drinkers. These results suggested that AB would play a role in the initiation of drinking episodes, but not in their perpetuation once initiated.

Influence of reflective processes on the relationship between AB and alcohol use. Four eye-tracking studies explored the association between inhibitory control and alcohol AB in subclinical drinkers. Weafer and Fillmore (2012) investigated the joint role of behavioural control and alcohol AB in moderate to heavy beer drinkers. Participants performed two novel laboratory tasks assessing alcohol AB (free viewing task) and inhibitory control (attentional bias-behavioural activation task). Regarding the inhibition task, participants in the alcohol go condition showed more inhibitory failures than those in the neutral go condition. Regarding the AB task, individuals who reported higher alcohol consumption showed longer dwell times towards alcohol-related scenes. Regarding the joint role of inhibition and AB, longer alcohol dwell times were associated with shorter RT for alcohol go condition but not with more inhibitory failures. Alcohol AB was thus related to alcohol consumption in adult beer drinkers, and predicted response activation, but not response inhibition, for alcohol images. Other studies took advantage of the features offered by the eye-tracking device to measure the inhibitory control component of AB through the use of a gaze contingency paradigm.

This novel eye-tracking task measures the ability to inhibit the orientation of attentional resources towards peripherally appearing alcohol-related stimuli. Wilcockson and Pothos (2015) found a positive correlation between break frequency (i.e., inability to inhibit saccade) for alcohol-related stimuli and weekly alcohol consumption in male undergraduate students. These findings provided preliminary support to the proposal that this gaze contingency paradigm might be useful to measure the inhibitory processes related to alcohol AB. In Qureshi et al. (2019), problem and non-problem drinkers performed a gaze contingency paradigm with appetitive alcohol, appetitive non-alcohol, and non-appetitive stimuli. For centrally-located stimuli, problem drinkers showed higher break frequency for non-appetitive stimuli compared to alcohol ones. In contrast, they observed, for peripheral stimuli, a higher break frequency towards both appetitive (i.e., alcohol and non-alcohol) stimuli among problem drinkers, compared to non-appetitive ones. These findings suggested that inhibitory control for appetitive stimuli might be improved when covert attentional processing is possible and that AB was not specifically related to alcohol stimuli. Finally, Brown et al. (2020) used the gaze contingency paradigm to investigate the impact of sleep quality on AB among university students. They found a positive correlation between AUDIT and alcohol-related break frequency, as well as higher break frequency for alcohol-related stimuli when comparing high against low hazardous drinkers. However, no relation was found between sleep quality and AUDIT or break frequency scores. High hazardous drinkers were more frequently distracted by alcohol-related stimuli, independently of their sleep quality.

3.3.1.4. Neuroscience data

Relationship between alcohol AB and alcohol use. Langbridge et al. (2019) assessed AB before intervention through cued-elicited event-related potentials. EEG data showed similar N1 amplitudes in response to neutral-probes or alcohol-probes among binge and non-binge drinkers, indexing the absence of AB in those groups.

Time course and components of AB. Gladwin et al. (2013) investigated the fMRI correlates of automatic engagement/disengagement processes of AB in social drinkers. Participants performed a spatial cueing task with approach-alcohol and avoid-alcohol blocks to evoke conflict between automatic alcohol AB and task instructions. The medial parietal region was activated when attention had to be directed toward alcohol cues (approach-alcohol blocks), which could reflect an attentional disengagement from alcohol stimuli features when interfering with task performance. Heavier drinkers showed a reduced activity in this area, which might reflect a weaker tendency to disengage from distracting alcohol cues. Therefore, the medial parietal region could play a role in attentional disengagement, which might partly explain the AB in heavier drinkers. Dickter et al. (2014) investigated how alcohol dependence and escape drinking influence the time course of AB in college students. EEG data were recorded while participants passively watched alcohol-related and soft drink pictures in active (human content) or inactive settings. They compared potential alcohol dependent and non-alcohol dependent participants, as well as escape and non-escape drinkers. Results showed that: (1) potential alcohol dependent participants showed larger N1 amplitudes for alcohol-related cues; (2) escape drinkers showed larger N2 amplitude to alcohol-related cues in active settings; (3) no differential neural responses for inactive cues; (4) no enhancement of P1 responses. Potential alcohol dependence is thus associated with neural AB early in processing while escape drinking is associated with neural AB at later processing stages.

Effect of training interventions on alcohol AB. Langbridge et al. (2019) investigated the effect of cognitive interventions on alcohol AB in binge drinkers, assessed through cued-elicited event related potentials. EEG data did not show any difference between binge and non-binge drinkers regarding alcohol AB at baseline or after ABM intervention, confirming the null effect of attentional training in binge drinking on behavioural and electrophysiological markers of AB.

3.3.2. Clinical population

3.3.2.1. Classical behavioral paradigms

Relationship between alcohol AB and alcohol use. Twenty-one studies used behavioural measures to explore AB in SAUD. Sharma et al. (2001) measured alcohol AB through an alcohol Stroop task among detoxified inpatients with SAUD and undergraduate students with light or heavy alcohol consumption. Compared to light drinkers, both patients and heavy drinking students showed an alcohol AB indexed by longer RT for alcohol-related words. Other studies found similar findings using the alcohol Stroop task with higher Stroop interferences (Fadardi & Cox, 2006; Lusher et al., 2004; Müller-Oehring et al., 2019) or higher error rates (Duka et al., 2002) for alcohol-related words in detoxified inpatients compared to CTL.

Nevertheless, several studies did not replicate these findings, and identified no AB in SAUD. Two studies compared the Stroop performance of abstinent outpatients with CTL and did not find a greater AB interference in SAUD (Fridrici et al., 2014; Ryan, 2002). Den Uyl et al. (2018) investigated the effect of training interventions on alcohol AB in detoxified patients. Their performance at baseline on the VPT did not correlate with alcohol problems. Fridrici et al. (2013) investigated the alcohol AB in detoxified outpatients with regard to individualized (i.e., preferred alcohol drink of each participant) versus general alcohol-related words in an alcohol Stroop task. They found similar RT for the different word categories in patients, while CTL showed slower RT for individualized alcohol words, thus indexing the presence of an AB toward individualized alcohol-related stimuli in CTL but not in patients. Using a VPT, Van Hemel-Ruiter et al. (2016) showed that adolescents with SAUD do not present alcohol AB just after detoxification or 6 months later. Moreover, changes in SAUD severity was not predicted by changes in AB. However, this might be explained by a substantial dropout rate for this part of the study. In contrast to theoretical models, Townshend and Duka (2007) have even supported the presence of an avoidance AB pattern in detoxified inpatients: they found a negative AB score in patients but not in CTL, suggesting the presence of an avoidance AB for alcohol-related stimuli in SAUD, potentially influenced by intensive psychotherapy.

Findings from other studies further suggested that the presence and extent of alcohol AB in SAUD might be related to treatment outcomes. Cox et al. (2002) assessed the variation of AB with time and treatment. Inpatients and matched CTL performed an alcohol Stroop task before starting treatment (T1), 4 weeks later (T2) and 3-month after discharge. Patients who remained abstinent or had only a brief drinking episode showed a similar pattern of alcohol AB than CTL across time. Relapsing patients showed a strong increase in alcohol interference scores from T1 to T2. However, the large number of heavy social drinkers in the control group call for caution when interpreting those results. In Rettie et al. (2018), while patients before discharge did not differ from CTL regarding alcohol interference scores, patients with successful detoxification had lower alcohol interference than relapsing ones, suggesting a predictive role of AB in relapse.

Time course and components of AB. Three studies (Beraha et al., 2018; Noël et al., 2006; Vollstadt-Klein et al., 2009) investigated AB time course in detoxified patients with SAUD by manipulating stimuli duration in the VPT. They used different duration of stimuli presentation to distinguish initial orienting (e.g., at 50ms) from attentional maintenance (e.g., at 500ms or 1250ms). While using similar methodologies, findings from Beraha et al. (2018) and Noël et al. (2006) suggested the presence of an approach-avoidance attentional pattern, dependent upon stimuli duration, specific to detoxified inpatients whereas Vollstädt-Klein et al. (2009) found this pattern in both CTL and outpatients with long-term abstinence. Noël et al. (2006) found an initial orienting AB toward alcohol-related stimuli in detoxified patients at very short stimuli duration, but not in CTL, followed at a stimuli duration of 500ms by an alcohol AB in CTL, but not in patients. No AB was found in both groups when stimuli were presented for 1250ms. Beraha et al. (2018), who explored the effect of Baclofen treatment on AB in detoxified inpatients, showed, at baseline, that patients presented an AB toward alcohol at 500ms and an avoidance AB away from alcohol at 1500ms. In contrast, Vollstädt-Klein et al. (2009) found faster RT for alcohol-related stimuli at very short stimuli duration in both groups, and an avoidance AB for alcohol-related stimuli for long stimuli duration in CTL and detoxified outpatients. Another study dissociated the fast/slow processes of alcohol AB (Clarke et al., 2015). Both patients and CTL showed a Stroop interference on alcohol-related words (indexing fast processes), but also on the following neutral words (indexing slow processes). Alcohol interference thus occurred on the alcohol-related cue itself, but was also carried over onto subsequent neutral words. The authors underlined the fact that instructions inadvertently primed participants to respond to alcohol-related cues, which might have raised expectancy salience and be responsible for the similar pattern of AB across groups.

Influence of the current state on the relationship between AB and alcohol use. Three studies investigating the relation between AB and subjective craving generated inconclusive findings (den Uyl et al., 2018; Field et al., 2013; Wiers et al., 2016). In Wiers et al. (2016), male detoxified inpatients and CTL did not differ regarding RT in the VPT and their performance was not correlated with craving. In den Uyl et al. (2018), patients' performance at VPT did not correlate with craving. In Field et al. (2013), while detoxified outpatients were overall slower at color-naming alcohol-related words compared to neutral ones (unlike CTL), no association was found between Stroop interference scores and craving. Conversely, VPT showed no general alcohol AB in patients compared to CTL, but patients with high craving showed greater AB scores, and patients with low craving showed lower AB scores than CTL for alcohol cues at 500ms. The weak evaluation of comorbidities and biasing variables, the small sample size and the hazardous consumption of CTL call for caution when interpreting those results. Moreover, the inconsistent findings on the relationship between AB and craving, even observed within the same experiment (Field et al., 2013), might be explained by the low level of craving usually reported by detoxified patients. Finally, Sinclair et al. (2016) investigated the influence of current drinking status by administrating a VPT to abstinent and non-abstinent outpatients. Results showed that alcohol-related AB was not correlated with SAUD or abstinence duration. Interestingly, an alcohol AB was present among drinking patients but not among abstinent ones, suggesting a robust association between alcohol AB and drinking status.

Influence of reflective processes on the relationship between AB and alcohol use. Two studies explored the contributing role of higher-level cognitive processes on alcohol AB among patients (Fadardi & Cox, 2006; van Hemel-Ruiter et al., 2016). Fadardi and Cox (2006) investigated whether alcohol AB, assessed through an alcohol Stroop task, might be a mere consequence of a general cognitive impairment presented by detoxified inpatients. They observed that: (1) patients showed more impaired cognitive functioning and larger alcohol interference scores than CTL, (2) cognitive functioning was associated with AB, (3) larger alcohol interference scores in patients were still present after controlling for cognitive functioning. These findings suggest that alcohol AB is not an artefact of a general cognitive impairment but, rather, a reliable phenomenon in SAUD. Van Hemel-Ruiter et al. (2016) investigated substance AB, through a VPT, in adolescents diagnosed with substance use disorder (SUD), and explored whether executive control moderated this relationship. Overall, adolescents with SUD showed a greater substance AB compared to CTL, and executive control did not moderate this relationship. However, adolescents with a primary diagnosis of SAUD did not show significant alcohol AB scores and did not differ from CTL. Those tested at follow-up 6 months after entering therapy did not show changes in their substance AB. Changes in SUD severity was not predicted by changes in AB or executive control. However, this might be explained by a substantial dropout rate for this part of the study. To conclude, while substance AB appears to be related to the severity of SUD -

independently of executive control - no specific-alcohol AB was identified in adolescents presenting a primary diagnosis of SAUD.

Effect of medical treatment on alcohol AB. As mentioned above, Beraha et al. (2018) explored the effect of Baclofen treatment on AB in detoxified inpatients with SAUD. They were assigned in baclofen or placebo groups and performed a VPT at baseline and after four weeks of baclofen or placebo treatment. A negative mood induction always took place before conducting the task. At baseline, patients showed an AB towards alcohol at 500ms and an avoidance AB away from alcohol at 1500ms. Patients who received the baclofen treatment showed a change in their AB after four weeks of treatment, as their avoidance AB was also found for alcohol-related stimuli presented for 500ms. This finding supports the positive effect of baclofen on alcohol AB, but it should be noted that the effect of negative mood induction on AB could not be determined as no control condition was performed. Moreover, the combination of medication with psychotherapy might have limited the additional effect of baclofen on AB.

3.3.2.2. Alternative behavioral paradigms

Relationship between alcohol AB and alcohol use. Four studies used novel behavioural paradigms to investigate the association between AB and alcohol-related problems. Using the flicker change induced-blindness paradigm, Jones and colleagues (2006) found that, unlike the matched control group, detoxified inpatients were quicker to detect alcohol-related changes compared to neutral changes, indexing an alcohol AB. Waters and Green (2003), using a dual task paradigm, showed that patients, but not CTL, were slower to perform peripheral lexical decisions concerning alcohol-related words compared to neutral words. This was also observed at the central odd/even decision task, when patients were exposed to peripheral alcohol-related words compared to neutral words. They concluded that patients show an automatic AB, as their performance was poorer in the presence of alcohol-related stimuli. Finally, Garland (2011) measured AB through a spatial cueing task in long-term abstinent patients. Patients did not show any AB, but AB score was positively associated with previous alcohol consumption.

Time course and components of AB. One study dissociated the engagement and disengagement components of alcohol AB in outpatients with SAUD using the Odd-One-Out task (Heitmann & de Jong, 2021). Results did not show higher engagement or disengagement biases in patients compared to CTL, but participants made many errors in the task which might have reduced its sensitivity to detect AB.

Influence of reflective processes on the relationship between AB and alcohol use. Waters and Green (2003) examined whether abstinent patients were characterized by either an alcohol AB or an enhanced schematic processing (i.e., automatic activation or enhanced accessibility to alcohol-related cognitive schemes) of alcohol-related cues compared to CTL, using a dual task paradigm. Patients were slower to perform peripheral lexical decisions concerning alcohol-related words compared to neutral words – an effect not found in CTL. This was also observed at the central odd/even decision task, when patients were exposed to peripheral alcohol-related words compared to neutral words. However, this latter finding did not reach significance when entering the severity of disorder as covariate. They concluded that detoxified patients show an automatic AB rather than enhanced schematic processing of alcohol-related cues, as their performance was poorer in the presence of alcohol-related stimuli.

3.3.2.3. Neuroscience data

Relationship between alcohol AB and alcohol use. Müller-Oehring et al. (2019) showed that detoxified patients presented a deactivation of frontal and premotor regions when exposed to alcohol words in a modified Stroop task combined with fMRI, indexing the presence of AB.

Effect of training interventions on alcohol AB. Den Uyl et al. (2018) investigated whether transcranial Direct Current Stimulation (tDCS) could enhance the ABM effects on implicit biases, craving and relapse rate. Groups received 4 sessions of control/real ABM training, combined with real/sham-tDCS using a VPT. At baseline, their AB score did not correlate with alcohol problems or craving. Moreover, while results from their online measures showed enhanced learning with stronger avoidance bias in the real ABM training with real-tDCS group, no positive effect of the ABM-tDCS combination was observed on alcohol AB.

4. Discussion

The main aim of this systematic review was to discuss the experimental validity of the assumptions made by dominant models regarding AB in alcohol-related disorders when confronted with existing behavioural, eye-tracking and neuroscience findings. We identified five major assumptions regarding alcohol-related AB, namely: (1) AB is a key and long-lasting characteristic of alcohol use disorders, its magnitude being directly associated with the severity/frequency of alcohol use; (2) AB is underpinned by automatic/early rather than controlled/later attentional processes, since AB is considered as a behavioural expression of reflexive/reward system's over-activation, giving rise to automatic and uncontrolled saccades towards alcohol-related stimuli (dual-process models; Bechara, 2005; Wiers et al., 2007); (3) AB is a stable feature of alcohol use disorders once established, due to an over-sensitized dopaminergic system following repeated alcohol exposures (IST; Robinson & Berridge, 1993) or is strongly affected by momentary motivational processes, either appetitive, aversive or both (Field et al., 2016); (4) AB is not influenced by the activity of high-level cognitive functioning, given the independency between the reflexive/reward and reflective/control systems postulated by dual process models; and (5) AB is specific to alcohol-related stimuli and does not generalized towards other appetitive stimuli.

The results section has shown the complexity of the current literature related to AB in alcohol-related disorders, and the large inconsistencies across experimental outputs. However, to move the field forward, we will identify the main conclusions that can be drawn from available studies, at theoretical (first to fourth assumptions), methodological (fifth assumption) and clinical levels. This will introduce the next chapter, in which we will propose recommendations for future studies and present those conducted in our thesis.

4.1. Results overview and theoretical implications

4.1.1. Is alcohol-related AB associated with the severity of alcohol use?

4.1.1.1. What do we know about subclinical populations?

Alcohol-related AB was positively related with alcohol consumption in most studies conducted in social drinkers, often recruited among students (e.g., Albery et al., 2015; Field et al., 2011; Hobson et al., 2013). Many studies also showed a stronger alcohol-related AB in more specific drinking patterns (e.g., heavy or binge drinkers) compared to light drinkers (Baker et al., 2014; DePalma et al., 2017; Tibboel et al., 2010), especially among adolescents (e.g., McAteer et al., 2015, 2018; McGivern et al., 2021). To sum up, studies conducted on subclinical populations appear consistent regarding the association between alcohol-related AB and alcohol consumption, most showing that AB is directly linked to the intensity of drinking habits. These findings therefore support the first theoretical assumption that the magnitude of AB would be related to consumption's intensity.

4.1.1.2. What do we know about patients with SAUD?

Among the 24 studies focusing on alcohol-related AB in SAUD, nine suggested a stronger alcohol-related AB in patients compared to CTL (e.g., Jones et al., 2006; Lusher et al., 2004; Müller-Oehring et al., 2019) or reported a positive correlation between AB scores and alcohol consumption (Garland, 2011). However, 14 studies did not observe such difference (e.g., Fridrici et al., 2014; Rettie et al., 2018; Vollstadt-Klein et al., 2009) or did not show any correlation between AB and alcohol consumption (den Uyl et al., 2018; Sinclair et al., 2016). Two studies even reported an avoidance bias in SAUD, indexed by lower AB scores for alcohol-related stimuli compared to CTL (Fridrici et al., 2013; Townshend & Duka, 2007). Beyond the SAUD diagnosis, alcohol-related AB appears related to higher quantity and frequency of alcohol consumption (e.g., Clarke et al., 2015; Fadardi & Cox, 2006; Garland, 2011), earlier age of SAUD onset (Müller-Oehring et al., 2019) and higher number of previous SAUD treatment (Jones et al., 2006; Noël et al., 2006). However, it is not associated with SAUD (Lusher et al., 2004; Noël et al., 2006; Sinclair et al., 2016) or abstinence (Garland, 2011; Sinclair et al., 2016; Wiers et al., 2016) duration.

Such findings question the key role played by AB in SAUD (Bechara, 2005; Robinson & Berridge, 1993; Wiers et al., 2007). Indeed, the first theoretical assumption resulting from dominant models is that the magnitude of AB would be related to the disorder's severity, individuals with SAUD presenting a stronger alcohol-related AB than moderate drinkers. Most studies were therefore expected to show an AB toward alcohol-related stimuli, since they focused on patients diagnosed with SAUD, presenting longer/stronger alcohol consumption. However, the mixed results observed, most studies showing no stronger AB (or even an avoidance AB) among detoxified patients with SAUD compared to light drinkers, do not support this theoretical assumption. Importantly, recent modifications of the incentive-sensitization theory highlighted individual variations in the extent to which incentive salience is attributed to alcohol-related cues (Robinson et al., 2014). Indeed, individuals prone to approach reward cues (sign-trackers) would attribute greater motivational value to interoceptive cues than do individuals less prone to approach reward cues (goal-trackers; see Colaizzi et al., 2020 for a review). Moreover, each motivational property acquired by incentive stimuli (i.e., alcohol-related AB, subjective craving and seeking behaviour) may contribute to alcohol use in different but complementary pathways (described as the "three routes to relapse"; Milton & Everitt, 2010). Therefore, AB might play a major role in the development of SAUD for some individuals but be far less crucial for others.

4.1.2. What is the time course of AB?

4.1.2.1. What do we know about subclinical populations?

AB in subclinical populations appeared mostly at the controlled stages of attentional processing. The maintenance of attention toward alcohol was reflected by AB at longer stimuli duration (Field et al., 2004), delayed Stroop interferences (Hallgren & McCrady, 2013), specific assessment of disengagement processes of AB (Gladwin et al., 2013; Heitmann et al., 2020; Sharbanee et al., 2013), larger attentional resources (i.e., N2 amplitude) dedicated to alcohol-related cues (Dickter et al., 2014) or by eye-tracking indexes such as dwell times or number of fixations (e.g., McAteer et al., 2015, 2018; Monem & Fillmore, 2017). Alcohol-related AB in subclinical populations would thus rely on later and controlled processes, suggesting that the automaticity in AB, postulated by dominant models, is absent in this population (McAteer et al., 2015).

4.1.2.2. What do we know about patients with SAUD?

Two studies suggested the presence of an approach-avoidance pattern depending on stimulus duration - with an initial approach AB towards alcohol-related stimuli, followed by attentional disengagement from these stimuli – specific to this population (Beraha et al., 2018; Noël et al., 2006). These preliminary results on patients with SAUD highlighted the relevance of investigating the time course of AB in populations usually characterized by motivational conflict regarding alcohol-related cues, and notably among patients in detoxification, frequently showing ambivalence towards alcohol consumption.

4.1.3. Is AB a stable index of the reflexive/reward system's over-activation?

4.1.3.1. What do we know about subclinical populations?

Alcohol-related AB is increased by craving (Field et al., 2004; 2005; 2007), in vivo alcohol cue exposure (Cox et al., 2003; Ramirez et al., 2015a; 2015b) and reward expectancies (Field et al., 2011; Jones et al., 2012). However, AB in heavy drinkers is not influenced by experimental procedure like subliminal priming or alcohol-related motivations (Baker et al., 2014). Hangover did not affect AB (Gunn et al., 2021) but alcohol intoxication might decrease it (Weafer & Fillmore, 2013), especially following high alcohol pre-load (Duka & Townshend, 2004).

4.1.3.2. What do we know about patients with SAUD?

AB might be increased by high craving at testing time (Field et al., 2013) and current drinking status (Sinclair et al., 2016). These findings provided experimental support for Field et al.'s (2016) proposal, as AB might fluctuate alongside motivational states related to craving and drinking status, rather than being a stable index of reflexive/reward system's over-activation. This could explain the inconsistencies across previous studies exploring AB in SAUD without measuring the psychological state at testing time. Indeed, most patients were abstinent and undergoing detoxification treatment, such states being frequently related to aversive or ambivalent alcohol evaluations. Therefore, the available results do not rule out the possibility that AB is present at some stages of SAUD, but they nonetheless suggest that, during the detoxification process, patients with SAUD do not present a strong and stable AB toward alcohol.

The discrepancies between clinical and subclinical populations regarding the presence of AB might be explained by the role of motivational conflict. Field et al. (2016) suggested that patients with SAUD in detoxification treatment might attempt to override alcohol-related AB to reduce concerns about drinking behaviour and suppress craving. This could lead to different patterns of AB than subclinical drinkers who are not attempting to reduce their consumption. Finally, while experimental manipulations of alcohol-related motivations failed to influence AB, AB increased with subjective craving and in vivo alcohol cue exposure. Again, these findings support the theoretical account whereby AB arises from momentary changes in alcohol-related stimuli evaluations (Field et al., 2016).

4.1.4. Is AB influenced by the reflective/control system?

4.1.4.1. What do we know about subclinical populations?

While alcohol AB is unaffected by working memory performance (Pieters et al., 2014; Sharbanee et al., 2013; van Duijvenbode et al., 2017b), the moderating role of executive control on the relationship between AB and alcohol use is more inconsistent. Indeed, AB is unaffected by executive control or impulsivity in some studies (van Duijvenbode et al., 2017b; Weafer & Fillmore, 2012a), but they appear strongly related in other ones (Field et al., 2007a; Murphy & Garavan, 2011; van Hemel-Ruiter et al., 2015; Willem et al., 2013). More particularly, heavy drinkers show more difficulty to inhibit saccade towards alcohol or appetitive stimuli (Brown et al., 2020; Wilcockson & Pothos, 2015), specifically when they are presented in their peripheral vision (Qureshi et al., 2019). Finally, stronger AB might be induced in social or heavy drinkers under increased cognitive load (Nikolaou et al., 2013; Tibboel et al., 2010) or by manipulating goal-driven mechanisms (Brown et al., 2018). These findings partly suggest the implication of reflective processes in alcohol-related AB, thus raising doubt regarding the validity of AB measures as specific indexes of the reflexive/reward system overactivation. Indeed, results show that AB could be influenced by the manipulation of the cognitive load recruited by the reflective/control system to perform a concurrent task. Nevertheless, the reflective abilities to deliberately inhibit the production of early saccadic movements are reduced (but not turned off) especially for alcohol-related cues, therefore showing that the reflective/control system cannot entirely take control over the over-activation of the reflexive/reward system and its alcohol-related AB.

4.1.4.2. What do we know about patients with SAUD?

Going beyond an enhanced schematic and elaborative processing of alcohol-related stimuli (Waters & Green, 2003) or an artefact of patients' impaired cognitive functioning (Fadardi & Cox, 2006), AB appears as a genuine phenomenon of SAUD, independently of higher-level cognitive processes such as executive functioning (Van Hemel-Ruiter et al., 2016). These few studies provide support to the proposal of an independence between the reflexive/reward and the reflective/control systems in patients with SAUD, as hypothesized by dual process models.

4.2. Methodological considerations

The inconsistencies between studies are mostly related to their variability regarding experimental choices and to several methodological shortcomings that cast doubt over the robustness of their findings. In line with recent proposals (Pennington et al., 2021), we identified these methodological issues and provided suggestions to address them, thus introducing the next chapter as well as the experimental part of this thesis.

4.2.1. Is AB specific to alcohol-related stimuli?

Many studies compared alcohol-related stimuli to non-alcoholic and non-appetitive ones (e.g., household objects, office stationery). Although this selection prevents participants from associating the control stimuli with alcohol use, contrary to non-alcohol appetitive stimuli (e.g., soft drinks, potentially associated with cocktails or mixed alcoholic drinks), this methodological choice does not elude the possibility that alcohol-related AB might not be specific to alcohol-related stimuli but would rather be generalized to other appetitive stimuli (soft drinks, monetary or erotic stimuli). Indeed, Qureshi and colleagues (2019) found stronger AB for both alcohol and non-alcohol appetitive cues in student drinkers. To isolate the mechanisms specifically related to the alcohol-related nature of AB, Pennington et al. (2021) suggested to consistently match experimental and control stimuli on incentive valence. Nevertheless, what can be considered as a neutral or appetitive non-alcohol stimulus remains unclear, since various studies used soft drinks or water pictures as neutral cues (Christiansen et al., 2015b; Heitmann et al., 2021), whereas others used them as appetitive cues (Pennington et al., 2020; Qureshi et al., 2019). Further work should clarify the concept of appetitiveness and determine what is appetitive for the population targeted before challenging AB specificity, as a generalized AB toward all appetitive cues without preference for alcohol-related ones would generate an in-depth revision of the current assumptions regarding AB in SAUD. Research should therefore carefully select their control stimuli and measure their appetitive nature in their specific sample.

4.2.2. Selection and validation of stimuli

Pennington et al. (2021) highlighted the frequent opacity of stimuli selection and validation in alcohol-related AB research. Most studies do not disclose the source of their selected stimuli and do not report validation procedure. The use of validated image databases is recommended to reduce the noise generated by the varying visual properties of stimuli. Future studies should thus consistently report stimulus validation procedures. Alcohol-related stimuli could also be individualized (i.e., focused on the alcohol preferentially consumed by each participant). The relevance of the experimental stimuli for the targeted population is also important to account for, as databases such as the Amsterdam Beverage Picture Set (Pronk et al., 2015) provide images of beverages consumed in specific countries, which brands might be unfamiliar for other cultures. New databases using images of alcohol and non-alcohol beverages should be developed and openly available. Finally, it should be underlined that most alcohol-related cues presented in experimental settings (e.g., pictures of beer, alcoholic beverages words) only present a part of the features related to the cues that people experience in naturalistic settings (e.g., the sight and smell of their preferred drink, in the context of expecting to be able to consume it imminently). Therefore, all AB cues are to some extent artificial, but pictures might have a better ecological validity than words (Jiang & Vartanian, 2018).

4.2.3. Reliability of AB measures and tasks

Most reviewed studies rely upon behavioural data, particularly percentage of correct answers (frequently related to ceiling effects, and thus of low informative value) and mean RT. RT measures are however affected by motor and cognitive processes, as the instructions request encoding stimuli, processing all the information needed for decision-making and finally executing the appropriate motor response (Hedge et al., 2018; Miller & Ulrich, 2013). Pennington et al. (2021) also highlighted measurement noises among studies relying upon difference scores to index AB. By subtracting two measures (i.e., RT for alcohol-related and control stimuli) usually intercorrelated, this method shows low reliability and potentially weakens the associations with other variables (Draheim et al., 2019; von Bastian et al., 2020). Altogether, the use of these biased measures, combined to the variability of the pictures used across studies, the reduced number of stimuli and their repetitions, highly impact the reliability of the tasks used and the replicability of their findings. Ataya et al. (2012) criticized the psychometric qualities of the RT-based VPT, after demonstrating its low internal consistency (α between .00 and .50; mean=.18). Several papers provided empirical recommendations to improve VPT reliability (Jones et al., 2018a; Pennington et al., 2021; Price et al., 2019), among which the systematic report of AB measures reliability indices. They also proposed the use of individualized stimuli and eye-tracking measures. Indeed, previous studies demonstrated improved internal reliability for individualized stimuli compared to general ones and for eye-tracking measures compared to RT ones (Christiansen et al., 2015b). The VPT therefore appears as a reliable task for assessing AB, but only when combined with individualized stimuli and/or eye-tracking indices.

4.2.4. Validity of AB measures and tasks

Beyond their ability to provide reliable measures (i.e., how the measure is performed), tasks also raise questions regarding their construct validity (i.e., which process is measured). Regarding the VPT, inferring AB through RT, as done in most studies, raises concerns as such measures only offer information about the location at which participants focused their attention at probe onset. It therefore provides no information about the successive steps of attentional processing (Field & Cox, 2008). Depending on the visual exploration strategy (e.g., initial focus on alcohol-related stimulus and then avoidance of this stimulus), a non-existing AB might be measured or, conversely, a real AB might be ignored. Regarding the modified Stroop task, slower responses to alcohol-related words are interpreted as an automatic allocation of increased attention to the semantic processing of these words. These could also result from patients' attempts to avoid processing alcohol-related words (Klein, 2007), leading to a completely different interpretation. However, RT measures prevent from testing the direction of alcohol-related AB (approach/avoidance AB). The same limits apply to other classical tasks. For example, the free viewing task combined with eye-tracking measures does not specifically request participants to pay attention to the cues, since they are neither presented as distractors nor goal-oriented stimuli. While being more ecological, the absence of goal-oriented instructions does not ensure that participants are paying attention to the cues when looking at the screen. Regarding the flicker induced-blindness paradigm, the structure of the grid might encourage the systematic use of strategic scanning, limiting attentional capture by the cues (Hobson et al., 2013).

4.3. Clinical perspectives

Beyond the experimental and conceptual issues addressed above, key questions are also raised regarding the clinical usefulness of AB in alcohol-related disorders. Namely, in order to determine its potential therapeutic interest, it has first to be determined whether AB towards alcohol cues is related to clinical outcomes and, if so, if we can reliably measure and reduce it among patients with SAUD.

4.3.1. Is AB related to key alcohol-related factors?

As described earlier, alcohol-related AB appears related to higher quantity and frequency of alcohol consumption in patients with SAUD (Clarke et al., 2015; Fadardi & Cox, 2006; Garland, 2011; Vollstadt-Klein et al., 2009), earlier age of SAUD onset (Müller-Oehring et al., 2019) and a higher number of previous SAUD treatment (Jones et al., 2006; Noël et al., 2006). However, it is not associated with duration of SAUD (Lusher et al., 2004; Noël et al., 2006; Sinclair et al., 2016) or abstinence length (Garland, 2011; Sinclair et al., 2016; Wiers et al., 2017). More centrally, we showed that alcohol-related AB might play a predictive role in relapse risk, as relapsers showed stronger AB at treatment time than non-relapsers (Cox et al., 2002; Rettie et al., 2018). While these results do not establish a formal causal link between the persistence of SAUD and AB towards alcohol, they suggest that higher AB might be related to higher relapse risk, and thus that reducing AB might promote prolonged abstinence. However, the relationship between AB measured during detoxification and subsequent relapse is inconsistent across studies (for a review, see Christiansen et al., 2015a), which might be partly due to the large variability in the criteria used to characterize relapse: some studies considered relapse through a dichotomous yes/no approach (with variable criteria to index relapse, from the consumption of a unique alcohol dose to the presence of a persistent re-consumption pattern) while others promoted a more continuous perspective by measuring the number of abstinence days or the quantity/frequency of consumption since detoxification. More centrally, AB presents an intra-individual variability notably related to the fact that it is partly related to the motivational state, as above-mentioned (Christiansen et al., 2015a). As a whole, in view of the persisting difficulties to validly measure AB towards alcohol and to establish the stable presence and extent of such AB at the individual level, it appears premature to conclude that AB can constitute a reliable factor to predict relapse in SAUD.

4.3.2. Can AB be modulated?

In our systematic review, very few studies investigated how clinical treatment can impact the AB towards alcohol (notably because we only included studies comparing performances with a healthy control group and/or exploring the links between AB and alcohol consumption). We showed that AB in patients with SAUD might be decreased by medication such as baclofen (Beraha et al., 2018), but did not receive any beneficial effect from ABM training, tDCS or their combination (den Uyl et al., 2018). In subclinical populations, AB might be reduced in social, hazardous or harmful drinkers through ABM training, which also shows beneficial effects on alcohol consumption, craving and motivation to change (Fadardi & Cox, 2009; Luehring-Jones et al., 2017). Nevertheless, the benefits derived from ABM training are not always observed (Langbridge et al., 2019). The effectiveness of ABM programs was thoroughly debated in previous reviews questioning its clinical relevance in addiction (Christiansen et al., 2015a; Cristea et al., 2016; Heitmann et al., 2018). Although previous studies reported positive effects of ABM on addiction symptoms, most of them were conducted on subclinical drinkers, hampering to test its effect on relapse in SAUD, and did not report any alcohol-related AB at baseline in the tested population (Heitmann et al., 2018).

4.3.3. Should AB constitute a treatment target in SAUD?

The implementation of clinical programs aiming at reducing AB in SAUD can only be justified if AB can be reliably measured and quantified at the individual level, is a recognized predictor of relapse and can be efficiently modified. In view of the available literature, it appears that none of these necessary conditions are currently fulfilled as (1) methodological issues, as well as the high intra-individual variability of AB with time and motivational state, hamper to obtain a reliable and stable evaluation of AB at the individual level; (2) the causal role of AB in the persistence of SAUD is not established, and (3) no recognized procedure or training allows to significantly and durably reduce AB in SAUD. This leads to the conclusion that, at the current state of knowledge, AB should not constitute a clinical priority in detoxification centres. While promising, the remediation programs proposed to reduce the intensity of AB through cognitive training have shown very limited effects. Moreover, the stability of alcohol-related AB through contexts and stages of SAUD is a pre-requisite for the clinical implementation of ABM programs. However, as AB fluctuates with internal or environmental demands, the reliability of its evaluation and the relevance of ABM training in clinical settings should be questioned. Instead, these short-term fluctuations might constitute therapeutic targets to efficiency intervene on alcohol-related expectancies and evaluations.

5. Conclusion

We provided a comprehensive review of the literature on the association between alcohol-related AB and alcohol use. We highlighted major findings on the time course and components of AB, as well as experimental support to address the assumptions made by theoretical models (Bechara, 2005; Robinson & Berridge, 1993; Wiers et al., 2007). More precisely, we aimed to determine whether AB is independent of the reflective/control system activity, and whether it is stable through contexts and time or fluctuates alongside motivational state or alcohol use severity. Findings in SAUD showed that AB is independent of disorder's severity or higher-level cognitive processes, but is unstable and influenced by craving or drinking status. Conversely, studies on subclinical drinkers supported the link between alcohol-related AB and alcohol consumption intensity and suggest the partial involvement of reflective processes. Although this population is not usually characterized by ambivalent motivations towards alcohol, experimental manipulations of motivational states also influenced AB, thus supporting the theoretical proposal of an overstatement of its stability (Field et al., 2016). When interpreting these outcomes, one should bear in mind that we focused on peer-review published studies, therefore excluding the grey literature. Although most studies did not find any association between AB and SAUD, a publication bias might have limited the publication of such null findings. In the same vein, a publication bias may have influenced conclusions regarding AB in easier-to-recruit subclinical populations. Furthermore, our methodological quality evaluation of the studies allowed us to provide recommendations for future research to address the main methodological shortcomings (i.e., appropriate use of stimuli, reliability and validity of AB measures). Finally, we discussed the therapeutic interest of evaluating and retraining AB in clinical population with SAUD. In view of the current findings, we cannot identify a strict causal link between AB and variables related to the development and persistence of SAUD (e.g., SAUD duration, number of detoxification treatment, duration of abstinence, relapse rate). Considering also the lively debates regarding the clinical effectiveness of ABM programs, its implementation as a therapeutic target appears premature and further work should rather focus on the causal role and stability of AB in SAUD, as well as on establishing reliable paradigms to evaluate it.

Chapter 3

Moving forward: Research avenues on alcohol-related AB

This chapter is adapted from:

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1. Introduction

In the previous chapters, we have identified the main theoretical assumptions made by dominant models in addiction regarding the nature and role of AB. We have then discussed the currently available evidence to establish their validity. We have demonstrated the complexity of the literature related to AB in alcohol use disorders, and the major discrepancy between experimental findings. We argue that experimentally addressing those theoretical assumptions would clarify the nature of AB in alcohol use disorders, and thus pave the way for theoretically grounded and experimentally valid research on this topic. To move the field forward and reach a comprehensive understanding of alcohol-related AB, the present chapter will propose five research avenues based on the above-mentioned limits of earlier studies. It will thus introduce to the experimental part of this thesis, directly implementing these research avenues.

2. Research avenues on alcohol-related AB

2.1. The association between AB and the severity of alcohol use

Most dominant models assume that alcohol-related AB progressively develops through associative learning and/or over-sensitization of the reflexive/reward brain system, finally constituting an enduring characteristic of SAUD (Hardman et al., 2021). Therefore, we expect AB to be more pronounced in patients who have been suffering from SAUD for many years than among light drinkers. However, most of the studies reviewed in the previous chapter did not show such difference, casting doubt on this first theoretical assumption. Whereas the association between alcohol use and AB appears more consistent in subclinical populations, the comparison across studies is dampened by discrepancies in terminology, inclusion criteria and consumption thresholds. Indeed, the sample is often poorly specified, as participants are mostly recruited among the general population or among University students, assuming the presence of high consumption levels in this population. Moreover, the control of potentially biasing variables (e.g., presence of psychiatric comorbidities, demographics) is usually limited. A key priority for future studies is to provide a better characterization of their experimental sample, through valid and standardized assessment of alcohol consumption. Since most studies used the AUDIT and TLFB, these two tools could constitute the minimal alcohol consumption measures, potentially complemented by tools evaluating specific drinking habits (e.g., binge drinking; Townshend & Duka, 2002, 2005). Furthermore, the terms labelling the targeted population are heterogeneous and should also be standardized (Maurage et al., 2021).

The present Ph.D. thesis will further explore this first assumption in all our experimental studies by comparing the performances of a well-established population of people presenting alcohol use disorders with matched CTL meeting a set of rigorous inclusion criteria. In Chapter 4 to 6, we will investigate the presence of AB in a specific population of binge drinkers, recruited according to an adapted version of the selection criteria proposed by Maurage et al. (2020a). In Chapter 7 to 9, we will assess its occurrence in a clinical population of patients with SAUD under detoxification treatment. In all studies, the recruitment method will systematically account for potential biasing variables and will integrate valid and standardized alcohol use assessment tools (i.e., DSM criteria, AUDIT, binge drinking score). Based on the continuum hypothesis between subclinical but excessive alcohol use and SAUD, we aim to explore those two populations in order to determine the role of AB in the development (binge drinking; Chapter 4-6) and persistence (SAUD; Chapter 7-9) of alcohol use disorders.

2.2. The time course and processes underlying AB

Prominent models in addiction hypothesize that the over-sensitization of the reflexive/reward system increases responsiveness to alcohol-related stimuli, this AB being considered as an early, automatic and uncontrollable hijacking of attentional resources. In the same vein, AB is considered by dual-process models as a behavioral output of reflexive/reward system's over-activation, giving rise to automatic and uncontrolled behaviors (Wiers et al., 2007). The automaticity of AB, while usually considered as obvious in most studies, has not been established in SAUD. Moreover, AB was mostly observed at the late and controlled stages of attentional processing (i.e., longer dwell time for alcohol) in subclinical drinkers, raising doubts about its automatic and uncontrolled nature.

To determine whether AB is early, involuntary and automatic, as assumed in most dominant models, future studies should systematically go beyond behavioral measures, centrally by using eye-tracking methods. Classical behavioral results (i.e., accuracy and RT) provide only the final output of all the successive stages involved in stimuli processing. Conversely, by precisely and directly measuring the consecutive cognitive treatment steps involved during such tasks, the eye-tracking technique provides major insights regarding the time course of AB (Armstrong & Olatunji, 2012; Popa et al., 2015). Indeed, eye-tracking indices allow early/automatic attentional processing stages to be separated from later strategy-guided ones. On the one hand, the first fixation measures inform about AB in the first stages of stimulus processing, reflecting the initial orientation of attentional resources that occurs quickly and early during a trial. On the other hand, the dwell time for alcohol-related stimuli reflects the modulation of attentional allocation between stimuli that are progressively deployed over time and that are related to the controlled maintenance of attention on these stimuli (McAteer et al., 2015, 2018). Since cognitive control is thought to increase with the successive processing stages, the distinction between early and late ones allows to appropriately measure the alcohol-related AB and to specify its core processes.

Eye-tracker thus clarifies the spatial and temporal dynamics of AB, from the initial orienting to the more controlled attentional processing stages, and therefore increases the understanding of the cognitive mechanisms involved in AB (McAteer et al., 2015). However, although several eye-tracking studies have been conducted in subclinical populations, no study has ever used eye-tracking in patients with SAUD or in a specific population of binge drinkers. Altogether, previous findings highlighted the need to refine theoretical assumptions regarding the time course of AB, since (1) it can fluctuate from approach to avoidance AB according to the duration of stimulus presentation in patients with SAUD, and (2) its automatic nature is strongly questioned in subclinical populations.

In the present Ph.D. thesis, we will systematically explore the time course of AB and its underlying processes by combining AB paradigm with eye-tracking measures in each experimental chapter. Hence, we will provide the very first experimental data assessing AB in SAUD and binge drinking through more reliable eye-tracking measures. Moreover, Chapter 5 will further investigate the automatic nature of AB in binge drinking through the use of a specific eye-tracking task recruiting the early processing stages of attention.

2.3. The stability of AB

To be considered as a core characteristic of SAUD, that plays an important role in SAUD evolution, AB should be fairly stable during the course of the disorder. Hence, demonstrating that AB cannot be totally modified by context variation is a compulsory pre-requisite to confirm its conceptual and clinical validity. However, recent theoretical proposals (e.g., Field et al., 2016) and findings from previous studies suggested that AB might highly fluctuate alongside motivational state in both clinical and subclinical populations. Future research should therefore determine whether AB is constant and consistent among those populations, or whether it is modulated by short-term environmental or internal contingencies.

To this end, different types of stability have to be addressed. First, we need to further explore the *inter-contextual stability* of AB, as previous studies showed that the extent of AB is influenced by external factors (e.g., alcohol cue exposure) or motivational states (e.g., craving, alcohol-related motivations). The influence of these contextual variables on AB could be investigated by manipulating craving intensity, either directly through alcohol priming procedures (Halsall et al., 2022) or indirectly through negative mood induction procedures (Bresin et al., 2018). Moreover, further studies should evaluate alcohol-related AB in individuals with SAUD not seeking treatment and/or not presenting motivational conflict regarding alcohol. Second, we need to address the *short-term intra-individual stability* of AB, as the vast majority of previous studies have only offered AB measures at one timepoint, without evaluating test-retest variations and more globally without testing the psychometric properties of the task (reliability and validity). Within-subject variability in AB, according to craving level and perceived value of alcohol at testing time (Field et al., 2016), might obscure between-groups differences.

The present Ph.D. thesis will investigate the *inter-contextual stability* of AB by exploring the role played by current subjective craving on the occurrence and magnitude of AB through correlational analyses (Chapter 7 and 9). Going further, we will also directly compare the performances of people presenting identical drinking patterns but solely differing on their level of reported craving at testing time (binge drinkers in Chapter 4, patients with SAUD in Chapter 8). Moreover, we will manipulate positive and negative mood through induction procedures in Chapter 6 to determine their (direct or indirect) influence on AB in binge drinkers. Finally, we will evaluate the *short-term intra-individual stability* of AB in Chapter 7 by assessing the test-retest variations of AB in patients with SAUD that perform a traditional AB paradigm combined with eye-tracking measures.

2.4. The influence of reflective abilities on AB

The alcohol-related AB is commonly considered as reflecting specific reflexive/reward system over-activation, independently of reflective functioning. However, a direct experimental testing of the influence of reflective functioning on AB is needed to determine its purely reflexive nature. Whereas a few studies investigated the direct influence of reflective functioning on AB in subclinical drinkers, its impact still need to be experimentally addressed in patients with SAUD to determine the purely impulsive nature of alcohol-related AB. Future research should thus address this crucial aspect of the dual-process models, by testing the validity of the firmly postulated dissociation between reflexive/reward and reflective/control systems. Moreover, they should also address the validity of alcohol-related AB to exclusively measure the processes related to the reflexive/reward system's overactivation, as repeatedly argued in previous work.

First, we should determine whether AB can be modulated when the reflective resources are recruited (e.g., when saturated under high cognitive load), thus indexing an influence of reflective abilities on the reflexive/reward system. It would require the use of a pure AB task (e.g., VPT or free viewing task with eye-tracking monitoring) combined with a concurrent cognitive task requesting low or high cognitive load. Therefore, the commonly used addiction Stroop task should be avoided, as it requires to inhibit a predominant response (i.e., reading the word) in favour of a largely less automated one (i.e., name the color of the word). It consequently involves reflective abilities such as inhibitory control and prevents the dissociation of the two systems postulated by dual process models.

Second, we should further investigate the possibility of direct involvement of reflective abilities to control saccadic movements through task-related requirements, testing the ability of reflective processes to deliberately control AB. This second aspect requires to combine AB task with eye-tracking monitoring, as well as an assessment of alcohol-related AB at baseline, without any instruction to exercise a voluntary control on attentional resources. In both cases, the observation that AB (a) are significantly modified by a concurrent task involving reflective abilities or (b) can be significantly reduced through a voluntary control on attentional resources would raise serious doubts regarding the validity of AB to exclusively index reflexive/reward system's over-activation, as suggested by earlier studies.

The present Ph.D. thesis will investigate both aspects of the research question regarding the influence of reflective abilities on AB. First, the modulation of AB through the saturation of the reflective/control system's resources will be explored in Chapter 8. Patients with SAUD will be asked to perform an eye-tracking AB task while simultaneously performing a concurrent cognitive task with different levels of cognitive load, thus directly measuring the influence of reflective/control system's saturation on AB. Second, the ability to control and inhibit saccadic movements towards alcohol-related cues will be assessed in Chapter 9 by using an avoidance task with gaze contingency procedure in patients with SAUD.

2.5. The alcohol specificity of AB

To be a core determinant of the persistence of alcohol use disorders, AB should have specificity for alcohol-related cues and not be generalized to other appetitive cues. However, most previous studies have exclusively faced alcohol-related stimuli with non-alcohol-related or emotionally neutral stimuli, and have not compared alcohol-related AB with a potential AB towards other appetitive stimulations. Thus, the reported alcohol-related AB is likely to be only a subset of a generalized AB towards every rewarding stimuli, reducing its experimental and clinical importance.

Future research should determine whether AB is found exclusively for alcohol-related stimuli or generalize to a larger set of appetitive stimuli. In this vein, adding a comparison between other appetitive stimuli and neutral or alcohol-related stimuli in classical AB tasks would offer a double insight. First, a reduced or suppressed alcohol-related AB when other appetitive stimuli are used as control instead of neutral ones would suggest that the alcohol-related AB reported in earlier studies might have been over-estimated through the use of non-appetitive stimuli as control. Second, the observation of a generalized AB towards other appetitive stimuli when compared to neutral ones would show that AB are not specifically related to alcohol in SAUD, reducing the empirical and clinical interest of the so-called alcohol-related AB.

In the present Ph.D. thesis, we will control for the specificity of AB by comparing alcohol-related stimuli (i.e., alcoholic beverages) with non-alcohol appetitive stimuli (i.e., soft drink beverages) in Chapters 4, 6, 7, 8 and 9. Moreover, we will further clarify whether AB could be generalized to other appetitive stimuli by comparing alcohol-related stimuli with other appetitive stimuli (i.e., high-calories food stimuli, Chapter 4) or non-appetitive stimuli (i.e., household products, Chapter 9).

3. Conclusion

After identifying the major assumptions made by theoretical models regarding alcohol-related AB and exploring their experimental validity in the current literature, the present chapter provided research avenues to enhance our understanding of AB in alcohol use disorders. Based on above-mentioned limits of previous studies, we proposed future research to respectively explore: (1) the relationship between the severity and frequency of alcohol use disorders and the magnitude of AB; (2) the time course of AB and its underpinning processes; (3) its inter-contextual and intra-individual stability over time; (4) the impact of reflective/control system's activity on its occurrence; (5) the specificity of AB for alcohol-related cues. Those methodological and theoretical recommendations provided the foundation for the experimental design of our six studies (see Table 3), which aimed to reach a comprehensive grasp of the nature and role of AB in alcohol use disorders.

Table 3. Summary of the populations and theoretical assumptions tested by each experimental chapter of the present thesis.

	Binge drinking studies			SAUD studies		
Theoretical assumptions on AB	Ch. 4	Ch. 5	Ch. 6	Ch. 7	Ch. 8	Ch. 9
The association between AB and the severity of alcohol use	**X**	**X**	**X**	**X**	**X**	**X**
The time course and underlying processes of AB	x	**X**	x	x	x	x
The inter-contextual and intra-individual stability of AB	x		**X**	**X**	**X**	x
The influence of the activity if the reflective/control system on AB					**X**	**X**
The specificity of AB for alcohol-related stimuli	**X**		x	x	x	**X**

Studies with a methodological design specifically chosen to explore the theoretical assumption concerned are indicated by an upper-case and bold X.

PART II: EXPERIMENTAL STUDIES

Chapter 4

Craving is everything: An eye-tracking exploration of AB in binge drinking

Background: AB towards alcohol-related stimuli is a core characteristic of SAUD, directly linked to clinical variables (e.g., alcohol consumption, relapse). Nevertheless, the extent of AB remains poorly documented in subclinical populations such as binge drinking, an alcohol consumption pattern highly prevalent in youth, characterised by an alternation between excessive intakes and withdrawal periods.

Aims: We used eye-tracking to measure AB in binge drinking and determine its time course by dissociating early/late processing stages. We also aim to clarify its specificity for alcohol-related stimuli compared to other appetitive stimulations and explore its modulation by current craving intensity.

Methods: Binge drinkers (BD; n=42) and matched CTL (n=43) performed a VPT, requiring visual targets preceded by pairs of pictures to be processed, with three conditions (i.e., alcohol vs. soft drink, alcohol vs. high-calorie food, high-calorie food vs. low-calorie food).

Results: No group difference was observed for early processing (i.e., first AOI visited). Dwell times highlighted an AB towards soft drinks and healthy food among CTL, without any global AB towards alcohol in BD. Centrally, a comparison of BD with low versus high current craving intensity indicated that binge drinking was associated with AB towards alcohol and high-calorie food only in the presence of a high craving for these stimuli.

Conclusion: AB towards alcohol is only found in BD in the presence of high craving and is generalised to other appetitive cues.

Reference: This chapter is an adapted version of:

Bollen, Z., Masson, N., Salvaggio, S., D'Hondt, F., & Maurage, P. (2020). Craving is everything: An eye-tracking exploration of attentional bias in binge drinking. *Journal of Psychopharmacology, 34*(6), 636–647.

Craving is everything: An eye-tracking exploration of AB in binge drinking

1. Introduction

Binge drinking, constituting a frequent excessive alcohol consumption pattern in adolescents and young adults (Archie et al., 2012), is now considered as a specific drinking habit. Its distinctive characteristics are the presence of excessive but episodic consumption, leading to a repeated alternation between intense intoxications and withdrawal periods, associated with a strong motivation to reach drunkenness rapidly (Rolland and Naassila, 2017). The multiple withdrawal periods related to binge drinking appear harmful at both cognitive and cerebral levels when compared to more regular consumption patterns without extreme alcohol intoxications (López-Caneda et al., 2013). Indeed, binge drinking has recently been the focus of a large range of psychological and neuroscience explorations (e.g., Scaife and Duka, 2009; Lannoy et al., 2019a), consistently showing its consequences on cognitive abilities such as memory and executive functions (for reviews, see Carbia et al., 2018 and Hermens et al., 2013). As a whole, binge drinking is thus a specific alcohol consumption pattern related to well-established neuropsychological and cerebral negative effects.

Although AB towards alcohol-related stimuli emerged during the two last decades as a key process in alcohol use disorders, only a few studies that focused on neurocognitive abilities in binge drinking has assessed the presence and extent of AB in a clearly defined sample of BD. AB is globally defined as the tendency to allocate one's attentional resources preferentially to alcohol cues when such cues are presented together with other stimuli (usually neutral or soft-drink cues). It is supposed to play a major role in the emergence and persistence of SAUD by attracting attention towards alcohol-related stimuli and thus leading to an increase in the incentive motivational properties of such stimuli. This subsequently leads to an increase in alcohol consumption, craving (i.e., the intense urge and desire to drink alcohol, constituting a primary subjective motivational state promoting compulsive consumption; Flaudias et al., 2019; Skinner and Aubin, 2010) and relapse risk (Cox et al., 2014; Field et al., 2014; Field and Eastwood, 2005; Manchery et al., 2017). Previous behavioural studies observed the presence of AB towards alcohol-related stimuli in SAUD (for a review, see Field and Cox, 2008). Moreover, several studies have revealed a direct link between the strength of AB and the severity of alcohol-related problems (Jones et al., 2006) or the relapse risk over a six-month follow-up period (Garland et al., 2012). Despite some currently ongoing debates (Boffo et al., 2019; Cristea et al., 2016; Wiers et al., 2018), this pivotal role of AB in SAUD has been reinforced by recent investigations (Heitmann et al., 2018; Rinck et al., 2018) showing that training paradigms able to reduce this AB efficiently diminished alcohol consumption and relapse risk, suggesting a causal link between AB and alcohol-related problems.

The presence of AB could go beyond SAUD, as it may also concern subclinical consumption patterns (e.g., heavy drinking, regular drinking or hazardous drinking). Several experimental investigations have shown AB in populations presenting subclinical chronic consumption habits (e.g., Cox et al., 2015; Fadardi and Cox, 2009; Field and Eastwood, 2005; Weafer and Fillmore, 2013). However, some inconsistencies remain regarding those populations (Ceballos et al., 2009; Field et al., 2005, 2011; Sharma et al., 2001), which could partly be explained by the serious lack of coherence regarding the terminology, inclusion criteria and thresholds chosen in these studies to categorise alcohol consumption patterns. The population explored is indeed often poorly specified: participants are mostly recruited among college students, assuming a high level of alcohol consumption in this population, and the control of potentially biasing variables (e.g., presence of co-morbid depressive/anxious states or other addictive disorders, variations in alcohol consumption frequency/intensity) is usually limited. To address this issue and to clarify the presence of AB towards alcohol in subclinical populations, the present paper will focus on binge drinking, as it is a very frequent consumption pattern in youth and constitutes a clearly defined and specific consumption pattern in which AB has been poorly explored. The definition criteria for binge drinking have long been a matter of debate, but a consensus has progressively emerged to promote the computation of a binge-drinking score evaluating the key characteristics of this habit (Crego et al., 2009; Townshend and Duka, 2002). This binge-drinking score, focusing on consumption speed, drunkenness frequency, and drunkenness ratio, has been largely used in recent papers (e.g., Bø et al., 2017; Gierski et al., 2017; Laghi et al., 2016; Smith et al., 2017), and we will also capitalise on this score to offer an optimal characterisation of BD.

The VPT (see Methods for a full description) is the most common task to study AB. Nevertheless, inferring the presence of AB exclusively through the classical VPT behavioural measures (i.e., RT and performance) is questionable, which could partly explain the very low internal reliability of the task (Ataya et al., 2012). Indeed, such measures only provide insights about the final output of all the successive stages involved in processing alcohol cues (Field and Cox, 2008), without dissociating early (i.e., initial orientation of attentional resources) and late (i.e., modulation of attentional allocation between stimuli) processing stages. Cognitive control is thought to increase with the successive stimulus processing stages, and it is thus essential to distinguish early and late stages to measure the AB induced by alcohol stimuli appropriately and to specify its core processes.

A reliable way to assess AB is to go beyond such classical measures by using eye-tracking. This tool provides insights regarding the time course of AB by measuring eye movements and gaze position throughout the entire task, with high temporal resolution (Popa et al., 2015). Eye-tracking directly and precisely measures the consecutive steps involved in attentional processing, thus offering a deeper understanding of the underlying processes (Armstrong and Olatunji, 2012). In particular, eye-tracking indices allow early processes to be separated from later ones. On the one hand, the first AOI visited informs about AB in the first stages of stimulus processing, reflecting an initial attentional capture that occurs quickly and early during a trial. On the other hand, the dwell time (i.e., overall fixation time on each stimulus) reflects processes that are progressively deployed over time and that are related to the controlled maintenance of attention on alcohol-related stimuli (McAteer et al., 2015, 2018; Monem and Fillmore, 2017). Therefore, the eye-tracking method clarifies the spatial and temporal dynamics of the reported AB, from the initial orienting to the more controlled attentional processing stages, and thereby improves the reliability of the traditional paradigms (Christiansen et al., 2015b; Miller and Fillmore, 2010). Results from studies using this technique among subclinical populations with excessive alcohol use (i.e., heavy, hazardous or regular drinkers) clearly showed that indices based on eye movements provide a more robust AB assessment than RT (e.g., Christiansen et al., 2015b; Field et al., 2011). While these results mainly indicated the presence of AB towards alcohol-related stimuli in heavy drinkers at the later and more controlled stages of information processing (McAteer et al., 2015, 2018; Miller and Fillmore, 2010; Monem and Fillmore, 2017), the time course of AB remains to be more deeply understood through the comparison between different eye-tracking indices.

Another uncertainty regarding AB in alcohol use disorders is its specificity towards alcohol-related stimuli. Previous studies have mostly investigated the presence of AB towards alcohol by presenting alcohol-related stimuli together with non-alcoholic non-appetitive or emotionally neutral stimuli. However, it is not clear whether AB is specifically caused by the alcohol-related nature of the cues or at least partly by their highly appetitive nature. Recent research exploring inhibitory control failure (presumably caused by AB) in young drinkers compared alcohol-related stimuli with non-alcoholic appetitive stimuli and non-alcoholic non-appetitive stimuli. A significant effect of both appetitive cues was shown, beyond their alcohol-related nature (Monk et al., 2017; Qureshi et al., 2019). The appetitive value of the stimuli should thus be further explored through AB paradigms, as a generalised AB towards all appetitive cues without any preference for the alcohol-related ones would imply a strong revision of the assumptions concerning AB in alcohol use disorders.

Finally, the role played by craving in the presence and intensity of AB is still unclear. The incentive-sensitisation theory (Robinson and Berridge, 1993) describes AB as the result of repetitive alcohol exposures, leading to a more sensitised dopaminergic system that subsequently enhances the incentive-motivational properties of alcohol cues. Becoming more salient, these cues grab the consumer’s attention. According to this theory, the sensitisation of the dopaminergic system also results in the emergence of a subjective craving towards the substance (i.e., an appetitive experienced motivational state) that is strongly related to AB. Similar predictions of a reciprocal excitatory relationship between the two processes can also be found in the extensions of this model (Franken, 2003; Ryan, 2002) and have been widely confirmed by the literature. Although most studies exploring alcohol-related AB in subclinical populations did not assess participants’ craving, a meta-analysis of 68 data sets demonstrated a significant association between the magnitude of AB and the strength of subjective craving (Field et al., 2009). One eye-tracking study (Hobson et al., 2013) has even suggested that craving intensity is a stronger determinant of AB than the level of alcohol consumption in regular drinkers. Nevertheless, these associations have not been supported by more recent studies (Van

Duijvenbode et al., 2017; Wilcockson et al., 2019) and thus need further investigation.

In view of the above-mentioned limits related to previous studies, the four main objectives of the present study were as follows. First, this study aimed to explore, for the first time, the presence of AB in a specific population of subclinical BD by using eye-tracking measures. We hypothesised that BD, when compared to CTL, would show an AB towards alcohol-related stimuli. Second, the study aimed to investigate the time course of the potential AB by combining the VPT with eye-tracking measures. This integration allowed us to explore the successive steps involved in attentional processing and to dissociate early and late components of AB. We hypothesised that AB would mostly occur during the later and more controlled stages of attentional processing (indexed by dwell times) in binge drinking, in line with previous results in other subclinical populations (McAteer et al., 2015; 2018; Miller and Fillmore, 2010). Third, the study sought to determine whether AB was exclusively related to alcohol or could be generalised to other appetitive stimuli. To do this, a comparison between alcohol-related stimuli, neutral ones (i.e., pictures of soft drink or healthy food) and other appetitive ones (i.e., pictures of high-calorie food) was performed. We hypothesised that AB would be present for other appetitive stimuli when compared to neutral ones, and thus that AB is not specifically related to alcohol in subclinical populations. The presence of such a generalised AB towards appetitive stimuli would question the experimental and clinical interest of the so-called alcohol-related AB. Fourth, the study explored the role played by subjective craving for alcohol or food on the magnitude of AB towards alcohol-related or food-related stimuli, as we hypothesised that the eye-tracking correlates of AB, and particularly those related to late processing stages (i.e., dwell time), would be strongly modulated by the current craving intensity towards appetitive cues.

2. Methods

2.1. Participants

Participants were recruited via an online screening questionnaire sent through social networks to students from UCLouvain (Belgium). The survey assessed sociodemographic (i.e., age, sex, mother tongue) and nutritional (i.e., diet, consumption frequency per food types) variables. A thorough evaluation of alcohol consumption characteristics during the last six months was also conducted, encompassing: the evaluation of the mean number of alcohol units per week and per occasion (an occasion being defined as an event lasting several hours, e.g., dinner with friends, evening party); the mean number of drinking and binge drinking occasions (defined as the consumption of more than six units of alcohol) per week; the consumption speed (in units per hour); the drunkenness frequency (i.e., number of drunkenness episodes: 'How many times have you been drunk during the last six months', drunkenness being defined as including the loss of motor/verbal coordination, the loss of self-control and/or nausea); the drunkenness ratio (i.e., percentage of drunkenness episodes compared to all drinking episodes); and the age when alcohol was first consumed. Participants were informed about the number of alcohol units per type of alcoholic beverages (an alcohol unit corresponding to 10 g of pure ethanol in Belgium) and were asked to fill in a questionnaire assessing alcohol-related disorders (AUDIT; French validation: Gache et al., 2005). Exclusion criteria for both groups were the presence of: a parental history of SAUD; a personal past or current SAUD (as diagnosed through DSM-5 criteria); daily alcohol consumption; a personal past or present psychological, addictive (except nicotine and occasional cannabis use) psychiatric or neurological disorder (including clinical depressive or anxious state); uncorrected visual deficits; low French speaking abilities; vegetarian or vegan diets.

Two groups of participants (BD, CTL) were constituted based on alcohol consumption characteristics, including binge-drinking score (Townshend and Duka, 2005) and AUDIT score (Gache et al., 2005). The binge-drinking score was computed using the following formula: (4×consumption speed) + drunkenness frequency + (0.2×drunkenness percentage). Following the online screening, 85 participants (75 right-handed) were selected to take part in the experiment: 42 BD (binge-drinking score ⩾22; AUDIT score ⩾9) and 43 CTL (binge-drinking score ⩽12; AUDIT score ⩽9). A power computation (performed in R v3.6.1; R Foundation for Statistical Computing, Vienna, Austria) indicated that a sample size of 53 was required to detect a conventional medium effect size (Cohen, 1992) with 0.80 power, as fulfilled by our sample size. To control for the influence of psychopathological co-morbidities, participants filled in questionnaires using Qualtrics software (Qualtrics, LLC, Provo, UT), assessing depressive symptoms (Beck Depression Inventory (BDI-13); French validation: Beck et al., 1998), anxiety (State–Trait Anxiety Inventory (STAI); French validation: Bruchon-Schweitzer and Paulhan, 1993) and impulsivity (UPPS-P Impulsive

Behavior Scale; French validation: Billieux et al., 2012). All participants were asked to refrain from consuming alcohol during the days preceding the experimental session and were questioned about their recent consumption before starting the experiment.

2.2. Procedure

Participants provided written informed consent to take part in the study and were not aware of the hypotheses being tested. Just before the task, online questionnaires evaluated current (i.e., right now) craving using Qualtrics software. Visual analogue scales (VAS; 0–100) assessed the craving intensity related to alcohol and salty and sugary food. A complementary craving measure was performed using the Alcohol Craving Questionnaire Short Form Revised (for alcohol craving) and adapted forms for salty and sugary food. We only report (see median split analyses below) the results related to the craving median split performed on the VAS, as the correlations between the two craving measures were high (i.e., alcohol craving: $r=0.634$, $p<0.001$; salty food craving: $r=0.675$, $p<0.001$; sugary food craving: $r=0.692$, $p<0.001$) and as similar results were obtained when performing the median split on craving questionnaires (see Supplemental Material). Then, participants were seated in front of a blank screen and tested individually in a quiet room. They received verbal instructions to perform the task, without being aware of its rationale. The experimental task was a computerised behavioural task composed of three blocks and lasted 45 minutes. A nine-point calibration of each participant's eye-gaze position was set up at the beginning of each block through a display screen. After the task, participants were asked to fill in the online questionnaires assessing psychological co-morbidities. The study protocol was performed in accordance with the ethical standards established by the Declaration of Helsinki and was approved by the Ethics Committee of the Psychological Sciences Research Institute (UCLouvain). At the end of the experiment, participants were debriefed and received a compensation of €10 for completing the experiment.

2.3. Apparatus

Participants were seated on an adjustable desk chair, facing an eye-tracker camera placed 60 cm away from a Dell PC equipped with a 21.5-inch LCD screen (resolution 1080×1920; refresh rate 60 Hz). Their head movements were reduced using a forehead and chin stabiliser. The presentation of the experimental task and its synchronisation with eye-tracking were controlled using OpenSesame software (Mathôt et al., 2012). Eye movements were recorded using an Eye-link 1000 tower-mounted eye-tracker (SR Research Ltd, Mississauga, Canada; sampling rate 1000 Hz; average accuracy range 0.25°–0.5°, gaze tracking range 32° horizontally and 25° vertically).

2.4. VPT

At the beginning of each trial, a central fixation dot appeared on the black background screen, and participants were asked to fixate their gaze on it. This instruction ensured that participants initially focused their visual attention at the centre of the screen in each trial. The fixation dot was also used as a drift check to confirm the reliability of the eye-gaze calibration. Once the participant's eyes were detected at the centre of the screen by the eye-tracking device, the fixation dot was removed and was directly followed by the presentation of two pictures. They were displayed randomly on the left and right side of the computer screen for a 2000 ms period and then replaced by a probe (i.e., a white arrow on a black background, pointing up or down) appearing at the location previously occupied by one of the pictures. Participants were instructed to respond to the orientation of the probe by pressing the 'up' or 'down' key on a keyboard as quickly and accurately as possible. Each trial was separated by an intertrial interval of random duration (between 500 and 1500 ms). Faster responses to probes replacing the alcohol-related stimulus (compared to the neutral one) are interpreted as an AB towards alcohol-related stimuli.

Participants completed three versions of the VPT: one presenting alcohol and soft-drink stimuli (i.e., drink block; see Figure 5), one presenting alcohol and food stimuli (i.e., drink–food block) and one presenting salty or sugary food and healthy food (i.e., food block). The three blocks were administrated in the following order: the drink block was presented first to obtain the standard measure of the alcohol-related AB, followed by the drink–food block or the food block in a counterbalanced order. Visual probes replaced the two types of pictures with equal frequency. Each block contained 84 trials in total, including four practice trials (i.e., the same task performed on stimuli not included in the experimental phase) that participants completed first.

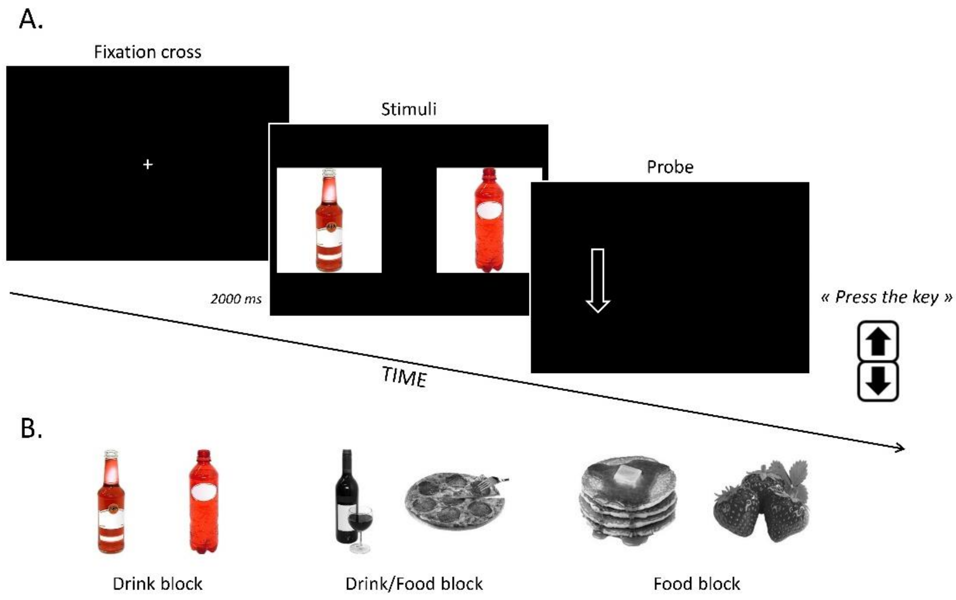

Figure 5. (a) Illustration of the alcohol-related VPT with alcohol-related versus non-alcohol-related (i.e., soft drink) stimuli. The task requires participants to respond as quickly as possible to the target probe by indicating on which side (left or right) the arrow appeared. The presence of AB towards alcohol is indexed by shorter RT when the probe appears at the same location as the alcohol-related stimulus (as illustrated here) in comparison with a probe appearing at the same location as the soft drink. (b) Example of stimuli pairs for each block of the VPT (from left to right: drink block with alcohol/soft drink, drink–food block with alcohol/food and food block with sugary/healthy food).

2.5. Stimuli

Three pictures sets were used for the VPT. For the drink block, 20 pairs of coloured pictures of alcoholic beverages (e.g., bottle of vodka, can of beer) and matched pictures of non-alcoholic beverages (e.g., bottle of water, soft drink can) without context, extracted from the validated ABPS pictures battery (Pronk et al., 2015), were displayed on a white background. The brand and writings of the beverage were systematically blurred, and each picture pair was matched on perceptual features such as size (250×250 pixels; 6.05×6.05° visual angle), brightness and salience. For the drink–food block, we used a set of pictures depicting other alcoholic drinks from the ABPS battery and high-calorie food from the Food-Pics battery (e.g., bowl of ice cream, hamburger; Blechert et al., 2014). All pictures were matched on luminance and spatial frequency using the SHINE toolbox (Willenbockel et al., 2010). The same matching procedure was used for the food block, including a set of other pictures from the Food-Pics battery depicting high-calorie food, all matched with pictures of low-calorie food (e.g., fruit, vegetables) on basic perceptual features such as size (250×250 pixels; 6.05×6.05° visual angle), luminance and spatial frequency using the SHINE toolbox. Stimuli were presented in black and white in the drink–food and food blocks. This is because the large variation in colours across food stimuli made it impossible to match them on this parameter, and it was thus decided to present these stimuli in black and white to avoid any strong perceptive difference (known to influence eye-tracking measures strongly) between stimuli types.

2.6. Data reduction and statistical analyses

A data-reduction procedure was performed for RT. Trials with incorrect responses (3.65% of trials) were removed prior to analysis, as well as trials with RT <200 ms (0.03% of trials) or >2000 ms (0.25% of trials). The spatial and temporal parameters of eye movements were extracted using Eyelink® Data Viewer (SR Research Ltd). Gaze samples were qualified as fixations or saccades according to the standard Eyelink algorithms. The dependent variables measured were the first AOI visited, which indicates the area that was first fixated at the beginning of each trial, and the dwell time, defined as the sum of fixation times on one of the areas during the whole trial. For the first AOI visited, the sum of the percentages for both stimuli is not equal to 100%, as the first fixation could be outside the two AOIs. Likewise, the sum of dwell times for both stimuli is not equal to 2000 ms, as the fixations could be outside the two AOIs.

All statistical analyses were performed using IBM SPSS Statistics for Windows v25.0 (IBM Corp., Armonk, NY). Between-group comparisons (i.e., independent t-tests) were performed on demographic and psychological characteristics, as well as on alcohol consumption variables. To estimate the internal reliability, we computed Cronbach's alpha for the following AB measures: (a) RT, (b) first AOI visited and (c) gaze dwell time. Following a well-established procedure (Ataya et al., 2012; Christiansen et al., 2015b; Van Ens et al., 2019), we calculated AB scores separately for each pair of pictures, leading to 20 AB scores for each AB measure within each version of the VPT (drink, drink–food and food blocks). Separate repeated-measures analyses of variance (ANOVAs) were performed on RT for each block, with group (BD vs.

CTL) as the between-subjects factor and type (alcohol vs. soft drink, alcohol vs. high-calorie food, salty or sugary food vs. healthy food) as the within-subjects factor. For each picture category, the type factor thus groups the trials in which the probe appeared at the same location as these pictures (e.g., all trials in which the arrow replaced the alcohol-related stimuli for 'alcohol' type). Eye-tracking measures were explored by using two 2×2 ANOVAs (first AOI visited and dwell time) performed for each version of the VPT, with group (BD vs. CTL) as the between-subjects factor and type (alcohol vs. soft drink, alcohol vs. high-calorie food, salty or sugary food vs. healthy food) as the within-subjects factor. For each ANOVA, comparisons within group and type were investigated, as well as interactions between the two factors. Regarding craving analyses, Pearson's two-tailed correlations with Bonferroni correction were first performed between AB measures (i.e., RT, first AOI visited, dwell time for each stimulus type) and craving measures (i.e., VAS scores) to investigate the influence of craving levels on the magnitude of AB towards alcohol and food-related stimuli in the whole sample. Multiple regressions for AB were then conducted in each version of the VPT to explore the predictive power of craving (for alcohol, salty food, and sugary food), alcohol-related factors (AUDIT score and BD score) and psychopathological co-morbidities (depression, state/trait anxiety, and impulsivity) on AB indexed by dwell times. Based on correlational results and in line with Hobson et al. (2013), median splits were then conducted on craving levels. Then, 2×2 ANOVAs were performed on RT, first AOI and dwell time separately for each group (BD and CTL) and each version of the VPT, with alcohol/salty food/sugary food craving (high cravers vs. low cravers) as the between-subjects factor and type (alcohol vs. soft drink, alcohol vs. high-calorie food, salty or sugary food vs. healthy food) as the within-subjects factor. Finally, complementary analyses were performed (see Appendix B for the results) on: (a) first fixation laterality for each version of the VPT to test for the presence of a potential pseudoneglect effect (Bowers and Heilman, 1980) by performing a 2x2 ANOVA with group as between-subjects factor and laterality (left, right) as within-subjects factor; (b) the time course of AB by performing 2x2 ANOVA (group as between-subjects factor, type as within-subjects factor) on dwell time in the drink block for the first (T1: 0–1000 ms) and second (T2: 1000–2000 ms) stimuli presentation time periods in order to distinguish early and late processing stages; and (c) gender effect regarding high-calorie food by performing 2x2x2 ANOVAs on dwell time (with gender as second between-subjects factor) in the drink-food and food blocks to account for any differential processing of high-calorie food between men and women, notably those related to different social norms/stereotypes regarding nutrition behaviours.

3. Results

3.1. Demographic and psychopathological measures

As shown in Table 4, BD and CTL did not differ for age [$t(83)=.620$, $p=.537$], sex ratio [$\chi^2(1,85)=.294$, $p=.588$], depression [$t(83)=.704$, $p=.483$], trait anxiety [$t(83)=1.096$, $p=.276$] or state anxiety [$t(83)=.046$, $p=.963$]. By contrast, BD showed higher impulsivity [$t(83)=2.476$, $p=.015$], alcohol craving [$t(83)=4.174$, $p<.001$] and salty-food craving [$t(83)=3.031$, $p=.003$]. Finally, and as expected, BD participants had larger BD scores [$t(83)=10.751$, $p<.001$] and AUDIT scores [$t(83)=13.978$, $p<.001$].

Table 4. Demographic, psychopathological, and alcohol consumption measures [mean (SD)] for BD and CTL.

	BD (n=42)	CTL (n=43)
Demographic measures		
Gender ratio (male/female) ^{ns}	20/22	20/23
Age ^{ns}	21.36 (2.20)	21.07 (2.00)
Psychopathological measures		
Beck Depression Inventory ^{ns}	4.61 (3.90)	4.29 (3.40)
State Anxiety Inventory ^{ns}	33.79 (10.00)	36.14 (9.70)
Trait Anxiety Inventory ^{ns}	42.36 (10.90)	42.47 (10.80)
UPPS-P *	46.05 (7.30)	42.16 (7.20)
Alcohol consumption measures		
AUDIT **	17.38 (5.00)	4.72 (3.10)
Binge Drinking Score **	43.91 (23.19)	5.35 (3.89)
Number of units per week **	22.74 (12.28)	3.15 (3.54)
Number of occasions per week **	3.51 (1.36)	1.47 (1.24)
Number of units per occasion **	5.71 (2.82)	2.20 (1.91)
Number of binge drinking episodes per week **	1.47 (1.50)	0.13 (0.17)
Consumption speed (units/hour) **	3.39 (1.07)	1.06 (0.74)
Number of drunkenness episodes (last 6 months) **	27.68 (19.36)	0.91 (1.31)
Drunkenness ratio (last 6 months) **	19.25 (28.92)	2.02 (6.17)
Age at first alcohol consumption ^{ns}	14.41(0.95)	14.68 (2.61)
Craving measure (VAS)		
Alcohol craving **	28.48 (27.0)	8.58 (15.5)
Salty food craving *	32.83 (25.6)	17.21 (21.8)
Sugary food craving ^{ns}	33.76 (25.3)	26.14 (20.6)

^{ns} Non-significant, * $p<.05$, ** $p<.001$.

3.2. Experimental measures

3.2.1. Internal reliability

Internal reliability is shown in Table 5. Cronbach's alpha was very low for classical measures (i.e., RT). Conversely, it was high for eye-tracking measures (i.e., first AOI visited and dwell time), being above the 0.70 cut-off conventionally considered as the minimum for acceptable internal reliability (Kline, 2000).

Table 5. Internal reliability (Cronbach's alpha) of the Drink, Drink-Food and Food blocks of the VPT, for RT and eye tracking measures.

	RT	First AOI visited	Dwell time
Drink block	.138	.781	.939
Drink-Food block	.082	.924	.911
Food block	.013	.970	.923

Note: Trials with RT outliers (i.e., lower than 200ms or higher than 2000ms) were excluded from the analyses.

3.2.2. RT

RT are shown in Table 6. We found a main effect of TYPE in the drink–food block [$F(1,83)=8.958$, $p=.004$, $\eta^2=.097$], showing shorter RT for food compared to alcohol. We found no main effect of TYPE in the drink and food blocks, nor a main effect of GROUP or interaction in any block ($p>.050$).

Table 6. RT [mean (SD)] for Drink, Drink-Food and Food VPT tasks [mean (SD)] for BD and CTL.

Variable	Condition	Type	BD (n=42)	CTL (n=43)
RT (ms)	Drink	Alcohol	582 (115)	574 (122)
		Soft Drink	582 (115)	572 (121)
	Drink-Food	Alcohol	586 (120)	573 (118)
		Food	577 (112)	564 (111)
	Food (salty)	Salty	572 (102)	571 (121)
		Healthy	570 (106)	566 (111)
	Food (sugary)	Sugary	572 (110)	570 (125)
		Healthy	579 (118)	568 (123)

3.2.3. Eye-tracking measures

First AOI visited. Eye-tracking measures are shown in Table 7. We found a main effect of TYPE in the drink–food block [$F(1,83)=60.566$, $p<.001$, $\eta^2=.422$], showing a higher frequency of first fixations on food compared to alcohol. We found no main effect of TYPE in the drink and food blocks, nor main effect of GROUP or interaction in any block ($p>.050$).

Dwell time. We found a main effect of TYPE in the drink [$F(1,83)=6.273$, $p=.014$, $\eta^2=.070$], drink–food [$F(1,83)=32.518$, $p<.001$, $\eta^2=.281$] and food [$F(1,83)=4.135$, $p=.045$, $\eta^2=.047$] blocks, showing a longer dwell time on soft drinks and food compared to alcohol, and on healthy food compared to sugary food. Centrally, we found an interaction between TYPE and GROUP in the drink [$F(1,83)=5.040$, $p=.027$, $\eta^2=.057$], drink–food [$F(1,83)=8.146$, $p=.005$, $\eta^2=.089$] and food [$F(1,83)=6.899$, $p=.010$, $\eta^2=.077$] blocks. In the drink block, CTL showed a longer dwell time on soft drinks compared to alcohol [$t(42)=2.884$, $p=.006$], while no difference was observed in BD. In the drink–food block, both groups showed a longer dwell time on food compared to alcohol [BD: $t(41)=2.523$, $p=.016$; CTL: $t(42)=5.217$, $p<.001$], with BD showing a smaller difference than CTL [$t(83)=2.702$, $p=.008$]. In the food block, CTL showed a longer dwell time on healthy food compared to salty [$t(42)=2.940$, $p=.005$] and sugary food [$t(42)=2.335$, $p=.024$], and compared to BD [$t(83)=2.445$, $p=.017$]. We found no main effect of GROUP in any block ($p>.050$).

Table 7. Eye tracking indexes for Drink, Drink-Food and Food VPT tasks [mean (SD)] for BD and CTL.

Variable	Condition	Type	BD (n=42)	CTL (n=43)
First AOI visited (%)	Drink	Alcohol	47.29 (8.8)	45.61 (8.5)
		Soft Drink	46.04 (8.7)	46.83 (9.4)
	Drink-Food	Alcohol	42.89 (7.4)	42.09 (10.8)
		Food	54.64 (5.9)	51.19 (10.5)
	Food (salty)	Salty	49.88 (8.0)	47.73 (9.4)
		Healthy	47.74 (7.1)	47.56 (8.1)
	Food (sugary)	Sugary	49.29 (6.3)	47.09 (10.9)
		Healthy	48.81 (6.8)	47.67 (8.2)
Dwell Time (ms)	Drink	Alcohol	578 (188)	526 (173)
		Soft Drink	584 (153)	638 (252)
	Drink-Food	Alcohol	578 (183)	471 (180)
		Food	657 (180)	709 (283)

	Food (salty)	Salty	673 (213)	641 (256)
		Healthy	645 (189)	777 (296)
	Food (sugary)	Sugary	648 (183)	657 (249)
		Healthy	663 (193)	761 (316)

3.3. Craving analyses

Craving-related correlations. Alcohol craving was significantly correlated with dwell time on alcohol-related stimuli (drink block: r=.533, p<.001; drink–food block: r=.355, p<.001). Sugary food craving was significantly correlated with dwell time on sugary food stimuli (food block: r=.411, p<.001), as well as salty food craving with dwell time on salty food stimuli (food block: r=.365, p<.001). No correlation was found between the first AOI visited measures or RT measures and any craving type (p>.050).

Craving-related regression. In the BD group, the dwell time on alcohol stimuli in the drink block was predicted by the full model [containing AUDIT, binge drinking, BDI, STAI-A, STAI-B, UPPS, and alcohol craving scores as predictors; F(7,41)=3.458, p=.007, R^2_{adj}=.296], but alcohol craving was the only variable significantly contributing to the prediction (β=.510, t=3.812, p=.001). In the drink–food block, dwell time on alcohol stimuli was also predicted by the full model [F(7,41)=3.162, p=.011, R^2_{adj}=.270], but here again, alcohol craving was the only predictor (β=.306, t=2.243, p=.032). Dwell time on food stimuli was not significantly predicted by the full model [F(7,41)=1.495, p=.197, R^2_{adj}=.003]. In the food block, dwell time on salty food stimuli was predicted by the full model [F(7,41)=3.417, p=.007, R^2_{adj}=.292], with the binge-drinking score being the only significant predictor (β=.666, t=3.316, p=.002). Similarly, dwell time on sugary food stimuli was predicted by the full model [F(7,41)=3.402, p=.007, R^2_{adj}=.291], with the binge drinking score (β=.519, t=2.562, p=.015) and sugary food craving (β=.452, t=3.230, p=.003) being the significant contributors. In the CTL group, dwell time on alcohol stimuli was predicted by the model in the drink block [F(7,42)=3.450, p=.007, R^2_{adj}=.290], with STAI-A (β=-.668, t=3.016, p=.005) and UPPS scores (β=.705, t=2.999, p=.005) significantly adding to the prediction. In the drink–food block, dwell times on alcohol stimuli [F(7,42)=1.175, p=.342, R^2_{adj}=.028] and food stimuli [F(7,42)=1.014, p=.445, R^2_{adj}=.003] were not predicted by the model. In the food block, the models did not significantly predict dwell time for salty food

[*F*(7,42)=1.324, *p*=.268, R^2_{adj}=.051] and sugary food [*F*(7,42)=.845, *p*=.558, R^2_{adj}=.027] stimuli.

3.4. Craving-related median split analyses

Median split procedure. Median splits were conducted in each group (BD and CTL) based on the craving scores observed for alcohol, salty and sugary food. Importantly, the resulting subgroups (i.e., BD and CTL subgroups presenting low vs. high alcohol/salty food/sugary food cravings) did not differ regarding alcohol-related or psychopathological variables (see Supplemental Material), ensuring that the differences observed between low and high cravers were specifically related to current craving intensity.

Median split on RT. In the drink and drink–food blocks, no significant interaction was found between TYPE and alcohol, salty or sugary food CRAVING (*p*>.050) in the BD and CTL groups. In the food block, an interaction between sugary food CRAVING and TYPE was found among BD [*F*(1,40)=5.193, *p*=.028, η^2=.115], but no difference was found when comparing BD with high and low craving [healthy food: *t*(40)=1.113, *p*=.272; unhealthy food: *t*(40)=.477, *p*=.636], and no difference was found in the CTL group.

Median split on first AOI visited. In the drink, drink–food and food blocks, no significant interaction was found between TYPE and alcohol, salty or sugary food CRAVING (*p*>.050) in the BD and CTL groups.

Median split on dwell time. In the drink block (see Figure 6), an interaction between alcohol CRAVING and TYPE was found among BD [*F*(1,40)=9.122, *p*=.004, η^2=.186], with the subgroup with low craving showing longer dwell times for soft drink stimuli compared to those with high craving [*t*(40)=3.175, *p*=.003] and compared to alcohol stimuli [t(20)=2.340, p=.030]. In the drink–food block, an interaction between alcohol CRAVING and TYPE was also found among BD [*F*(1,40)=8.007, *p*=.007, η^2=.167], with the subgroup with low craving showing longer dwell times for food stimuli compared to those with high craving [*t*(40)=2.057, *p*=.046] and compared to alcohol stimuli [t(20)=3.470, p=.002]. No significant interaction was found between TYPE and salty and sugary food CRAVING (*p*>.050). In the food block, an interaction between salty food CRAVING and TYPE was found among BD [*F*(1,40)=5.585, *p*=.023, η^2=.123], with the subgroup with high craving showing a longer dwell time on salty food compared to those with low craving [*t*(40)=2.629, *p*=.012].

The same interaction was found for sugary food CRAVING [$F(1,40)=5.996$, $p=.019$, $\eta^2=.130$], with the subgroup with low craving showing a longer dwell time on healthy food compared to those with low craving [$t(40)=3.485$, $p=.001$] and compared to sugary food [t(20)=2.401, p=.026]. Finally, a main sugary food CRAVING effect was found in BD [$F(1,40)=4.170$, $p=.048$, $\eta^2=.094$] and CTL [$F(1,41)=9.310$, $p=.004$, $\eta^2=.185$], with the subgroup with high craving showing a longer dwell time. No significant interactions between alcohol/sugary/salty CRAVING and TYPE were found among CTL in any block ($p>.050$).

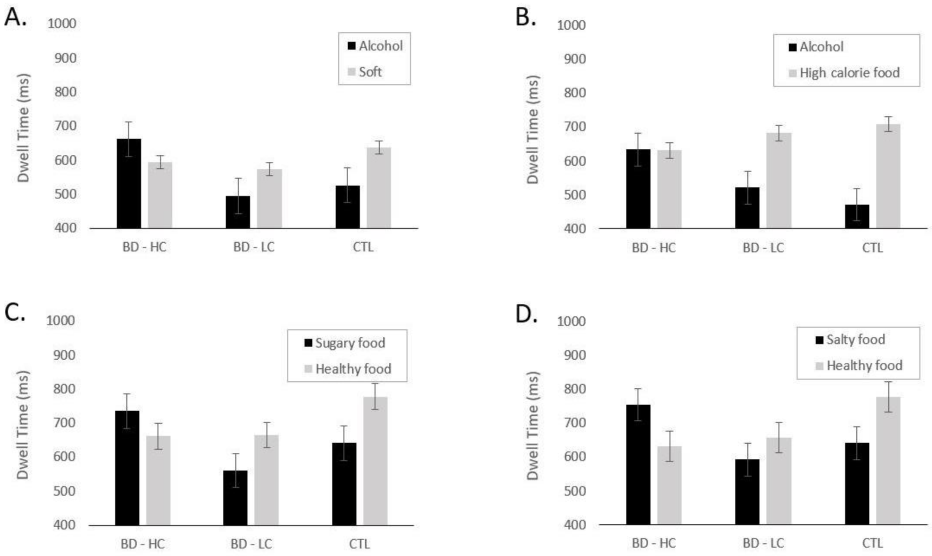

Figure 6. Dwell times observed in BD with high craving (BD – HC), BD with low craving (BD – LC) and CTL in the drink block (a), drink–food block (b) and food block (c) for the sugary/healthy food comparison and (d) for the salty/healthy food comparison.

4. Discussion

The presence of AB towards alcohol-related cues in SAUD is assumed by most dominant models in addiction (Field and Cox, 2008). Its investigation has recently been extended to various drinking patterns, and its assessment has been improved through the use of innovative techniques. The present paper aimed to extend this research field by exploring the presence and extent of AB in binge drinking using combined RT and eye-tracking measures.

Regarding RT, no general (i.e., independent of craving) AB was observed in BD, as no significant difference was shown between BD and CTL in any block. This absence of RT results, contrasting with the differences previously found on eye-tracking measures in subclinical populations, might be partly explained by the low reliability of RT measures, whereas the complementary use of eye-tracking provides a more reliable and robust AB assessment (Marks et al., 2015; Miller and Fillmore, 2010, 2011). The internal reliability analyses performed in the present paper offered strong support to this proposal by showing a very poor reliability for RT measures (Cronbach's α <0.2), and conversely a very high reliability for eye-tracking indices (Cronbach's α >0.75), particularly for dwell time measures (Cronbach's α >0.90). Regarding eye-tracking results, indices reflecting the initial and early processes (i.e., first AOI visited) and the late ones (i.e., dwell time) did not demonstrate any global AB towards alcohol cues in BD. This is inconsistent with most previous studies showing the presence of AB in diverse subclinical populations with excessive alcohol consumption patterns (Field et al., 2004; Hallgren and McCrady, 2013; Miller and Fillmore, 2011; Townshend and Duka, 2001; van Duijvenbode et al., 2017; Weafer and Fillmore, 2013). Nevertheless, it should be noted that these earlier studies were not focusing on binge drinking habits but were rather exploring heavy drinking samples, with large variability in the alcohol consumption patterns considered and in the inclusion/exclusion criteria determined. Moreover, the present study is not the first failing to replicate these earlier findings. The only previous study focusing on binge drinking (DePalma et al., 2017) did not report any AB towards alcohol among BD for RT. In the same vein, Schoenmakers et al. (2008) did not observe a longer dwell time on alcohol-related pictures in sober heavy drinkers.

Importantly, while no dwell time difference was observed between alcohol-related and soft-drink stimuli in BD, CTL presented a higher dwell time for soft drinks, suggesting the presence of AB towards healthier stimuli (or away from alcohol-related ones) in CTL, absent in BD. This AB should lead to reconsider the so-called alcohol-related AB reported in earlier studies. For example, McAteer et al. (2015) stated the presence of an alcohol-related AB in heavy drinkers, but this result was due to the fact that CTL showed a strong AB for neutral stimuli and not to a real alcohol-related AB in the experimental group (as dwell times for alcohol and neutral stimuli did not differ in heavy drinkers). In the present study, longer dwell time on soft-drink pictures in CTL (when compared to BD) was only observed during the latter half of the stimuli presentation. No AB was observed during early attentional processing (considered as the automatic processing stage in earlier studies), explored by first AOI visited and T1 dwell time. Similar results were observed by McAteer et al. (2015), who suggested that the automaticity of AB, postulated by several theoretical models, would not be present in regular drinkers but rather would be specific to SAUD. Actually, previous studies using RT and variations in stimuli presentation time observed an automatic capture of attention towards alcohol-related stimuli in SAUD when stimuli were presented for 50–100 ms, while this alcohol-related AB was only measured in regular drinkers after longer presentation times (Field et al., 2004; Noël et al., 2006). In our study, the similar patterns between groups appeared to vanish during the late processing stages, since a longer dwell time for soft drinks (when compared to alcohol-related ones) was observed for CTL and not for BD. These findings clarify the time course of attentional processing by showing that the difference between CTL and BD only appeared during the later processing stages, and are not related to an early automatic capture of attentional resources by alcohol-related stimuli, as observed in SAUD. The absence of an early AB among BD could, however, be partly due to the classical dominance of the left side of the visual field (see Supplemental Material) related to reading/writing habits (i.e., left-gaze bias), leading the participants to orient their attention preferentially to the left side of the screen at early processing stages, regardless the type of stimuli presented on the left side (Foulsham et al., 2013; McAteer et al., 2015).

Regarding the specificity of AB for alcohol, results indicated that BD are also strongly attracted by other appetitive stimuli as shown by results from the drink–food block (i.e., RT, first AOI visited and dwell time) which revealed that both groups were more attracted by high-calorie food when compared to alcohol. It thus appears that the potential AB (beyond being present only when high craving levels are reported, as discussed below) is not specific to alcohol-related cues: BD also have a preferential allocation of attentional resources towards other appetitive stimuli, and even a stronger attraction towards high-calorie food stimuli than alcohol-related ones. Nevertheless, the higher percentage of first fixations on food (when compared to alcohol) in all participants might be partly explained by a general complexity effect, with food stimuli presenting a higher degree of visual complexity, potentially influencing the initiation of the first saccade. Future studies should thus further explore the generalisation of AB towards other appetitive stimuli.

No AB was found here in BD when considered as a homogeneous group. However, in line with earlier studies (e.g., Hobson et al., 2013), our results showed that alcohol craving widely influenced the magnitude of AB towards alcohol-related stimuli in BD. The subgroup of high cravers presented a significant AB towards alcohol, while low cravers presented an avoidance AB for alcohol, as found in CTL. AB towards alcohol was thus only found among BD when combined with a high level of craving. The intensity of alcohol craving at the testing time is thus the core determinant of AB magnitude in BD. This finding is in line with evidence from Field et al. (2013), who also used a median split on craving levels among patients with SAUD to show that a far stronger AB was found among patients with high craving. Similarly, previous studies reported that regular drinkers with high craving presented an AB towards alcohol cues, while regular drinkers with low craving did not (Field et al., 2005; Hobson et al., 2013). Hobson et al. (2013) also demonstrated that eye-tracking indices of AB were related to craving but not alcohol consumption, which is consistent with the present multiple regression analysis showing that dwell time was significantly predicted by craving but not alcohol consumption or psychopathological variables. Moreover, the impact of craving on AB among BD is found here when considering dwell time but not when considering the first AOI visited. The theoretical and experimental proposal, emerging from SAUD studies, that craving influences the early attentional capture might thus not apply to binge drinking, where craving intensity would rather influence later and more controlled processes.

As a whole, these findings suggest that AB observed in populations with subclinical alcohol consumption, and particularly in binge drinking, is not explained by alcohol consumption but rather by an interaction between the drinking pattern (i.e., binge drinking) and craving level during the task. The role of craving in the intensity of AB had already been suggested in earlier work (Hobson et al., 2013; Field et al., 2004, 2005), but we show here that in subclinical samples, craving levels are not merely intensifying AB, but rather that AB is absent among BD with low craving. At the initial stages of excessive alcohol consumption, AB thus might not yet constitute a core and stable characteristic but rather would be influenced by the motivational state. This assumption is in line with the theoretical account proposed by Field et al. (2016) regarding the role of AB in addictive disorders. They indeed questioned its stability and rather suggested that this AB would be determined by momentary evaluations of substance-related stimuli, which fluctuate with current motivational tendencies to consume. Interestingly, the association between craving and AB has also been observed between the level of craving for salty or sugary food and AB towards these cues. The AB towards food appears in all participants with a high craving for salty or sugary food, while it only occurs in BD regarding alcohol cues. Future work should extend these results to other appetitive cues and drinking patterns (centrally by comparing BD with heavy drinkers). They should also explore the influence of other alcohol-related variables (e.g., time since last binge-drinking episode, alcohol consumption during the days preceding the experiment, withdrawal symptoms), craving-related factors (e.g., explicit liking, satiation level) and psychopathological co-morbidities (while they did not influence the experimental results, the depression and anxiety scores obtained in our sample were quite high, in line with earlier studies among university students; e.g., Beiter et al., 2015; Ibrahim et al., 2013).

At the methodological level, the following limitations should be underlined. First, we used identical stimuli for all participants, but variations in preferred alcohol drinks might have influenced AB. Upcoming studies should explore such influence, notably by using personalised stimuli when exploring AB among BD, as recently recommended (Christiansen et al., 2015b, but see also Jones et al., 2018a). Second, our design did not propose total randomisation of the experimental blocks (i.e., the drink block was systematically presented first). While this choice allowed us to have an uncontaminated measure of the classical AB towards alcohol-related stimuli, it might have influenced the results observed for the drink–food block. Indeed, despite the fact that different alcohol-related stimuli data sets were presented in the drink block and drink–food block, participants had already been confronted with alcohol-related stimuli when starting the drink–food block, while food stimuli were presented for the first time. Third, although the use of black and white pictures in the drink-food and food blocks was justified by the large variation in colours across food stimuli (leading to probable differences in the early mobilization of attentional resources), it hampered us to explore the role played by variations in terms of arousal and salience, reported for the original alcohol and high-calories food pictures in Blechert et al. (2014) and Pronk et al. (2015) but modified following the transition to black and white pictures. Future studies should control for this potential effect on AB, notably by asking participants to evaluate the arousal of the selected stimuli. Despite these limitations, this study is the first to demonstrate that AB towards alcohol-related in binge drinking is (a) strongly determined by craving intensity and (b) not specific to alcohol, as it is also found for other appetitive cues.

Chapter 5

Does alcohol automatically capture drinkers' attention? Exploration through an eye-tracking saccadic choice task

Rationale: Dominant models postulate the presence of an automatic AB towards alcohol-related stimuli in alcohol use disorder, such AB constituting a core feature of this disorder. An early AB has been documented in subclinical populations such as binge drinking (i.e., a drinking pattern prevalent in youth and characterized by repeated alternation between alcohol intoxications and withdrawals). However, the automatic nature of AB remains to be established.

Objectives: We investigated the automatic nature of AB in BD through the saccadic choice task. This eye-tracking paradigm consistently highlights the extremely fast and involuntary saccadic responses elicited by faces in humans, relative to other object categories. Through an alcohol-related adaptation of the saccadic choice task, we tested whether the early capture of attentional resources elicited by faces can also be found for alcohol-related stimuli in BD, as predicted by theoretical models.

Methods: Forty-three BD and 44 CTL performed two versions of the saccadic choice task. In the original version, two images (a face, a vehicle) were displayed on the left and right side of the screen. Participants had to perform a saccade as fast as possible towards the target stimulus (either face or vehicle). In the alcohol-related version, the task was identical but the images were an alcohol-related and a non-alcohol stimulus.

Results: We replicated the automatic attraction toward faces in both groups, as faces generated higher saccadic accuracy, speed and amplitude than vehicles, as well as higher corrective saccade proportion. Concerning the alcohol-related adaptation of the task, groups did not differ for the accuracy, speed and amplitude of the first saccade towards alcohol. However, BD differed from CTL regarding the proportion of corrective saccade towards non-alcoholic stimuli after an error saccade towards alcohol, suggesting the presence of an alcohol disengagement AB specific to BD.

Conclusions: Alcohol-related AB in BD is not characterized by an early and automatic hijacking of attention towards alcohol. This AB rather relies on later and more controlled processing stages, namely a difficulty to disengage attentional resources from alcohol-related stimuli.

Reference

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Does alcohol automatically capture drinkers' attention? Exploration through an eye-tracking saccadic choice task

1. Introduction

AB refers to the tendency to preferentially orient one's attentional resources towards salient or behaviourally-relevant stimuli when presented in the environment. Prominent addiction models (Bechara, 2005; Wiers et al., 2007) suggested that alcohol-related stimuli would hijack the attention of individuals with alcohol use disorder through associative learning, ending up in an AB towards alcohol. The influential incentive-sensitization theory (Robinson & Berridge, 1993) notably posits that repetitive alcohol exposures sensitize the reflexive/reward system, thus enhancing the motivational properties (i.e., incentive salience) of the stimuli associated with alcohol use. Becoming more salient, these alcohol-related stimuli automatically and rapidly grab drinker's attention and result in AB. This theory was then refined by a psychopharmacological model (Franken, 2003), suggesting that, when alcohol-related stimuli are present in the environment, they increase the dopaminergic response in the reward circuit, which in turn serves to automatically capture one's attention toward those stimuli. Such alcohol AB is thought to have clinical consequences, as it would increase craving (i.e., the intense urge and desire to consume alcohol), favour increased alcohol consumption, and enhance relapse risk. Hence, AB would play a crucial role in the onset and persistence of SAUD, and is now considered as a key process in this disorder. Indeed, current prominent models postulate that the over-sensitivity of the reflexive/reward system, caused by repeated alcohol use, makes the user highly reactive to alcohol-related stimuli, this AB being considered as an early, automatic and uncontrollable hijacking of attentional resources.

However, the empirical evidence supporting such strong theoretical assumptions remains limited in SAUD. Previous behavioural studies showed very heterogeneous findings regarding the presence and extent of AB in the classical population of interest, namely recently detoxified patients with SAUD (for a review, see Bollen et al., 2022). Indeed, some findings revealed the presence of AB in this clinical population (e.g., Müller-Oehring et al., 2019), but others rather revealed an avoidance pattern (e.g., Townshend and Duka, 2007), and most did not show any difference in the attentional processing of alcohol-related stimuli compared with CTL presenting low/moderate alcohol consumption (e.g., Field et al., 2013; Wiers et al., 2016). These disparate findings might be partly explained by the heterogeneity (e.g., various stimuli presentation times) and low reliability (due to RT measures; Ataya et al., 2012) of the AB paradigms used, as well as by the lack of inclusion criteria (e.g., alcohol doses per week) for recruiting CTL. The presence of alcohol-related AB appears more consistent in subclinical populations (i.e., individuals presenting excessive alcohol consumption but who do not present the diagnosis of SAUD), since AB was positively related with alcohol use intensity in most studies conducted among social drinkers (Albery et al., 2015; Field et al., 2011), and was found to be stronger in more specific drinking patterns (e.g., heavy or BD) compared to light drinkers (DePalma et al., 2017; Tibboel et al., 2010), especially in the presence of high subjective craving (Bollen et al., 2020). Nevertheless, the inter-studies comparison is dampened by a lack of coherence regarding the terminology and inclusion criteria to characterize these drinking patterns. To address this issue, we will focus on binge drinking, because it constitutes a clearly defined and specific drinking pattern (Maurage et al., 2020a), and because it has been repeatedly associated with alcohol AB (Elton et al., 2021; Langbridge et al., 2019), thus constituting the ideal population to reliably test the features of AB in a subclinical population. Popular in youth, binge drinking is characterized by intense alcohol consumptions in short periods of time to reach drunkenness (Lannoy et al., 2021). The repeated alternation between intense intoxications and withdrawal periods appears particularly harmful for the brain, leading to well-established neuropsychological and cerebral negative effects (Crego et al., 2009; Lannoy et al., 2019a; López-Caneda et al., 2013). The definition criteria for binge drinking usually relies on the computation of a binge drinking score evaluating the key characteristics of this habit: consumption speed, drunkenness frequency, and drunkenness ratio per drinking occasions (Townshend and Duka, 2002).

As mentioned above, a key models' assumption is that AB towards alcohol is early, involuntary and automatic. To date, studies focusing on the time course of AB in subclinical populations revealed, however, that it mostly appears at later and more controlled attentional stages (Bollen et al., 2022). For example, Field et al. (2004) reported an alcohol-related AB (i.e., shorter RT for probes appearing on the side of the screen previously occupied by alcohol-related stimuli) in heavy drinkers (compared to light drinkers) when using the VPT, but only for stimuli with longer presentation duration (i.e., 500-2000ms versus 200ms). The maintenance of attention towards alcohol was also reflected by specific assessment of disengagement processes of AB through alternative paradigms (see Bollen et al., 2022 for a detailed description): the spatial cueing task, the Odd-One-Out task and the selective attention/action-tendency task (Gladwin et al., 2013; Heitmann et al., 2020; Sharbanee et al., 2013). Such findings suggested that AB would be characterized by a difficulty to disengage attention from alcohol-related stimuli once detected, potentially caused by the disrupted activity of higher-level and controlled processes (i.e., inhibitory control, executive functions; Carbia et al., 2018; Lees et al., 2019; López-Caneda et al., 2014). The automaticity in AB, postulated by dominant models, thus appears questionable in these populations. Some discrepancies were however found regarding the time course of AB when focusing on BD. Indeed, BD showed delayed interferences for color-naming alcohol-related words in an alcohol Stroop task, reflecting an AB at later and more controlled stages of processing (Hallgren & McCrady, 2013), but were more efficient to process alcohol-related cues at early encoding levels in an attentional blink task, reflecting more automatic AB processes (DePalma et al., 2017; Elton et al., 2021). A major limitation of these previous studies is that they exclusively relied on behavioural measures (i.e., manual RT) showing very low reliability (Ataya et al., 2012). Beyond the issue that such measures relied on hand movements and could thus be biased by potential deficits in motor responses, inferring AB through manual RT raises concerns since it only provided information about where participants focused their attention at the specific time of probe onset, without indexing the global stream and successive steps of attentional processing involved in AB (Field and Cox, 2008). Therefore, their methodology did not allow determining whether AB relies on a genuine automatic hijacking of the attentional resources by alcohol or whether it is rather characterized by an increase in the controlled processing of alcohol-related stimuli when consciously perceived.

To address this issue, recent studies used neuroscience tools to determine the neural activation underlying the different processes of alcohol-related AB. For example, the study of brain electrical activity through EEG allows to measure the neurofunctional brain response evoked by alcohol-related stimuli with high temporal resolution, thus providing major insights on the early brain processes involved when exposed to alcohol-related stimuli (Almeida-Antunes et al., 2022). Most EEG studies reported consistent findings by showing higher alcohol-related cue-reactivity and altered inhibitory processes (e.g., Blanco-Ramos et al., 2019; Petit et al., 2012; Ryerson et al., 2017). Nevertheless, this method does not allow to investigate the specific processes involved in the preferential allocation of attentional resources towards alcohol-related stimuli when confronted with neutral ones. Recent studies thus used eye-tracking measures to directly and precisely assess and distinguish the successive cognitive processes underlying AB, by detecting eye movements and gaze positions with a high temporal and spatial resolution throughout the task (Popa et al., 2015). Whereas manual RT only offer an indirect AB measure (i.e., the final processing output), eye-tracking allowed deepening the understanding of the time course and core mechanisms of AB and enhancing the reliability of its assessment (Bollen et al., 2020; Christiansen et al., 2015b). Eye-tracking findings suggested the presence of alcohol-related AB in subclinical populations (e.g., heavy or regular drinkers) at later processing stages, as indexed by longer dwell times (i.e., overall fixation time) or higher number of fixations towards alcohol-related stimuli (e.g., McAteer et al., 2015, 2018; Monem and Fillmore, 2017). While these studies did not index any early AB (e.g., alcohol preference in the first fixation), they used free exploration tasks with relatively long presentation times and without any "attentional task" *per se*, which does not make them suitable for measuring the early and automatic capture of attention towards alcohol-related stimuli. To date, only one study (Bollen et al., 2020) has explored the time course of AB in a specific population of BD, by combining the VPT with eye-tracking. They documented an AB among BD with high current craving, AB being related to late controlled attentional stages (i.e., longer dwell times for alcohol-related stimuli compared to neutral ones). However, the VPT is usually characterized by long stimuli presentation duration before the appearance of the probe, with participants not receiving any specific instruction on how to process these stimuli, thus potentially masking the early processing stages of AB. The present study will overcome this limit through a paradigm specifically dedicated to the exploration of early and automatic AB, namely the saccadic choice task, which will allow the first specific exploration of AB automaticity.

This paradigm was initially developed to explore the speed of visual processing (Kirchner & Thorpe, 2006) and was later adapted to address the speed of face processing (Crouzet et al., 2010). Indeed, human faces are naturally salient stimuli automatically capturing attention at very early processing stages. In this saccadic choice task, two images, a target (e.g., a face) and a distractor (e.g., a vehicle) are simultaneously displayed on the left and right of the screen. Participants have to perform a saccade as fast as possible towards the target stimulus. Studies have repeatedly reported shorter saccadic latencies when the target is a face [minimum saccadic RT (SRT) of 100-120ms for face targets vs. 130-150ms for other target categories e.g., vehicles], demonstrating the presence of a very strong automatic AB for faces compared to other stimuli (Crouzet et al., 2010; Guyader et al., 2017; Kauffman et al., 2019; 2021). Furthermore, they also reported that participants made more error saccades (i.e., saccades toward the distractor) when the distractor was a face than when it was another stimulus. These experimental results suggest that fast saccades toward attention-grabbing stimuli (i.e., faces) are automatic and beyond voluntary control. It should however be noted that other paradigms that directly involved more controlled processes (e.g., the antisaccade task) led to different results, notably reporting that facial stimuli are easier to avoid (i.e., generate stronger inhibitory control) than circles or scrambled facial stimuli (Hoffmann et al., 2021). The saccadic choice task thus constitutes an ideal paradigm to explore the early preferential processing of specific stimuli. This is further illustrated by the fact that, after an error saccade in this task, participants present more frequent and faster corrective saccades (i.e., second saccades directed towards the target when first saccades were directed towards the distractor) when the target is a face (indexing a re-engagement AB towards faces) than when it is another stimulus (indexing a disengagement AB from faces, Kauffmann et al., 2019). This corrective saccade towards the target was performed automatically by participants, as they did receive explicit instructions to correct their erroneous saccades and disengage from the distractor stimuli. Finally, they explored the amplitude (i.e., distance between the saccadic starting and ending points) of the saccade and observed larger saccades directed towards faces (either as target or distractor; Kauffmann et al., 2019), suggesting that the content of the stimuli influences the programming of saccade amplitude prior to its execution. As a whole, the saccadic choice task constitutes a powerful paradigm to test the early, automatic and involuntary capture of attentional resources by salient stimuli, and thus the presence of an AB towards such stimuli.

We thus used an adapted version of the saccadic choice task with alcohol-related stimuli to explore the automatic aspects of alcohol-related AB. If theoretical models' assumptions are correct, alcohol-related stimuli should hijack attentional resources and generate the same response pattern than the one reported above for faces (i.e., shorter saccadic latencies, increased error saccades when alcohol-related stimuli are the distractor, re-engagement and disengagement AB). We investigated this assumption in BD, since the presence of AB has been more consistently reported in subclinical populations than among patients diagnosed with SAUD. The advantages of the saccadic choice task are multiple. First, it is combined with eye-tracking, thus offering more reliable AB measures than manual RT. Second, it uses very short stimuli presentation times, thus forcing participants to perform their saccade towards stimuli as fast as possible and providing more insights regarding the early processes of AB compared to paradigms with longer presentation times. Finally, the assessment of the first saccades and the corrective ones offer important insights on the engagement, disengagement and re-engagement aspects of AB. We firstly administered the original version of the saccadic choice task to all participants to ensure the absence of any attentional dysfunction for the detection of highly salient stimuli in BD. The simultaneous use of both the original and the adapted alcohol version of the task led to two hypotheses: (1) BD and CTL will present the classical automatic capture of attention by universally salient stimuli (i.e., faces); (2) this automatic AB will also be present for alcohol-related stimuli among BD (but not among CTL), as these stimuli are supposed to acquire incentive salience in these populations (Robinson & Berridge, 1993).

2. Methods

2.1. Participants

We recruited participants via an online screening survey sent through social networks to students from UCLouvain (Belgium). Participants had to fill in questionnaires assessing alcohol-related disorders (AUDIT; Saunders et al., 1993; French validation: Gache et al., 2005), binge drinking habits [i.e., consumption speed, drunkenness frequency and ratio, number of binge drinking episodes (i.e., drinking more than 6 units) per week], socio-demographic (e.g., age, sex) and other alcohol consumption variables (i.e., number of alcohol units consumed per week, number of units per occasion, number of drinking occasions per week). Before completing them, they were provided with information about equivalences in terms of the number of alcohol units per type of alcoholic beverages (an alcohol unit corresponding to 10 gr of pure ethanol in Belgium). To be included in the study, they had to meet the following criteria: absence of parental history of SAUD, absence of current or past psychological or neurological disorders, normal or lens corrected vision.

For each participant, we then computed the binge drinking score (Townshend and Duka, 2005) by using the following formula: (4 x consumption speed) + drunkenness frequency + (0.2 x drunkenness ratio). We recruited 44 BD (AUDIT score ≤ 20; binge drinking score ≥ 24; 2-4 drinking occasions per week; binge drinking episodes per week ≥ 1) and 45 CTL matched on gender (AUDIT score ≤ 8; binge drinking score ≤ 16; units per week ≤ 10; units per occasion ≤ 3; no binge drinking episodes). Regarding the sample size determination, no reliable a priori power computation was possible as this study constituted the first using the SRT with alcohol-related stimuli in a subclinical population. We thus decided to include a larger sample size per group than all previous studies using this paradigm with facial stimuli among healthy populations (Kauffmann et al., 2019; 2021), to increase our ability to detect smaller effects of alcohol-related stimuli in the second task.

All participants provided their informed written consent before taking part in the study and were not aware of the hypotheses tested. We performed the study protocol in accordance with the ethical standards established by the Declaration of Helsinki for experiments involving humans and the Ethics Committee of the Psychological Sciences Research Institute (UCLouvain) approved it.

We asked participants to refrain from consuming alcohol during the day preceding the experimental session and we questioned them about their recent consumption before starting the experiment[2]. Before performing the two experimental tasks, we asked participants to fill in questionnaires using Qualtrics software (Qualtrics, LLC), assessing state anxiety (STAI-A) and current alcohol craving [Alcohol Craving Questionnaire Short Form Revised, ACQ-SF-R and VAS: "Indicate how much you want to drink alcohol right now (from 0 = not at all, to 100 = terribly wanting)"]. To control for psychopathological comorbidities, they filled in other questionnaires between the tasks assessing depressive symptoms (Beck Depression Inventory, BDI-II; French validation: Beck et al., 1998) and anxiety (State-Trait Anxiety

[2] We performed correlations between alcohol consumption the day before the experiment (i.e., number of alcohol units) and alcohol-related AB, since previous studies showed that acute alcohol consumption could induce alcohol-related AB in social drinkers (Duka & Townshend, 2004). For the alcohol vs flower task, results showed no correlation with the accuracy of the first saccade (r=.180, p=.103), the proportion of corrective saccade (r=.148, p=.183), the latency of the first saccade (r=-.087, p=.432) or the latency of the corrective saccade (r=.113, p=.307).

Inventory, STAI A-B; French validation: Bruchon-Schweitzer and Paulhan, 1993). At the end of the experiment, we debriefed participants, who received financial compensation.

2.2. Stimuli

Stimuli were 128 coloured pictures depicting human faces, vehicles, alcoholic beverages or flowers with context (32 pictures of each category), extracted from the free-from copyright “Pixabay” stock image base (https://pixabay.com/) under CC0 License. We chose the faces, vehicles and flowers pictures from the stimuli used in Kauffman et al. (2019; 2021) that were matched on perceptual features such as luminance and RMS contrast[3]. Faces were presented with vehicles pictures to replicate the version of the saccadic choice task used in Kauffmann et al. (2019). In the alcohol saccadic choice task, we chose flower pictures as neutral stimuli instead of non-alcoholic beverages pictures since they sufficiently differ from alcoholic beverages in terms of shape and are not related with alcohol through associative learning, contrarily to non-alcoholic beverages (e.g., orange juice might hijack attentional resources through its visual similarity with alcoholic cocktails). Moreover, we conducted preliminary tests showing that the use of flower stimuli compared with alcohol stimuli facilitated the categorization of the two stimuli, resulting in a similar level of difficulty than the initial face *versus* vehicle task, thus increasing the comparability across tasks. Finally, a previous study comparing face with flower pictures in a saccadic choice task showed that they were appropriate neutral stimuli as they elicited similar saccadic performance than vehicle pictures and did not contain features salient enough to capture attention like faces (Kauffmann et al., 2021). All pictures were matched on size (600×600 pixels; 11x11° visual angle) and spatial position of the main object in the picture.

[3] Alcohol-related pictures presented higher luminance (0.51±0.12 vs 0.42±0.12; t_{62}=2.943, p=.005, d=.736) than flower pictures but they were matched on RMS contrast (p=.394). This resulted in 72% of trials containing a pair of stimuli with alcohol-related pictures showing higher luminance than flower pictures. This difference however did not interfere with participants’ performance, as SRT of the first saccade did not correlate with the luminance of the picture fixated (r=-.060, p=.576).

2.3. Procedure

Stimuli were displayed using the Psychtoolbox (Brainard, 1997; Pelli, 1997) implemented in MATLAB R2021a (MathWorks, Natick, MA, USA) against a grey background (luminance of 0.44). Participants seated on a desk chair placed 60cm away from an Asus Display Laptop PC equipped with a 17.3-inch FHD screen (resolution 1080 × 1920 pixels; refresh rate 120 Hz) and facing an eye tracker camera. We used a chinrest to stabilize participants' head position and we recorded eye movements using the pupil-corneal reflection and remote mode of an EyeLink Portable Duo eye-tracker (SR Research, Canada; sampling rate of 1000 Hz; average accuracy range 0.25°-0.5°, gaze tracking range of 32° horizontally, 25° vertically). Eyelink software automatically detected saccades with the following thresholds: speed >30°/s, acceleration >8000°/s2, and saccadic displacement >0.15°. Blinks were detected during partial or total occlusion of the pupil. A 9-point calibration of participant's eye gaze position was set up at the beginning of each block.

All participants completed two experimental phases consisting of the faces vs. vehicles saccadic choice task and the alcohol vs. flowers saccadic choice task. They received verbal instructions to perform the tasks, without being informed about their rationale. All participants systematically started by performing the *faces vs. vehicles* saccadic choice task, which was replicated from Kauffmann et al. (2019, 2021) and Guyader et al. (2017). The task comprised two blocks, one for which the targets were images containing human faces (the distractors being vehicle images) and the other one for which the targets were images containing vehicles (the distractors being human face images). In a second phase, participants underwent the *alcohol vs. flowers* saccadic choice task, with one block presenting alcoholic beverages as targets (and flowers as distractors), and the other block presenting flowers as targets (and alcoholic beverages as distractors). We simply asked participants to make a saccade as fast as possible toward the target image and did not provide instructions about the correction of any erroneous saccade towards distractor stimuli. We counterbalanced the order of blocks within the tasks to avoid potential learning and/or training effects.

At the beginning of each trial, a white fixation cross subtending 0.73° of visual angle was displayed centrally on a grey background screen (mean luminance of 0.5 for pixel intensity values between 0 and 1). We used the fixation cross as drift check to confirm the reliability of the eye-gaze calibration.

This instruction ensured that participants initially focused their visual attention at the centre of the screen in each trial. We carried out a drift correction every ten trials. The fixation cross was followed by a gap (mean grey-level screen) of 200ms. Two images (a target and a distractor) were then simultaneously displayed on the left and right side of the central fixation cross for 400ms. The centre of each image was lateralized at 8° from the screen centre. The inter-trial interval (uniform grey background) was fixed at 1000ms (Figure 7). Each block comprised 64 trials, with each image being presented twice, once on the left and once on the right side, randomly. Each block lasted approximately 5 minutes and the total experimental task 20 minutes.

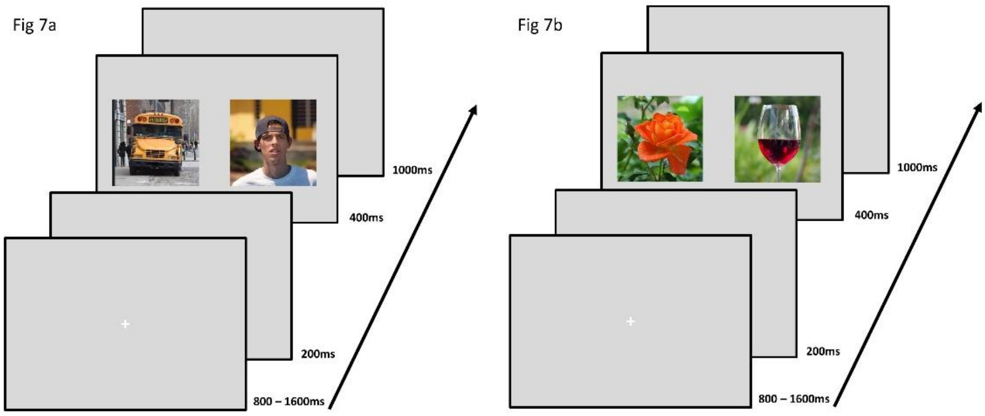

Figure 7. Time course of a trial in the face vs. vehicle (Fig 7a) and alcohol vs. flower (Fig 7b) saccadic choice task.

2.4. Statistical analyses

We performed the same data reduction procedure than Kauffmann et al. (2021) by removing trials in which (1) a blink occurred during stimulus presentation, (2) SRT was shorter than 50ms, (3) saccades were initiated from more than 2° around the fixation cross, (4) saccades had an amplitude below 1° or (5) saccades duration were above 100ms. These criteria were based on the distributions of eye movement parameters consistently reported in the literature (e.g., Devillez et al., 2020). This procedure resulted in removing two participants (1 BD, 1 CTL), as more than half of their trials were invalid (due to poor calibration), and discarding 8.38% of the trials from the remaining participants. It should be noted that the percentage of remaining trials was similar between groups (BD: 92.59±0.06%; CTL: 90.68±0.08%; t_{85}=1.219, p=.226) and was higher than those reported in previous studies using the same paradigm, thus ensuring the validity of our experimental procedure. We performed all statistical analyses using MATLAB R2021a (MathWorks, Natick, MA) and R (R Core Team, 2021).

We performed between-group comparisons (i.e., independent t-tests) on demographic, psychopathological characteristics and alcohol consumption variables. We analysed the error rate (percentage of erroneous saccadic movement), latency (in milliseconds from the onset of stimuli - also called SRT) and amplitude (distance between the positions of the start and the end of saccades, in degrees of visual angle) of the first saccade. We also examined whether erroneous first saccades were followed by corrective saccades. When applicable, we analysed the percentage (%) and SRT of corrective saccades. We considered saccades as corrective if they ended on the target side of the display. For both tasks (face *versus* vehicle, alcohol *versus* flower), we performed analyses of covariance (ANCOVAs) with TARGET (alcohol or face, flower or vehicle) as within-subject factor, GROUP (BD, CTL) as between-subject factor and AGE as covariate (as age differed across groups, see below). We performed them on eye-tracking measures related to the first saccade (accuracy, SRT, amplitude) and the corrective saccade (proportion, SRT) when applicable. We conducted Post-Hoc tests (independent samples t-tests) for the interpretation of significant Target x Group interactions. We estimated effect sizes by calculating partial eta-squared (η_p^2) for ANCOVAs and Cohen's d for Post Hoc t-tests. We also reported in Appendix C (1) results for the alcohol vs flower task when including only CTL with AUDIT score ≤ 4 to exclude any women participants with potential risky drinking, (2) methods and results regarding the minimum SRT for both tasks and (3) methods and results for the exploratory correlations between eye-tracking measures (i.e., accuracy and SRT of the first saccade, proportion of corrective saccades) and alcohol consumption (i.e., AUDIT and binge drinking score, craving).

3. Results

3.1. Demographic, psychopathological and alcohol-related measures

As showed in Table 8, BD were younger [$t(85)=2.288$, $p=.025$, $d=.491$] and reported higher craving as assessed through VAS [$t(84)=3.096$, $p=.003$, $d=.668$] or ACQ [$t(84)=4.156$, $p<.001$, $d=.896$] than CTL. Groups did not significantly differ regarding gender ratio [$\chi^2(2,87)=.988$, $p>.050$], state anxiety ($p=.580$), trait anxiety ($p=.087$) and depression ($p=.295$).

Table 8. Group differences on demographic, psychopathological and alcohol consumption measures (mean ± standard deviation) between BD and CTL.

	BD (N=43)	CTL (N=44)	*t or χ2*	*p-value*
Demographic measures				
Sex ratio (male/female)	24/19	24/20	.989	.610
Age	20.88 ± 1.94	22.07 ± 2.80	2.298	.024
Psychopathological measures				
Beck Depression Inventory	5.21 ± 4.26	4.28 ± 3.92	1.054	.295
State Anxiety Inventory	33.53 ± 10.02	32.44 ± 8.15	.555	.580
Trait Anxiety Inventory	43.56 ± 10.26	39.86 ± 9.54	1.731	.087
Alcohol consumption measures				
AUDIT	15.65 ± 6.02	3.36 ± 2.10	12.645	<.001
Binge drinking score	43.27 ± 21.22	5.64 ± 4.13	11.419	<.001
Craving (VAS)	18.30 ± 18.59	7.58 ± 13.04	3.096	.003
Craving (Alcohol Craving Questionnaire)	31.77 ± 11.22	22.63 ± 9.06	4.156	<.001

3.2. Face vs vehicle Saccadic Choice Task (Figure 8)

Accuracy. The 2x2 ANCOVA on mean error rates for the first saccade revealed a main effect of TARGET [$F(1,84)=88.78$, $p<.001$, $\eta_p^2=.514$]. Participants made significantly less error saccades when the target stimulus was a face (14.05±8.96%) than when it was a vehicle (24.61±12.94%). We observed neither GROUP effect ($p=.644$), nor interaction between GROUP and TARGET ($p=.589$).

Latency and amplitude of the correct first saccade. The 2x2 ANCOVA on mean SRT for the correct first saccade showed a main effect of TARGET [$F(1,84)=139.22$, $p<.001$, $\eta_p^2=.624$]. Participants initiated their correct first saccade faster when the target stimulus was a face (180±20ms) than when it was a vehicle (203±26ms). We observed neither GROUP effect ($p=.578$), nor interaction between GROUP and TARGET ($p=.657$). The 2x2 ANCOVA on mean amplitude for the correct first saccade showed a main effect of TARGET [$F(1,84)=124.95$, $p<.001$, $\eta_p^2=.598$]. Participants performed a longer correct saccade when the target stimulus was a face (7.62±0.53°) than when it was a vehicle (7.03±0.72°). We observed neither GROUP effect (p=.237), nor interaction between GROUP and TARGET (p=.986).

Proportion and latency of the corrective saccade. The 2x2 ANCOVA performed on proportion of corrective saccade revealed a main effect of TARGET [$F(1,82)=5.08$, $p=.027$, $\eta_p^2=.058$]. Participants made significantly more corrective saccades when the target stimulus was a face (89.97±17.73%) than when it was a vehicle (83.72±15.27%). We observed neither GROUP effect (p=.404), nor interaction between GROUP and TARGET (p=.775). The 2x2 ANCOVA performed on mean SRT for the corrective saccade revealed a main effect of TARGET [$F(1,82)=20.41$, $p<.001$, $\eta_p^2=.201$]. Participants initiated their corrective saccade faster when the target stimulus was a face (110±23ms) than when it was a vehicle (122±19ms). We observed neither GROUP effect (p=.737), nor interaction between GROUP and TARGET (p=.064).

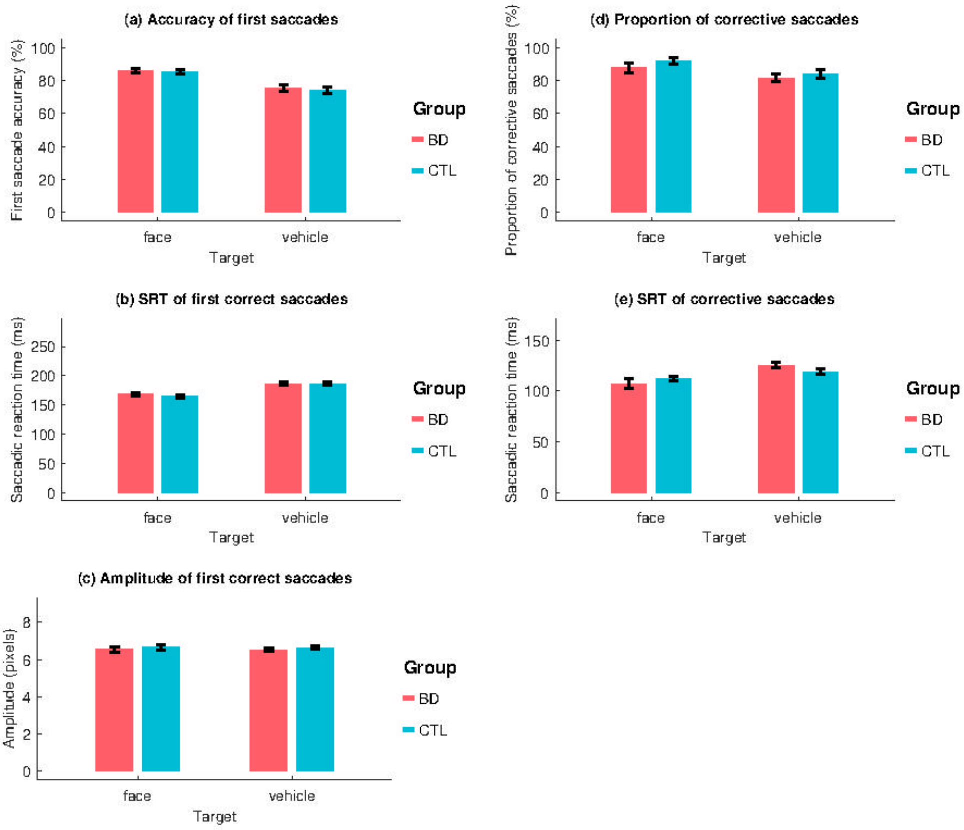

Figure 8. (a) Mean accuracy (in percentage of correct saccadic responses) of the first saccades, (b) mean latency or SRT (in milliseconds) of the first correct

saccades, (c) mean amplitude (in degrees) of the first correct saccades, (d) mean proportion of corrective saccades and (e) mean latency or SRT (in milliseconds) of corrective saccades according to the Target category (Face, Vehicle) and the Group (BD, CTL). Error bars correspond to ± 1 SE

3.3. Alcohol vs flower Saccadic Choice Task (Figure 9)

Accuracy. The 2x2 ANCOVA on mean error rates for the first saccade revealed no main effect of TARGET (p=.276), GROUP (p=.599) or interaction between these two factors (p=.849).

Latency and amplitude of the correct first saccade. The 2x2 ANCOVA on mean SRT for the correct first saccade showed a main effect of TARGET [F(1,84)=7.51, p=.007, η_p^2=.082]. Participants initiated their correct first saccade faster when the target stimulus was an alcoholic beverage (191±26ms) than when it was a flower (197±27ms). We observed neither GROUP effect (p=.573), nor interaction between GROUP and TARGET (p=.987). The 2x2 ANCOVA on mean amplitude for the correct first saccade showed no main effect of TARGET (p=.726), GROUP (p=.194) or interaction between these two factors (p=.157).

Proportion and latency of the corrective second saccade. The 2x2 ANCOVA performed on proportion of corrective saccade revealed a significant interaction between TARGET and GROUP [F(1,84)=5.96, p=.017, η_p^2=.066]. Post-Hoc independent sample t-tests showed that BD made fewer corrective saccades than CTL when the target stimulus was a flower [BD: 63.15±22.22%; CTL: 73.71±21.61%; t(85)=2.248, p=.027, d=.482] but groups did not differ when the target stimulus was an alcoholic beverage (p=.868). We observed neither TARGET (p=.401) or GROUP (p=.322) effects. The 2x2 ANCOVA performed on mean SRT for the corrective saccade revealed no main effect of TARGET (p=.462), GROUP (p=.971) or interaction between these two factors (p=.815).

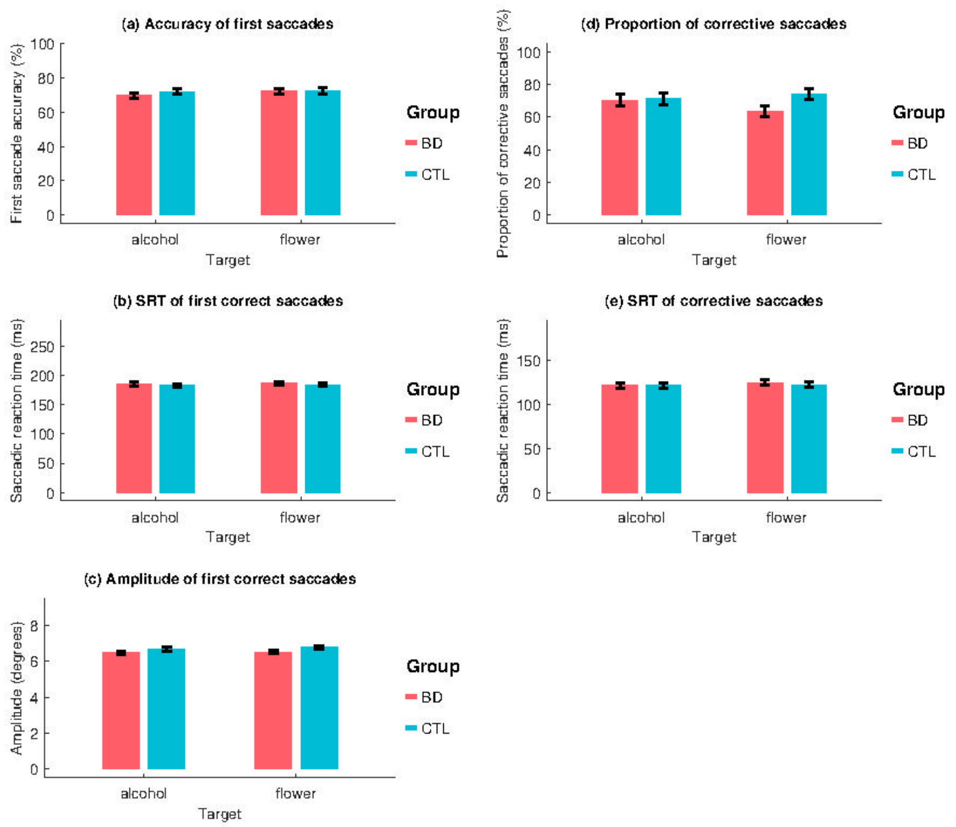

Figure 9. (a) Mean accuracy (in % of correct saccadic responses) of the first saccades, (b) mean latency or SRT (in milliseconds) of the first correct saccades, (c) mean amplitude (in degrees) of the first correct saccades, (d) mean proportion of corrective saccades and (e) mean latency or SRT (in milliseconds) of corrective saccades according to the Target category (Alcohol, Flower) and the Group (BD, CTL). Error bars correspond to ± 1 SE

4. Discussion

Dominant theoretical models hypothesized the presence of an automatic AB towards stimuli with acquired salience (e.g., alcoholic beverages) in chronic drinkers. Such AB is not consistently documented in the literature, since previous studies showed heterogeneous findings among individuals with SAUD (Bollen et al., 2022). While the literature is more consistent in subclinical populations, most studies showing the presence of an alcohol-related AB, its automaticity remains to be proven. We thus applied the saccadic choice paradigm, commonly used to evaluate AB towards faces, in a population of BD and matched CTL to investigate the automatic aspects of the alcohol-related AB.

First, we replicated previous findings regarding AB towards faces, since both groups processed these stimuli more rapidly and efficiently compared to vehicles (Guyader et al., 2017; Kauffmann et al., 2019; 2021). Indeed, they made less incorrect saccades and performed quicker and larger first saccades when the target was a face than when it was a vehicle. Corrective saccades were also more frequent and rapid when faces were the targets. By replicating these findings in both BD and CTL, we showed that (1) saccadic choice task constitutes a valid eye-tracking paradigm to evaluate the automatic nature of AB, and (2) BD have an automatic preference for processing faces similar to CTL, and do not present any generalized dysfunction of the reflexive/reward system responsible for the detection of salience (Franken, 2003). The similar performance between groups is in line with King and Byars (2004), who showed that heavy drinking habits did not impact the saccadic latency and velocity measured in a prosaccade task.

Second, in contradiction with theoretical models' predictions, we found no early, automatic and involuntary hijacking of attention provoked by alcohol-related stimuli (indexed by the accuracy and latency of the first saccade) specific to BD, since our findings revealed shorter SRT for alcohol-related stimuli in both groups. Whereas our findings regarding facial stimuli clearly demonstrate the saccadic choice task as an appropriate measure of the automatic hijacking processes related to AB, further research could explore the involuntary aspects of attentional processing by using other paradigms and/or measures. For example, other saccadic paradigms are known to explicitly request to inhibit saccadic responses towards alcohol when no second stimulus is on the target side of the screen, thus directly involving both automatic and controlled processes (e.g., antisaccade task; Hoffmann et al., 2021). In the same line, recent studies investigated the interaction between automatic (e.g., alcohol cue-reactivity) and controlled (e.g., inhibition abilities) processes in BD at the electrophysiological level, thus providing important insights on the underlying processes of mechanisms related to AB (i.e., alcohol-related cue-reactivity; Almeida-Antunes et al., 2022; Blanco-Ramos et al., 2019; Lannoy et al., 2018). Beyond these perspectives, our findings already showed that BD had more difficulty to disengage from alcohol-related stimuli when their gaze was erroneously directed towards alcohol. Indeed, they corrected less frequently their saccade than CTL after having performed an error first saccade towards alcohol-related stimuli when the target was a flower, revealing the presence of a late and controlled disengagement AB related to alcohol cues. While the presence of a disengagement AB in subclinical drinkers was already demonstrated in previous studies (Gladwin et al., 2013; Heitmann et al., 2020; Sharbanee et al., 2013), we strengthen these findings through the use of an eye-tracking paradigm in a specific population of BD.

These joint results thus demonstrate that AB in BD is not characterized by an automatic capture of attention by alcohol-related cues, but by an increased willingness to process these cues once detected. In line with previous studies (Field et al., 2004; Hallgren & McCrady, 2013), we thus suggest that alcohol-related AB relies on late and controlled processes rather than early and automatic ones. The different effect between faces and alcoholic beverages might be partly explained in terms of differential exposure and behavioural relevance between these two classes of stimuli during life. Faces stimuli are salient for humans since the very beginning of life, as the human brain requires to quickly detect and preferentially process those socially relevant stimuli to interact with the social world. Conversely, the increased salience properties of alcohol-related stimuli would result from repeated alcohol exposures and are thus acquired through alcohol-related experiences (Robinson & Berridge, 1993). As we tested young BD who have been usually drinking for a few years only, alcohol-related AB might thus have not achieved an automatic stage yet. Future research should test the automatic aspects of alcohol-related AB in individuals with SAUD, since this population has been exposed to excessive and chronic alcohol consumption for a longer time and might thus have developed an automatic capture of attention for alcohol-related stimuli. Nevertheless, this remains to be established as most previous studies did not show any strong and stable AB among patients with SAUD compared to CTL, some of them even revealing an avoidance AB (Bollen et al., 2022). While the aim of this study was to determine whether the automatic AB for faces could be also found for alcohol-related stimuli in BD, future studies should also directly compare the attractiveness of faces *versus* alcoholic beverages by confronting these two types of stimuli in different populations of drinkers. Indeed, alcohol-related stimuli could reduce or counter the AB towards faces, although our results suggest that the incentive salience of alcohol is much lower than faces in BD.

5. Limitations

First, whereas the number of trials per block chosen in previous studies using the saccadic choice task (Guyader et al., 2017; Kauffmann et al., 2019; 2021) was sufficient to explore AB towards highly attractive stimuli like faces, it might have been too small to detect smaller effects from less salient stimuli like alcoholic beverages. Second, the shorter SRT for alcohol-related stimuli in both groups could be partly explained by the higher luminance of the alcohol-related stimuli compared to flower stimuli. Moreover, while the size of the pictures was standardized, we did not control for the size of the main object within the alcohol-related and flower pictures, although bigger stimuli are known to be detected easier and faster (Hoffmann et al., 2021). Finally, the use of flower rather than non-alcoholic beverages as neutral stimuli, although justified by physical aspects, did not allow for dissociating the alcohol-related and appetitive nature of alcoholic beverages pictures. Nevertheless, these potential effects should be found in all participants, and thus would not impact the Target x Group interactions we were interested in to detect the presence of an automatic alcohol-related AB specific to BD.

6. Conclusion

The present study demonstrates that, while BD present a preserved early salience processing (as confirmed by the replication of the effects previously established for faces), the AB towards alcohol-related stimuli in binge drinking is not characterized by an automatic capture of attention but rather appears on later and more controlled attentional processing stages.

Chapter 6

Tell me how you feel, I will tell you what you look at: Impact of mood and craving on AB in binge drinking

Background: Alcohol-related AB is thought to play a key role in the emergence and maintenance of excessive alcohol use. Recent models suggest that AB, classically considered as a stable feature in alcohol use disorders, is rather modulated by temporary motivational states.

Aims: We explored the influence of current mood and craving on AB in binge drinking, through a mood induction procedure (MIP) combined with eye-tracking measures.

Methods: In Experiment 1, we measured AB (VPT with eye-tracking measures) among BD (n=48) and light drinkers (LD; n=32) following a positive, negative and neutral MIP. Participants reported subjective craving and mood before/after induction. In Experiment 2, we measured AB among the same BD compared with 29 moderate drinkers (MD) following alcohol-related negative, non-alcohol-related negative and neutral MIP.

Results: In Experiment 1, induced negative mood and group positively predicted subjective craving, which was positively associated with AB. We found no effect of induced positive mood nor a direct mood-AB association. In Experiment 2, the relationships that AB presented with both induced negative mood and group were again mediated by craving. Inducing alcohol-related negative mood did not modify the mood-craving association.

Conclusions: Alcohol-related AB are not a stable binge drinking characteristic but rather vary according to transient motivational (i.e., craving) and emotional (i.e., negative mood) states. This study provides important insights to better understand AB in subclinical populations and emphasizes the importance of considering motivational and affective states as intercorrelated, to offer multiple ways to reduce excessive alcohol use.

Reference

Bollen, Z., Pabst, A., Masson, N., Suárez-Suárez, S., Carbia, C., & Maurage, P. Tell me how you feel, I will tell you what you look at: Impact of mood and craving on alcohol attentional bias in binge drinking. *Journal of Psychopharmacology*. Accepted.

Tell me how you feel, I will tell you what you look at: Impact of mood and craving on AB in binge drinking

1. Introduction

Binge drinking, characterized by repeated alternations between intense intoxication episodes and abstinence periods, is an established alcohol consumption habit with specific characteristics (Archie et al., 2012; Crego et al., 2009; Maurage et al., 2020a; Townshend & Duka, 2002). It is particularly widespread in youth and keeps on growing in prevalence among older adults in Western countries (Dormal et al., 2019). Many studies have underlined the early and long-lasting harmful consequences of this consumption pattern on cognitive and cerebral functioning (see Carbia et al., 2018; De Goede et al., 2021; Lannoy et al., 2019a for recent critical reviews). In view of this harmful impact, it appears crucial to understand the psychological mechanisms contributing to the emergence and persistence of binge drinking.

AB, reflecting the preferential orientation of one's attentional resources towards alcohol-related stimuli, may constitute one such mechanism. Importantly, AB is posited to be part of a vicious circle in which repeated alcohol consumption leads to greater attraction towards alcohol-related cues, enhancing the desire to consume alcohol (i.e., craving) and ending up in increased drinking (Field & Cox, 2008; Field et al., 2009). Dominant theories in addiction have postulated that AB would develop by associative learning, where alcohol-related stimuli acquire incentive-motivational properties caused by repeated alcohol exposures that progressively sensitize the dopaminergic system (Franken, 2003; Robinson & Berridge, 1993). These models further postulated that the neuroadaptations underlying behavioural sensitization (e.g., alcohol-related AB) are long-lasting and potentially permanent, and have not discussed the intra-individual variability of AB once installed. Field and colleagues (2016) have thus suggested that AB fluctuates alongside motivational states between and within individuals. They proposed that AB is the expression of the momentary motivational evaluation of alcohol-related stimuli, and would thus arise from momentary changes in evaluations of these stimuli that can be positive (e.g., when the incentive value of the substance is high), negative (e.g., when individuals have a goal to stop drinking), or both (e.g., when individuals experience motivational conflict).

Recent reviews corroborate this assumption by underlining the presence of intrapersonal AB fluctuations, particularly according to current motivational states affected by environmental and internal factors (e.g., stress or subjective craving; see Bollen et al., 2022; Christiansen et al., 2015a for reviews). Indeed, two between-subjects studies showed increased AB following stress induction in participants with coping motives for alcohol use (Field & Powell, 2007; Field & Quigley, 2009). More importantly, recent studies relying on eye-tracking measures showed that alcohol-related AB was only observed in regular and BD reporting high craving at testing time (Bollen et al., 2020; Field et al., 2005; Hobson et al., 2013). Subjective craving would thus be a core determinant of the magnitude of alcohol-related AB in subclinical populations. Altogether, the above-mentioned studies highlighted the key role played by current stress or motivational state on AB, and the need to consistently assess them when exploring AB, such states being stronger AB predictors than global alcohol consumption characteristics.

Another fluctuating factor that could influence AB is mood. Cognitive processes related to AB (e.g., approach biases, implicit memory associations) are increased following negative emotional priming (Cousijn et al., 2014) or associated with mood-congruent motives (Salemink & Wiers, 2014). However, few studies investigated how mood could influence AB, either directly or through craving increase. In their between-subjects study, Emery & Simons (2015) randomly allocated participants to positive, negative or neutral mood conditions and asked them to perform a classical AB paradigm (i.e., VPT) before and after MIP (i.e., combined emotional picture slides and music). Alcohol-related AB, assessed through RT, did not differ across MIP conditions, but the reliability of the VPT was very low, which might explain the null findings. Following musically induced positive and anxious mood, Grant et al. (2007) showed that students with coping motives presented increased AB in the anxious condition (compared to positive mood condition), whereas students with enhancement motives showed the opposite findings. Using ecological momentary assessment (EMA), Emery & Simons (2020) then explored whether positive or negative changes of affective states led to increased AB by assessing their mood and alcohol Stroop interferences for 28 consecutive days through smartphone reports. While no association was found between negative mood and AB, positive mood predicted increases in AB and alcohol use over the same day at within-person level. Moskal et al. (2022) used a similar design with EMA for 15 days to investigate the role of alcohol-related AB (assessed by a VPT) as a craving predictor. They showed that AB-craving associations were stronger as momentary positive mood and trait-like sad mood increased among men and, on the opposite, decreased among women. While those studies offered important insights on the influence of momentary states on alcohol-related AB, they were weakened by the very low reliability of their AB measures (i.e., manual RT). Moreover, previous studies had a very unspecific sample, as they recruited college students without further inclusion criteria related to alcohol consumption, simply assuming high consumption levels in this population. Finally, they did not investigate whether mood explicitly associated with alcohol use might impact differently craving and AB.

The present study aimed to further investigate the effects of craving and mood (both direct and through craving increase) on alcohol-related AB, by improving the reliability of AB measures in a specific population of BD with beer as favourite alcoholic beverage. To this end, we performed two experiments using personalized VPT (i.e., only beer pictures as alcohol-related stimuli) combined with eye-tracking measures, known to improve the reliability of AB measures (Bollen et al., 2020; Christiansen et al., 2015b; Field et al., 2009). All participants performed three sessions. For each session, the task was preceded by a combined MIP with autobiographical recall and self-selected music listening, which successfully induced both positive and negative affective states (Ellard et al., 2012; Vuoskoski & Eerola, 2012; Zhang et al., 2014). In Experiment 1, BD and LD underwent positive, negative and neutral MIP. We firstly hypothesized that BD would present stronger alcohol-related AB compared to LD (h1). Second, we wondered whether AB could be caused by changes in mood and craving (then leading to AB through the influence of drinking pattern) rather than being the direct consequence of the drinking pattern. In other terms, we hypothesized that induced positive and negative mood would enhance the magnitude of alcohol-related AB, especially among BD, and that this relationship between mood and AB would be mediated by subjective craving (h2). We indeed reflected that mood can either have a direct influence on AB or an indirect one through craving increase (Figure 10). In Experiment 2, to explore the influence of alcohol-related mood, we compared BD with MD and allocated them to alcohol-related negative mood, non-alcohol-related negative mood and neutral mood conditions. We recruited MD rather than LD or non-drinkers to make sure that all participants would be able to recall autobiographical memories related to alcohol consumption. We hypothesized that BD would present stronger alcohol-related AB compared to MD (h3). We also hypothesized that AB would be strengthened by non-alcohol-related negative MIP but reduced by alcohol-related negative MIP, as a result of alcohol devaluation (h4). Once again, the association between negative mood and alcohol-related AB would be mediated by subjective craving and moderated by group status.

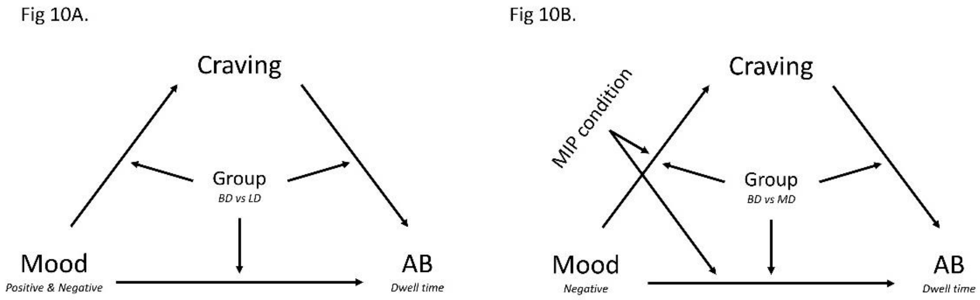

Figure 10. Conceptual models predicting alcohol-related AB. In Experiment 1 (Fig 10A), positive and negative mood predict AB, with craving as mediator variable, and group status (BD versus LD) as moderator variable. In Experiment 2 (Fig 10B) negative mood predict AB with craving as mediator variable, and group (BD versus MD) and MIP condition (alcohol-related, non-alcohol-related, neutral) as moderator variables.

2. Methods of Experiment 1

2.1. Participants

We recruited participants via an online screening questionnaire sent through social networks to students from UCLouvain (Belgium). First, we informed them that, following this screening, they may be invited to participate to a paid experience exploring the link between emotions and alcohol consumption. Second, we asked them to fill in questionnaires assessing alcohol-related disorders (AUDIT; Saunders et al., 1993; French validation: Gache et al., 2005), binge drinking habits [i.e., consumption speed, drunkenness frequency and ratio, number of binge drinking episodes (i.e., drinking more than 6 units, a unit corresponding to 10 gr of pure ethanol in Belgium) per week], socio-demographic (e.g., age, sex), drinking motives (Drinking Motives Questionnaire-Revised Short Form, DMQ-R-SF; French validation: Cooper, 1994) and other alcohol consumption variables (i.e., beverage preferences, number of alcohol units consumed per week, number of units per occasion, number of drinking occasions per week).

To be included in the study, they first had to meet the following criteria (evaluated through self-reported measures): having beer as preferred alcoholic beverage, absence of parental history of SAUD, absence of current psychological or neurological disorder, normal or lens-corrected vision, fluent French speaking. Moreover, we invited participants to take part in the experimental session only if they met the inclusion criteria for one of the two groups (BD *vs*. LD). We constituted the inclusion criteria based on drinking habits and binge drinking score (Townshend and Duka, 2005), computed through the following formula: (4 x consumption speed) + drunkenness frequency + (0.2 x drunkenness percentage). Eighty-five participants (50 women and 35 men) took part in the experiment: 51 BD (binge drinking score >24, 2-3 drinking occasions per week, units per occasion >6, binge drinking episodes per week >1, beer drinkers) and 34 LD (binge drinking score <12, 0.25-1 drinking occasions per week, units per week <3, units per occasion <3, no binge drinking episodes). People presenting a binge drinking score between 12 and 24 were thus not included.

We asked participants to refrain from consuming alcohol during the 24 hours preceding the experimental sessions. To control for psychopathological comorbidities, they filled in questionnaires between sessions assessing depressive symptoms (Beck Depression Inventory, BDI-II; Beck et al., 1996) and anxiety (State-Trait Anxiety Inventory, STAI A-B; French validation: Bruchon-Schweitzer & Paulhan, 1993). All participants provided their informed written consent before participating in the study and were not aware of the hypotheses tested. The study protocol adhered to the ethical standards established by the Declaration of Helsinki, and was approved by the Ethics Committee of the Psychological Sciences Research Institute (UCLouvain). At the end of the experiment, we debriefed participants, who received a financial compensation of ten euros per hour.

2.2. Procedure

The experiment consisted of three 40-min sessions with different MIP, each separated by at least 24 hours. The sessions' order was counterbalanced across participants to avoid potential learning and/or training effects. Participants were seated on a desk chair in front of a computer and tested individually in a quiet laboratory. The procedure (Figure 11) was identical across sessions: participants had to fill in online questionnaires assessing current alcohol craving (VAS) and emotional state (PANAS; Watson et al., 1988) using Qualtrics software, before and after completing the MIP and after performing the VPT.

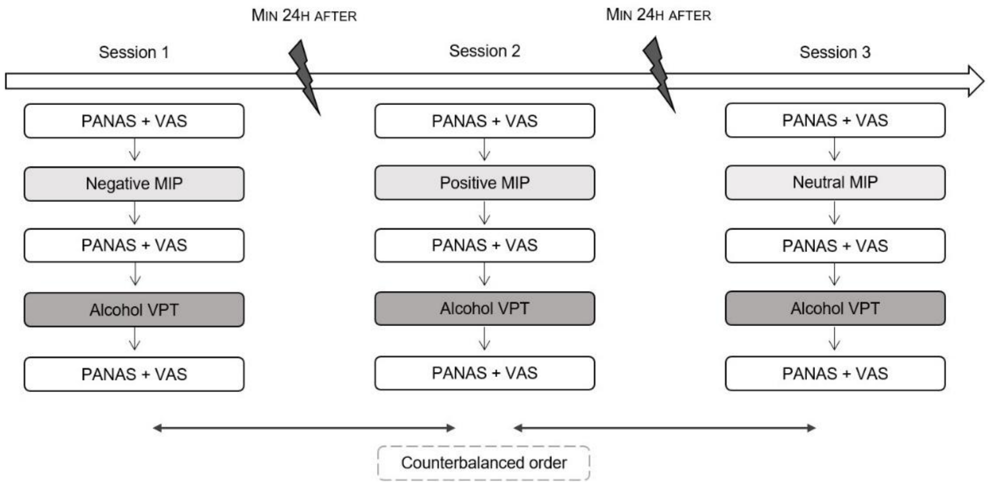

Figure 11. General experimental procedure of the Experiment 1.

We used combined MIP with autobiographical recall and music listening for inducing each mood. A few days before the experiment, participants sent by email the title of three music tracks making them feel in a positive mood, as well as three music tracks making them feel in a negative mood. At the start of the experiment, participants received instructions (Appendix D1) to write down a happy memory (for positive MIP) or sad memory (for negative MIP), in which they did not consume any alcoholic beverage. For the neutral MIP, they were asked to write the itinerary they followed to arrive at the laboratory (Appendix D2). After reading the instructions, participants received headphones and started listening to the correspondent playlist prepared by the experimenter. One playlist was made for each condition, comprising the music tracks selected by the participant for the negative and positive MIP and one song selected by the experimenter for the neutral MIP. We chose the song «Common Tones in Simple Time» by John Adam for the neutral MIP, as this song was reported to not evoke any emotion (Vastjall, 2001). Participants were then asked to complete the recall task within 10 minutes. The experimenter stayed quiet and away from the participants to give them privacy during MIP.

For the experimental task, participants seated on a desk chair, facing a desktop eye-tracker camera, and placed 60cm away from a Dell PC equipped with a 21.5-inch LCD screen (resolution 1920 x 1080; refresh rate 60Hz). We reduced their head movements using a forehead and chin stabilizer. We controlled the presentation of the experimental task and its synchronization with the eye-tracking using OpenSesame software (version 3.1.6; Mathôt et al., 2012). We recorded eye movements using an Eye-link 1000 desktop-mounted eye-tracker (SR Research, Canada; sampling rate of 1000 Hz; average accuracy range 0.25° to 0.5°, gaze tracking range of 32° horizontally and 25° vertically). We set up a 9-point calibration of participant's eye gaze position at the beginning of the personalized VPT.

At the beginning of each trial, a central fixation dot appeared on the black background screen and participants had to fixate their gaze on it. Moreover, the fixation dot was used as drift check to confirm the reliability of the eye-gaze calibration. This instruction ensured that participants initially focused their visual attention at the centre of the screen in each trial. Once the eyes of the participant were detected at the centre of the screen, the fixation dot was removed and directly followed by the onset of two pictures (i.e., beer and soft drink pictures). They were displayed randomly on the left and right side of the computer screen for a random duration (1500-2500ms) and then replaced by a probe (i.e., a white arrow on a black background, pointing up or down) appearing at the location previously occupied by one of the pictures. Participants had to respond to the orientation of the probe by pressing the "up" or "down" key on a keyboard, as quickly and correctly as possible. Each trial was separated by an inter-trial interval of random duration (500-1500ms). Visual probes replaced the two types of pictures with equal frequency. The task contained 68 trials, including four practice trials that participants first completed, and lasted for 15 minutes. For each session, we presented a different set of stimuli to participants, leading to 3 versions of the task, administered in a counterbalanced order. This allowed to reduce a potential learning and practice effect in the last block of the last session.

2.3. Stimuli

We used 48 pairs of beer pictures (i.e., beer bottles) and matched non-alcoholic beverages pictures (i.e., water and soft drink bottles) without context for the different versions of the VPT (16 pairs per task). We used internet image search to develop stimulus sets including beer (by far the most consumed alcoholic drink among Belgian University students) and non-alcoholic beverages of familiar brands in Belgium. We systematically blurred the brand and writings of the beverage to avoid reading or semantic processing. We computed the physical properties of images using customized MATLAB scripts (The Mathworks, Inc. Natick, United States). We then matched each picture pair on the following physical features: size (375x375 pixels), object size (proportion of non-white pixels), color (contribution of red, green and blue color channels to the non-white pixels), and complexity [proportion of pixels representing contour outlines as determined by a Canny edge detection algorithm (Canny, 1986)]. We performed mean comparisons (i.e., independent t-tests) to control for the influence of perceptual aspects on AB, but we observed no significant difference between beer and soft drink pictures for all these physical features ($p>.05$).

2.4. Data analysis

We performed a data reduction procedure for RT by removing trials with incorrect responses (0.014% of trials) and RT lower than 200ms (0.002% of trials) or higher than 2000ms (0.002% of trials). We removed the data from five participants before performing the analyses, as they did not make any eye movements towards stimuli in the different blocks, leading to a sample of 80 (48 BD, 32 LD).

The dependent variables measured were (1) the *RT* to respond to probes appearing on the side of the screen congruent versus incongruent with alcohol-related stimuli, (2) the *first fixation location*, indicating the stimulus that was first fixated at the beginning of each trial (i.e., initial attentional capture), (3) the *second fixation proportion,* indicating how frequently the participant fixated a second stimulus after visiting the first one (i.e., attentional switch) and (4) the *dwell time*, the sum of fixation times on one of the stimuli during the whole trial (i.e., maintenance of attention). We computed AB scores for each measurement: the difference between the RT for probes congruent and incongruent with alcohol-related stimuli for *RT*, the percentage of first fixations towards alcohol-related stimuli for *first fixation*, the percentage of second fixation on alcohol compared to no fixation after a first fixation on non-alcohol for *alcohol second fixation*, the percentage of second fixation on non-alcohol compared to no fixation after a first fixation on alcohol for *non-alcohol second fixation,* and the percentage of fixation time spent on alcohol-related stimuli compared to non-alcohol stimuli for *dwell time*. We extracted the spatial and temporal parameters of eye movements using Eyelink® Data Viewer (SR Research Ltd). We qualified gaze samples as fixations or saccades according to the standard EyeLink algorithms.

We performed all statistical analyses using SPSS software package (version 27.0). First, we performed between-group comparisons (independent samples t-tests) on demographic and psychological variables. Second, we examined the efficacy of the MIPs by estimating linear mixed-effect models for positive and negative mood, including TIME [just before MIP (pre-MIP) and just after MIP (post-MIP)] and CONDITION (positive, negative, neutral MIP) as within-subjects factors, GROUP (BD, LD) as between-subjects factors and a random intercept by subject. We performed post-hoc analyses by rerunning the analysis separately for the different levels of TIME or CONDITION with a Bonferroni-corrected p-value of $\alpha_{altered}$=.05/3=0.017. Third, we estimated the internal reliability of our AB measures by computing Cronbach's alpha and considered it acceptable when being above the 0.70 conventional cut-off (Kline, 2000). Following a well-established procedure (Ataya et al., 2012; Christiansen et al., 2015b; Van Ens et al., 2019), we calculated AB scores separately for each pair of pictures, leading to 48 AB scores for each AB measure within each version of the VPT. Fourth, we investigated our first hypothesis (h1: stronger alcohol-related AB among BD than LD) by estimating linear mixed-effect models for behavioural (RT) and eye-tracking (first fixation position, alcohol second fixation, non-alcohol second fixation and dwell time) indices of alcohol-related AB with GROUP (BD, LD) as between-subjects factor and a random intercept by subject. Fourth, we explored our second hypothesis (h2: induced positive/negative mood strengthen AB in BD) by estimating linear mixed-effect models for each AB measure. We investigated the relationship between post-MIP mood (positive or negative) and AB by including GROUP as moderator variable and post-MIP CRAVING as mediator variable in the model. To do so, we firstly estimated an initial linear mixed-effect model for CRAVING with GROUP, POSITIVE MOOD, NEGATIVE MOOD and their interactions (GROUP*POSITIVE MOOD, GROUP*NEGATIVE MOOD) as predictors. Then, we reran the model by removing each time the less significative interactions, until reaching a final model with exclusively significative interactions or no interaction (significance level set to .05). We estimated the indirect effects between mood and AB using the joint significance approach (RMediation package for mediation analysis; Tofigui & MacKinnon, 2011). We used the same procedure when predicting each AB measure with CRAVING, GROUP, POSITIVE MOOD and NEGATIVE MOOD and their interactions (GROUP*POSITIVE

MOOD, GROUP*NEGATIVE MOOD, GROUP*CRAVING) as predictors. A power computation (performed in G*Power v3.1.9.7) indicated that a total sample size of 67 was required to perform linear multiple regressions with a total number of 7 predictors, assuming a medium (f = 0.25) effect size with 0.90 power and α = 0.05, thus suggesting that our study was sufficiently powered.

3. Results of Experiment 1

3.1. Demographics and psychological variables

BD and LD did not significantly differ regarding age [$t(44)=.987$, $p=.329$], anxiety [$t(78)=1.242$, $p=.218$] and depression [$t(78)=1.625$, $p=.108$]. BD showed higher scores for impulsivity [$t(63)=3.339$, $p=.001$], and for enhancement [$t(53)=8.074$, $p<.001$] and coping [$t(43)=4.271$, $p<.001$] drinking motives[4] (Table 9). BD showed higher craving before MIP [VAS; $t(78)=4.278$, $p<.001$] and after MIP [$t(76)=3.918$, $p<.001$].

Table 9. Means and standard deviation of demographical and psychological variables in BD, LD (Experiment 1) and MD (Experiment 2).

	BD (n=48)	LD (n=32)	MD (n=29)
Age	20.77 ± 1.84	21.41 ± 3.32	21.90 ± 2.38
Gender (M/W)	17/31	12/20	10/19
Depression	6.96 ± 5.46	5.19 ± 3.48	5.14 ± 5.07
Anxiety trait	45.67 ± 10.31	42.84 ± 9.39	43.59 ± 9.28
Impulsivity	49.27 ± 7.62	42.28 ± 9.84	46.41 ± 5.47
Enhancement motives	9.71 ± 2.84	4.45 ± 2.02	6.27 ± 2.86
Coping motives	5.38 ± 2.66	3.27 ± 0.88	3.53 ± 0.91

3.2. Efficacy of MIP

Positive mood. The linear mixed model for positive mood revealed a CONDITION x TIME interaction [$F(2,356)=33.101$, $p<.001$]. Consistent with our predictions, positive mood increased from pre- to post-MIP in the positive condition [$b=3.28$, $t(60)=6.069$, $p<.001$], while it decreased after negative condition [$b=-4.14$, $t(78)=7.374$, $p<.001$] and did not significantly change after

[4] Considering the major differences between groups on mood-congruent drinking motives (i.e., enhancement motives for positive mood, coping motives for negative mood), as well as the very low variability of scores of drinking motives in LD, we decided to not include these motives in our multilevel approach model.

the neutral condition (*p*>.050). Moreover, post-MIP positive mood was higher in the positive condition relative to negative [*b*=-6.87, *t*(144)=8.674, *p*<.001] and neutral [*b*=-2.15, *t*(145)=2.712, *p*=.007] conditions. We found no main effect of GROUP nor significant interaction between GROUP, CONDITION and TIME (all *p*>.050).

Negative mood. The linear mixed model for negative mood revealed a CONDITION x TIME interaction [*F*(2,349)=35.815, *p*<.001]. Consistent with our predictions, negative mood increased from pre- to post-MIP in the negative condition [*b*=3.91, *t*(78)=7.310, *p*<.001], while it decreased after positive [*b*=-1.62, *t*(60)=3.351, *p*<.001] and neutral conditions [*b*=-1.75, *t*(79)=5.203, *p*<.001]. Moreover, post-MIP negative mood was higher in the negative condition relative to positive [*b*=-5.46, *t*(142)=8.904, *p*<.001] and neutral [*b*=-5.27, *t*(137)=9.422, *p*<.001] conditions. We also found a GROUP main effect [*F*(1,77)=7.598, *p*=.007], showing that BD generally reported higher negative mood than LD [*b*=3.047, *SE*=1.194]. Nevertheless, the efficacy of MIPs to induce negative mood did not differ between BD and LD as no interaction was found between GROUP and CONDITION and TIME (all *p*>.050).

3.3. Alcohol-related AB

Internal reliability was low for RT (α=-.301), first fixation direction (α=-.084) and second fixation towards non-alcohol (α=.620). Conversely, it was high for other eye-tracking measures related to more controlled AB measures (second fixation towards alcohol: α=.834; dwell time: α=.910).

To test h1, we performed linear mixed-effect models to investigate group differences on alcohol-related AB. Models for the different AB scores revealed no main effect of GROUP, neither for RT [$F_{1,215}$=0.081, p=.776], first fixation orientation [*F*(1,76)=0.076, *p*=.783], second fixation on alcohol [*F*(1,78)=1.383, *p*=.243], second fixation on non-alcohol [*F*(1,79)=.029, *p*=.866] nor dwell time [*F*(1,72)=1.769, *p*=.188].

To test h2, we then included the moderator and mediator variables in linear mixed-effect models (Table 10). Our final models for craving and AB no longer contained any interaction terms. First, there was an indirect effect of NEGATIVE MOOD on dwell time AB score through CRAVING [*b*=.077, *SE*=.035, 95%CI=.15 to .22]. The intensity of negative mood increases craving [*b*=.670, *SE*=.214, *F*(1,212)=9.784, *p*=.002], which in turn positively predicts alcohol-related AB [*b*=.115, *SE*=.035, *F*(1,206)=10.857, *p*=.001]. Second, CRAVING was also predicted by the GROUP [*F*(1,79)=9.586, *p*=.003], as BD showed stronger craving than LD [*b*=10.075, *SE*=3.254]. We found no moderation effect of GROUP, no mediation effect of CRAVING between POSITIVE MOOD and AB, nor direct effect of GROUP, POSITIVE MOOD or NEGATIVE MOOD on dwell time AB score. We found no direct or indirect effect of those predictors on the other AB measures (all *p*>.050).

Table 10. Linear mixed-effect models on craving and AB in Experiment 1.

Variables	*B*	*S.E.*	*t*	*p*	*95% CI*	
1.Craving predicted from group, sex and emotions						
Step 1 – Initial model						
Group	6.238	14.546	.429	.668	-22.439	34.915
Positive affect	.343	.250	1.372	.172	-.150	.837
Negative affect	.238	.393	.606	.545	-.537	1.014
Group × Positive affect	-.163	.348	.470	.639	-.849	.522
Group × Negative affect	.588	.469	1.252	.212	-.338	1.513
Step 2 – Final model						
Group	10.075	3.254	3.096	.003	3.598	16.553
Positive affect	.281	.173	1.623	.106	-.060	.623
Negative affect	.670	.214	3.128	.002	.248	1.093
2.AB predicted from group, sex, craving and emotions						
Step 1 – Initial model						
Group	-1.119	7.523	-.149	.882	-15.958	13.719
Craving	.152	.079	1.927	.056	-.004	.307
Positive affect	-.006	.137	-.046	.964	-.276	.264
Negative affect	-.104	.204	-.509	.611	-.506	.298
Group × Positive affect	.022	.184	.121	.903	-.340	.385
Group × Negative affect	.122	.244	.500	.617	-.359	.604
Craving × Group	-.048	.088	-.542	.589	-.221	.126
Step 2 – Final model						
Group	.887	1.636	.542	.589	-2.370	4.144
Craving	.115	.035	3.295	.001	.046	.184
Positive affect	.013	.090	.148	.883	-.164	.191
Negative affect	-.021	.111	-.190	.850	-.241	.198

4. Discussion of Experiment 1

Our results revealed that the group (BD *vs.* LD) did not predict alcohol-related AB differences, regardless of the AB measures used. However, both being BD and being in a negative mood predicted positively subjective craving, which in turn was positively associated with alcohol-related AB when measured through dwell time. In other terms, the relationships between binge drinking and negative mood and AB were not direct but mediated by subjective craving.

Surprisingly, we did not find any effect of positive mood on craving or on alcohol-related AB. As previous studies consistently reported that most young drinkers are motivated to drink for positive drinking-related reinforcements (i.e., enhancement and social drinking motives; Kuntsche et al., 2004; 2005; 2014), we expected most of our participants to present more craving and be more attracted by alcohol-related cues when being in a positive mood. However, such links might represent acquired associations between specific contexts (i.e., parties, social events) and the presence of alcohol (O'Hara et al., 2015). The pictures used as stimuli in our study, presenting isolated alcohol beverages without depicting any of these contexts, might not result in stronger AB following positive mood.

Capitalizing on the observed increased craving following negative MIP, we further investigated this relationship in Experiment 2 and tested whether it could be modified if participants were explicitly asked to recall a negative autobiographical memory directly linked to alcohol (conversely to the memories evoked in Experiment 1). Indeed, using a MIP that directly associates negative mood and alcohol consumption might lead participants to evaluate alcohol negatively, and thus increase their negative alcohol expectancies. Similar to previous studies using taste devaluation, this procedure of alcohol devaluation could then reduce their subjective craving and/or visual attraction towards alcohol-related stimuli (Rose et al., 2013). To explore these hypotheses (h3-4), we conducted a second experiment with a novel negative MIP, in which participants had to recall an autobiographical memory characterised by strong negative emotions and intense alcohol use (i.e., alcohol-related negative MIP) and compared it with the non-alcohol-related negative and neutral MIP used in Experiment 1.

5. Methods of Experiment 2

5.1. Participants

The same group of BD took part in Experiment 2. We also selected 29 MD (19 women, 10 men; binge drinking score < 12, drinking occasions per week > 1, units per week < 22, units per occasion < 3, no binge drinking episodes) using the same procedure as in Experiment 1.

5.2. Procedure

We used combined MIP with autobiographical recall and music listening for inducing alcohol-related negative mood. Participants were asked to send by email three music tracks making them feel in a negative mood. At the start of the experiment, participants received instructions (Appendix D3) asking them to write down a sad memory, in which they consume a high level of alcohol. The procedure for the non-alcohol-related negative and neutral MIPs and AB task were identical to Experiment 1 (Figure 12).

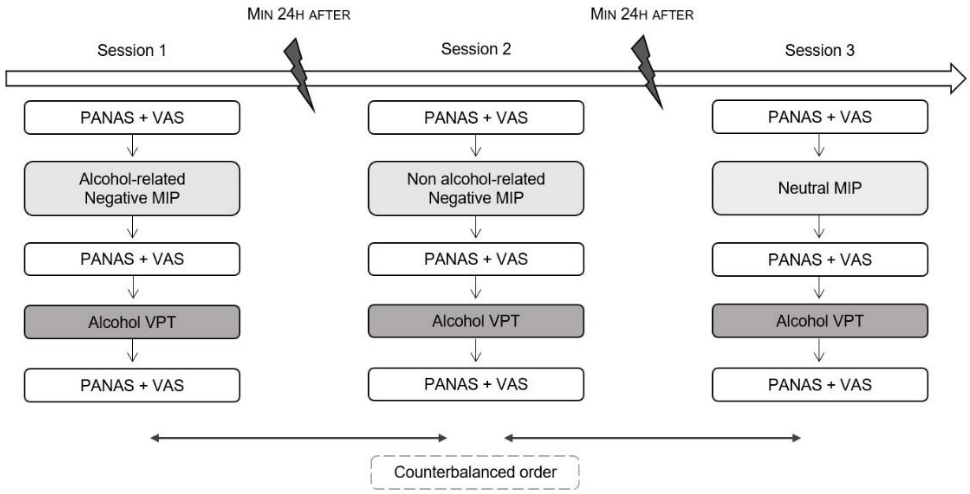

Figure 12. General experimental procedure of the Experiment 2.

5.3. Data analysis

We performed data reduction procedure for RT by removing trials with incorrect responses (0.009% of trials), RT lower than 200ms (0.001% of trials) or higher than 2000ms (0.006% of trials).

We performed the same data analyses than Experiment 1 but also included the MIP (alcohol-related, non-alcohol-related, neutral) as within-subjects moderator variable in the models to test h4 (i.e., the alcohol-related nature of MIP would reverse the association between negative mood and craving or AB).

6. Results of Experiment 2

6.1. Demographics and psychological variables

BD and MD did not differ regarding anxiety [$t(75)=.890$, $p=.376$], depression [$t(75)=1.455$, $p=.150$] and impulsivity [$t(75)=1.762$, $p=.082$]. However, BD were younger [$t(75)=2.327$, $p=.023$] than MD and showed higher scores of enhancement [$t(47)=3.892$, $p<.001$] and coping [$t(45)=3.596$, $p<.001$] drinking motives[5].

BD showed higher negative mood before MIP [$t(75)=2.007$, $p=.048$] and after MIP [$t(75)=2.575$, $p=.014$] than MD. They also showed higher craving before MIP [$t(75)=3.417$, $p=.001$] and after MIP [$t(75)=2.665$, $p=.009$]. They did not differ regarding positive mood before MIP [$t(75)=1.603$, $p=.113$] or after MIP [$t(75)=.909$, $p=.366$].

6.2. Efficacy of MIP

Positive mood. The linear mixed model for positive mood revealed a CONDITION x TIME interaction [$F(2,370)=12.893$, $p<.001$]. Consistent with our predictions, positive mood decreased from pre- to post-MIP in the alcohol-related [$b=-3.28$, $t(66)=6.779$, $p<.001$] and non-alcohol-related [$b=-3.32$, $t(79)=6.126$, $p<.001$] negative conditions but did not change significantly after the neutral condition ($p>.050$). Moreover, post-MIP positive mood was lower in the alcohol-related [$b=-3.45$, $t(148)=4.877$, $p<.001$] and non-alcohol-related [$b=-3.71$, $t(145)=5.594$, $p<.001$] negative conditions relative to the neutral condition. We found no main effect of GROUP nor significant interaction between GROUP, CONDITION and TIME (all $p>.050$).

[5] Considering the major differences between groups on mood-congruent drinking motives and the low variability of scores of drinking motives in MD, we decided to not include these motives in our multilevel approach model.

Negative mood. The linear mixed model for negative mood revealed a CONDITION x TIME interaction [$F(2,370)=19.932$, $p<.001$]. Consistent with our predictions, negative mood increased from pre- to post-MIP in the alcohol-related [$b=3.21$, $t(66)=4.780$, $p<.001$] and non-alcohol-related [$b=3.25$, $t(79)=6.499$, $p<.001$] negative conditions, while it decreased after neutral condition [$b=-1.73$, $t(80)=4.975$, $p<.001$]. Moreover, post-MIP negative mood was higher in the alcohol-related [$b=5.42$, $t(150)=7.235$, $p<.001$] and non-alcohol-related [$b=5.04$, $t(146)=7.153$, $p<.001$] negative conditions relative to the neutral condition. We also found a GROUP main effect [$F(1,79)=8.230$, $p=.005$], showing that BD generally reported higher negative mood than MD [$b=2.986$, $SE=1.335$]. Nevertheless, the efficacy of MIPs to induce negative mood did not differ between BD and LD as no interaction was found between GROUP and CONDITION and TIME (all $p>.050$).

6.3. Alcohol-related AB

Internal reliability was low for RT (α=-.520), first fixation direction (α=.004), second fixation towards alcohol (α=.536) and non-alcohol (α=.212) measures, and high for dwell time (α=.908).

To test h3, we performed multilevel models to investigate group differences on alcohol-related AB. Models for the different AB scores revealed no main effect of GROUP, neither for RT [$F(1,211)=0.418$, $p=.519$], first fixation orientation [$F(1,67)=0.872$, $p=.354$] second fixation on alcohol [$F(1,72)=1.194$, $p=.278$], second fixation on non-alcohol [$F(1,73)=1.409$, $p=.239$] nor dwell time [$F(1,73)=.004$, $p=.949$].

We then included the moderator and mediator variables in models to test h4 (Table 11). Our final models for craving and AB no longer contained any interaction terms. First, there was a significant indirect effect of NEGATIVE MOOD on dwell time AB score, mediated by CRAVING [$b=.055$, $SE=.027$, 95%CI=.009 to .115]. The intensity of negative mood increases the level of craving [$b=.747$, $SE=.197$, $F(1,205)=14.441$, $p<.001$], which in turn positively predicts alcohol-related AB [$b=.073$, $SE=.030$, $F(1,205)=6.057$, $p=.015$]. Second, CRAVING was also directly predicted by the GROUP [$F(1,78)=5.465$, $p=.022$], as BD showed stronger craving than MD [$b=7.206$, $SE=3.083$]. We found no moderation effect of GROUP or MIP CONDITION, nor direct effect of GROUP, NEGATIVE MOOD or MIP CONDITION on dwell time AB score. We found no direct or indirect effect of those predictors on the other AB measures (all *p*>.050).

Table 11. Linear mixed-effect models on craving and AB in Experiment 2.

Variables	*B*	*S.E.*	*t*	*p*	*95% CI*	
1.Craving predicted from group, sex, MIP and negative emotions						
Step 1 – Initial model						
Group	2.169	6.791	.319	.750	-11.224	15.562
MIP	2.460	3.561	.691	.491	-4.573	9.494
Negative affect	.678	.436	1.553	.122	-.183	1.538
Group × Negative affect	.312	.382	.816	.415	-.441	1.064
MIP x Negative affect	-.109	.215	-.504	.615	-.534	.317
Step 2 – Final model						
Group	7.206	3.083	2.338	.022	1.069	13.344
MIP	.766	1.358	.564	.573	-1.916	3.448
Negative affect	.747	.197	3.800	<.001	.359	1.135
2.AB predicted from group, sex, craving, MIP and negative emotions						
Step 1 – Initial model						
Group	-2.947	2.999	-.983	.327	-8.861	2.966
Craving	.064	.058	1.096	.275	-.051	.178
MIP	-1.644	1.475	-1.114	.267	-4.558	1.271
Negative affect	-.282	.186	-1.519	.131	-.649	.084
Group × Negative affect	.138	.170	.812	.418	-.197	.473
MIP x Negative affect	.148	.089	1.653	.100	-.029	.325
Craving × Group	.015	.068	.219	.827	-.119	.149
Step 2 – Final model						
Group	-.717	1.498	-.479	.633	-3.699	2.264
Craving	.073	.030	2.461	.015	.015	.132
MIP	.595	.565	1.053	.294	-.521	1.711
Negative affect	.001	.089	.001	.999	-.175	.175

7. Discussion of Experiment 2

In line with Experiment 1, the group (BD *vs.* MD) did not predict alcohol-related AB differences for any measure used. However, both binge drinking habit and negative mood were positively associated with subjective craving - regardless of the negative MIP used -, which in turn positively predicted AB when assessed through dwell time AB score. These findings again highlight the mediating role of subjective craving in the relationship between AB and negative mood. Importantly, the explicit instructions of recalling a negative memory related to strong alcohol consumption did not reverse the association between negative mood and craving as hypothesized, since participants were still more prone to report higher craving following the two types of negative MIPs.

The present findings could be explained by the fact that negative mood, whatever its source, played a higher role on the emergence of craving for alcohol than the devaluation of alcohol *per se*. This strong association between negative emotions and the desire to consume to reduce these emotions usually explain how the negative consequences of alcohol use (e.g., increased of anxious and depressive symptoms; Anker & Kuchner, 2019) do not result in functional avoidance of alcohol among BD, but rather in a persistent maladaptive attraction towards alcohol. Another explanation is that participants might not have directly associated their negative mood with their alcohol consumption during this memory. Hence, the alcohol-related negative MIP did not change their alcohol expectancies and did not impact their craving or AB.

8. General discussion

Altogether, results from our two experiments provide important insights into the understanding of alcohol-related AB in subclinical populations with excessive alcohol use. First, they replicate findings from many previous studies regarding the major role of craving on the intensity of alcohol-related AB. Indeed, a meta-analysis of 68 studies highlighted the positive association between craving level and AB magnitude (Field et al., 2009). More importantly, previous studies relying on eye-tracking measures even suggested that the intensity of subjective craving is a stronger determinant of AB than drinking habits, since they did not find any AB among regular or BD reporting no craving at testing time (Bollen et al., 2020; Hobson et al., 2013). In the same vein, the present study did not find any direct association between group status (BD *vs.* LD or MD) and AB, as this relationship was mediated by subjective craving. All these findings support the model of Field and colleagues (2016), defining AB as the expression of momentary motivational states regarding alcohol-related stimuli. Altogether, they posit that the presence of alcohol-related AB highly fluctuates according to transient state such as craving.

Since the presence and magnitude of AB depend on subjective craving in BD, it is important to highlight the core determinants of craving *per se*. The present study provides initial insights on this question by showing that participants were more likely to report craving when they endorsed binge drinking habits and experienced negative mood. Our findings relate with previous studies showing that laboratory manipulations of negative mood can provoke subjective craving, and that this effect was stronger in heavier drinkers compared to moderate ones (Blaine et al., 2019; Fox et al., 2007). This is consistent with the affective processing model of negative reinforcement (Baker et al., 2004), which suggests that the desire for consumption is predominantly motivated by the escape and avoidance of negative mood. Several meta-analyses supported this model by showing that experiencing negative mood was a relevant factor to elicit craving (Bresin et al., 2018; Cyr et al., 2022; Heckman et al., 2013; van Lier et al., 2017).

In line with previous studies in subclinical populations (see Bollen et al., 2022 for a review), alcohol-related AB in the present study was only predicted by our selected variables when indexed by eye-tracking measures, and more specifically by dwell time (i.e., overall fixation time on alcohol *vs.* non-alcohol stimuli). As this latter measure is known to reflect the processes related to controlled maintenance of attention, AB would thus appear at the later and more controlled stages of attentional processing in subclinical drinkers rather than being characterized by an early and involuntary hijacking of attention provoked by alcohol-related stimuli as postulated by dominant models in addiction (Bechara, 2005; Wiers et al., 2007). However, this could also be due to the higher reliability of dwell time measure reported in the present study and in previous ones (Bollen et al., 2020, 2021; Christiansen et al., 2015b). Future studies on AB should systematically go beyond behavioural measures, centrally by using eye-tracking methods, but also develop novel paradigms to more reliably determine the automatic nature of AB.

Finally, our findings showed that BD reported higher negative mood at baseline and after MIP than MD or LD, which might be a direct after-effect of repeated alcohol exposures and binge drinking patterns (Koob, 2013) or related to differences in emotional regulation abilities highlighted by many previous studies in binge drinking (Lannoy et al., 2019a). Whereas the efficacy of MIP was similar between groups, this finding makes it difficult to differentiate the respective impact of negative mood and drinking group status on craving or AB. Our study also bares some limitations. First, while our experimental sample presented the classically reported binge drinking consumption pattern, the use of the same BD participants in the two experiments might have limited the generalizability of our findings. Second, we did not include drinking motives in our main analyses for statistical reasons, which prevented us from determining the role of this potential predictor. Third, our study might have not been sufficiently powered to detect smaller interaction effects. Fourth, while Experiment 2 investigated the role of negative devaluation on craving and AB through an alcohol-related negative MIP, we did not include explicit measures of negative alcohol expectancies. Finally, the MIP effect might have been partly related to demand characteristics and might have progressively vanished during the VPT task, the influence of MIP thus potentially varying along the task. Future studies should extend the present results to other stimuli (e.g., beverages in a drinking context) and alcohol types (e.g., wine, spirits) and explore the influence of other variables (e.g., drinking motives) on the links between mood, craving and AB. However, our work draws some clinical avenues regarding prevention and intervention of excessive alcohol use. In view of these results, an ample panel of strategies (i.e., emotion regulation, cognitive regulation of craving, ABM training) could show promises as targeted interventions on the interlinked determinants of alcohol use (i.e., negative mood, craving and AB; Gratz et al., 2015; Naqvi et al., 2015).

9. Conclusion

We provided insights on the interactions between alcohol-related AB, craving, drinking status and mood in a population of student drinkers, by showing that the association between negative mood, binge drinking habits and AB are mediated by subjective craving. These findings support previous studies and theoretical models suggesting that alcohol-related AB is not a stable characteristic of excessive alcohol use but are rather the behavioural artefact of transient evaluative states (e.g., craving). Additionally, our multilevel modelling approach identified which variables directly determine craving, and thus indirectly influenced the magnitude of alcohol-related AB. Overall, these findings emphasize the importance of considering different motivational and affective states (i.e., subjective craving, mood and AB) as intercorrelated to offer multiple ways to reduce excessive alcohol use.

Chapter 7

Alcohol-related AB in recently detoxified inpatients with SAUD: an eye-tracking approach

Background: Dominant theoretical models consider that AB towards alcohol-related stimuli plays a key role in the development and maintenance of alcohol use disorder. Its assessment has however showed high inconsistencies and has been mostly based on unreliable behavioural measures. This study evaluated the presence and extent of alcohol-related AB in recently detoxified inpatients with SAUD by combining the VPT paradigm with eye-tracking measures, known to improve the VPT reliability in subclinical populations.

Methods: We recruited 24 patients with SAUD and 27 matched CTL. They performed the VPT (measuring RT when processing visual targets preceded by alcoholic and matched non-alcoholic pictures) combined with eye-tracking measures (dwell times, first fixation direction/duration, second fixation direction) during two sessions. Estimates of internal consistency, split-half reliability, and test-retest reliability were measured.

Results: Patients with SAUD showed shorter dwell times for alcohol cues (p=.004, d=.853) and reduced number of fixations towards alcohol after a first fixation on non-alcohol cues (p=.012, d=.758) compared to CTL. These findings suggest the presence of alcohol-related avoidance AB in detoxified patients with SAUD. The VPT achieved excellent reliability for these eye-tracking measures. RT and first fixation measures did not indicate any AB pattern and showed poor reliability.

Conclusions: The VPT, when combined with dwell time and second fixation direction, constitutes a reliable method for assessing AB in detoxified patients. It showed the presence of an alcohol-related avoidance AB in this clinical population, in contradiction with the approach AB predicted by theoretical models.

Reference

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Alcohol-related AB in recently detoxified inpatients with SAUD: an eye-tracking approach

1. Introduction

AB is the tendency to orient one's attention towards salient or goal-directed stimuli. Prominent models (Bechara, 2005; Wiers et al., 2007) proposed that AB is present for alcohol-related stimuli in alcohol use disorder. The incentive-sensitization theory (Robinson & Berridge, 1993) suggests that repeated alcohol consumption sensitizes the reward system, enhancing the incentive properties of alcohol-related cues. By becoming more salient, these cues capture attention and generate AB. This AB would subsequently be related to higher craving and elevated relapse risk. Most influential models thus assume that AB plays a key role in SAUD onset and persistence (Volkow et al., 2019; Yücel et al., 2019).

Capitalizing on this background, behavioural paradigms have emerged to measure alcohol-related AB. The most commonly used tasks are the addiction Stroop task (Cox et al., 2006) and the VPT (Ehrman et al., 2002). In the addiction Stroop task, participants name the color of alcohol-related or neutral words. Detoxified patients with SAUD are slower than CTL to name the color of alcohol-related words (Duka et al., 2002; Lusher et al., 2004). This is usually interpreted as alcohol-related AB, based on the rationale that the automatic capture of attention to process the semantic content of alcohol-related words slows down color naming. However, such interpretation is discussed, as this interference could also result from the mobilization of attention to inhibit alcohol-related words processing, then rather indexing avoidance AB of alcohol-related cues (Klein, 2007). Regarding the VPT (see Methods section for a full description), some previous studies suggested the presence of AB in SAUD, detoxified patients responding faster to probes replacing alcohol-related stimuli (Loeber et al., 2009). However, other studies rather revealed an avoidance pattern in detoxified inpatients (Townshend & Duka, 2007), or did not show any difference with CTL (Field et al., 2013; Wiers et al., 2016). Similar inconsistencies exist across studies exploring AB in subclinical populations without SAUD (e.g., heavy or binge college drinkers; for a review, see Field & Cox, 2008).

Such incoherence hampers the sound testing of theoretical assumptions and the emergence of empirically-based therapies. An underlying factor, which might explain such discrepancies, is that previous studies have inferred AB in detoxified patients with SAUD exclusively from RT measures. The focus on behavioural data prevents testing the alternative proposal (i.e., the existence of avoidance AB) in the Stroop task. In the VPT, RT only inform about the location of attention at probe onset, not providing insight about the successive stages involved in attentional deployment over time (Field & Cox, 2008). A further weakness of VPT-based RT is their low internal reliability (Ataya et al., 2012) and high variability according to stimulus duration (Beraha et al., 2018): short durations (e.g., 50ms) appear related to AB toward alcohol while longer ones (e.g., 500ms) generate avoidance AB (Vollstadt-Klein et al., 2009). Despite these limitations, also underlined in other psychopathological states (Kruijt et al., 2019), the VPT paradigm is frequently implemented in clinical settings to improve SAUD treatment by retraining AB (Heitmann et al., 2018). Its therapeutic efficacy nevertheless appears weak and its clinical relevance is debated (Christiansen et al., 2015a; Cristea et al., 2016).

A promising tool to overcome these mitigated findings is eye-tracking, providing an optimized measure of AB by detecting eye movements and gaze position with a high temporal resolution (Popa et al., 2015). Unlike behavioural measures, eye-tracking offers insights on the time course of AB and clarifies its core mechanisms by measuring the consecutive steps involved in attention (Armstrong & Olatunji, 2012): the direction and duration of the first fixation index early attentional capture, whereas dwell time (i.e., overall fixation time on a stimulus) reflects the latter and controlled maintenance of attention. Combining traditional paradigms with eye-tracking would thus clarify the spatial and temporal dynamics of AB, improving their measure's reliability (Christiansen et al., 2015b). Studies assessing AB in subclinical populations through combined VPT/eye-tracking (Maurage et al., 2020b for a review) showed that eye-tracking indexes are more reliable than RT (Christiansen et al., 2015b), and suggested the presence of alcohol-related AB in these populations (Fernie et al., 2012; Miller & Fillmore, 2010; Weafer & Fillmore, 2013), particularly under alcohol intoxication (Schoenmakers et al., 2008) or high craving (Bollen et al., 2020). These results were mostly observed at the late and controlled stages of attentional processing (i.e., longer dwell times for alcohol). Another eye-tracking study showed that hazardous drinkers with ambivalence (i.e., both positive and negative evaluations of alcohol) initially oriented their attention towards alcohol, and then redirected it away from alcohol later during the trial, while those without ambivalence showed alcohol-related AB throughout the trial (Lee et al., 2014). Novel theoretical predictions (Field et al., 2016) emerged regarding the role played by the perceived valence of alcohol cues on AB, suggesting that this approach-avoidance pattern of AB would appear in patients with SAUD experiencing motivational conflict (e.g., detoxified patients receiving treatment). This pattern can only be observed with eye-tracking (Field et al., 2016), through measures indexing attentional shift or disengagement. There is thus a need to test the reliability of a combined VPT/eye-tracking approach in patients with SAUD to obtain the first reliable measure of AB in this population (Jones et al., 2018a).

We explored the presence of alcohol-related AB among recently detoxified inpatients diagnosed with SAUD by combining VPT with eye-tracking measures to disentangle two contradictory hypotheses: (1) eye-tracking findings in subclinical populations suggest that individuals with SAUD might present AB towards alcohol, which is also predicted by theoretical models; (2) as AB is related to motivational states (e.g., craving, ambivalence) and as detoxified patients have motivational conflicts regarding alcohol cues (Field et al., 2016), they might present initial approach AB (i.e., early automatic attraction towards alcohol) followed by avoidance AB (i.e., reduced dwell times on alcohol), as suggested earlier (Vollstadt-Klein et al., 2009). At the methodological level, we postulated that eye-tracking will increase VPT reliability (Christiansen et al., 2015b).

2. Methods

2.1. Participants

Patients with SAUD were recruited from an inpatient treatment unit during their second/third detoxification weeks (Psychiatric Hospital of Beau Vallon, Belgium) and screened using the Mini International Neuropsychiatric Interview (MINI; Sheehan et al., 1998). Twenty-six detoxified inpatients (12 females) were selected as they met the DSM-V criteria for SAUD, indicated by the presence of 6 or more symptoms. They had all abstained from alcohol for at least 7 days and were free of other psychiatric comorbidities (except nicotine dependence). It should be noted that none of the patients had followed a cognitive remediation therapy such as ABM during their treatment. Patients with SAUD were matched for age and sex with a group of 28 CTL (13 females), free of any past or present psychiatric disorder or personal/family history of SAUD. CTL were recruited through social networks and emails and were selected if they did not usually consume more than ten alcohol units (i.e., one unit corresponding to 10gr of pure ethanol) per week and did not exceed three units per day. They were excluded if they scored higher than 8 at the AUDIT (Babor & Robaina, 2016). Exclusion criteria for both groups included polysubstance use disorder and major past or present neurological disorder and/or trauma. They all had normal/corrected vision and were fluent French speakers. An a priori power computation (performed in G*Power v3.1.9.4) indicated that a sample size of 46 was required to detect a group x type of stimuli interaction (two measurements) in repeated-measures ANOVA, assuming a medium (f=0.25) effect size with 0.90 power and α=0.05, as fulfilled by our sample size.

2.2. Apparatus

Participants seated on an adjustable chair, facing an eye-tracker camera and an Asus Display Laptop PC equipped with a 17.3-inch FHD screen (resolution 1080x1920p; refresh rate 120Hz). The presentation of the experimental task and its synchronization with eye-tracking were controlled using OpenSesame software (Mathôt et al., 2012). Eye movements were recorded using an EyeLink Portable Duo remote mode eye-tracker (SR Research, Canada; sampling rate 1000 Hz; average accuracy range 0.25°-0.5°, gaze tracking range of 32° horizontally, 25° vertically).

2.3. Procedure

Participants attended a test-retest experimental design with two sessions separated by four days. They provided written informed consent to participate in the study and were not aware of the hypotheses tested. They were seated 60cm away from a laptop and were tested individually in a quiet room. At the first session, participants first filled in questionnaires assessing state anxiety (State Anxiety Inventory; Spielberger, 1993) and alcohol craving [Obsessive-Compulsive Drinking Scale (OCDS; Anton et al., 1995) and VAS: "Indicate how much you want to drink alcohol right now (from 0=not at all, to 100=strong desire)"], before performing the task. The procedure was repeated for the second session. The task was a computerized VPT lasting about 15 minutes. Prior to each block, the eye-tracker was calibrated to the screen using a built-in 9-point protocol. Between sessions, participants filled in questionnaires assessing depressive symptoms (Beck Depression Inventory-II; Beck et al., 1996), anxiety (Trait Anxiety Inventory; Spielberger, 1993), and impulsivity (UPPS-P Impulsive Behavior Scale; Billieux et al., 2012). The study protocol was performed in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of the Saint-Luc-UCLouvain Clinics and the local Ethics Committee of Beau Vallon Hospital. At the end of the two sessions, participants were debriefed and CTL received financial compensation.

2.4. Stimuli

Twenty pairs of alcoholic beverage pictures (e.g., bottle of vodka) and matched non-alcoholic beverage pictures (e.g., bottle of water) without context, extracted from the validated Amsterdam Beverage Picture Set (ABPS; Pronk et al., 2015), were displayed on a black background. The picture sets were identical to those used in Bollen et al. (2020). Brands and writings were blurred to avoid reading and each picture pair was matched on color, size (444x444 pixels or 10.7x10.7° angle), brightness, and salience.

2.5. VPT

The VPT procedure was identical to those used in Bollen et al. (2020). Each trial started with a central fixation dot on a black background and participants had to fixate their gaze on it. The fixation dot was used as a drift check to confirm the reliability of the eye-gaze calibration. This instruction also ensured that participants initially focused their visual attention at the center of the screen in each trial. Two pictures (i.e., alcoholic and non-alcoholic beverage pictures) were then displayed in a counterbalanced order on the left and right side of the screen for a 2000ms period, and then replaced by a probe (i.e., white arrow) appearing at the location previously occupied by one of the pictures (Figure 13). Participants had to respond to the orientation of the probe by pressing the "up" or "down" key on the keyboard, as quickly and correctly as possible. Visual probes replaced the two types of pictures with equal frequency. Each trial was separated by an inter-trial interval of random duration (500-1500ms). The task contained 84 trials, including four practice trials excluded from the analyses.

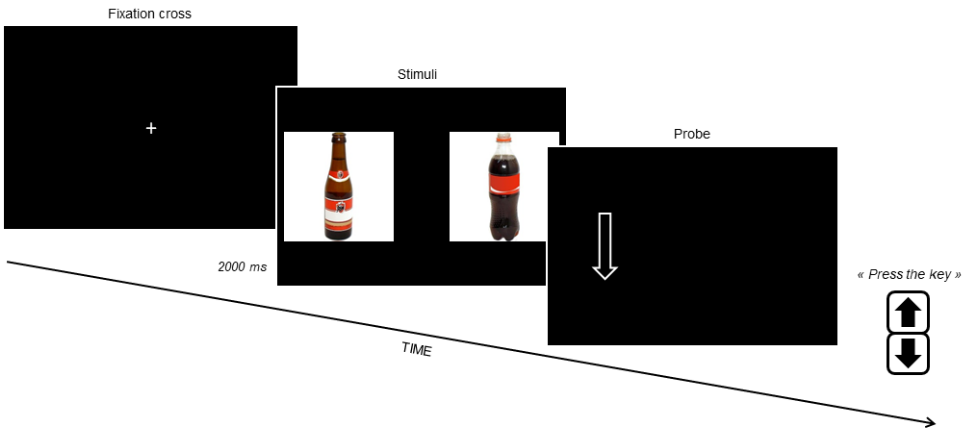

Figure 13. Illustration of the VPT with alcohol-related and non-alcohol stimuli.

The performance was assessed through behavioural (RT) and eye-tracking measures (first fixation direction, first fixation duration, second fixation direction, dwell times). The RT for probes replacing alcohol pictures compared to those replacing non-alcohol pictures are the commonly used AB index. The first fixation direction indicates the stimulus that was first fixated during each trial (i.e., initial attentional capture). The first fixation duration indicates the duration of the first fixation made on a stimulus (i.e., persistence of attentional focus). The second fixation direction indicates how frequently the participant fixated a second stimulus after visiting the first one (i.e., attentional switch). The dwell times are the sum of fixation times on each stimulus during the whole trial (i.e., maintenance of attention). Gaze samples were qualified as fixations or saccades according to the standard Eyelink algorithms.

2.6. Data reduction and statistical analyses

We performed data reduction procedure for RT by removing trials with incorrect responses (3.58% of trials), RT lower than 200ms (0.56% of trials) or higher than 2000ms (0.07% of trials). Starers (i.e., participants not making any eye movements towards stimuli in more than half of the trials; van Ens et al., 2019) were removed before performing the analyses (2 patients with SAUD, 1 CTL), leading to a sample of 51 (24 patients with SAUD, 27 CTL) for the first session. 11 participants dropped out during the testing period, leading to a sample size of 40 (19 patients with SAUD, 21 CTL) for the second session. To measure task reliability, we computed AB score for each measurement: RT (non-alcohol minus alcohol), first fixation direction (proportion of first fixation on alcohol compared to non-alcohol), first fixation duration (alcohol minus non-alcohol), second fixation direction for alcohol/non-alcohol (proportion of second fixation on alcohol/non-alcohol compared to no second fixation after a first fixation on non-alcohol/alcohol), and dwell times (alcohol minus non-alcohol). A positive/negative AB score for RT, first fixation duration, and dwell times indicated AB towards alcohol/non-alcohol.

We performed all statistical analyses using the SPSS software package (version 27.0). We performed between-group comparisons (i.e., independent t-tests) on demographic, psychopathological characteristics and alcohol consumption variables. We also performed Pearson's correlations to explore the influence of psychopathological variables on the magnitude of alcohol-related AB (as indexed by dwell times) in the first session. These analyses were however conducted with an exploratory aim as the present study was not sufficiently powered to contrast correlations. We indexed the internal consistency of the task by (1) computing Cronbach's alpha for the 20 pairs of pictures; (2) computing bivariate Spearman-Brown correlations between AB score of the odd and even trials (split-half reliability). We indexed test-retest reliability by computing Pearson's correlations between AB score of the first and second sessions. For both sessions, we performed five 2x2 repeated-measures analyses of variance (ANOVAs) on behavioural (RT) and eye-tracking (First fixation direction, First fixation duration, Second fixation direction and Dwell times) indices with Group (patients with SAUD, CTL) as between-subjects factor, Type (alcohol, non-alcohol) as within-subjects factor, and depression, anxiety and impulsivity scores as covariates (as they differed across groups and might influence AB). For RT, the Type factor encompassed, for each picture category, the trials in which the probe appeared at the same location as these pictures. We conducted Post Hoc tests (independent and paired samples t-tests) with a Bonferroni-corrected p-value of ($\alpha_{altered}$=.05/2)=0.025. We also carried out complementary analyses on first fixation laterality and trial-by-trial variability in the test session, the methods and results of which are described in Appendix E.

3. Results

3.1. Demographic, psychopathological and alcohol-related measures (Table 12)

Patients with SAUD and CTL did not differ for age, sex, state anxiety and both assessments of subjective craving (p>.050). Patients with SAUD showed higher depression [$t(29)$=6.524, p<.001, d=1.955], trait anxiety [$t(49)$=5.564, p<.001, d=1.619], impulsivity [$t(47)$=2.718, p=.009, d=1.287], AUDIT scores [$t(25)$=14.040, p<.001, d=4.277] and alcohol doses per day [$t(23)$=9.322, p<.001, d=2.775] than CTL. Regarding OCDS subscales, patients with SAUD scored higher on obsessive thoughts (but not on compulsive desires) in the first session compared to CTL [$t(24)$=3.661, p=.001, d=1.087]. We found positive correlations between dwell time AB scores at first session and (1) depression (r=.450) and OCDS craving (r=.407) in patients; (2) impulsivity (r=.410) in CTL.

Table 12. Demographic, psychopathological, alcohol consumption and craving measures [M (SD)] for detoxified patients with SAUD and CTL, and their correlations with dwell time AB scores during the first session.

	SAUD (n=24)		CTL (n=27)	
	M (*SD*)	*r*	*M* (*SD*)	*r*
Demographic measures				
Sex ratio (male/female) ^{ns}	12/12		14/13	
Age ^{ns}	49.88 (8.7)	-.177	49.52 (10.1)	.035
Psychopathological measures				
Beck Depression Inventory **	20.04 (10.2)	.450*	4.70 (4.6)	-.047
Trait Anxiety Inventory **	49.29 (8.6)	.336	35.48 (8.0)	-.141
State Anxiety Inventory ^{ns}	37.13 (13.8)	.118	31.11 (8.1)	-.110
UPPS-P *	43.90 (6.2)	-.224	38.30 (8.2)	.410*
Alcohol consumption measures				
AUDIT **	27.00 (7.6)	.358	4.00 (2.0)	.156
Number of units per day **	14.08 (7.0)	-.339	0.74 (0.6)	.053
Craving measures				
VAS ^{ns}	4.42 (10.5)	.244	1.52 (6.0)	.235
OCDS ^{ns}	6.19 (6.7)	.407*	3.30 (2.8)	.316

^{ns} non-significant, * p<.050, ** p<.001.

3.2. Reliability estimates (Table 13)

RT showed low and negative internal consistency, under the 0.70 cut-off score of acceptable internal reliability (Kline, 2000). They also presented low and negative split-half and test-retest reliabilities. First fixation direction and duration measures did not reach the cut-off score for acceptable reliability in terms of internal, split-half, or test-retest reliability. Conversely, dwell times and both indices of second fixation direction showed excellent internal consistency and split-half reliability. They also presented significant and positive correlations between test and retest sessions.

Table 13. Internal consistency (Cronbach's alpha), split-half reliability (bivariate Spearman-Brown correlations) and test-retest reliability (bivariate Pearson correlations) for the first and second sessions of the VPT for RT and eye-tracking measures.

	RT	Dwell Time	1st Fixation	1st Fixation Duration	2nd Fixation alcohol	2nd Fixation non-alcohol
Internal consistency						
First session	-.156	.967	.027	.643	.870	.806
Second session	-.947	.980	.370	.437	.977	.811
Split-half reliability						
First session	.058	.804**	-.197	-.101	.830**	.840**
Second session	-.126	.763**	-.051	.326*	.875**	.762**
Test-retest reliability						
Both sessions	-.798**	.536**	.124	.304	.637**	.463**

Note. * p<.050, ** p<.001

3.3. AB measures (Table 14)

RT. In both sessions, we found a GROUP effect [session 1: $F(1,46)=5.741$, $p=.021$, $\eta_p^2=.111$; session 2: $F(1,35)=6.877$, $p=.013$, $\eta_p^2=.164$], showing longer RT for patients with SAUD compared to CTL. Main effect of TYPE and its interaction with GROUP were inconclusive (p>.050).

First fixation direction. In both sessions, main effects of TYPE, GROUP and their interaction were inconclusive (p>.050).

First fixation duration. In both sessions, main effects of TYPE, GROUP and their interaction were inconclusive (p>.050).

Second fixation direction. In session 1, we found a marginal TYPEXGROUP interaction [$F(1,46)=4.028$, $p=.051$, $\eta_p^2=.081$] (Figure 14). Patients with SAUD less frequently performed a second fixation towards alcohol after a first fixation on non-alcohol compared to CTL [$t(39.00)=2.640$, $p=.012$, $d=.758$], while groups did not differ regarding the second fixation on non-alcohol after a first fixation on alcohol (p>.050). Main effects of TYPE and

GROUP were inconclusive (p>.050). In session 2, we found a TYPE effect [F(1,35)=6.333, p=.017, η_p^2=.153], showing a higher proportion of second fixations for non-alcohol compared to alcohol. We found a GROUP effect [F(1,35)=4.119, p=.050, η_p^2=.105], showing that CTL performed a second fixation more frequently than patients with SAUD. We found a TYPEXGROUP interaction [F(1,35)=16.657, p<.001, η_p^2=.322]. Patients with SAUD less frequently performed a second fixation towards alcohol after a first fixation on non-alcohol compared to CTL [t(38)=2.846, p=.007, d=.901]. Groups did not differ regarding second fixation on non-alcohol after a first fixation on alcohol (p>.050).

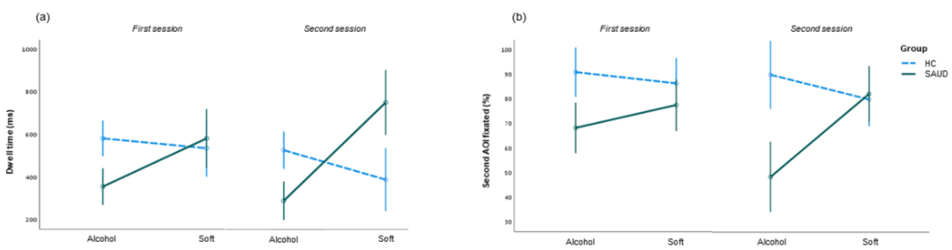

Figure 14. (a) Dwell times and (b) proportion of second fixations for alcohol and non-alcohol stimuli observed in detoxified patients with SAUD and CTL during the first and second sessions when controlling for depression, anxiety and impulsivity.

Dwell Time. In session 1, we found a TYPEXGROUP interaction [F(1,46)=6.016, p=.018, η_p^2=.116]. Patients with SAUD presented shorter dwell times on alcohol than CTL [t(49)=3.041, p=.004, d=.853], while groups did not differ regarding dwell times on non-alcohol (p>.050). Main effects of TYPE and GROUP were inconclusive (p>.050). In session 2, a TYPE effect [F(1,35)=4.931, p=.033, η_p^2=.123] showed longer dwell times for non-alcohol than alcohol. We also found a significant TYPEXGROUP interaction [F(1,35)=19.235, p<.001, η_p^2=.355]. Patients with SAUD presented shorter dwell times on alcohol than CTL [t(38)=3.322, p=.002, d=1.052] and compared to non-alcohol [t(18)=2.466, p=.024, d=.566]. Groups did not differ regarding dwell times on non-alcohol (p>.050). Main effect of GROUP was inconclusive (p>.050).

Table 14. Behavioural and eye-tracking indexes for the first and second sessions of the VPT (M [SD]) for detoxified patients with SAUD and CTL.

	First session		Second session	
Variable	SAUD (n=24)	CTL (n=27)	SAUD (n=19)	CTL (n=21)
RT (ms)				
Alcohol	824 (439)	625 (145)	756 (214)	579 (147)
Non-alcohol	795 (329)	634 (166)	789 (324)	588 (151)
First fixation direction (%)				
Alcohol	37.33 (6.4)	37.59 (6.0)	36.00 (6.4)	37.95 (6.2)
Non-alcohol	35.96 (5.8)	37.70 (5.9)	37.79 (8.0)	35.81 (6.2)
First fixation duration (ms)				
Alcohol	227 (47)	253 (79)	220 (47)	259 (73)
Non-alcohol	241 (95)	253 (81)	241 (72)	261 (75)
Second fixation direction (%)				
Alcohol	71.70 (24.4)	87.17 (16.0)	58.87 (28.4)	82.10 (23.1)
Non-alcohol	76.99 (22.9)	86.74 (18.5)	76.76 (21.2)	85.20 (19.7)
Dwell Time (ms)				
Alcohol	393 (193)	543 (158)	319 (156)	491 (169)
Non-alcohol	525 (337)	586 (214)	579 (391)	537 (223)

4. Discussion

The presence of AB towards alcohol in SAUD is a core proposal of theoretical models. However, its experimental validation still faces issues as available data rely on unreliable RT-based measures. We investigated the presence and extent of AB in a population of detoxified inpatients diagnosed with SAUD, by using a combined VPT/eye-tracking approach presenting higher reliability.

Regarding RT and first fixation indices, we did not observe any alcohol-related AB among patients. This null finding appears related to the poor reliability of RT (Ataya et al., 2012). Regarding the eye movements indices of initial attentional capture, neither first fixation direction nor duration reached acceptable reliability, in coherence with earlier results (Lazarov et al., 2018; Soleymani et al., 2020). The absence of early automatic attraction towards alcohol among patients could partly be caused by the classical dominance of the left visual field related to Western reading and writing habits (Foulsham et al., 2013). This left-gaze bias early orients attention towards the left hemifield, regardless of the stimuli (only 33% of first fixations directed rightwards in the current study). We thus found no support for an automatic and early AB towards alcohol in SAUD.

Researchers have suggested that, instead of being based on attention-grabbing properties of alcohol stimuli, AB may be characterized by a difficulty to disengage attention from them (Field et al., 2016; Soleymani et al., 2020). The second fixation direction indexes whether patients: (1) show difficulty to redirect attention away from alcohol cues, as indexed by a lower proportion of second fixation towards non-alcohol stimuli after a first fixation on alcohol stimuli, or (2) avoid processing alcohol-related stimuli after a first fixation on non-alcohol stimuli, as indexed by a lower proportion of second fixation towards alcohol. Our findings supported the latter proposal, revealing the presence of avoidance AB in detoxified patients with SAUD. In the same vein, we showed shorter dwell times for alcohol-related stimuli among patients, which aligns with previous VPT studies reporting avoidance AB of alcohol in this population (Townshend & Duka, 2007). Both measures (second fixation direction, dwell time) provided excellent reliability (internal consistency, split-half reliability). Eye-tracking indexes thus highly increase VPT reliability (Bollen et al., 2020; Christiansen et al., 2015b), these sound results suggesting that detoxified inpatients present avoidance AB at later processing stages.

Such findings question theoretical assumptions regarding the role of AB in SAUD (Bechara, 2005; Robinson & Berridge, 1993; Wiers et al., 2007). Based on the dominant models, our clinical sample was expected to present AB towards alcohol-related stimuli, since it was exclusively composed of patients diagnosed with the most severe pattern of alcohol use disorders, usually characterized by massive cognitive dysfunctions (Stavro et al., 2011). AB towards alcohol might be observed in other AUD populations (e.g., untreated individuals) but the opposite pattern observed here among recently detoxified patients invalidates the proposal of consistent and stable AB in SAUD. Previous findings in subclinical populations suggested that AB fluctuates alongside motivational state related to subjective craving (Bollen et al., 2020), stress (Field & Quigley, 2009) or ambivalence (Lee et al., 2014). Similarly, currently drinking patients with SAUD presented RT-based AB towards alcohol, while abstinent patients rather showed avoidance AB (Sinclair et al., 2016). In the present study, the avoidance bias might be explained by patients' negative thoughts about alcohol, as they were involved in an abstinence process at testing time. Altogether, these findings suggest that AB varies with contexts and disease course. To experimentally test this assumption, further studies should evaluate alcohol-related AB in individuals with SAUD not seeking for treatment and/or not presenting motivational conflict regarding alcohol.

Our findings thus offer experimental support to the proposal of Field et al. (2016) that most models might have overstated the stability of AB in SAUD: AB in addictive disorders might be driven by temporary changes in appetitive and/or aversive motivational states. The subjective valence [positive, negative, or both (i.e., ambivalence)] of the evaluation of substance cues might determine whether individuals maintain and/or override their gaze on them, resulting in different AB patterns. This provides a better explanation of the inconsistencies in the aforementioned VPT studies, where patients with SAUD could either show approach or avoidance alcohol-related AB. In our sample, patients were all abstinent and most reported low craving and high abstinence motivation at testing time. These variables being related to negative evaluation and aversive state towards alcohol, they might explain why detoxified patients present avoidance AB. Moreover, our correlational analyses indicate that higher craving is associated with higher AB score, further supporting the impact of the motivational state on AB. Beyond the motivational state, the intensity of SAUD presented by the experimental sample may vary between studies, both in terms of the number of diagnostic criteria encountered and the intensity/frequency of alcohol use, which could also influence the intensity of AB. Researchers and clinicians should thus reconsider the conditions in which attentional training should be conducted. Some patients might present genuine AB towards alcohol, and increasing the avoidance AB through attentional training might have a beneficial therapeutic impact, but the absence of AB towards alcohol in detoxified patients with SAUD when using valid measures raises doubts regarding the usefulness of generalized attention training in this population.

The present study bares some limitations. First, our sample size was relatively small and statistical power was unsufficient for correlational analyses. Although these analyses were defined as exploratory, their results should be interpreted with caution. Second, we did not explicitly evaluate the patient’s feelings and thoughts about alcohol use at testing time, preventing us from evaluating their impact on AB.

5. Conclusion

Capitalizing on reliable data combining VPT and eye-tracking, we showed that recently detoxified patients with SAUD present avoidance AB of alcohol-related stimuli rather than approach AB, as suggested by most theoretical models. Avoidance AB appears at later and controlled processing stages (i.e., second fixation direction, dwell time) without influencing the initial capture of attention. There findings should lead to reconsider the interest of the therapeutic programs reducing AB in SAUD, notably by reserving such intervention to patients presenting a genuine approach AB and/or high craving levels.

Chapter 8

Craving modulates AB toward alcohol in SAUD: An eye tracking study

Background and Aims: Competing models disagree on three theoretical questions regarding alcohol-related AB, a key process in SAUD: (1) is AB more of a trait (fixed, tied to alcohol use severity) or state (fluid, tide to momentary craving states) characteristic of SAUD?; (2) is AB purely reflecting the over-activation of the reflexive/reward system or is it also related to the under-activation of the reflective/control system?; (3) does AB rely on early or later processing stages? We addressed these issues by investigating the time course of AB and its modulation by subjective craving and cognitive load in SAUD.

Design and Setting: A free viewing eye-tracking task was performed in a laboratory setting, presenting pictures of alcoholic and non-alcoholic beverages, combined with a concurrent cognitive task with three difficulty levels.

Participants: Ninety participants were included, 60 patients with SAUD (30 self-reporting craving at testing time; 30 reporting a total absence of craving) and 30 matched CTL.

Measurements: AB was assessed through early and late eye-tracking indexes. The modulation of AB by craving (i.e., comparison between patients with/without craving) and cognitive load (i.e., variation of AB with the difficulty level of the concurrent task) was evaluated.

Findings: Measures of late AB stages indicated that patients with craving allocated more attention towards alcoholic stimuli than patients without craving, resulting in opposite approach/avoidance AB according to craving presence/absence. Patients without craving even showed a stronger avoidance AB for alcohol than CTL. AB did not vary according to the cognitive resources requested by the concurrent task.

Conclusions: The direction of alcohol-related AB (approach/avoidance) is determined by patients' subjective craving at testing time and does not function as a stable SAUD trait. While relying on later/controlled attentional stages, AB is not modulated by the saturation of the reflective/control system.

Reference

Bollen, Z., Pabst, A., Masson, N., Wiers, R.W., Field, M., & Maurage, P. Craving modulates attentional bias toward alcohol in severe alcohol use disorder: An eye tracking study. *Addiction*. Submitted.

1. Introduction

Alcohol-related AB is the preferential allocation of attention toward alcohol-related stimuli. Prominent theoretical models assume that AB plays a causal role in the onset and persistence of SAUD (Bechara, 2005; Volkow et al., 2019; Yücel et al., 2019). The incentive-sensitization theory (Robinson & Berridge, 1993) postulates that repeated alcohol exposures sensitize the reflexive/reward system, enhancing the incentive properties of alcohol-related cues through conditioning. Becoming more salient, these cues capture attention (i.e., generate AB) and guide individuals towards alcohol consumption. Hence, interventions targeting AB emerged, postulating that reducing AB through attentional retraining would reduce consumption and relapse risk. These interventions, while increasingly implemented in clinical settings with some promising effect on clinical outcomes, led to inconsistent results regarding their impact on AB (Cox et al., 2014; Rinck et al., 2018). Such discrepancies might result from the fact that several theoretical questions remain to be clarified in this research field, namely is AB: (1) mostly a trait (fixed, tied to SAUD severity) or state (fluid, tide to momentary motivational states) characteristic of SAUD?; (2) purely reflecting the over-activation of the reflexive/reward brain system or also influenced by the under-activation of the reflective/control system, hampering voluntary control on AB?; (3) characterized by an early/automatic hijacking of attention by alcohol-related stimuli or rather relying on later and more controlled processing stages?

Regarding the first question, traditional models assume that AB progressively develops through associative learning and reflexive/reward system over-sensitization, finally constituting an enduring and potentially permanent SAUD characteristic (Hardman et al., 2021; Robinson & Berridge, 1993). These models thus understated the sensitivity of AB to momentary motivational states compared to the influence of stable factors related to SAUD (e.g., duration, severity). In the past decade, there has been more emphasis (Hofmann et al., 2008) on how fluctuating factors would moderate the behavioral expression of the reflexive/reward system (i.e., AB). Taking a step further, Field and colleagues suggested that AB is partly driven by temporary changes in appetitive and/or aversive states (Field et al., 2016). AB would then result from the momentary motivational evaluation of alcohol-related stimuli, hence constituting a state rather than trait SAUD marker. The subjective evaluation (positive, negative, ambivalent) of alcohol-related cues would lead individuals to maintain their attention on it or conversely ignore it, resulting in different AB patterns (Field et al., 2016). The reported intra-individual AB fluctuation according to current motivational value of alcohol (e.g., subjective craving or drinking status; Field et al., 2013; Sinclair et al., 2016) supports this proposal (Christiansen et al., 2015a; Field et al., 2014). Patients with SAUD might present an AB strongly affected by their current states, which would hence not constitute a key causal factor for SAUD persistence, raising doubt on the rationale of AB retraining. However, the very few studies exploring AB in SAUD only used unreliable measures (Ataya et al., 2012), applied on recently detoxified patients (known to frequently present aversive/ambivalent alcohol evaluation and low craving), which might explain the inconsistent results (Bollen et al., 2022). The only study using reliable eye-tracking measures showed both an avoidance bias in recently detoxified patients with SAUD and a positive correlation between AB and craving (Bollen et al., 2021). These results call for directly addressing the inconsistent theoretical assumptions regarding AB fluctuations (Field et al., 2016; Robinson & Berridge, 1993).

The second question relates to the dual-process models (Bechara, 2005; Wiers et al., 2007), postulating that SAUD emerges from (1) the under-activation of the “reflective/control system”, responsible for deliberative and controlled responses; (2) the over-activation of the “reflexive/reward system”, initiating automatic and appetitive behaviors. In this view, AB results from the overactivation of the reflexive/reward system, but the role played by the reflective/control system remains unclear. Indeed, dual-process models stated that situational factors such as cognitive load could selectively impair the reflective/control system, leading the reflexive/reward system to take the lead (therefore assuming a continuous interaction between systems). Nevertheless, they simultaneously stated that reflexive/reward processes operate in an effortless manner, independently from the availability of cognitive resources (Hofmann et al., 2008; Strack & Deutsch, 2004). Previous studies also suggested that AB is not an artefact of patients’ impaired cognitive/executive functioning (Fadardi & Cox, 2006) but rather a genuine consequence of the reflexive/reward system’s over-activation (van Hemel-Ruiter et al., 2016). Still, studies in other psychopathological states showed that AB might be increased by executive dysfunction (Heeren et al., 2017;

Judah et al., 2013; Liu et al., 2011), suggesting that AB is affected by the activity of the reflective/control system. The under-activation of this system (e.g., through reduction of cognitive resources) could therefore reduce the voluntary control on AB, thus increasing it.

The third question is whether AB relies on early and automatic attentional processes (generating an uncontrolled capture of attention towards alcohol; Bechara, 2005; Wiers et al., 2007), or on later and more controlled processes (being related to longer processing time for alcohol cues and/or to a difficulty to disengage attention from them; Schoenmakers et al., 2010). Eye-tracking allows to dissociate, with high temporal/spatial resolution, (1) the initial attentional capture quickly following the appearance of alcohol-related cues (first saccade latency, first fixation direction); (2) the controlled maintenance of attention towards alcohol (dwell time, total number of fixations). Eye-tracking studies showed that AB mostly appears at the late processing stages in subclinical and clinical populations (McAteer et al., 2015, 2018; Monem & Fillmore, 2017), thus questioning its early/automatic nature.

Here, we directly address these three conceptual questions, as we (1) clarify whether AB is stable or affected by motivational states, by comparing recently detoxified patients with SAUD with or without craving in a free viewing eye-tracking task assessing AB; (2) investigate whether under-activating the reflective/control system increases AB (through the reduction of the cognitive resources available to control AB), by combining AB measure with a concurrent cognitive task requesting no, low or high cognitive load; (3) determine the temporal dynamics of AB by dissociating early/automatic and late/controlled processing steps.

2. Methods

2.1. Participants

We recruited thirty patients with SAUD (15 women) who self-reported craving just before starting the experiment ("craving SAUD" who scored higher than zero at a craving VAS, 0 = not at all, to 100 = terribly wanting) and thirty patients with SAUD (10 women) who did not report craving at testing time ("non-craving SAUD", who scored zero at the VAS). All patients fulfilled DSM-5 criteria for SAUD and were tested during their detoxification treatment in three Belgian hospitals. They had all been abstinent for at least 7 days and were free of other psychiatric comorbidities (except tobacco use disorder). We recruited thirty CTL (15 women) through social networks and e-mails. CTL were free of any past/present psychiatric disorder and personal/parental SAUD history. They consumed less than ten standard alcohol units (10gr of pure ethanol per unit) per week and never exceeded three units per day. They scored lower than 8 at the AUDIT (Babor & Robaina, 2016) and refrained from consuming alcohol the day before testing. Exclusion criteria for both groups included polysubstance use disorder and major past/present neurological disorder and/or trauma. They all had normal or lens corrected vision and were fluent in French.

2.2. Procedure

Participants provided written informed consent and were tested individually. They filled out questionnaires, assessing state anxiety (STAI-S) and current alcohol craving (Alcohol Craving Questionnaire Short Form Revised, ACQ-SF-R and VAS), before testing. The computerized experimental task comprised three parts and lasted 20-30 minutes. We re-assessed craving through the VAS after each part.

We performed a standard 9-point eye-gaze calibration at the beginning of each block. Between experimental parts, participants filled out questionnaires measuring psychopathological variables, namely depressive symptoms (BDI-II; Beck et al., 1996), trait anxiety (STAI-T; Bruchon-Schweitzer & Paulhan, 1993) and impulsivity (UPPS-P; Billieux et al., 2012). The study protocol followed the Declaration of Helsinki and was approved by the Ethics Committee of UCLouvain. After the experiment, we debriefed participants and CTL received a financial compensation. This study was not pre-registered.

2.3. Apparatus

Participants seated on a desk chair, facing an eye-tracker camera and an Asus Display Laptop PC with a 17.3-inch FHD screen (resolution 1080x1920; refresh rate 120Hz, placed 60cm away from the eyes). We controlled the presentation of the task and its synchronization with eye-tracking using OpenSesame (Mathôt et al., 2012). We recorded eye movements using an Eye-link Portable Duo (SR Research, Canada; sampling rate 1000Hz; average accuracy range 0.25°-0.5°, gaze tracking range 32° horizontally, 25° vertically).

2.4. Free viewing eye-tracking task

The AB task was replicated from Soleymani et al. (2020). In each trial, participants had first to fixate a central fixation dot appearing on the background screen for at least 100ms. We used this dot as drift check for eye-gaze calibration, and to ensure that participants focused their attention at the center of the screen. Once the eye-tracking device detected the eyes at the center of the screen, a 4x4 matrix replaced the dot for 6000ms. The matrix presented 16 full color 250x250 images of eight alcoholic and eight non-alcoholic beverages without context. The four inner pictures always consisted of two alcohol and two non-alcohol pictures, while we randomized the 12 outer pictures. Participants were asked to freely look at the pictures. To support participants' task engagement, we presented three types of stimuli: bottles, bottles with empty glass, bottles with filled glass. A total of 218 pictures were extracted from the ABPS battery (Pronk et al., 2015), the selected stimuli being culturally relevant for the Belgian population.

2.5. Concurrent auditory cognitive task

In *Level 1,* we presented series of digits orally through headphones and participants had to detect the appearance of a digit target ("5") by mouse-clicking. In *Level 2*, we presented other series of digits orally and participants had to mouse-click each time the sum of the two last digits was 10. A male French voice (Andres et al., 2020) pronounced each digit with the same pace. We used Audacity® software to mark the onset/offset of each digit and then compressed the sampled period in an OGG file. The duration of enunciation and silent periods for each digit was set to 2000ms. In both levels, we presented the series of digits in a continuous way to keep the difficulty level constant.

Participants completed three parts, each containing 54 trials: one presenting solely the free viewing task (i.e., *Baseline*, see Figure 15) and two presenting the free viewing task alongside cognitive tasks of increasing difficulty (i.e., low cognitive load, *Level 1* and high cognitive load, *Level 2*). We always presented the *Baseline* first, followed by *Levels 1* and *2* in counterbalanced order.

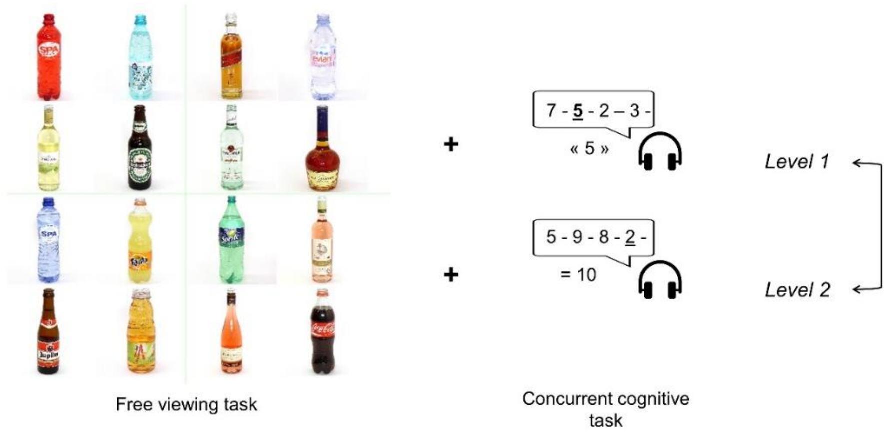

Figure 15. Illustration of a trial from the eye-tracking free viewing task and of the concurrent cognitive task with low (Level 1) and high (Level 2) cognitive load.

2.6. Data analysis

We set our sample size to 30 participants per group based on previous work exploring AB in SAUD (Bollen et al., 2021; den Uyl et al., 2018; Field et al., 2013; Fridrici et al., 2014; Wiers et al., 2016). The power analysis indicated that a total sample size of 66 was required to detect medium (f=0.25) within-between groups interactions (power of 0.95; alpha of 0.05) in repeated-measures ANOVAs, which was fulfilled by our sample size. We defined AOI for the free viewing task as the zone in pixels covered by each image, leading to 16 AOIs per trial. We assessed early AB processes through the *first saccade latency* (i.e., time between the matrix onset and the first saccade towards an alcohol/non-alcohol AOI) and *first visited AOI* (i.e., percentage of trials in which alcohol/non-alcohol AOIs were fixated first) eye-tracking indexes, and late AB processes through *dwell time* (i.e., sum of fixation times on alcohol/non-alcohol AOIs during the whole trial) and *number of visited AOIs* (i.e., number of alcohol/non-alcohol AOIs fixated during the whole trial) eye-tracking indexes. Eyelink algorithms qualified gaze samples as fixations or saccades. For the concurrent task, we assessed performance through behavioral measures: correct responses, false alarms, and delayed responses (i.e., response to the target digit after the onset of the next one).

We performed all statistical analyses using SPSS 27.0. We performed between-group comparisons (independent t-tests; chi-square tests) on demographic, psychopathological and alcohol-related variables. As an estimate of reliability, we computed Cronbach's alpha for the 54 trial-level at baseline. We performed four 3x3x2 ANOVAs on AB indices with GROUP (craving/non-craving/CTL) as between-subjects factor, LEVEL (baseline/1/2) and TYPE (alcohol/non-alcohol) as within-subject factors. We performed three 3x2 ANOVAs on concurrent task's results with GROUP (craving/non-craving/CTL) as between-subjects factor and LEVEL (1/2) as within-subject factor. We conducted Post-Hoc tests with a Bonferroni-corrected p-value of $\alpha_{altered}$=.05/3=0.017. Finally, we performed Pearson's correlations to explore the influence of demographic, psychological and alcohol-related variables on AB magnitude (indexed by dwell time) and on craving at baseline. We calculated difference scores or percentage for AB measures to perform reliability and correlational analyses.

3. Results

3.1. Demographic, psychopathological and alcohol use measures (Table 15)

Table 15. Demographic, psychopathological and alcohol use measures (mean ± standard deviation) and independent samples t-test or chi square test comparing patients with SAUD reporting craving, patients with SAUD reporting no craving and CTL.

	Craving (N=30)	Non-craving (N=30)	CTL (N=30)	Craving vs Non-craving	Craving vs CTL	Non-craving vs CTL
				t or χ^2	*t or* χ^2	*t or* χ^2
Demographic measures						
Sex ratio (M/F)	20/10	15/15	15/15	1.714	1.714	.000
Age	42.90±10.66	48.07±9.35	47.87±10.39	1.996	1.827	.078
Years of education	12.47±2.85	13.07±4.23	16.07±2.83	.644	**4.873 ****	3.192
Psychopathological measures						
BDI-II	11.56±7.03	8.68±8.29	2.93±3.69	1.324	**5.778 ****	**3.449 ***
STAI-S	40.47±15.28	36.12±16.76	28.83±7.56	1.050	**3.737 ****	**2.170 ***
STAI-T	52.24±9.18	45.52±12.5	32.30±11.99	**2.145 ***	**6.617 ****	**4.109 ****
UPPS-P	48.79±8.28	44.39±9.33	37.43±7.51	1.773	**5.274 ****	**3.114 ***
Alcohol use measures						
AUDIT	33.50±5.43	30.75±6.68	3.30±1.70	1.516	**28.532 ****	**21.769 ****
First alcohol use (age)	13.85±3.16	15.72±4.89	15.28±1.89	1.756	**2.092 ***	.454
Doses per week	32.12±24.22	21.90±13.15	0.47±0.43	1.802	**6.833 ****	**8.919 ****
Years of SAUD	13.40±9.70	9.67±8.58	N/A	1.580	N/A	N/A
Previous detoxification	2.28±2.88	3.00±4.21	N/A	.770	N/A	N/A
Days of abstinence	35.50±39.51	39.07±43.86	N/A	.331	N/A	N/A
Craving (VAS)	22.73±23.40	0.00±0.00	2.30±4.84	**5.322 ****	**4.684 ****	**2.601 ***
Craving (ACQ-SF-R)	35.70±14.13	17.97±7.78	18.17±5.07	**6.019 ****	**6.396 ****	.118

* *p*<.050, ** *p*<.001, N/A, not applicable to this group.

Craving and non-craving SAUD groups did not differ except for craving and trait anxiety. Both groups showed less education years and higher alcohol doses per week, AUDIT score, state and trait anxiety, depression and impulsivity than CTL. Craving SAUD also showed earlier age at first consumption and higher craving than CTL.

3.2. Free viewing task (Table 16)

3.2.1. AB reliability

Internal consistency was high for dwell time (α=.976) but low for the number of visited AOIs (α=.385) and the first visited AOI (α=.047) [6].

3.2.2. Early AB stages

First saccade latency. We found a TYPE effect [$F(1,85)=5.842$, $p=.018$, $\eta_p^2=.064$] showing that participants performed their first saccade faster when directed towards alcoholic than non-alcoholic stimuli. We also found a GROUP effect [$F(2,85)=3.120$, $p=.049$, $\eta_p^2=.068$] showing that craving SAUD presented faster first saccades than CTL [$t(58)=2.117$, $p=.039$, $d=.547$]. Other main effects and interactions were inconclusive.

First visited AOI. We found a TYPE effect [$F(1,85)=13.467$, $p<.001$, $\eta_p^2=.137$] showing that participants performed first fixations more frequently towards non-alcoholic than alcoholic stimuli. Other main effects and interactions were inconclusive.

3.2.3. Late AB stages

Dwell Time. We found a TYPE effect [$F(1,85)=18.279$, $p<.001$, $\eta_p^2=.177$] showing longer dwell time for non-alcoholic than alcoholic stimuli (Figure 16). We also found a TYPEXGROUP interaction [$F(2,85)=9.688$, $p<.001$, $\eta_p^2=.186$]: craving SAUD presented longer dwell time on alcohol [$t(58)=4.234$, $p<.001$, $d=1.093$], and shorter dwell time on non-alcohol than non-craving SAUD [$t(58)=3.586$, $p<.001$, $d=.926$]. Moreover, both non-craving SAUD and CTL showed longer dwell time on non-alcohol than alcohol-related stimuli [non-craving: $t(29)=5.635$, $p<.001$, $d=1.029$; CTL: $t(29)=2.775$, $p=.010$,

[6] Internal reliability for first saccade latency could not be calculated as the number of observations was too small when separated per type of stimuli, trial and participant.

d=.507], but this difference was higher in non-craving SAUD than CTL [alcohol: *t*(58)=3.122, *p*=.003, *d*=.806; non-alcohol: *t*(58)=2.826, *p*=.007, *d*=.730]. Other main effects and interactions were inconclusive.

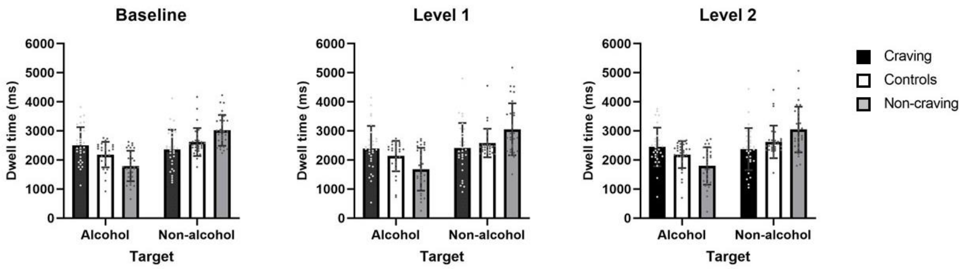

Figure 16. Dwell time observed in patients with SAUD reporting craving, patients with SAUD reporting no craving and CTL in the free viewing task at baseline, level 1 and level 2 for alcohol and non-alcohol stimuli.

Number of visited AOIs. We found a TYPE effect [*F*(1,85)=16.791, *p*<.001, η_p^2=.165] showing a larger number of fixations for non-alcoholic than alcoholic stimuli. We also found a TYPEXGROUP interaction [*F*(2,85)=9.314, *p*<.001, η_p^2=.180]. Both non-craving SAUD and CTL visited fewer alcohol than non-alcohol AOIs [non-craving: *t*(29)=5.882, *p*<.001, *d*=1.074; CTL: *t*(29)=3.115, *p*=.004, *d*=.569]. This difference between stimuli was inconclusive in craving SAUD, as well as group differences regarding alcohol or non-alcohol (all *p*>.050). We also found a LEVEL effect [*F*(2,170)=183.892, *p*<.001, η_p^2=.684] showing that the number of visited AOIs decreased with cognitive load. Other main effects and interactions were inconclusive.

Table 16. AB eye-tracking measures for the three levels of cognitive load (mean ± standard deviation) comparing patients with SAUD reporting craving, patients with SAUD reporting no craving and CTL.

	Craving (N=30)		Non-craving (N=30)		CTL (N=30)	
	Alcohol	Non-alcohol	Alcohol	Non-alcohol	Alcohol	Non-alcohol
First saccade latency (ms)						
Baseline	468±115	467±111	490±120	502±130	507±129	525±139
Level 1	455±125	476±145	482±170	487±166	577±201	619±222
Level 2	462±168	476±157	487±160	510±142	546±290	539±205
First visited AOI (%)						
Baseline	25.73±4.76	27.27±4.58	27.03±3.37	26.87±3.42	25.93±3.80	27.93±3.73
Level 1	26.73±3.22	27.03±3.28	25.07±3.50	28.87±3.57	24.57±4.65	27.80±4.83
Level 2	26.14±3.06	27.59±3.12	25.14±3.55	28.76±3.52	26.07±4.13	27.63±4.13
Dwell time (ms)						
Baseline	2495±631	2355±688	1794±523	3018±531	2184±437	2617±480

Level 1	2387±784	2406±865	1681±735	3054±864	2137±522	2582±489
Level 2	2447±665	2375±723	1796±641	3048±785	2184±463	2622±561
Number of visited AOIs						
Baseline	5.27±1.10	5.23±1.21	4.85±1.13	5.51±0.99	5.49±0.92	5.79±0.76
Level 1	4.28±1.52	4.20±1.63	3.85±1.55	4.46±1.54	4.52±1.40	4.74±1.31
Level 2	3.22±1.53	3.16±1.63	2.56±1.27	3.04±1.48	3.27±1.62	3.41±1.61

3.3. Concurrent cognitive task

Correct responses. We found a LEVEL effect [$F(1,73)=38.380$, $p<.001$, $\eta_p^2=.345$] showing higher rates of correct responses in Level 1 than 2. Other main effects and interactions were inconclusive.

False alarms. We found a LEVEL effect [$F(1,73)=9.880$, $p=.002$, $\eta_p^2=.119$] showing more false alarms in Level 2 than 1. Other main effects and interactions were inconclusive.

Delayed responses. We found a LEVEL effect [$F(1,73)=9.175$, $p=.003$, $\eta_p^2=.112$] showing more delayed responses in Level 2 than 1. Other main effects and interactions were inconclusive.

3.4. Correlations

Dwell Time. In SAUD, we found positive correlations between dwell time at baseline and craving (1) before (VAS: $r=.443$, $p<.001$; ACQ: $r=.546$, $p<.001$) and after (VAS: $r=.486$, $p<.001$) the task. All other correlations in SAUD and CTL were inconclusive.

Craving. In SAUD, we found a negative correlation between craving VAS score at baseline and age ($r=-.289$, $p=.025$). All other correlations in SAUD and CTL were inconclusive.

4. Discussion

Addiction models postulate that AB is a major index of the reflexive/reward system overactivation (Robinson & Berridge, 1993; Wiers et al., 2007), causally involved in SAUD persistence. In the past decade, concurrent models placed greater emphasis on the moderating role of situational factors (e.g., craving, cognitive load) on the links between alcohol use severity and AB (Field et al., 2016; Hofmann et al., 2008). Nevertheless, a theoretical blur persists on the nature and role played by AB in SAUD. We thus experimentally addressed three remaining questions on AB, namely how is it affected by current motivational state and cognitive load, and what is its time course.

First, we unequivocally show the role played by craving in the magnitude and direction of AB, offering experimental support to the theoretical proposal that AB is strongly affected by current motivational state rather than stable. Indeed, craving patients with SAUD spent more time fixating alcohol stimuli than patients without craving, while the reverse was found for non-alcohol stimuli. Moreover, both CTL and non-craving patients showed an avoidance bias for alcohol-related stimuli (i.e., shorter dwell times and smaller number of AOIs fixated for alcohol stimuli), this bias being even stronger in the latter group. These results are in line with recent findings showing an avoidance bias in patients with SAUD reporting low craving and high abstinence motivation (Bollen et al., 2021). Altogether, our findings undermine the proposal of a long-lasting and potentially permanent AB in SAUD, since we could not find any AB among recently detoxified patients when using reliable eye-tracking measures. The opposite AB patterns between the two groups of patients supported the theoretical account that AB is driven by temporary changes in appetitive/aversive motivational states regarding alcohol, and that its stability along the disorder has been overstated (Field et al., 2016). The subjective momentary evaluation of alcohol-related cues (indexed here by craving) determines whether individuals maintain and/or override their gaze on them, resulting in avoidance/approach AB. The model rightly predicts that, in a treatment context (i.e., abstinent patients in clinical setting, highly motivated to avoid alcohol outside the clinic), non-craving patients would present a negative evaluation and aversive state towards alcohol, resulting in avoidance AB, while craving patients would rather show motivational conflict (i.e., craving associated with abstinence motivation), thus not leading to a strong AB towards alcohol. Correlational analyses support this proposal as AB was not associated with any index of SAUD severity except craving.

The concurrent cognitive task supported the proposal that AB relies on an over-activation of the reflexive/reward and is quite independent from the reflective/control system, as AB patterns were not influenced by the extent of cognitive resources available. However, while we checked the increase of cognitive load across conditions (i.e., lower performance in Level 2 than 1), the cognitive resources of the reflective/control system might have been insufficiently saturated to impact the reflexive/reward system and AB, and our sample size might have been insufficient to detect small effect size of cognitive load's impact on AB.

Finally, we demonstrated that AB, regardless of its direction (approach/avoidance), is only underlid by later and controlled attentional stages (i.e., dwell times, number of AOIs fixated). This casts doubt on the postulated automatic/early nature of AB in SAUD (Wiers et al., 2007), already questioned by heterogeneous findings when manipulating stimuli duration in behavioral experiments (Beraha et al., 2018; Vollstadt-Klein et al., 2009). This inconsistency regarding early components of AB might however be explained by the usually low reliability of the related measures. In contrast, our results regarding the late component are in line with eye-tracking studies in subclinical (see Maurage et al., 2020b for a review) and clinical (Bollen et al., 2021) populations, as well as with earlier studies targeting such malleable late components in attentional retraining (Rinck et al., 2018; Schoenmakers et al., 2010). We also showed that patients' performances were not explained by globally impaired perceptive abilities as craving patients presented faster saccadic latency than CTL. We thus highlighted the relevance of eye-tracking measures to investigate the temporal dynamics of AB and we encourage future studies to increase the reliability of early eye-tracking indexes by developing AB tasks specifically exploring the early attentional capture by alcohol-related cues (Bollen et al., 2023).

Our findings should lead researchers and clinicians to reconsider the role of AB in SAUD and the conditions in which ABM programs should be conducted. Some patients with high craving and/or low abstinence motivation might present genuine AB and could thus benefit from attentional training (Rinck et al., 2018). Indeed, since AB is more easily triggered by specific motivational states (i.e., high craving, positive alcohol evaluation), interventions could have stronger effects by administrating attentional training when patients are currently in this state, or by using other interventions directly modifying this state (e.g., mindfulness or visual cognitive interference; Skorka-Brown et al., 2015). However, most recently detoxified patients already avoid alcohol-related cues, raising doubts regarding the usefulness of generalized attention training in this population. Importantly, the increasing accessibility of reliable AB measures by using low-cost eye-tracker or newly developed AB paradigms (Wiechert et al., 2021) helps clinicians to identify patients who will benefit most from attention training. Finally, the strong relationship between AB and craving observed here and previously (Field et al., 2009) highlights the need to identify and target psychological factors triggering craving in SAUD to break the vicious circle between craving, AB and alcohol-seeking behavior, traditionally described as the three pathways to relapse (Milton & Everitt, 2010).

5. Conclusion

We used eye-tracking measures to clarify three theoretical questions on AB in SAUD, namely whether AB is stable, independent of the reflective/control system and early/automatic. We showed that AB is not stable in detoxified patients with SAUD, but is rather determined by the presence of craving, patients with/without craving presenting opposite AB patterns. The absence of craving results in a strong avoidance AB for alcohol-related cues, thus questioning most theoretical frameworks proposing that AB constitutes a central and long-lasting SAUD feature (Robinson & Berridge, 1993). We thus argue, in line with alternative theoretical proposals, that AB rather expresses momentary changes in appetitive/aversive evaluation of alcohol-related cues (Field et al., 2016). We also highlighted that AB is not influenced by increased cognitive load (and might thus be quite independent from reflective/control system's activity) and is mostly related to later and more controlled stages of attentional processing (thus not being related to early/automatic attentional capture).

Chapter 9

Stay focused!
Modulation of AB by inhibitory control in SAUD

Background: Prominent models postulate that AB towards alcohol-related stimuli is a core characteristic of SAUD, playing a key role in its development and persistence. Yet, debates remain whether AB is compulsive and driven automatically or is also partly influenced by controlled and inhibitory processes.

Aims: We administered an eye-tracking avoidance task using a gaze contingency procedure in patients with SAUD to measure their ability to voluntarily inhibit eye movements towards alcohol-related distractors, and to determine whether such inhibition of AB could be affected by craving and by the predictability of the stimuli to inhibit. We also calculated the convergent validity of the task with a classical measure of AB (i.e., VPT combined with eye-tracking), and we finally explored the potential covert attentional shifts (i.e., without eye movement) towards alcohol.

Methods: Patients with SAUD (n=30) and matched CTL (n=30) performed a VPT combined with eye-tracking measures, and two versions (mixed *versus* predictable) of the avoidance task. This task requires to focus on a specified target and measures the break frequency, namely the number of times participants fail to inhibit saccades towards alcoholic, appetitive or non-appetitive distractors.

Results: Patients with SAUD showed an avoidance AB for alcohol-related cues in the VPT, as indexed by eye-tracking measures related to later attentional processing stages (i.e., dwell time and proportion of second fixation). In the mixed version of the avoidance task, we observed higher break frequency in patients with SAUD, regardless of the distractor, indicating a general inhibition impairment. In the predictable version of the avoidance task, where stimuli categories were presented separately, we conversely observed lower break frequency for alcohol in both groups as well as fixational eye movements further away from alcohol in patients with SAUD, suggesting an avoidance AB for alcohol-related stimuli when their appearance was predictable. We found no correlation between tasks, or between AB and craving.

Conclusion: Using two complementary assessments of AB, we show that detoxified patients with SAUD do not present the AB towards alcohol predicted by theoretical models but rather exhibit an avoidance AB. Indeed, patients showed reduced late overt attentional resources dedicated to alcohol-related stimuli, as well as increased inhibitory processes and reduced cover attention (indexed by fixational eye movements) towards them. This coherent pattern of results questions both the theoretical assumption that AB plays a key role in SAUD, and the usefulness of implementing ABM programs in clinical settings.

1. Introduction

SAUD is a key public health concern, being among the most prevalent psychiatric conditions worldwide (Rehm & Shield, 2019) and contributing massively to the global burden of disease and mortality (Rehm et al., 2017). Numerous studies have underlined its damaging consequences on cognitive (Stavro et al., 2013) and cerebral (Bühler & Mann, 2011) functioning. In view of this harmful impact, it is crucial to better understand the key mechanisms responsible for the emergence and persistence of SAUD, notably to develop new interventions reducing the persistently high relapse rates related to this condition.

Alcohol-related AB, reflecting the tendency to orient one's attentional resources towards alcohol-related stimuli, may constitute one such mechanism. AB constitutes an important process in the dominant models of addiction. For example, the incentive sensitization theory (Robinson & Berridge, 1993) posits that repetitive alcohol exposures sensitizes the dopaminergic response in the reflexive/reward system, enhancing the incentive properties of alcohol-related cues. Becoming more salient, these cues hijack attention (generating AB) and guide behaviour toward alcohol consumption. In the same vein, dual-process models (Bechara, 2005; Wiers et al., 2007) suggest that SAUD would rely on altered interactions between two brain systems: the reflective/control system, responsible for high-level functioning and deliberative behaviour, becomes under-activated (through the neurotoxic effects of excessive alcohol consumption, notably on frontal structures) while the reflexive/reward system, involved in the appetitive evaluation of stimuli, becomes sensitized and over-activated (by the repeated reward emerging from alcohol-related cues exposure). This systems' dysregulation results in reduced executive abilities among patients with SAUD (Stavro et al., 2013) and increased attention towards alcohol when confronted with alcohol-related cues, namely AB. Most theoretical frameworks thus assume that AB, indexing the over-activation of the reflexive/reward system, is a central feature of SAUD.

However, the key role of AB in SAUD has been questioned by experimental data, as most studies in recently detoxified patients with SAUD did not document stronger AB compared to healthy CTL (see Bollen et al., 2022 for a review). Some studies even reported an avoidance AB for alcohol-related stimuli in this population (Fridrici et al., 2013; Townshend & Duka, 2007). Among them, a study using more reliable eye-tracking measures showed lower time spent on alcohol-related stimuli and less second fixations (indexing lower reengagement AB) towards these stimuli in a VPT in SAUD (Bollen et al., 2021). These findings question the proposal that the magnitude of AB would be strongly associated with the severity and frequency of alcohol use, as it disregards the key role of the context in which the individual finds him/herself (i.e., drinking or clinical context). Indeed, there is actually a massive gap between the SAUD population described by traditional models (i.e., individuals with current alcohol consumption) and the SAUD population included in most experimental studies (i.e., recently detoxified patients under treatment), which might explain the discrepancy between the pattern of AB expected by models and the one observed in previous findings. In fact, some studies showed that AB in SAUD would be highly affected by current craving or drinking status (Bollen et al., 2021; Field et al., 2013; Sinclair et al., 2016), supporting recent theoretical proposals that AB might be driven by temporary changes in motivational states towards alcohol rather than by long-lasting and stable SAUD-related factors (Field et al., 2016). AB would then reflect the momentary subjective evaluation (positive, negative, ambivalent) of alcohol-related stimuli, hence leading individuals to maintain their attention on them and/or conversely avoid them, resulting in different AB patterns. Most patients tested in previous studies were abstinent and undergoing detoxification treatment. Such states are frequently related to aversive or ambivalent alcohol evaluations, which could explain the inconsistencies across previous studies exploring AB in SAUD without measuring the motivational state towards alcohol at testing time.

A remaining question is whether this modulation of AB by appetitive and/or aversive motivational states is compulsive and driven automatically or whether it requires the recruitment of higher-level functions related to the reflective/control system's activity (e.g., inhibitory control) to direct attention towards stimuli congruent with these states. The two most widely used AB paradigms (i.e., visual probe task and addiction Stroop) do not allow to disentangle the involvement of automatic versus controlled processes in AB modulation. For example, the VPT only requires participants to freely explore alcohol and non-alcohol stimuli without instructions forcing them to control their visual exploration. In the same vein, whereas the addiction Stroop task requires inhibiting a predominant response (i.e., reading the word) in favour of a less automatic one (i.e., naming the colour of the word), this measure does not allow to determine AB direction. Indeed, it was argued that higher Stroop interferences for alcohol-related words could result from either the automatic allocation of attention to the semantic processing of alcohol-related words, or conversely from an attempt to avoid processing these words (Klein, 2007). Moreover, the latter paradigm solely relies on RT to measure AB, known to show very poor reliability (Ataya et al., 2012).

An avoidance task using a gaze contingency procedure was recently developed to further investigate the possibility of direct control of reflective abilities on early saccadic movements toward alcohol-related cues, by measuring people's ability to inhibit orientation of attention towards alcohol-related distractors when focusing on a specified target (Qureshi et al., 2019; Wilcockson and Pothos, 2015). In this eye-tracking paradigm, participants receive explicit instructions to deliberately inhibit AB (i.e., the production of early saccadic movements toward alcohol-related stimuli), thus testing the ability of reflective abilities to modulate alcohol-related AB, and hence clarifying the automatic or controlled nature of AB. When applied to subclinical populations, this paradigm showed that heavy and problem drinkers were more likely to break their central focus and produce saccadic eye movements (termed break frequency) towards alcohol-related distractors compared to neutral non-appetitive distractors (Qureshi et al., 2019; Wilcockson et al., 2015). Qureshi et al. (2019) further demonstrated that these findings may be partly attributable to the appetitive content of the stimuli used, as this inability to avoid the automatic processing of stimuli was generalized towards other appetitive stimuli (i.e., non-alcoholic beverages). They also showed that higher break frequency for appetitive stimuli was only observed when stimuli appeared in peripheral vision (as opposed to stimuli adjacent to the target), which they explained by the impossibility to recruit covert attention to process remote stimuli. However, one may argue that participants would exhibit more random than content-specific AB when they are unable to attentionally process and categorize the distractors.

While the use of this gaze contingency paradigm is promising, it still needs to be tested and validated in a clinical population of patients with SAUD, notably by comparing the break frequency with reliable and more classical measures of AB (e.g., dwell time towards alcohol in the VPT). While the VPT and the avoidance task both aim to assess alcohol-related AB, they explore it under different conditions (free exploration *versus* forced avoidance), and might thus tap into distinct attentional processes (attentional monitoring and controlled processes *versus* inhibitory processes). Hence, the association between those AB measures remains to be determined. Finally, the potential recruitment of covert attention to process nearby *vs.* remote distractors could be experimentally investigated through innovative eye-tracking measures. Indeed, eyes are in constant motion even when the gaze is maintained on a fixated point, resulting in micro eye movements like tremors, drifts and microsaccades (Engbert, 2006; Hafed et al., 2015). Among those fixational eye movements, microsaccades direction has been widely claimed to reflect shifts in covert attention (Laubrock et al., 2007; Lv et al., 2022; Yuval-Greenberg et al., 2014).

The present study aims to better apprehend the inhibitory and controlled processes of AB in SAUD by using the paradigm developed by Qureshi et al. (2019) in a population of recently-detoxified patients with SAUD. Moreover, we explored the convergent validity of this novel paradigm with the VPT combined with eye-tracking measures, since both paradigms investigate distinct but complementary processes of AB. We also aimed to determine the impact of current motivational state (i.e., subjective craving) on those different AB measures and, since the potential impossibility to covertly process remote distractors, whether break frequency could be affected by the predictability of the type of stimuli presented. To do so, we used a predictable version of this avoidance task in which we separated the trials in three blocks according to the type of distractors (alcohol-related, appetitive, non-appetitive), and informed participants which type of distractors will appear. Finally, we conducted exploratory analyses to track putative covert AB that we measured by tracking gaze position of fixational eye movements (i.e., when participants maintained their gaze on the target).

Regarding the VPT, we expected to replicate our previous findings (Bollen et al., 2021) by showing an avoidance AB for alcohol-related stimuli in patients with SAUD, this AB appearing on later processing stages (indexed by dwell time and second fixation). For the avoidance task, we hypothesized that patients with SAUD would present higher mean break frequency than CTL regardless of the stimulus type, as SAUD is related with executive control deficits. In line with our first hypothesis, we expected patients with SAUD to also present an avoidance AB for alcohol-related stimuli in this task in overt (indexed by lower break frequency for alcohol-related distractors) and covert AB measurements (indexed by fixational eye movements). Finally, we expected mean break frequency towards alcohol to increase as a function of reported craving at tested time.

2. Methods

2.1. Participants

We recruited thirty inpatients (17 women, 13 men) fulfilling DSM-5 criteria for SAUD during their detoxification treatment in Belgian hospital facilities (Psychiatric Hospital of Beau Vallon in Namur, Saint-Thérèse Hospital in Charleroi). They had all abstained from alcohol for at least 7 days, were free of other psychiatric comorbidities (except nicotine use disorder) and were not involved in any attentional training program. We matched patients for age and gender with a group of 30 CTL (16 women, 14 men). CTL were free of any past or present psychiatric disorder as well as any personal or parental history of SAUD. They consumed less than ten alcohol units (i.e., one unit corresponding to 10gr of pure ethanol in Belgium) per week and never exceeded three units per day. They scored lower than the cut-off score of 8 at the AUDIT (Babor et al., 2016). Exclusion criteria for both groups included polysubstance use disorder and major past or present neurological disorder and/or trauma. They all had normal or lens corrected vision and were fluent French speakers.

2.2. Procedure

Participants provided written informed consent to take part in the study, were not aware of the hypotheses tested and were tested individually in a quiet room. They first completed questionnaires assessing state anxiety (State Anxiety Inventory, STAI-A; Bruchon-Schweitzer & Paulhan, 1993) and current alcohol craving [Alcohol Craving Questionnaire Short Form Revised, ACQ-SF-R and VAS: "Indicate how much you want to drink alcohol right now (from 0 = not at all, to 100 = strong desire)"], before performing the experimental tasks. These tasks were a computerized VPT and two versions of an avoidance task using a gaze contingency procedure, each lasting about 15 minutes. Prior to each experimental task, we calibrated the eye-tracker to the screen using a built-in 9-point protocol. Between tasks, participants completed questionnaires assessing depressive symptoms (Beck Depression Inventory, BDI-II; Beck et al., 1998), trait anxiety (Trait Anxiety Inventory, STAI-B; Bruchon-Schweitzer & Paulhan, 1993), and impulsivity (UPPS-P Impulsive Behavior Scale; Billieux et al., 2012) to control for the influence of psychopathological symptoms. The study protocol was performed in accordance with the ethical standards established by the Declaration of Helsinki and was approved by the Ethics Committee of the Saint-Luc-UCLouvain Clinics. At the end of the experiment, participants were debriefed and CTL received financial compensation.

2.3. Apparatus

Participants seated 60cm away from a laptop, facing an eye-tracker camera and an Asus Display Laptop PC equipped with a 17.3-inch FHD screen (resolution 1080 x 1920p; refresh rate 120Hz). We controlled the presentation of the experimental tasks and their synchronization with the eye-tracking using OpenSesame (Mathôt et al., 2012) and Experiment Builder (SR Research Ltd.). We recorded eye movements using an Eye-link Portable Duo remote mode eye-tracker (SR Research, Canada; sampling rate of 1000 Hz; average accuracy range 0.25° to 0.5°, gaze tracking range of 32° horizontally and 25° vertically). We performed a 9-point calibration of participant's eye position at the beginning of each block of the tasks.

2.4. VPT

At the start of each trial, a central fixation dot appeared on a black background and participants had to fixate their gaze on it. The fixation dot was used as a drift check to confirm the reliability of the eye-gaze calibration, and ensure that participants initially focused their visual attention at the centre of the screen in each trial. Once the eyes were detected at the centre of the screen by the eye-tracking device, the fixation dot was removed and directly followed by the onset of two pictures (i.e., alcoholic beverage picture and soft drink beverage picture). They were displayed in a counterbalanced order on the left and right side of the computer screen for 2000ms and then replaced by a probe (i.e., a white arrow on a black background, pointing up or down) appearing at the location previously occupied by one of the pictures. Participants were instructed to respond to the orientation of the probe by pressing the "up" or "down" key on the keyboard, as quickly and correctly as possible. Visual probes replaced the two types of pictures with equal frequency. Each trial was separated by an inter-trial interval of random duration (between 500 and 1500ms). The task contained 84 trials in total, including four practice trials that were excluded from the analyses.

Twenty pairs of alcoholic beverage pictures (e.g., bottle of vodka, can of beer) and matched non-alcoholic beverage pictures (e.g., bottle of water, soft drink can) without context were extracted from the validated Alcohol Beverage Picture Set battery (ABPS; Pronk et al., 2015). The visible brands and writings of the beverage were blurred to avoid reading. Each picture pair was matched on the following perceptual features: colour, size (444x444 pixels or 10.7x10.7° angle), brightness, and salience using the SHINE toolbox (Willenbockel et al., 2010). We presented each pair of stimuli four times during the task (2 stimuli position x 2 probe position).

We assessed performance through behavioural (RT) and eye-tracking measures (first fixation direction, first fixation duration, second fixation direction, dwell time). The RT for probes replacing alcohol pictures compared to the ones replacing non-alcohol pictures are the commonly used AB index. The first fixation direction indicates the stimulus that was first fixated during each trial (i.e., initial attentional capture). The first fixation duration indicates the duration of the first fixation made on a stimulus (i.e., persistence of attentional focus). The second fixation direction indicates how frequently the participant fixated the second stimulus after visiting the first one (i.e., attention switch). The dwell time is the sum of fixation times on each stimulus during the whole trial. We qualified gaze samples as fixations or saccades according to the standard Eyelink algorithms.

2.5. Avoidance task

We replicated the task from Qureshi et al. (2019), who used three categories of alcoholic appetitive, non-alcoholic appetitive, and non-alcoholic non-appetitive visual cues. Participants received instructions to maintain their gaze on a fixation target and ignore the distractor stimuli. The target and distractor were randomly presented within one of the nine regions on the screen. Half of the trials presented a nearby distractor (i.e., the distance between each stimuli centre varied between 209 and 385 pixels), and the other half a remote distractor (i.e., distance from 514 to 784 pixels). For each trial, the distractor appeared on the screen only after participants gazed at the target for a set interval of 1000ms. If participants performed a saccade away from the target, the distractor disappeared and only reappeared when they returned their gaze to the fixation target for 10ms. For each trial, the fixation target was displayed for 5000ms, the maximum onscreen time for the distractor being 4000ms.

We used 90 images as distractor stimuli, with 30 non-alcoholic appetitive stimuli, 30 alcoholic appetitive stimuli and 30 non-appetitive stimuli. All distractor stimuli were equivalent in size (225×225 pixels) and the resolution of the computer screen was set to 1280x1024 to use the same visual angle than Qureshi et al. (2019). They were matched on valence, arousal, angles of objects, luminance and colour. Pictures of alcoholic and non-alcoholic beverages were extracted from the ABPS (Pronk et al., 2015) and were matched with non-appetitive products (e.g., fabric softener, cleaning items) from Qureshi et al. (2019).

We presented 91 trials (30 per category of distractors and 1 initial blank distractor) in each version of the task. In the mixed version, we randomized the distractor stimuli to provide a strict replication of Qureshi et al. (2019). In the predictable version, we dissociated trials based on the distractor type and presented them sequentially (each block presented in a randomized order the 30 distractor stimuli from the same category). We informed participants about the distractor type before starting each block. We calculated the mean number of times that participants performed a saccade outside the target area and directed towards the distractor stimuli and took it as the dependent variable of break frequency.

2.6. Data reduction and statistical analyses

We performed a data reduction procedure for RT for the VPT. Before the analysis, we removed trials with incorrect responses (0.039% of trials) and with RT higher than 2000ms (0.003% of trials). No trial with RT lower than 200ms was recorded. We performed all statistical analyses using the SPSS software package (version 27.0). We performed between-group comparisons (i.e., independent t-tests) on demographic and psychopathological characteristics, as well as on alcohol consumption variables. For the VPT, we indexed the internal consistency of the task by computing Cronbach's alpha for the 20 pairs of pictures on all AB measures. We then performed repeated-measures analyses of variance (ANOVAs) on behavioural (RT) and eye-tracking (First fixation direction, First fixation duration, Second fixation direction, Dwell time) indices with GROUP (SAUD, CTL) as between-subjects factor and TYPE (Alcohol, Non-alcohol) as within-subjects factor. For RT, the TYPE factor encompasses, for each picture category, the trials in which the probe appeared at the same location as these pictures (e.g., all trials in which the arrow replaced the alcohol-related stimuli for "Alcohol" type). For the avoidance task, we computed Cronbach's alpha for the 90 trials on the mean break frequency for each version of the task and each stimuli type. we performed an ANOVA on the proportion of saccades performed towards the distractor stimuli (Break frequency) with GROUP (SAUD, CTL) as between-subjects factor, TYPE (Alcoholic, Non-alcoholic, Non-appetitive), DISTANCE (Nearby, Remote) and TASK (Mixed, Predictable) as within-subject factors. We conducted Post Hoc tests (independent samples t-tests) on stimuli types and performed Pearson's correlations to explore the convergent validity of the two AB tasks and their association with craving.

For our exploratory analyses on fixational eye movements, we split the total time presentation of distractors (5000ms) into 50ms bins for each trial and then calculated the distance (in pixels) between gaze position and target centre in each bin (positive values indexed fixational eye movements directed towards distractor, negative value indexed fixational eye movements directed away from distractor). We excluded trials in which gaze position was located out of the target by removing distances higher than target radius. For each remaining trial, we centred our measures on the distance between eye position and target centre 100ms before distractor onset. We performed independent and paired samples t-tests on each bin to explore the effects of DISTANCE (Nearby, Remote), TYPE (Alcohol, Non-alcoholic, Non-appetitive) and GROUP (SAUD, CTL). In these exploratory analyses, we used a more restrictive p-value threshold (.010) and reported significant differences only when they constituted a coherent pattern occurring in minimum five consecutive bins.

3. Results

3.1. Demographic, psychological and alcohol-related measures (Table 17)

As expected, patients with SAUD showed higher AUDIT scores than CTL [$t(51)=18.886$, $p<.001$, $d=5.234$]. They also showed higher scores of depression [$t(51)=6.490$, $p<.001$, $d=1.799$], trait anxiety [$t(52)=5.904$, $p<.001$, $d=1.617$] and impulsivity [$t(50)=3.064$, $p=.004$, $d=.855$]. Groups did not differ regarding age, state anxiety and craving (assessed through ACQ or VAS; p>.050).

Table 17. Demographic, psychological and alcohol-related measures (mean ± standard deviation) of patients with SAUD and CTL.

	SAUD (N=30)	CTL (N=30)
Demographic measures		
Gender ratio (women/men)	17/13	16/14
Age ^{ns}	47.23±9.63	44.07±11.71
Psychopathological measures		
Beck Depression Inventory ***	9.54±4.86	2.47±3.05
State Anxiety Inventory ^{ns}	34.38±10.36	30.83±10.36
Trait Anxiety Inventory ***	51.30±10.18	35.23±9.74
Impulsivity **	45.30±9.19	38.72±6.26
Alcohol consumption measures		
AUDIT ***	28.70±7.07	3.33±1.84
Craving (VAS) ^{ns}	7.83±21.92	4.50±11.68
Craving (Alcohol Craving Questionnaire) ^{ns}	21.75±9.53	20.63±8.79
MINI	7.93±1.93	N/A
SAUD duration (in years)	9.85±9.28	N/A
Previous detoxification stays	1.68±2.20	N/A

Note: ^{ns} non-significant; * p<.05; ** p<.01; *** p<.001; N/A, not applicable to this group.

3.2. VPT

3.2.1. Reliability estimates

Internal consistency was low for RT (α=.517), first fixation direction (α=.221) and duration (α=.507) measures, under the 0.70 cut-off score of acceptable internal reliability (Kline, 2000). Conversely, it was excellent for dwell time (α=.981) and both indices of second fixation (alcohol: α=.967; non-alcohol: α=.906) measures.

3.2.2. AB measures (Table 18)

RT. We found a main effect of GROUP [$F(1,58)=12.357$, $p<.001$, $\eta_p^2=.176$], showing longer RT for SAUD compared to CTL. We found a main effect of TYPE [$F(1,58)=4.234$, $p=.044$, $\eta_p^2=.068$], showing faster RT for alcohol compared to non-alcohol. The TYPEXGROUP interaction was inconclusive ($p=.670$).

First fixation direction. Main effects of TYPE (*p*=.456), GROUP (*p*=.583) and their interaction (*p*=.385) were inconclusive.

First fixation duration. Main effects of TYPE (*p*=.073), GROUP (*p*=.087) and their interaction (*p*=.578) were inconclusive.

Table 18. Behavioral and eye-tracking indexes (mean ± standard deviation) for the visual probe task in patients with severe alcohol use disorder (SAUD) and control participants (CTL).

	SAUD (N=30)	CTL (N=30)
Reaction time (ms)		
Alcohol	756±211	591±129
Non-alcohol	757±223	596±138
First fixation direction (%)		
Alcohol	48.25±7.00	47.82±5.65
Non-alcohol	46.19±8.02	47.98±6.38
First fixation duration (ms)		
Alcohol	261±73	240±48
Non-alcohol	280±81	250±55
Second fixation direction (in %)		
Alcohol	54.62±33.23	87.54±13.73
Non-alcohol	76.69±29.37	87.54±15.61
Dwell time (ms)		
Alcohol	398±238	525±175
Non-alcohol	700±409	611±215

Second fixation direction. We found a main effect of TYPE [$F(1,58)=11.534$, $p=.001$, $\eta_p^2=.166$], showing a higher proportion of second fixations for non-alcohol compared to alcohol. We also found a main effect of GROUP [$F(1,58)=16.274$, $p<.001$, $\eta_p^2=.219$], showing that CTL performed a second fixation more frequently than SAUD. We found a TYPEXGROUP interaction [$F(1,58)=11.530$, $p=.001$, $\eta_p^2=.166$] (Figure 17a). SAUD less frequently performed a second fixation towards alcohol after a first fixation on non-alcohol compared to CTL [$t(58)=5.015$, $p<.001$, $d=1.295$], while groups did not differ regarding the second fixation towards non-alcohol (*p*=.079). Moreover, SAUD performed a higher percentage of second fixations towards non-alcohol than alcohol [$t(29)=3.601$, $p=.001$, $d=.657$] while this difference was not evident in CTL (*p*=.999).

Dwell Time. We found a main effect of TYPE [$F(1,58)=14.133$, $p<.001$, $\eta_p^2=.196$], showing longer dwell times for non-alcohol than alcohol. We found a significant TypeXGroup interaction [$F(1,58)=4.430$, $p=.040$, $\eta_p^2=.071$] (Figure 17b). SAUD presented shorter dwell times on alcohol than CTL [$t(58)=2.362$, $p=.022$, $d=.610$], while groups did not differ regarding dwell times on non-alcohol ($p=.292$). Moreover, SAUD showed shorter dwell times on alcohol compared to non-alcohol [$t(29)=3.204$, $p=.003$, $d=.585$], while this difference was not evident in CTL ($p=.049$). Main effect of Group was inconclusive ($p=.698$).

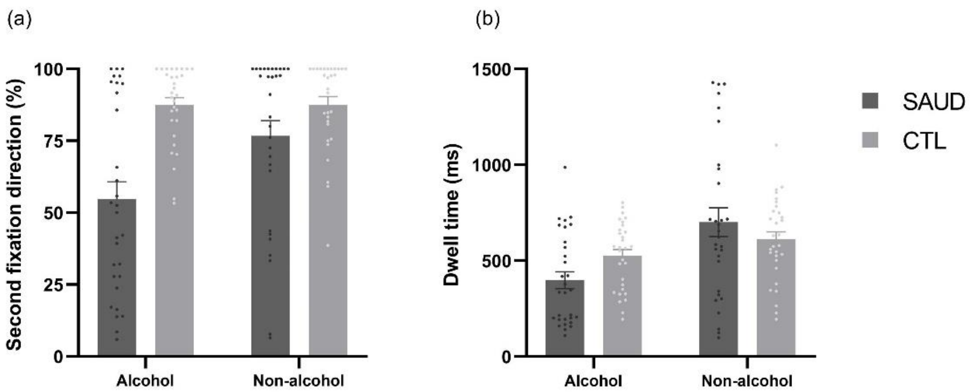

Figure 17. Mean (SEM) comparison of (a) proportion of second fixations and (b) dwell times for alcohol and non-alcohol stimuli in detoxified patients with SAUD and CTL in the VPT.

3.3. Avoidance task

3.3.1. Reliability estimates

Internal consistency was high for break frequency towards alcoholic (mixed task: α=.930; predictable task: α=.876), non-alcoholic (mixed task: α=.930; predictable task: α=.891) and non-appetitive (mixed task: α=.936; predictable task: α=.934) distractors.

3.3.2. Overt attention – Break frequency (Table 19)

Mixed avoidance task. We found a main effect of Group [$F(1,58)=4.140$, $p=.046$, $\eta_p^2=.067$], showing higher mean break frequency in SAUD compared to CTL (Figure 18). We also found a main effect of Distance [$F(1,58)=38.331$, $p<.001$, $\eta_p^2=.398$], showing higher mean break frequency for nearby distractors compared to remote ones. Main effects of Type and interactions were inconclusive (all $p>.050$).

Predictable avoidance task. We found a main effect of DISTANCE [$F(1,53)=41.011$, $p<.001$, $\eta_p^2=.436$], showing higher mean break frequency for nearby distractors compared to remote ones. We also found a main effect of TYPE [$F(2,106)=7.621$, $p<.001$, $\eta_p^2=.126$], showing lower mean break frequency for alcoholic stimuli compared to non-alcoholic [$t(55)=2.207$, $p=.032$, $d=295$] and non-appetitive stimuli [$t(55)=3.966$, $p<.001$, $d=.530$] (Figure 18). Main effects of GROUP and interactions were inconclusive (all $p>.050$).

Table 19. Break frequency (mean ± standard deviation) for the mixed and separated blocks of the gaze contingency paradigm in patients with severe alcohol use disorder (SAUD) and control participants (CTL).

	SAUD (N=30)		CTL (N=30)	
	Close	Far	Close	Far
Mixed block				
Alcohol	0.56±0.61	0.34±0.50	0.32±0.36	0.14±0.16
Non-alcohol	0.62±0.76	0.27±0.34	0.34±0.35	0.12±0.18
Non-appetitive	0.64±0.75	0.33±0.44	0.38±0.37	0.15±0.21
Separated block				
Alcohol	0.36±0.40	0.20±0.25	0.27±0.30	0.09±0.13
Non-alcohol	0.51±0.50	0.23±0.23	0.28±0.25	0.13±0.20
Non-appetitive	0.57±0.63	0.32±0.41	0.35±0.36	0.16±0.23

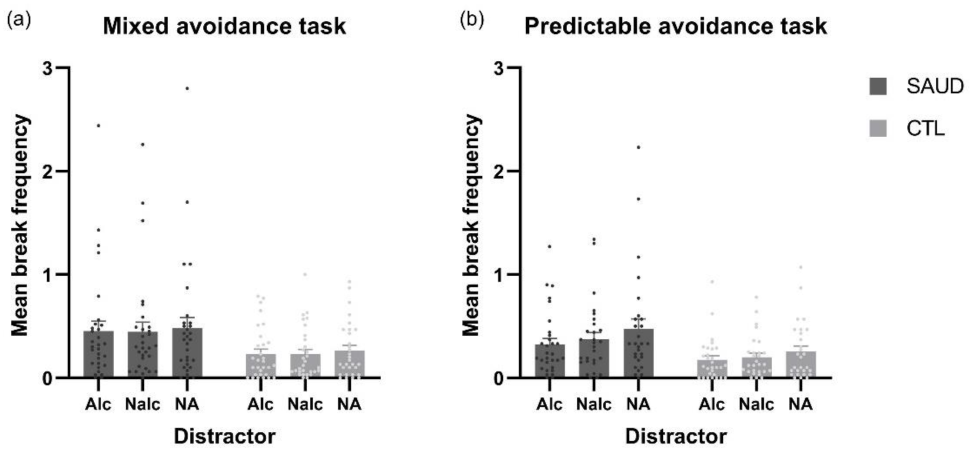

Figure 18. Mean (SEM) comparison of the number of break frequencies per trial in (a) the mixed and (b) predictable versions of the avoidance task for alcohol (Alc), non-alcohol (Nalc) and non-appetitive (NA) distractors in detoxified patients with SAUD and CTL.

3.3.3. Covert attention – Fixational eye movements

Mixed avoidance task. We found a DISTANCE effect, showing that fixational eye movements were positioned closer to nearby than remote distractors, from 200 to 500ms after distractor onset (6 consecutive 50ms bins with $p<.01$; Figure 19).

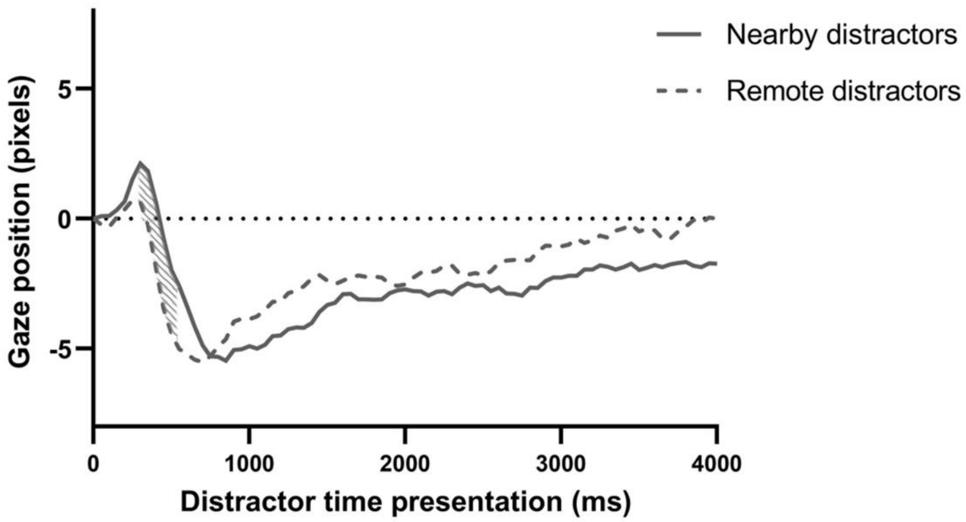

Figure 19. Gaze position of fixational eye movements (centred distance in pixels from target centre) in the mixed version of the avoidance task as a function of the time bins after distractor onset (1 bin = 50ms) with significant differences between nearby and remote distractors in grey stripes.

Predictable avoidance task. We found a DISTANCE effect, showing that fixational eye movements were positioned closer to nearby than remote distractors, from 250ms to 650ms after distractor onset (8 bins with $p<.01$). When focusing on nearby distractors, we showed that fixational eye movements of patients with SAUD were positioned farther away from alcoholic distractors compared to non-appetitive distractors, from 2750 to 3000ms (5 bins) and from 3050ms to 3300ms (5 bins) and compared to non-alcoholic distractors, from 3700ms to 3950ms (5 bins; Figure 20).

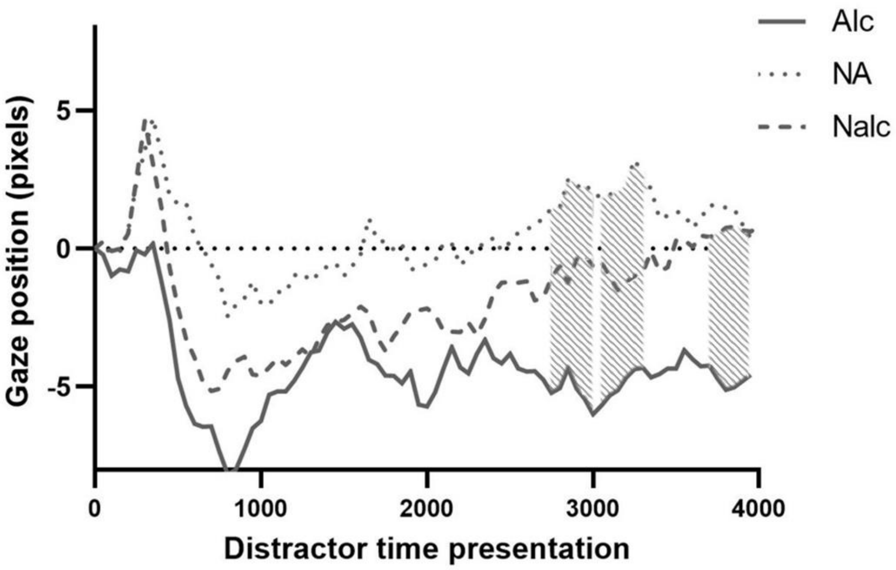

Figure 20. Gaze position of fixational eye movements (centred distance in pixels from target centre) in patients with SAUD in the predictable version of the avoidance task, as a function of the time bins after distractor onset (1 bin=50ms) with significant differences between alcoholic (Alc) and non-appetitive (NA) distractors in grey stripes.

3.4. Correlational analyses

3.4.1. Convergent validity

Dwell time AB score in the VPT did not correlate with the mean break frequency towards alcohol in the mixed (*r*=.165, *p*=.216) and predictable (*r*=.227, *p*=.089) versions of the avoidance task.

3.4.2. AB - Craving

Craving (assessed through VAS and ACQ) did not correlate with the dwell time AB score [VAS: *r*=.200, *p*=.126; ACQ: *r*=.082, *p*=.531] in the VPT or the mean break frequency towards alcohol in the mixed version of the avoidance task [VAS: *r*=.054, *p*=.681; ACQ: *r*=.100, *p*=.448]. It did correlate with mean break frequency towards alcohol in the predictable version of the avoidance task when assessed through ACQ [*r*=.265, *p*=.042] but not VAS [*r*=.240, *p*=.067].

4. Discussion

Dominant models traditionally considered alcohol-related AB as a core characteristic of SAUD, being a key contributor in its emergence and persistence (Robinson & Berridge, 1993; Wiers et al., 2007). However, little is known about the automatic and/or controlled processes underlying AB. Capitalizing on an avoidance task using a gaze contingency procedure, our first aim was to investigate the compulsive *versus* reflective nature of AB (regardless of its direction) by exploring how inhibitory control might play a role in its occurrence in detoxified patients with SAUD. Going a step further, we manipulated the expectancy of stimuli type by presenting trials with alcoholic, non-alcoholic and non-appetitive stimuli either in a randomized (i.e., mixed version) or sequential (i.e., predictable version) order. Second, we determined the convergent validity of this novel AB paradigm compared to the traditional VPT combined with reliable eye-tracking measures. Finally, we explored how motivational state (i.e., current craving) could impact AB magnitude.

In the mixed version of the avoidance task, patients with SAUD showed more difficulty than CTL to maintain focus on the target and inhibit eye movements towards distractors (as indexed by higher mean break frequency). These findings were predictable in view of the theoretical assumptions made by dominant models regarding the under-activation of the reflective/control system and the resulting self-regulation deficit in patients with SAUD (Wiers et al., 2007; Bechara, 2005), but also given the large number of previous studies showing impaired executive control in this population (Smith et al., 2014; Stavro et al., 2013; Wilcox et al., 2014). The avoidance task thus provides a new and reliable measure to further investigate (oculo-)motor inhibition in SAUD and go beyond the pure cognitive aspect of inhibitory control (Quoilin et al., 2018). Importantly, this difficulty to inhibit eye movements was not increased by the exposure to alcoholic or appetitive stimuli but was rather generalized to all type of distractors, suggesting an absence of specific AB towards alcohol. There is a controversy on that matter, some previous studies showing higher neuronal activity and more pronounced inhibitory failures in patients with SAUD and heavy drinkers when alcohol-related stimuli are presented compared to neutral ones (Czapla et al., 2017; Petit et al., 2012; Stein et al., 2018; Weafer & Fillmore, 2012b) while other showed no stimuli-specific differences in response inhibition (Mainz et al., 2012; Nederkoorn et al., 2009). A recent meta-analysis nevertheless demonstrates that exposure to alcohol-related cues prompts small but robust impairments in inhibitory control (Jones et al., 2018b). However, cue exposure might have been restrained in the present study by the task instructions (i.e., maintain focus on the target), the distractors' appearance in peripheral vision in half of the trials (known to be more difficult to process through covert attention; Thorpe et al., 2001), and their disappearance once participants break the focus on the target.

In contrast, we found an effect of the type of stimuli in the predictable version of the task, in which participants were explicitly told, before starting each block, which type of distractors they will be exposed to. We showed that all participants were less likely to break their focus and attend to alcoholic distractors compared non-alcoholic and non-appetitive ones. These findings are opposite to previous studies using the avoidance task in subclinical populations (Qureshi et al., 2019; Wilcockson et al., 2015), as they found higher break frequencies towards alcoholic and non-alcoholic appetitive stimuli among heavy and problem drinkers. In contrast, we showed that both CTL and patients with SAUD deliberately avoided to process alcohol-related stimuli once aware that they will be exclusively exposed to these stimuli. These findings are in line with our results from the VPT, showing the presence of an avoidance AB for alcohol at later and more controlled processing stages of attention. Indeed, we observed shorter dwell times towards alcohol compared to non-alcohol stimuli in the VPT, especially among patients with SAUD. Moreover, patients with SAUD were also less likely to direct their gaze towards alcohol-related stimuli after a first fixation on the non-alcohol stimuli. In contrast, this avoidance AB was not observed at the earlier and automatic processing stages (as indexed by first saccadic latency and first fixation direction measures). However, these measures were characterized by a very low reliability in the present study and previous ones (Bollen et al., 2020; 2021). Low reliability was also observed for RT measures, whose results went in the exact opposite direction than much more reliable eye-tracking indexes. Hence, those behavioural measures are unreliable and could thus be misleading.

We thus perfectly replicate our previous findings regarding AB in SAUD (Bollen et al., 2021) by showing the presence of an avoidance AB for alcohol in SAUD through eye-tracking indexes of the later processes of AB (i.e., dwell time and second fixation direction). Although these results are in contradiction with the theoretical assumption made by dominant models (Robinson & Berridge, 1993; Franken, 2003) that the magnitude of AB would be strongly associated with the severity and frequency of alcohol use, they are not counterintuitive since the presence of an avoidance AB pattern in detoxified patients under treatment could appear as a functional and adaptive process. Indeed, spontaneously avoiding to process alcohol-related stimuli might help them to regulate the negative affect associated with the exposure to those stimuli, and would be even more easy to implement in clinical contexts in which the exposure to alcohol-related stimuli would not result in subsequent alcohol use. Hence, we provide further experimental support to the recent proposal (Field et al., 2016) that approach alcohol-related AB is not a long-lasting and stable feature of SAUD, as postulated by theoretical models. Instead, they propose that AB rather fluctuates alongside subjective evaluations of alcohol-related cues, thus resulting in an avoidance AB in detoxified patients under treatment, usually characterized by negative (or ambivalent) evaluation of alcohol, low craving (only 5 patients reported craving higher than zero in the present study) and high motivation to abstain (Field et al., 2016). While this effect was stronger in patients with SAUD than CTL in the VPT, we did not find such significant group difference in the predictable version of the avoidance task, potentially because the generalized higher break frequency in SAUD (due to massive inhibitory difficulties) masked this subtler effect (i.e., patients with SAUD being more likely to inhibit break frequency towards alcohol than other distractors). Altogether, we demonstrated, by the use of a VPT and a predictable version of the avoidance task, that detoxified patients do not present a strong AB towards alcohol but rather exercise cognitive control over the visual exploration and processing of these stimuli, resulting in an avoidance AB. Nevertheless, we did not find significant correlations between the most reliable indexes of those tasks, most probably because their opposite instructions actually tapped into drastically distinct processes of AB. On one hand, the VPT invites participants to freely explore the presented stimuli, therefore measuring the spontaneous and natural trend of the reflexive/reward system when exposed to alcohol-related stimuli. On the other hand, the avoidance task explicitly asks participants to refrain from looking the appearing stimuli, thus assessing their ability to control this trend through inhibitory processes. Since the various components of AB might be underpinned by distinct and uncorrelated mechanisms, AB assessment might require the use of complementary tasks to get a comprehensive understanding of this multi-dimensional construct.

In contrast with Qureshi et al. (2019), we observed higher break frequencies for nearby compared to remote distractors in both versions of the task. In their study, they argued that inhibitory processes of AB were affected by the ability to covertly process stimuli, and that higher break frequencies for remote stimuli might be explained by the impossibility to recruit covert attention to process these stimuli without eye movements. Although central vision is indeed much more suited to fine discrimination than peripheral vision, their latter argument is countered by many studies showing that peripheral vision still allows coarse discrimination such as object categorization, even at eccentricities up to 60-70° (Boucart et al., 2013; D'Hondt et al., 2016; Thorpe et al., 2001). Moreover, our opposite findings rather suggest that stimuli which are easier to covertly process and categorize (i.e., nearly located stimuli) might be a further incentive to be distracted by those stimuli and thus direct gaze towards them. Finally, the post-hoc interpretation proposed by Qureshi et al. (2019) remained speculative, as they did not propose covert attention measures in their study. Going a step further, we directly explored covert attention by measuring the gaze position of fixational eye movements when participants maintained their focus on the target object (Engbert, 2006; Laubrock et al., 2007; Lv et al., 2022). First, we showed that participants actually recruit covert attention to process nearly located distractors in both versions of the task, as indexed by fixational eye movements getting closer to those stimuli compared to remote ones shortly after their onset. Second, we showed that fixational eye movements of patients with SAUD were positioned further away from alcoholic distractors compared to non-appetitive distractors throughout the whole trial period in the predictable version of the task. In line with results regarding overt attention (i.e., break frequency in the predictable avoidance task, dwell time and second fixation direction in the VPT), these exploratory findings suggest that the avoidance AB of alcohol-related stimuli might also be indexed by covert attention. Future works should deepen these exploratory results by using paradigms directly dedicated to covert attention measurements, such as the pupil light response while manipulating the luminance of stimuli or area on the screen (e.g., Mathôt & Van der Stigchel, 2015; Salvaggio et al., 2022; Strauch et al., 2022). Indeed, the pupil size is not only modulated by the actual amount of light entering the eye but also reacts to the luminance of stimuli presented in peripheral vision, therefore revealing the locus of covert attention. Using pupillometry, in addition to spatial eye movements research, could thus allow to better appraise our understanding of covert attentional shifts in alcohol-related AB, especially in ambivalent drinkers that might attempt to override eye movements towards alcohol.

Importantly, this avoidance AB appears to be specific to the alcohol-related content of the stimuli and does not generalize to other appetitive stimuli, since it was not observed for the non-alcoholic appetitive beverages used in our tasks. This is in line with previous findings showing an avoidance AB for alcohol-related stimuli in patients with SAUD compared to non-alcoholic appetitive stimuli (Bollen et al., 2021). However, it contrasts with Qureshi et al. (2019), who showed an AB generalized to all appetitive stimuli in subclinical problem drinkers. The specific alcohol-related AB, regardless of its direction, might thus only be found in clinical alcohol use disorder, while subclinical populations would still present a more diversified approach AB to various kinds of rewarding stimulations.

Finally, the main AB measures derived from the VPT and the avoidance task did not correlate with subjective craving at testing time, except for the predictable version of the avoidance task. This latter finding indicated that higher craving was associated with a higher tendency to break attentional focus towards alcohol distractors, but only when participants were explicitly aware that only alcohol-related stimuli would appear in the following trials. It further suggests that participants might have been unable to process and categorize the distractors in the mixed avoidance task, especially those in peripheral vision, and thus call future research to include the predictable version in their protocol to strengthen potential effects of AB. The absence of association between craving and other AB measures might be explained by the very few patients with SAUD reporting craving level higher than zero (five out of 30), thus resulting in very small variance. We still believe that the avoidance AB presented in detoxified patients with SAUD and, at a lower level, in healthy CTL is an adaptive behaviour set up to stay in line with their low reported craving, their negative evaluations of alcohol, their low consumption or abstinence as well as their high motivation to maintain it in the long term. While these motivational states are known to characterize most patients under detoxification treatment, future work using the avoidance task should compare patients with SAUD with or without subjective craving and ambivalent evaluation of alcohol at testing time, in order to better understand the role played by reflective abilities on individuals more prone to actually present AB towards alcohol-related stimuli. Indeed, it remains difficult to determine the compulsive nature of AB in patients with SAUD, and their difficulty to voluntary inhibit this AB, when instruction requirements of the avoidance task are not in contradiction with their spontaneous eye movements (i.e., tendency to avoid processing alcohol-related stimuli in the VPT without receiving explicit instructions to do so; Bollen et al., 2021).

5. Conclusion

Using eye-tracking measures, we provide experimental support to the proposal that alcohol-related AB (1) is not a long-lasting and stable characteristic of detoxified patients with SAUD, and (2) is actually underpinned by distinct attentional mechanisms that can be measured through different tasks and indexes. Indeed, we showed, through multiple experimental indexes, the robust presence of an avoidance AB specific to alcohol-related stimuli in patients with SAUD. This avoidance AB was underpinned by later and more controlled processes of AB in the VPT (as indexed by shorter dwell time and lower proportion of second fixation towards alcohol), but also by inhibitory processes (as indexed by lower break frequency for alcohol distractors) and covert attention shifts (as indexed by fixational eye movements positioned further away from alcohol distractors) in the predictable avoidance task. Future studies should clarify the role played by inhibitory abilities in AB among patients with SAUD reporting positive or ambivalent motivational states for alcohol and thus being more prone to present a compulsive AB towards alcohol.

GENERAL DISCUSSION

This thesis was built upon the postulate that individuals with excessive alcohol consumption present an AB towards alcohol-related stimuli, characterized as a key determinant of the development and maintenance of alcohol use disorders. We had the ambition to determine the theoretical and clinical relevance of AB in alcohol use disorders by experimentally testing the validity of five main theoretical assumptions made by dominant models in addiction. To do so, we conducted six empirical studies, using eye-tracking measures for the first time in a population of BD and recently detoxified patients with SAUD. Our main findings provided innovative and reliable data on AB in these critical populations and might therefore have major implications in the field compared to previous behavioural studies.

The general discussion will be organized as follows: We will first discuss the empirical validity of the five theoretical assumptions by briefly describing our experimental evidence related to each of them, before comparing and confronting our results with previous findings. As a reminder, the main assumptions were: (1) AB magnitude is associated with the severity of alcohol use; (2) AB appears at early and automatic processing stages of attention; (3) AB is stable and not strongly influenced by transient motivational states; (4) AB is a pure index of the reflexive/reward system's overactivation, independently of reflective/controlled processes; and (5) AB is specific to alcohol-related stimuli and does not generalize to other appetitive ones. We will then review the major theoretical, methodological and clinical implications of our results before considering their main limitations. Finally, we will discuss the perspectives opened up by this thesis, in order to provide avenues for continuing and extending the work initiated here.

1. Comparison and integration of the main findings

1.1. The association between AB and the severity of alcohol use

Dominant models in addiction postulated that alcohol-related AB would progressively develop as a consequence of associative learning and/or over-sensitization of the reflexive/reward system from repeated alcohol exposures (Anderson, 2013; Robinson & Berridge, 1993; Wiers et al., 2007). In this respect, the magnitude of AB would be strongly associated with the severity (i.e., intensity and frequency) of alcohol use and would finally constitute a long-lasting and persisting characteristic of SAUD once the disorder is established.

We explored this assumption in our six experimental studies by systematically comparing performances from a population of individuals presenting alcohol use disorders with matched healthy CTL. We investigated the presence of alcohol-related AB in a population of BD in Chapters 4, 5 and 6 and in a clinical population of detoxified patients with SAUD in Chapters 7, 8 and 9. The inclusion criteria used in all our studies accounted for potential biasing variables (e.g., psychopathological comorbidities, other substance use) and integrated valid and standardized alcohol use assessment tools (i.e., DSM-V criteria, AUDIT, binge drinking score).

1.1.1. Summary of the results

What did we learn about binge drinking? In Chapters 4 and 6, we did not demonstrate any global AB towards alcohol-related stimuli in BD compared to LD and MD. This absence of significant difference was observed regardless of the AB measures used in the VPT (i.e., behavioural and eye-tracking indexes). Nevertheless, BD were more likely than LD to erroneously maintain their attention towards alcohol in the saccadic choice task used in Chapter 5, thus indexing a disengagement AB for alcohol. Altogether, these findings highlight the inconsistencies regarding alcohol-related AB in a population of BD presenting comparable drinking patterns and suggest that other variables, and centrally current motivational states, might better predict the occurrence of AB than chronic binge drinking habits *per se* (see assumption 1.3 below).

What did we learn about SAUD? The VPT combined with eye-tracking measures revealed the presence of an avoidance AB for alcohol-related stimuli in detoxified patients with SAUD in Chapters 7 and 9. Patients maintained their attention for less time (i.e., shorter dwell time) and reengage less frequently (i.e., fewer second fixations) towards alcohol than CTL in both chapters. Moreover, findings from the avoidance task used in Chapter 9 also showed the presence of an avoidance AB for alcohol, indexed by both overt and covert attentional processes. First, patients with SAUD (but also CTL) less frequently “broke” their focus towards alcohol-related distractors compared to non-alcohol ones (i.e., overt AB). Second, patients with SAUD performed fixational eye movements that were positioned farther away from alcoholic distractors than non-alcohol ones when their gaze was maintained on the target (i.e., covert AB). In Chapter 8, we further demonstrated that the AB directed towards alcohol-related stimuli was not homogenous across patients with SAUD. Instead, it only occurred in some patients and/or in a specific context or state (see assumption 1.3 below), while other patients exhibited an avoidance bias similar to the one found in Chapter 7 and 9. Altogether, we highlighted, by the use of three reliable eye-tracking tasks, that detoxified patients with SAUD would not present a strong and enduring AB towards alcohol but would be more likely to present an avoidance bias towards these stimuli.

1.1.2. Integration with previous findings and theoretical implications

Our systematic review in Chapter 2 showed that most previous studies detected the presence of AB towards alcohol in diverse subclinical populations with excessive drinking patterns (e.g., Hallgren and McCrady, 2013; Miller and Fillmore, 2011; Weafer and Fillmore, 2013). Those studies were consistent regarding the direct link between AB and the intensity of drinking habits, and therefore supported the theoretical assumption that AB magnitude is strongly related to alcohol consumption's severity. This is in contrast with our findings from Chapter 4 and 6 showing that binge drinking habits did not predict the occurrence of AB. Nevertheless, it should be noted that previous studies were not focusing on binge drinking habits but were rather exploring heavy drinking samples, with a large variability in terms of drinking patterns and selection criteria, and that these latter populations might differ from BD in certain aspects potentially linked to AB (e.g., duration of consumption, drinking contexts and motivations, intensity of craving). Moreover, the only previous study focusing on binge drinking also failed to detect the presence of AB (DePalma et al., 2017). Altogether, persistent discrepancies between findings derived from highly reliable measures do not provide support for this first theoretical assumption and rather lead us to wonder whether drinking patterns, such as binge drinking habits, is actually the best predictor of the occurrence of alcohol-related AB.

Regarding AB in SAUD, our systematic review in Chapter 2 revealed that most studies in recently detoxified patients with SAUD did not documented stronger AB compared to CTL, or even reported the presence of an avoidance AB for alcohol (e.g., Fridrici et al., 2013; Townshend & Duka, 2007). Although relying solely on unreliable behavioural measures, these null findings already questioned the theoretical assumptions regarding the key role played by AB in SAUD (Bechara, 2005; Robinson & Berridge, 1993; Wiers et al., 2007). Capitalizing on the use of eye-tracking measures, we provided further experimental support to the reconsideration of the association between AB and the severity of alcohol use by showing the presence of an avoidance AB for alcohol in all our experimental studies conducted in patients with SAUD. Based on this first theoretical assumption, the population tested in Chapters 7 to 9 was expected to exhibit a stronger AB towards alcohol than LD, since the former sample was composed of patients diagnosed with the most severe pattern of alcohol use disorder and presenting much longer and stronger alcohol consumption. However, it must be stressed that all previous studies exploring AB in SAUD, including our own, were exclusively conducted on recently detoxified patients with SAUD, a population widely overlooked by dominant models when describing the role and nature of alcohol-related AB in SAUD. The differences between people with SAUD respectively presenting current drinking habits *versus* recent detoxification in terms of drinking contexts and motivational states prevent us to generalize the coherent findings found here in detoxified patients towards the most prevalent and problematic population of SAUD (i.e., untreated and/or currently drinking individuals with SAUD). In any case, while stronger AB towards alcohol might actually be observed in this latter population, the opposite pattern exhibited in recently detoxified patients with SAUD considerably invalidates the proposal of theoretical models of a long-lasting and consistent AB directed towards alcohol in SAUD (Bechara, 2005; Robinson & Berridge, 1993; Wiers et al., 2007). Furthermore, it calls for a better consideration of detoxified patients under treatment in dominant models of addiction, to better understand the adaptive/maladaptive nature of avoidance/approach AB patterns in their clinical outcomes and subsequent relapse risk.

1.1.3. Limits and perspectives

Most studies focusing on SAUD actually evaluated the relationship between the severity of alcohol use (recruiting only patients with DSM criteria of SAUD) and AB through between-group comparisons. Conversely, studies on subclinical populations usually mixed consumption-related measures (evaluating the intensity/frequency of alcohol consumption, mostly through the TLFB or AUDIT-C) with dangerousness/problems measures (evaluating the consequences and issues resulting from alcohol consumption, mostly through the AUDIT or the Short-Michigan Alcoholism Screening Test) for their correlational or between-group analyses. Future studies should distinguish the respective effects of alcohol consumption from those related to alcohol-related problems on AB, as these aspects differentially predict addictive behaviours and could explain the mixed findings in previous studies.

A valid assessment of alcohol consumption and its associated variables is also needed in SAUD, since self-reported measures are usually unreliable in this population. Future studies could provide for example additional measures reported from relatives. Moreover, the intensity and severity of alcohol use disorder presented by the experimental sample may vary between studies, both in terms of the number of diagnostic criteria encountered and the intensity/frequency of alcohol use, which could also influence the intensity of AB. To enable the comparison across studies and test the first theoretical assumption in the most representative sample, future studies exploring AB in clinical population should only recruit patients fulfilling the minimum six DSM-V criteria for SAUD (NIAAA, 2021). Finally, future research might account for the different pathways to addiction when exploring AB in a certain population and distinguish individuals more or less prone to rewards cues (i.e., sign-trackers versus goal-trackers; Robinson et al., 2014), in order to clarify the conditions and psychological factors determining the individual involvement of AB in the emergence of alcohol use disorders.

1.2. The time course and processes underlying AB

Dominant models in addiction usually consider AB as the behavioural output of the over-sensitization of the reflexive/reward system, resulting in impulsive and automatic behaviours (Bechara, 2005; Wiers et al., 2007). Hence, the second theoretical assumption is that AB relies on early and automatic attentional processes that generate an uncontrolled capture of attention towards alcohol. However, AB might rather be underpinned by later and more controlled processes and thus be related to longer processing time for alcohol cues and/or to a difficulty to disengage attention from them (Schoenmakers et al., 2010).

To experimentally test this question, we explored the time course of AB and its underlying processes in each study by combining different AB paradigms with eye-tracking measures, this tool allowing to dissociate, with high temporal and spatial resolution, the initial attentional capture quickly following the appearance of alcohol-related cues (e.g., first saccade latency, first fixation direction) and the controlled maintenance of attention towards alcohol (e.g., dwell time, second fixation direction). Hence, we provided the very first data exploring AB in binge drinking and SAUD through more reliable eye-tracking measures. Moreover, we further investigated the genuine automatic nature of AB in binge drinking in Chapter 5 through an eye-tracking paradigm specifically recruiting the early and automatic processes of attention.

1.2.1. Summary of the results

What did we learn about binge drinking? When exploring the time course of AB through the VPT combined with eye-tracking measures in Chapters 4 and 6, indices reflecting the initial and early processes (i.e., first fixation direction) and the late and more controlled ones (i.e., dwell time, second fixation direction) did not demonstrate any global AB towards alcohol-related cues in binge drinking. Nevertheless, the similar AB patterns observed in BD and LD in Chapter 4 appeared to vanish during the late processing stages, as showed by longer dwell times for non-alcohol cues only in the latter group. These findings suggested that the differential processing of alcohol and non-alcohol cues in BD would appear at the later processing stages, and are at least not related to an early automatic capture of attentional resources by alcohol-related stimuli. In the same vein, alcohol-related AB in Chapter 6 was only predicted by our selected variables (i.e., craving, binge drinking habits and negative mood) when indexed by eye-tracking measures reflecting processes underpinning the controlled maintenance of attention (i.e., dwell time). Finally, when more specifically exploring the automatic nature of AB through a saccadic choice task, our findings did not demonstrate any early, automatic and involuntary hijacking of saccadic movements provoked by alcohol-related stimuli that would be specific to BD. Instead, we found that they had difficulty to disengage from those stimuli once their gaze was erroneously directed on them, thus revealing the presence of a late and controlled disengagement bias related to alcohol cues in binge drinking. Altogether, these coherent pattern of results highlights that AB in binge drinking is not characterized by an automatic capture of attention by alcohol-related cues, but rather by an increased willingness to process these cues once detected and a difficulty to disengage from them.

What did we learn about SAUD? We explored the temporal dynamics of AB in SAUD through three different eye-tracking paradigms. In Chapter 7, the initial fixation indices in the VPT did not demonstrate the presence of an alcohol-related AB among patients with SAUD, thus questioning the existence of an automatic and early AB in this clinical population. In contrast, we observed a differential processing of alcohol-related stimuli in SAUD at later processing stages. We investigated the second fixation direction index to determine whether patients with SAUD showed difficulty to redirect attention away from alcohol cues once their first fixation was directed towards them (i.e., disengagement bias for alcohol), and we found actually that they rather avoided processing alcohol-related stimuli after a first fixation on non-alcohol stimuli. Our findings, together with shorter dwell times for alcohol-related stimuli in this clinical population, suggested that detoxified patients present avoidance AB at later processing stages. These findings were perfectly replicated in Chapter 9 by also showing the presence of an avoidance bias for alcohol in SAUD through eye-tracking indexes of the later processes of AB when using the same paradigm, AB measures and testing populations. Finally, we demonstrated in Chapter 8 that AB, regardless of its direction (approach/avoidance), was only evidenced by indexes of later and controlled attentional stages (i.e., dwell time, number of AOIs fixated) in an eye-tracking free-viewing task.

1.2.2. Integration with previous findings and theoretical implications

Although the association between AB and binge drinking is inconsistent across studies (see assumption 1.1), its expression appeared exclusively related to later and more controlled stages of attentional processing in all our experimental chapters. This is in line with most previous studies showing longer maintenance of attention towards alcohol indexed by various behavioural (e.g., delayed interferences in the modified Stroop task or shorter RT in the VPT with longer stimuli duration; Field et al., 2004; Hallgren & McCrady, 2013), eye-tracking (e.g., longer dwell times or higher number of fixations; McAteer et al., 2015, 2018) and other neuroscience (e.g., larger attentional resources indexed by N2 amplitude in electrophysiological studies; Dickter et al., 2014) measures. Researchers then claimed that, instead of being based on attention-grabbing properties of alcohol stimuli, AB in subclinical populations may be better characterized by a difficulty to disengage attention from them (Soleymani et al., 2020).

Considering the whole range of alcohol use disorders, McAteer et al. (2015) further proposed that alcohol-related AB would rely on late and controlled processes in subclinical populations and that the automaticity of AB, postulated by dominant theoretical models, would be specific to SAUD. This proposal received preliminary support from previous behavioural studies that manipulated the stimuli presentation time in the VPT and showed faster RT for alcohol-related stimuli in patients with SAUD when stimuli were presented for 50–100ms, while this alcohol-related AB was only observed in regular drinkers after longer presentation times (Field et al., 2004; Noël et al., 2006). However, the only eye-tracking data that were collected in patients with SAUD and provided in the present thesis did not demonstrate any differential processing of alcohol-related cues at the early and automatic stages of attention (as indexed by first saccade and fixation measures). Instead, we systematically showed that patients with SAUD exhibit AB patterns (approach or avoidance) for alcohol-related cues when indexed by eye-tracking measures reflecting later and more controlled processing stages. In the same vein, the first study exploring the efficiency of ABM in this clinical population showed that attentional retraining was efficient to decrease the late components of AB (i.e., the difficulty to disengage attention from alcohol) while no effect was found on the early components of AB (i.e., the speeded detection of alcohol; Schoenmakers et al., 2009). These coherent results thus cast doubt on the postulated early, automatic and involuntary nature of AB in SAUD, since it appears underpinned by later and more controlled processes of attentional processing. In this sense, one may wonder whether this absence of automatic capture of attention might be a first clue for the influence of higher-level processes on AB, directed by the activity of the reflective system (see assumption 1.4).

1.2.3. Limits and perspectives

Throughout this thesis, we assumed that AB occurring in the first milliseconds after stimuli onset, and thus underpinned by early processes and early measures (e.g., first fixation, first saccade), can be considered as automatic and impulsive. In other words, we postulated that when attentional resources are captured quickly by alcohol-related stimuli, it is caused by automatic processes beyond the individual's control. However, this assumption does not rely on a sufficiently robust theoretical and empirical basis and is therefore open to question. Similarly, the distinction between automatic and controlled processes when measuring AB through eye-tracking measures related to earlier (i.e., first saccade and fixation indices) and later (i.e., dwell time and second fixation indices) processing stages of attention may not be so clear-cut. To date, there is actually a lack of consensus in the scientific literature regarding which attentional processing stages can be linked to the different eye-tracking measures. Moreover, this terminology might be confusing, as it can easily be associated with the distinction between the reflexive/reward system and the reflective/control one. However, a genuine blur persists on whether the later and more controlled processing stages of attention (as considered in this thesis) might be partly underpinned by higher-level functions insured by the reflective/control system, or whether they fully result from the over-activation of the reflexive/reward system as well as the early and automatic ones.

One way to clarify these aspects might be to take a look at research in anxiety, which makes a clearer distinction between (1) the observed components of AB, and (2) the stage of information processing during which AB occurs (Cisler & Koster, 2010). The components of AB refer to the observable and measurable characteristics of AB and comprise the facilitated attention (i.e., speeded detection of threatening stimuli), the impaired disengagement (i.e., difficulty to shift attention away from threatening stimuli) and the attentional avoidance (i.e., allocation of attention away from threatening stimuli; Koster et al., 2006). These components would be tied to specific stages of information processing that are either automatic (i.e., occurring without intent, control or awareness) or strategic (i.e., intentional, controllable, capacity-limited and dependent of awareness; Moors and De Houwer, 2006). After reviewing empirical evidence of AB towards threat in anxiety and discuss dominant models, Cisler and Koster (2010) argued that facilitated attention would mostly rely on automatic processes, whereas attentional avoidance would be a mostly strategic process, and difficulty in disengagement would be considered as a mixture of automatic and strategic processing. Importantly, this literature considers the difficulty to disengage from threat as the most maladaptive aspect of AB, as it was frequently associated with higher anxiety symptoms and a higher frequency of functional disorders (disengagement hypothesis; Amir et al., 2008; Heeren et al., 2011). In the same vein, we can easily infer that difficulty in disengaging from alcohol could result in more SAUD-related symptoms (e.g., increased craving, approach behaviour) than simply faster alcohol detection. Therefore, the fact that our results seem to unanimously show that AB towards alcohol is only related to later processes and would manifest itself as a disengagement bias (when actually direct towards alcohol) is even more clinically challenging.

Overall, our results clearly show that the alcohol-related AB is not manifested by a faster detection of alcohol but by a disengagement and/or avoidance bias for alcohol. In this vein, future research exploring AB should not over-invest in specific tasks testing the facilitated attentional capture of alcohol (e.g., saccadic choice task, food-house task; Chen et al., 2022a), but rather use eye-tracking paradigms specifically dedicated to the exploration of the later components of AB. Although our measures related to the proportion of second fixations and corrective saccades towards alcohol provided robust findings on the disengagement component of AB, future studies should use paradigms that specifically measure the extent to which participants are able to rapidly disengage from alcohol stimuli compared to other stimuli. Indeed, a meta-analysis conducted on eye-tracking studies in affective disorders clearly underlined that increased maintenance of attention towards threatening stimuli was best observed in paradigms that explicitly required participants to disengage attention from those stimuli (Armstrong & Olatunji, 2012). As an example, research in dysphoria has developed an eye-tracking paradigm, easily adaptable to alcohol-related stimuli, in which they measured the time needed to engage or disengage from emotional stimuli after a 3000ms of natural processing stimuli presentation (Sanchez et al., 2013). Finally, we should stop using behavioural paradigms such as the modified Stroop task that do not allow to distinguish unequivocally the direction of AB (approach/avoidance), but rather combine the use of tasks that allow to investigate different processes of AB (e.g., combining the VPT and the avoidance task as in Chapter 9).

1.3. The stability of AB

Dominant traditional models assume that AB emerges gradually through associative learning and/or over-sensitization of the reflexive/reward system, ultimately constituting a stable and potentially permanent feature of SAUD once the disorder is established (Hardman et al., 2021; Robinson & Berridge, 1993; Wiers et al., 2007). However, these models did not consider the sensitivity of AB to momentary motivational states and underestimated their impact on the magnitude and direction of AB relative to the influence of stable SAUD-related factors (e.g., duration, severity). Over the past decade, there has been increased interest in the impact of fluctuating factors on the behavioural expression of the reflexive/reward system (i.e., AB; Hofmann et al., 2008). Going further, Field and colleagues (2016) claimed that the stability of AB along the disorder has been overstated by traditional models and rather suggested that AB is mostly driven by temporary changes in appetitive and/or aversive states. AB would then result from momentary motivational evaluation of alcohol-related stimuli and would thus not constitute a stable SAUD marker. Importantly, the subjective evaluation (positive, negative, ambivalent) of alcohol-related cues would lead individuals to maintain their attention on it or conversely ignore it, resulting in opposite AB patterns (Field et al., 2016).

In the present thesis, we investigated the stability of AB according to internal and contextual factors across BD and patients with SAUD, by first exploring the role played by current subjective craving on the occurrence and magnitude of AB, either through correlational analyses (Chapter 7 and 9) or by comparing groups of drinkers differing solely on their level of reported craving at testing time (BD in Chapter 4, patients with SAUD in Chapter 8). Second, we induced positive and negative mood through emotion induction in BD (Chapter 6) to determine how they can influence subjective craving and AB. Finally, we evaluated the short-term intra-individual stability of AB in SAUD (Chapter 7) by assessing the test-retest variations of AB when measured by VPT combined with eye-tracking measures.

1.3.1. Summary of the results

What did we learn about binge drinking? Although we did not find any general AB towards alcohol in binge drinking when using the VPT combined with eye-tracking (see assumption 1.1), our results from Chapters 4 and 6 showed that subjective craving for alcohol at testing time widely influenced the occurrence and magnitude of AB in this population. In Chapter 4, BD reporting high level of craving exhibited an AB towards alcohol-related stimuli on one hand, while on the other hand BD with low craving actually presented an avoidance AB for alcohol, similar to CTL. Moreover, we showed that craving was the only predictor of AB, psychological and alcohol consumption variables not appearing as significant predictors. In the same vein, we showed in Chapter 6 that binge drinking habits were not directly associated with alcohol-related AB, since this association was mediated by subjective craving. Altogether, our findings demonstrate that the intensity of alcohol craving at testing time is a core determinant of AB in binge drinking. In contrast to the first theoretical assumption (i.e., AB is strongly associated with the severity of alcohol use), we demonstrated that AB in subclinical populations such as binge drinking was not explained by the severity/frequency of alcohol use but rather by an interaction between the drinking pattern and current craving level.

In contrast to the second assumption (i.e., AB relies on early and automatic processes), the impact of craving on AB was found when exploring late processing stages of attention (i.e., dwell time measures) but not early ones (i.e., first fixation indices), thus suggesting that craving intensity would influence later and more controlled processes in binge drinking rather than the potential early attentional capture towards alcohol. Finally, we highlighted the major role played by craving in the occurrence of AB relative to other transient states, since negative mood did not show a direct association with AB in binge drinking, but was rather mediated by craving.

What did we learn about SAUD? In Chapters 7 and 9, the presence of an avoidance bias in detoxified patients with SAUD (rather than an AB directed towards alcohol as postulated by the first theoretical assumption) led us to wonder whether this avoidance AB might be caused by patients' negative thoughts and aversive states about alcohol, as they were all involved in an abstinence process and most of them reported low craving and high abstinence motivation at testing time. The proposal that AB would fluctuate alongside subjective evaluation of alcohol-related cues was reinforced by our correlational analyses in Chapter 7 showing that higher craving was associated with higher AB score. In Chapter 8, we clarified the stability of AB with respect to motivational states by comparing patients with SAUD reporting the presence *versus* absence of craving at testing time and unequivocally showed the major role played by craving in the magnitude and direction of AB in a free viewing eye-tracking task. Indeed, patients with craving spent more fixation time on alcohol stimuli and less fixation time on non-alcohol stimuli than patients without craving. Moreover, the latter group showed an avoidance AB for alcohol (i.e., lower fixation time on alcohol compared to non-alcohol stimuli) stronger than CTL. The opposite AB patterns between the two groups of patients were further supported by correlational analyses showing that AB was not associated with any index of SAUD severity except craving. Finally, AB might also be subject to short-term intra-individual variations in detoxified patients with SAUD (Chapter 7), since they exhibited stronger avoidance AB at the retest session compared to test session four days earlier. Importantly, these intra-individual variations in SAUD were not observed on a very short-term basis, as patients did not differ from CTL when exploring the dynamic nature of dwell time AB scores through an innovative computing method capturing trial-by-trial variability (Appendix E of Chapter 7). This increased avoidance AB after a few days might be partly explained by the positive outcomes related to their detoxification treatment (e.g., increased motivation for abstinence, enhanced self-regulation). Overall, we demonstrated that alcohol-related AB was not a stable characteristic of excessive alcohol use but are rather the behavioural artefact of transient evaluative states (e.g., craving).

1.3.2. Integration with previous findings and theoretical implications

The role of craving in the intensity of AB had already been suggested in earlier work conducted in SAUD or subclinical populations. First, a meta-analysis of 68 studies highlighted the positive association between craving level and AB magnitude (larger effect being observed when assessing AB through eye-tracking measures), regardless of the treatment-seeking status of participants (Field et al., 2009). Second, our findings from Chapter 4 were in line with a previous eye-tracking study showing that AB towards alcohol only occurred in subclinical drinkers with high craving (Hobson et al., 2013). In other words, these results showed that craving levels would not merely intensify AB in subclinical populations, but rather that AB, at the initial stages of excessive alcohol use, is absent without craving. Regarding our results in Chapter 8, these opposite AB patterns between patients with SAUD reporting high/low craving was actually already found in a behavioural study using median split on craving levels (Field et al., 2013). In opposition to the present assumption, all these findings suggested that AB is not a stable and permanent feature of alcohol use disorders but highly affected by current motivational states such as craving. More importantly, they suggested that the intensity of subjective craving is a stronger determinant of AB than drinking habits, in opposition with the first theoretical assumption.

Therefore, these findings clearly provide experimental support to the proposal of Field and colleagues (2016) that most models might have overstated the stability of AB. Instead, AB might rather be defined as the expression of momentary evaluations of alcohol-related stimuli, which fluctuate with current motivational tendencies to consume. Hence, AB would be driven by temporary changes in appetitive and/or aversive motivational states. The subjective valence (positive, negative, ambivalent) of the evaluation of substance cues (indexed here by craving) might determine whether individuals maintain and/or override their gaze on them, resulting in approach/avoidance AB. Based on this proposal, we could easily predict that abstinent patients in clinical settings would not present a stable AB towards alcohol because of their high motivation to pursue avoiding alcohol after their treatment. More specifically, we can expect these non-craving patients to present negative thoughts and aversive states for alcohol (i.e., a negative evaluation of alcohol-related cues), thus resulting in avoidance AB, while craving patients would be characterized by motivational conflict thus leading to a small AB towards alcohol. Although one might argue that a dissociation could be found between alcohol-related AB and thoughts (i.e., patients thinking more about alcohol might be the ones with the stronger avoidance AB), our findings regarding the links between craving and AB, together with previous ones, support the common assumption that gaze orientation reflects the course of one's thoughts. According to these proposals, it makes sense that previous studies exploring AB in SAUD without assessing the impact of current motivational states showed inconsistencies in the magnitude and direction of AB among their tested patients.

1.3.3. Limits and perspectives

While all our studies provided an assessment of subjective craving at testing time to investigate the influence of this motivational state on AB, we did not explicitly assess the alcohol expectancies of our participants, nor their positive/negative evaluation of alcohol use. Yet, exploring their impact on AB could provide further insights on the validity of Field et al. (2016)'s theoretical proposal, as the overlap between alcohol expectancies/evaluations and craving might not be total. Moreover, it could address the issue raised about the usually low reported craving in patients with SAUD, resulting in a very small variance for this measure. Future research should thus systematically account for the *inter-contextual stability* of AB by assessing relevant motivational states such as craving, mood and alcohol expectancies. Moreover, since low craving and negative alcohol evaluation usually characterized detoxified patients under treatment, one may wonder whether AB might also vary with drinking contexts and disease course. Indeed, all our recruited patients were tested in clinical settings, a context not associated with drinking behaviour or the presence of alcohol-related stimuli, and which could rather devalue alcohol by itself, as it can easily remind them of the problematic nature of their alcohol use and the negative consequences it had on their personal lives. In contrast, we could expect detoxified patients to present less aversive motivational states and higher craving for alcohol in naturalistic settings (e.g., at home or in a bar), and therefore a higher probability to exhibit an AB directed towards alcohol. To experimentally test these aspects of the *inter-contextual stability* of AB, it is crucial for future studies to test detoxified patients in drinking contexts, but also to evaluate AB in the population most likely to direct their attention towards alcohol, namely individuals with current alcohol use disorders not seeking for treatment and/or not presenting motivational conflict regarding alcohol. Nevertheless, the exploration of AB in these currently drinking populations is hampered by the difficulty to dissociate the effects of acute intoxication from chronic drinking habits. Indeed, our systematic review on the eye-tracking correlates of acute alcohol consumption (Maurage et al., 2020b) showed that alcohol intoxication had been repeatedly associated with AB towards alcohol-related cues, but that results were not coherent regarding the influence of chronic consumption on this AB following acute consumption.

Although our test-retest procedure and trial-by-trial analyses in Chapter 7 offered preliminary findings on the intra-individual variability of AB, most results from the present thesis did not allow to determine the *intra-individual stability* of AB. Indeed, it remains unclear whether one patient with SAUD could exhibit an AB towards alcohol at one time and not at another (indexing intra-individual variability of AB) or whether alcohol-related AB would characterize a certain type of patients but not all of them (indexing inter-individual variability of AB). In the latter case, some patients would constantly present AB and craving once exposed to alcohol-related stimuli, which would subsequently increase their relapse risk, while other patients might be led to relapse due to other psychological processes. This proposal is actually supported by recent adaptations of the incentive-sensitization theory accounting for the individual variations in the propensity to attribute incentive salience to alcohol-related cues (Robinson et al., 2014). They proposed that individuals prone to approach reward cues (sign-trackers) would attribute greater motivational value to cues than do individuals less prone to approach reward cues (goal-trackers), meaning that for different individuals there are different pathways to addiction (Colaizzi et al., 2020; Milton & Everitt, 2010). Therefore, AB might play a major role in the development of SAUD for some individuals but be far less crucial for others. To investigate the *short-term intra-individual stability* of AB, future studies could use (1) repeated measures at a timescale interval of several days or weeks (given the opposite results obtained in Chapter 7 on a trial-by-trial and week-by-week basis), and/or (2) craving induction in clinical and subclinical population to clarify whether AB might vary within an individual across time or conditions. Future studies should also explore the *long-term intra-individual stability* of AB, as it might vary through disease course. AB thus has to be tested across multiple sessions during the successive stages of the disease (e.g., non-abstinent patients, early/late withdrawal, post-detoxification).

1.4. The influence of reflective abilities on AB

Dual-process models in addiction (Bechara, 2005; Wiers et al., 2007) postulated that alcohol use disorders emerge from the under-activation of the reflective/control system, responsible for deliberative and controlled responses, and the over-activation of the reflexive/reward system, initiating automatic and appetitive behaviours. In this view, AB would be the behavioural expression of the overactivation of the reflexive/reward system, but the role played by the reflective/control system remains unclear. Indeed, dual-process models simultaneously stated that (1) reflexive/reward processes operate in an effortless manner, independently from the availability of cognitive resources, and that (2) situational factors such as cognitive load could selectively impair the reflective/control system, leading the reflexive/reward system to take the lead (hence assuming a continuous interaction between systems; Hofmann et al., 2008; Strack & Deutsch, 2004). Therefore, the question remains whether AB is a genuine index of the overactivation of the reflexive/reward system, independent from the reflective/control system's activity. In relation with the two previous assumptions, we also wondered whether the modulation of AB by appetitive and/or aversive motivational states is completely compulsive and driven automatically (although it has been systematically indexed by controlled processes), or whether its modulation and occurrence at later and more controlled processing stages of attention might be partly explained by the recruitment of higher-level functions (e.g., inhibitory control) related to the reflective/control system.

This question was investigated in two complementary studies conducted among patients with SAUD. In Chapter 8, we explored the modulation of AB through the saturation of the reflective/control system's resources. In Chapter 9, we explored the ability of patients with SAUD to control and inhibit saccadic movements towards alcohol-related cues.

1.4.1. Summary of the results

What did we learn about SAUD? In Chapter 8, we investigated whether recruiting the reflective/control system for a concurrent task could increase the magnitude of AB towards alcohol (through the reduction of the cognitive resources available to control AB). However, we clearly observed similar AB patterns in the three free-viewing tasks combined with no, low and high cognitive load task, suggesting that AB was not influenced by the extent of cognitive resources available. Indeed, patients with SAUD reporting an absence of craving at testing time continued to avoid processing alcohol even when the concurrent task was recruiting a significant part of their attentional and cognitive resources. In the same vein, patients reporting craving spent longer fixation time on alcohol than other participants and continued to do so even when engaged in the higher difficulty level of the concurrent task. These findings thus suggested that, even if AB is the behavioural expression of personal motivations and expectancies related to alcohol, and occurs at later and more controlled processing stages, it might not be driven by higher-level or goal-directed processes operated by the reflective/control system. Another explanation might be that the direction and maintenance of attention towards or away from alcohol-related cues might require little or no cognitive resources, especially in AB tasks involving free exploration of stimuli, such as the VPT used in Chapter 8, without specific instructions requesting cognitive resources. Therefore, the role of the reflective/control system on AB might have not been tested by our design, since we taxed the cognitive resources of participants with the concurrent task without requiring them to use these resources for the visual exploration of the stimuli displayed in the VPT.

To better appraise the independency of AB from cognitive control, we further investigated in Chapter 9 whether patients with SAUD could recruit their reflective and inhibitory abilities to directly control early saccadic movements toward alcohol-related cues. Using an avoidance task with a gaze contingency procedure (Qureshi et al., 2019; Wilcockson and Pothos, 2015), we measured people's ability to deliberately inhibit orientation of attention towards alcohol-related distractors when focusing on a specified target. We found that our sample of patients with SAUD, which was characterized by very low craving and avoidance bias in natural processing (indexed through dwell time and second fixation measures in the VPT), did not show more difficulty to inhibit their saccades towards alcohol compared to other distractors in the original version of the task. Importantly, we showed that both CTL and patients with SAUD deliberately avoided to process alcohol-related stimuli once aware that they will be exclusively exposed to these stimuli. Given the natural occurrence of an avoidance AB in a free processing of alcohol-related stimuli (i.e., the VPT), it was quite expected that our sample of patients would present no difficulty to deliberately inhibit their saccades towards alcohol once clearly aware of their appearance. The absence of difference between groups in the latter task could be partly explained by the well-established impairment of inhibitory control in this clinical population leading to higher break frequency regardless of the type of distractors appearing. Moreover, the exploration of covert attentional processing showed that fixational eye movements of patients with SAUD were positioned farther away from alcoholic distractors than non-alcoholic ones. Altogether, these findings provided further support to the frequent occurrence of avoidance AB in this clinical population, as well as the presence of inhibitory impairment, but they could not help us determine how reflective abilities might modulate AB as patients had spontaneously initiated its avoidance on their own.

1.4.2. Integration with previous findings and theoretical implications

The absence of findings regarding the modulation of AB through the saturation of the reflective/control system in Chapter 8 is consistent with previous findings in SAUD showing that AB is independent from higher-level cognitive processes such as executive functioning (Van Hemel-Ruiter et al., 2016) and is not an artefact of patients' poorer cognitive performance (Fadardi & Cox, 2006) but rather appears as a genuine phenomenon of SAUD. These few studies therefore supported the proposal that AB relies on an over-activation of the reflexive/reward system and is quite independent from the reflective/control system. However, they are not in line with previous behavioural findings in subclinical populations showing that stronger AB might be induced in social or heavy drinkers under increased cognitive load (Nikolaou et al., 2013; Tibboel et al., 2010). As described in Chapter 2, Nikolaou et al. (2013) investigated whether alcohol AB was modulated by top-down cognitive control mechanisms using a dual flanker task. The concurrent presentation of alcohol-related background images, in comparison with neutral and grey background displays, led to longer RT in the most demanding incongruent condition of the task. Alcohol AB thus attenuates cognitive control mechanisms, participants needing to exert more cognitive control to focus on the target and ignore both the task-irrelevant alcohol-related stimuli and the incongruent flankers. Importantly, this interference effect was associated with higher alcohol consumption. In the same vein, Tibboel et al. (2010) examined alcohol AB using an attentional blink paradigm in light and heavy drinkers. They showed that alcohol-related stimuli were processed more efficiently than soft drinks in heavy drinkers under high cognitive load, reflecting an alcohol AB at the encoding level.

Likewise, our findings regarding the avoidance task in Chapter 9 are not consistent with previous ones conducted in subclinical populations

(Qureshi et al., 2019; Wilcockson et al., 2015). In contrast to detoxified patients with SAUD in our study, heavy and problem drinkers in previous explorations showed more difficulty to maintain their focus on the target and inhibit saccadic movements towards alcohol-related distractors compared to neutral non-appetitive ones. The opposite AB patterns in subclinical and clinical populations (i.e., approach *versus* avoidance AB) would therefore extend to the inhibitory processes of AB. Moreover, our findings are in contrast with a recent meta-analysis of 35 alcohol studies demonstrating that exposure to alcohol-related cues significantly impaired inhibitory control (Jones et al., 2018b). However, it should be highlighted that alcohol-cue exposure might have been restrained in Chapter 9 by the design of the task (as distractors were presented in the peripheral vision half of the time, had to be ignored and disappeared once being glanced). In contrast with our findings, previous studies therefore suggested that the reflective abilities needed to deliberately inhibit processing goal-irrelevant cues are reduced when exposed to alcohol-related cues, further suggesting that the reflective/control system might not entirely take control over the reflexive/reward system and the occurrence of alcohol-related AB.

Altogether, these findings raised doubts about the potential implication of reflective processes in alcohol-related AB, thus questioning the validity of AB measures as specific indexes of the reflexive/reward system overactivation. Indeed, our results are inconsistent with previous findings in subclinical populations regarding how AB can be modulated by the manipulation of the cognitive resources recruited by the reflective/control system. Moreover, the respective role of aversive motivational states and reflective abilities in the mechanisms underlying the avoidance of overt and covert attentional processing of alcohol-related cues remains unclear.

1.4.3. Limits and perspectives

Although they offer interesting preliminary findings, results from Chapters 8 and 9 remain too premature and open to criticism to draw clear conclusions on the validity of this fourth theoretical assumption. In line with Tibboel et al. (2010), the exploration of the cognitive load's impact on AB might have been hampered by the methodological choices we made in Chapter 8. Indeed, the cognitive resources of the reflective/control system might have been insufficiently saturated in the high cognitive load condition of our concurrent task to significantly impact the reflexive/reward system and/or AB.

As mentioned above, it also remains difficult to determine the compulsive nature of AB, and the ability to deliberately inhibit its occurrence in patients with SAUD, when the instruction requirements of the avoidance task are in line with their spontaneous eye movements (i.e., tendency to avoid processing alcohol-related stimuli without receiving explicit instructions to do so). Considering the different AB patterns that patients with SAUD could exhibit according to their craving, future work using the avoidance task should compare patients with SAUD with or without subjective craving by following similar recruitment procedure than the one applied in Chapter 8, to better understand the role played by reflective abilities on individuals more prone to actually present AB towards alcohol-related stimuli. By doing so, we might clarify whether the respective role of appetitive/aversive motivational states and impaired/preserved reflective abilities in the occurrence of an approach/avoidance AB in patients with SAUD.

One complementary way to determine the influence of reflective abilities on AB is to combine the exploration of the two research questions related to this fourth theoretical assumption (i.e., is AB modulated by the saturation of the reflective/control system's resources and can we exert voluntary control on AB?) in a single task. For example, we could design a gaze contingency paradigm (such as the avoidance task) requiring participants to perform a low *versus* high cognitive load task in central vision, while ignoring alcohol-related distractors in peripheral vision. This paradigm would offer supplementary insights on the relationship between the reflexive/reward system and the reflective/control system, by exploring whether the inhibitory processes of AB might be modulated by the reduced availability of cognitive resources in the reflective/control system. It would also offer further insights on the apparent contradiction between the fact that alcohol-related AB mostly relies on later and more controlled processing stages of attention but would also be totally independent from the activity of the reflective/control system.

1.5. The specificity of AB towards alcohol-related stimuli

The final assumption intuitively made by theoretical models is that the facilitated capture of attentional resources towards alcohol-related stimuli is specifically and exclusively driven by their alcohol-related nature. However, previous studies were not consistent in their selection of control stimuli, most of them confronting alcohol-related stimuli with non-alcohol and non-appetitive stimuli, thus preventing us to determine whether AB is specifically caused by the alcohol-related nature of the cues or is just part of a generalized AB towards every rewarding stimuli. The latter case would strongly reduce the experimental and clinical relevance of AB in alcohol use disorders, since a generalized overactivation of the reflexive/reward system would question the alleged hijacking of this system by alcohol-related stimuli as well as the usefulness of using ABM for those stimuli.

In the present thesis, we controlled for the specificity of AB by comparing alcohol-related stimuli (i.e., alcoholic beverages) with non-alcohol appetitive stimuli (i.e., soft drink beverages) in every chapter except Chapter 5 (for perceptual reasons). Moreover, we further clarified whether AB could be generalized to other appetitive stimuli by comparing alcohol-related stimuli with other appetitive stimuli (i.e., high calories food stimuli, Chapter 4) and non-appetitive stimuli (i.e., household products, Chapter 9).

1.5.1. Summary of the results

What did we learn about binge drinking? In Chapter 4, we performed three blocks of the VPT using different types of stimuli to determine the specificity of AB in binge drinking (i.e., alcohol versus soft drink for the drink block, alcohol versus high calories food for drink-food block, high versus low calories food for the food block). In the drink block, no difference was found in terms of AB measures for alcoholic beverages compared to soft drinks in BD, which might be explained by their attraction towards other appetitive stimuli, except when they feel craving for alcohol. In the drink-food block, all AB measures revealed that both BD and CTL were more strongly attracted by other appetitive stimuli (i.e., high-calories food) than alcohol. Nevertheless, this preference for food stimuli disappeared in BD reporting high alcohol craving. It thus appears that the potential AB is not specific to alcohol-related cues in binge drinking, since BD also present a preferential allocation of attentional resources towards other appetitive stimuli, and even a stronger attraction towards high-calorie food stimuli than alcohol-related ones when reporting no alcohol craving. In Chapter 6, we did not observe the presence of a specific bias for alcohol-related stimuli in BD when compared to soft drinks, which might be partly explained by the generalization of AB towards other appetitive stimuli in this population.

What did we learn about SAUD? The avoidance AB systematically observed among patients with SAUD in all our studies appeared specific to alcohol-related stimuli compared to non-alcohol appetitive stimuli (i.e., soft drink pictures). Nevertheless, one may wonder whether the avoidance AB could become even more apparent when alcohol-related stimuli are compared to non-appetitive stimuli that are not related with alcohol through associative learning (e.g., mixtures of soft drink and alcohol in cocktail beverages). Findings from Chapter 9 provided preliminary data on this question by showing no difference between non-alcohol appetitive stimuli and non-appetitive stimuli in terms of break frequency or covert attentional processing. However, the design of the task did not allow to directly confront those stimuli to alcohol-related ones, as it presents only one type of stimuli per trial, thus preventing us from giving a clear answer to this question.

1.5.2. Integration with previous findings and theoretical implications

Many studies compared alcohol-related stimuli to non-appetitive ones (e.g., household objects, office stationery) in order to prevent participants from associating the control stimuli with alcohol consumption, contrary to non-alcoholic beverages. Nevertheless, this methodological choice does not elude the possibility that alcohol-related AB might not be specific to alcohol-related stimuli but would rather be generalized to other appetitive stimuli. Indeed, Qureshi et al. (2019) demonstrated through the use of a gaze contingency paradigm in subclinical drinkers that AB (indexed by break frequency) may be partly attributable to the appetitive content of the stimuli used, as the inability to inhibit their saccadic movements towards distractors was generalized towards all appetitive stimuli (i.e., alcoholic and non-alcoholic beverages). In our studies, we did not find any specific AB towards alcohol-related stimuli in BD (except for those reporting high craving for alcohol at testing time, see assumption 1.3) when compared to non-alcohol appetitive ones (i.e., soft drink, food), thus suggesting that their attention might be captured equally (or even more strongly in the case of high-calories food) by other appetitive cues. Importantly, the suppressed alcohol-related AB observed in our studies when other appetitive stimuli are used as control stimuli also suggests that the AB reported in previous studies might have been over-estimated through the use of non-appetitive stimuli as control stimuli.

Previous studies in SAUD were not consistent in their selection of control stimuli according to their appetence (among studies reviewed in

Chapter 2, six of them used soft drink pictures while four studies used non-appetitive pictures), which may partly explain the high heterogeneity of their findings, in addition to the low reliability of their AB measures (exclusively based on RT and/or accuracy measures). Moreover, the only previous study using both soft drink and non-appetitive stimuli (Heitmann & De Jong, 2021) did not make the distinction between the two types of control stimuli in the analysis, thus preventing us to draw conclusion regarding the specificity of AB in SAUD. Therefore, we provided the very first data exploring the specificity of AB towards alcohol compared to appetitive and non-appetitive stimuli in SAUD. Our findings showed opposite results than those testing subclinical drinkers (Qureshi et al., 2019), since we found an avoidance AB specific to alcohol-related distractors and no differential processing of other appetitive and non-appetitive ones. To sum up, the specificity of AB for alcohol-related cues, regardless of its direction (approach or avoidance), might thus only be found in SAUD, while subclinical populations would still present a more diversified AB directed towards various kinds of rewarding stimulations.

1.5.3. Limits and perspectives

A major concern related to this last theoretical assumption is the lack of convergence in the literature regarding what can be considered as a non-appetitive or non-alcoholic but appetitive control stimuli, since some studies viewed soft drinks pictures as neutral, non-appetitive stimuli (e.g., Christiansen et al., 2015b; Heitmann et al., 2021) while others defined them as appetitive stimuli (e.g., Pennington et al., 2020; Qureshi et al., 2019). To address this issue, the first step should be to determine which type of stimuli can be considered as appetitive among healthy and (sub-)clinical populations, at least by systematically measuring the self-reported appetence level associated with each stimulus type in each participant. In this view, future research should clarify the concept of appetence and determine which stimuli can be considered as appetitive in the targeted population before challenging AB specificity. A second step suggested by Pennington et al. (2021) is to consistently match alcohol-related stimuli with non-alcoholic appetitive stimuli, in order to isolate the mechanisms specifically related to the alcohol-related nature of AB. There is thus an urgent need to address more seriously these methodological shortcomings, since the existence of a generalized AB towards other appetitive stimuli would show that AB is not specifically related to alcohol in alcohol use disorders, reducing the empirical and clinical interest of the so-called alcohol-related AB.

2. Main implications

We reviewed the five main assumptions made by theoretical models about alcohol-related AB in the previous section by reporting the associated empirical evidence provided by studies from the present thesis, before integrating them with the existing literature. We also discussed the theoretical implications of these findings, highlighted the remaining limitations and provided avenues for future research exploring each of these theoretical assumptions. In the following section, we will discuss the main implications of our work for research on alcohol-related AB. First, we will highlight the theoretical insights brought by our experimental studies to renew the conceptualization of AB in alcohol use disorders. Second, we will argue how our methodological approach considerably improved the investigation of AB and its underlying processes. Third, we will discuss the extent to which our main results can strongly impact our therapeutic view of AB and how we should consider its rehabilitation in clinical settings.

2.1. Theoretical implications

Following findings from the present thesis and from previous studies, we casted doubts on several proposals made by theoretical models regarding alcohol-related AB. We showed that the way individuals preferentially process alcohol-related cues was actually better predicted by their motivational states at testing time than by the severity of their chronic alcohol use. Moreover, we demonstrated, through eye-tracking measures, that AB was not characterized by an automatic hijacking of attentional resources towards alcohol but rather appeared at later and more controlled stages of attentional processing. Furthermore, we could not provide clear-cut answers to the relationship between the reflexive/reward system and the reflective/control system, as some controlled and inhibitory processes appear involved in alcohol-related AB while it would not be affected by the activation of the reflective/control system to perform an independent task. Finally, we showed that the avoidance/approach AB presented by patients with SAUD was specific to alcohol-related stimuli but this level of specificity was not yet reached in subclinical populations since BD presented a more diversified AB towards various kinds of appetitive stimuli.

To put the present findings into perspective with the main theories about AB in alcohol use disorders, we will now review the dominant theoretical models introduced in Chapter 1 in the light of our empirical evidence. We will discuss the implications of the present thesis for the validity of these models and, more generally, for the theoretical conceptualization of alcohol-related AB.

2.1.1. Reappraisal of theories regarding the reflexive/reward system

According to the incentive-sensitization theory (Robinson & Berridge, 1993), chronic and excessive alcohol use over-sensitizes the dopaminergic response in brain areas related to the reflexive/reward system, enhancing the incentive-motivational properties of alcohol-related stimuli through associative learning. Becoming more salient, these stimuli automatically capture attention (generating an alcohol-related AB), acquire an attractive and desirable value, and lead to drinking behaviour. Importantly, the incentive salience of alcohol-related stimuli would increase gradually through associative learning, until these properties are settled permanently among individuals presenting well-established SAUD. Although the main rationale of this theory regarding the over-sensitization of the reward/reflexive system was evidenced by many neuroscience studies, their assumption that the sensitization of the incentive motivational properties of drugs would be very long-lasting and persistent did not rely on strong experimental evidence and was therefore speculative. This latter speculation assumes that the long-lasting nature of this acquired incentive salience would constantly lead to the occurrence of an AB towards those highly attractive stimuli. The theory thus clearly asserted that alcohol-related AB would be a stable feature of SAUD, and did not offer any insights on its consistency over time nor its level of malleability when faced with transient motivational states or specific contexts. Since we showed that these latter aspects could drastically change the direction of AB in our experimental samples (i.e., from approach to avoidance AB according to current craving), this issue seriously impairs the validity of the incentive-sensitization theory to predict the occurrence and magnitude of alcohol-related AB.

It should be noted that the incentive-sensitization theory, as well as its extensions (Franken, 2003; Ryan, 2002), appropriately highlighted the crucial association between AB and craving by considering them as the emotional and cognitive outputs of the overactivation of the reflexive/reward system. Moreover, they postulated a reciprocal excitatory relationship between those processes by arguing that the facilitated capture of attention by alcohol-related cues would enhance craving, which would in turn lead to greater attention paid to these cues, and so on until eventually leading to alcohol consumption (Franken, 2003; Ryan, 2002). However, the timeline of this relationship remains unclear. According to the incentive-sensitization theory, it might seem that the over-sensitization of the dopaminergic system would lead to increased salience of alcohol-related stimuli, which would generate AB, which would increase craving and then lead to approach behaviour. It could also be argued that this whole process is not sequential and linear but that these hyper-connected mechanisms rather happen in parallel. Nevertheless, both arguments raise many questions that are not sufficiently addressed by these traditional models. Indeed, one may wonder which mechanisms provoke the emergence of craving and AB in the first place, especially if these processes would occur at the same time. Considering the intra-individual variability of AB and craving suggested by our findings (rather than their long-lasting and permanent nature), what internal or external factors could determine the occurrence of these processes in SAUD and subclinical populations? What can possibly cause the sudden reactivation of the reflexive/reward system, especially among detoxified patients with SAUD in clinical settings?

The “elaborated intrusion” theory of desire (Kavanagh et al., 2005) offered further insights on these questions by suggesting that craving would appear before AB and that it would be either caused by internal states (e.g., negative mood, withdrawal symptoms) or external cues (e.g., exposition to alcohol-related cues). Then, the awareness of this craving would lead the individual to direct and maintain their attention to those triggering external cues when available, creating an AB, which in turn would further increase craving. This proposal received experimental support from our Chapter 6, in which we showed that negative mood significantly predicts current craving in BD, which was a reliable predictor of alcohol-related AB. Whereas negative mood indeed caused higher craving, the cross-sectional design of this study for AB assessment did not allow us to draw conclusions on the temporality between craving and AB. The allostatic model developed by Koob & Le Moal (2005) also claimed for a key role of negative affect in craving and alcohol seeking behaviour, and highlighted the importance of emotional regulation for the prevention and treatment of addiction. In their model, they suggested that the development of negative emotional states during drug abstinence drives the negative reinforcement of addiction by triggering substance use as a coping mechanism (Koob & Le Moal, 2008). While this use may temporarily relieve emotional symptoms, it also reinforces the association between negative affect and substance use, leading to addiction (i.e., the dark side of addiction).

This introduces the notion of a vicious cycle, in which substance use leads to negative consequences that may in turn lead to negative affect, resulting in drug craving (and potentially alcohol-related AB) and further use.

Finally, Field et al. (2016) further addressed these intraindividual variabilities by asserting that AB would arise from momentary changes in the evaluations of alcohol-related cues, and that the overall strength of these evaluations, rather than their valence (positive, negative, or both [ambivalent]), would determine the magnitude of AB. According to their new theoretical account of AB in addictive disorders (see Figure 21), positive evaluations would result from the incentive salience of alcohol-related stimuli at that moment (just like craving and drinking behaviour) while negative evaluations would arise from motivational conflict between their desire to consume alcohol and their goal to remain abstinent. The former would result in AB directed towards alcohol, the latter would lead to an attempt to override or control this AB and their combination would result in an approach-avoidance AB pattern.

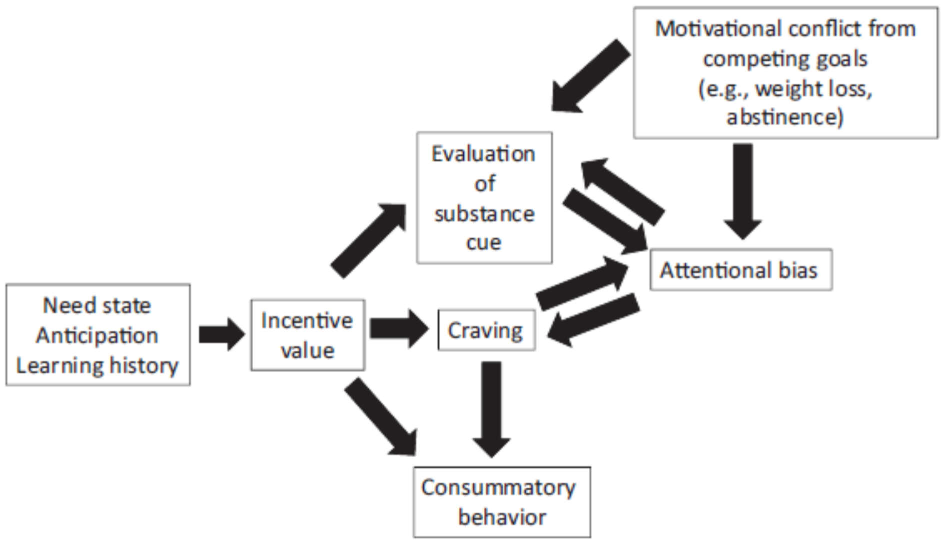

Figure 21. Illustration of the model proposed by Field et al. (2016) on the role of AB in addiction.

The present thesis repeatedly offered empirical support to the overall assertions of this model by demonstrating that AB highly fluctuates alongside transient motivational states in SAUD and binge drinking. However, we did not include direct measurements of these positive and negative momentary evaluations of alcohol-related cues in our studies, which prevented us to experimentally test the role played by the determinants of AB proposed here and to clarify the links between alcohol-related thoughts and AB. For example, we presume that the opposite AB patterns found in Chapter 8 in the two groups of patients with SAUD could be explained by their positive *versus* negative momentary evaluations of alcohol-related stimuli. Nevertheless, these two groups of patients were constituted according to the presence/absence of craving, and we did not measure alcohol-related evaluations and/or thoughts. Since the direction of AB was robustly explained by this variable, we argue that the evaluation of current craving might indirectly assess those evaluations of alcohol-related cues and that the two mechanisms should be linked in the model. Moreover, findings from Chapter 8 also revealed that the avoidance AB exhibited by patients with craving was not modulated by the cognitive resources available in the reflective/control system, thus suggesting that the avoidance AB might not be characterized by an attempt to voluntary override or control an AB directed towards alcohol as described in Field et al. (2016)'s model.

Altogether, we observed over the years that theoretical proposals about the overactivation of the reflexive/reward system are increasingly in line with the empirical evidence provided by reliable AB measures. Thirty years ago, theoretical models argued that alcohol-related stimuli automatically captured attention in problematic drinkers and led to drinking behaviour in the absence of consciousness, awareness and/or controllability (e.g., Tiffany, 1990; Robinson & Berridge, 1993). In the last decade, recent models considered the available empirical data to reframe AB in addiction as the expression of appetitive and/or aversive motivational states regarding alcohol-related cues (e.g., Field et al., 2016). In the same vein, the assessment methods of AB have evolved with the definition of AB made by addiction models. At first, traditional paradigms used single behavioural measures of AB indexing the final output of attentional processing, as traditional models considered AB as a one-dimensional concept. Later, alternative and eye-tracking paradigms aimed to provide different measures disentangling the time course of AB and notably explore the potential approach-avoidance pattern suggested by recent models (Field et al., 2016) in ambivalent patients with SAUD. However, the development of novel assessment methods is getting ahead of the current theoretical conceptualization of AB by dissociating the different components (e.g., facilitated capture of attention by the saccadic choice task, disengagement/reengagement bias by the eye-tracking paradigm in Sanchez et al., 2013) and processes (e.g., spontaneous process by free-viewing task, inhibitory processes by the avoidance task) of AB, while this distinction has not yet raised the interest of addiction models.

2.1.2. Reappraisal of theories regarding the relationship between the reflexive/reward and reflective/control systems

Dual-process models state that SAUD would emerge from an imbalance between two brain systems: (1) the reflective/control system is impaired by the neurotoxic effects of chronic and excessive alcohol use; (2) the reflexive/reward system is over-sensitized by repeated reward resulting from alcohol-related cues exposure. In this view, SAUD is characterized by an under-activated reflective/control system, resulting notably in impaired inhibitory control of drinking behaviours, coupled with an overactivated reflexive/reward system, leading to the occurrence of alcohol-related AB and increased craving (Bechara, 2005; Wiers et al., 2007).

While executive dysfunctions and memory deficits were consistently found among patients with SAUD (Bernardin et al., 2014; Stavro et al., 2013), we showed in the present thesis that one behavioural expression of the overactivation of the reflexive/reward system (i.e., alcohol-related AB) appears highly dependent from the presence of appetitive and/or aversive motivational states in detoxified patients with SAUD as well as among subclinical populations. Although the high variability of AB in detoxified patients might hamper its therapeutic rehabilitation, it could be profitable and actually helpful for maintaining their abstinence, since the continuous overactivation of the reflexive/reward system would request the constant recruitment of their strongly damaged reflective abilities to maintain a control over their attentional and behavioural attraction towards alcohol. Unfortunately, findings from the present thesis were limited to detoxified patients with SAUD and subclinical drinkers, and thus do not allow us to speculate on the level of intra-individual variability regarding the over/under-activation of these two systems when individuals with SAUD were currently drinking and not seeking for treatment.

As described in the previous section (assumption 1.4), dual-process models did not make clear statement regarding whether alcohol-related AB, considered as the behavioural output of the overactivation of the reflexive/reward system, would occur independently (or not) from the activity of the reflective/control system (Hofmann et al., 2008; Strack & Deutsch, 2004). The biased competition model of selective attention (Kastner and Ungerleider, 2000) made a clearer statement about the interaction between those systems by claiming that AB is determined by both bottom-up sensory mechanisms sensitive to stimuli salience and top-down control mechanisms prioritizing the processing of task relevant stimuli. In the same vein, Goldstein and Volkow (2002) described the "impaired response inhibition and salience attribution" syndrome as an inhibition deficit and an increased salience toward alcohol-related cues, both caused by frontal cortex disruption and involved in AB. The present findings provided a preliminary answer to this question, by showing that approach/avoidance AB was not influenced by the saturation of the reflective/control system (Chapter 8) and that inhibitory control abilities were not reduced by the exposure to alcohol-related cues (Chapter 9). Hence, AB would only be determined by bottom-up mechanisms and the different stages of attentional processing (from early/automatic to later/controlled ones) would purely reflect the overactivation of the reflexive/reward system. Nevertheless, limitations regarding the ability of the concurrent task to saturate cognitive resources in Chapter 8 and the recruitment of patients with SAUD mostly reporting low or no craving in Chapter 9 call for caution when interpreting these findings.

Finally, it was suggested, based on the continuum hypothesis (Enoch, 2006), that the dual-process perspective might help to better understand subclinical patterns of excessive alcohol use (Lannoy et al., 2014). However, the exploration of alcohol-related AB in SAUD and binge drinking did not allow us to better appraise this continuity hypothesis, since the severity of alcohol use was much less predictive of the magnitude and direction of AB than transient motivational states. While we observed differential processing of alcohol-related cues among these two populations, it is more likely to be related to the fact that detoxified patients with SAUD frequently present motivational conflict and aversive motivational states towards alcohol, while BD are not seeking for treatment or reduction of their alcohol consumption, as most of them only perceive the positive consequences of their alcohol use (De Wever, & Quaglino, 2016; Kuntsche et al., 2004). As a whole, our data support the idea that the continuum hypothesis does not apply to AB in alcohol-related disorders.

2.2. Methodological implications

2.2.1. Increased reliability of AB measures

The reliability of AB measures has been a frequently raised issue in the literature, as most previous studies investigated AB exclusively through behavioural paradigms (e.g., VPT, addiction Stroop task) which RT measures have been demonstrated as highly unreliable (Ataya et al., 2012). To address this issue, recent research recommended the use of eye-tracking measures as well as the more routine report of reliability estimates in future studies (Christiansen et al., 2015b; Jones et al., 2018a). They argued that this tool would provide a more direct and reliable assessment of AB by exploring consecutive gaze positions throughout the task with a high temporal and spatial resolution, thus informing on the time course of eye movements (Popa et al., 2015).

Following these recommendations, we combined eye-tracking with computerized AB tasks in all our experimental studies and calculated the internal reliability of our measures in each of them (except Chapter 5 because of randomized pairing of stimuli across participants). Eye-tracking indexes of late and more controlled processing stages of AB (i.e., dwell time, second fixation direction) provided excellent reliability, either when combined with the VPT (Chapters 4, 6, 7, 9) or when applied to novel paradigms using strictly eye-tracking measures (Chapter 8). Moreover, they systematically showed much higher reliability than RT measures in the VPT, thus giving much more weight to the avoidance AB systematically observed in our SAUD studies than to the heterogeneous findings regarding AB in previous behavioural research.

However, we failed to provide reliable eye-tracking measures of early and automatic processing stages, since our indexes of the first saccade latency and first fixation duration/direction never reached acceptable reliability (except in Chapter 4). In the case of the VPT, low reliability could be partly due to the horizontal presentation of stimuli which facilitates the appearance of the classical left-gaze bias, leading participants to preferentially orient their attention to the left side of the screen at early processing stages, regardless of the stimuli presented at this side, because of their reading/writing habits (Foulsham et al., 2013). To prevent this effect, future studies could rather use a vertical presentation of stimuli in the VPT (Hakamata et al., 2010). However, this might not be sufficient for the first fixation measures to reach acceptable reliability, as the same problem was found in a free-viewing task using 4x4 matrices of stimuli (Chapter 8). Another reason might be that the VPT and free exploration task used in our studies were characterized by long presentation times of stimuli and no specific instruction on how to process them, thus making them unsuitable for measuring the early attentional capture by alcohol-related stimuli. An attempt to address this issue was provided in Chapter 5 among BD, but the design of the saccadic choice task prevents us from reporting the internal reliability of its eye-tracking indexes. In the same vein, the adaptation of the house-food task described earlier (Chen et al., 2022a) is promising to investigate these early stages but its reliability remains to be estimated. In sum, although all our experimental studies seem to demonstrate the absence of a facilitated attention toward alcohol-related cues at early processing stages, these findings should be supported by studies reporting reliable measures of this specific component of AB.

Altogether, our findings clearly highlighted the need to move away from traditional AB paradigms relying solely on RT measures and encourage the systematic use of neuroscience tools such as eye-tracking to explore AB through more reliable measures. We also encourage researchers to systematically report reliability estimates of their AB measures, in order to quickly identify reliable measures of each component of AB. Moreover, the necessity to ensure sufficient reliability in eye-tracking measures is crucial for correlational studies where the upper bound of the observable correlations depends on the reliability of both variables. Low between-subject variability causes low reliability for individual differences, hampering the likelihood to observe replicable correlations with other factors and potentially undermining published conclusions drawn from correlational relationships. This might be one of the reasons why results regarding correlations between AB measures and other measures such as craving, are not consistent across previous studies, and why null correlations are observed despite sometimes being theoretically highly plausible. The reliability of AB measurements should thus be estimated and reported mandatorily before interpreting significant or non-significant correlations with other variables.

2.2.2. AB evidence through between and/or within-subject comparisons

A statistical question that seems crucial to address, although widely overlooked by previous studies, is related to the criteria chosen to determine the presence of alcohol-related AB among a certain group of drinkers. Could we assume that our experimental group of drinkers effectively show an AB when our statistical analyses demonstrate significant differences in their attentional processing of alcohol-related stimuli compared to the CTL (i.e., between-group comparisons)? Or is the presence of a significant difference in the way alcohol-related stimuli are processed by the experimental group compared to non-alcohol stimuli (i.e., within-group comparisons) sufficient to conclude the presence of AB in this group? Or should we stand by the presence of both significant differences to provide a genuine evidence of AB, i.e., a stronger AB for alcohol-related stimuli in our experimental group compared to non-alcohol stimuli AND compared to the CTL group (i.e., within and between-group comparisons).

The first option might lead to similar situations than in Chapter 4, in which we found longer fixation times for alcohol-related stimuli in BD compared to CTL, thus suggesting the presence of an AB towards alcohol in the experimental group. However, on closer inspection, we observed that this difference was actually related to the fact that CTL spent significantly less time on alcohol compared to non-alcohol stimuli, while BD processed them equally. Although we did not conclude for the presence of alcohol-related AB in binge drinking, one may wonder whether this avoidance of alcohol-related cues in CTL should be considered as “the norm”, meaning that our group of BD were indeed showing a problematic AB for not avoiding them, or whether it rather reflects particularly negative evaluations of alcohol-related cues from our group of LD, thus questioning their validity as a CTL group (see limitations section below). In any case, these findings call for caution when interpreting between-group comparisons regarding AB and invite to reconsider the so-called alcohol-related AB reported in earlier studies. As an example, McAteer et al. (2015) concluded the presence of an alcohol-related AB in heavy drinkers based on between-group differences regarding dwell times on alcohol-related stimuli, although heavy drinkers showed very similar dwell times for alcohol and neutral stimuli (the difference being in how the CTL group processed them).

The second option might raise important issues about the stimuli selection made across studies, since more attention paid to alcohol-related stimuli compared to neutral stimuli in drinkers might not index an alcohol-related AB *per se*, but could rather be due to the appetitive nature of the stimuli (further supporting the relevance of using non-alcohol appetitive stimuli as control stimuli) and/or their perceptual properties (hence demonstrating the importance of controlling stimuli for visual aspects such as colour, luminance or shape). Moreover, by relying only on within-group comparisons and not comparing performances with a CTL group, we cannot conclude that the alcohol-related AB is specific to drinkers, especially given the overexposure to alcohol-related stimuli in Western countries. Therefore, we highly recommend the inclusion of CTL in AB studies, or at least performing correlational analyses between AB measures and validated assessment of the severity/frequency of alcohol use (e.g., AUDIT or binge drinking scores; Maurage et al., 2020a; Saunders et al., 1993).

Given the issues raised by the first two options, the last option clearly appears as the most reliable one to provide genuine evidence of the presence of alcohol-related AB in a specific group of drinkers. Hence, we consistently considered both between- and within-group comparisons in the present thesis when interpreting our results. For example, we argued in Chapter 8 that patients without craving were presenting a genuine avoidance AB for alcohol-related stimuli, since they spent less fixation times on alcohol-related stimuli compared to non-alcohol stimuli and compared to the two other groups (i.e., CTL and patients with craving), but we did not state the presence of an AB directed towards alcohol in patients with craving since they did not show significantly shorter fixation times on alcohol compared to non-alcohol stimuli. While we acknowledge that this recommendation of a joint within/between group approach could considerably increase the number of null findings and would request larger sample size to get sufficient power to detect those interactive effects, we strongly believe that it would enhance the scientific robustness of AB research.

2.3. Clinical implications

2.3.1. The relevance of modifying a non-existent AB

The present thesis highlighted the absence of a robust, long-lasting and permanent AB towards alcohol-related stimuli in detoxified patients with SAUD postulated by dominant models, since most of them were actually more likely to avoid processing these stimuli. In light of these findings, there might be a need for researchers and clinicians to reconsider the clinical relevance of systematizing the inclusion of ABM in the rehabilitation programs offered to patients with SAUD under detoxification treatment. Indeed, some patients might present genuine AB towards alcohol, and training them to override it through ABM might have a beneficial therapeutic impact, but most detoxified patients with SAUD already avoid alcohol-related cues, inevitably raising doubts regarding the usefulness of generalized attention training in this population. In this sense, clinicians should identify patients who will benefit the most from ABM, notably by taking advantage of the increasing accessibility of reliable AB measures such as low-cost eye-tracker.

This questioning about the absence of AB in SAUD was surprisingly not new and usually overlooked by studies on ABM, as underlined by a systematic review on their effectiveness in substance use disorder (Heitmann et al., 2018). Among the nine studies exploring the efficacy of single and multiple sessions of ABM in alcohol use disorders, one of them did not observe a significant AB towards alcohol in their patients at baseline (Field et al., 2007b) and, much more challenging, six of them did not even assess and/or report the presence of AB at baseline (Cox et al., 2015; Field & Eastwood, 2005; McGeary et al., 2014; Schoenmakers et al., 2007; 2010; Wiers et al., 2015). This is of particular concern since it strongly limits the interpretation of findings and prevents from drawing firmer conclusions on the effectiveness of ABM to modify AB. It should be noted that the few estimations conducted by Heitmann et al. (2018) on the available graphs and descriptive statistics actually indicated the absence of AB in their tested population. We therefore recommend future studies on ABM to routinely assess and report the presence/absence of AB at baseline as a minimum standard practice. Furthermore, the largest study exploring ABM in SAUD (Rinck et al., 2018) did not show any alcohol-related AB among their patients at baseline (most of them rather showing an avoidance AB) or any reduction of AB following multiple sessions of ABM. Although one may rightly argue that the null findings regarding AB at baseline could be partly explained by the poor reliability of their AB measures (none of them using eye-tracking measures to assess AB at baseline or at post-test), it seems hard to speculate that the use of more reliable measures in ABM studies would have demonstrated the presence of an AB directed towards alcohol, given the results of the present thesis.

One way to increase the usefulness of ABM in SAUD is to determine their inclusion in the neuropsychological training programs offered to patients with SAUD during their detoxification treatment according to a more patient-tailored approach. Indeed, a recent revision of the incentive-sensitization theory focused on the individual variations regarding the acquisition of incentive salience by alcohol-related cues (Robinson et al., 2014). They suggested that some individuals are more or less prone to approach reward cues (sign-trackers and goal-trackers respectively) and would thus attribute greater or lesser motivational value to these cues (Colaizzi et al., 2020). In the same vein, Milton and Everitt (2010) described alcohol-related AB, subjective craving and seeking behaviour as the “three routes to relapse”, by explaining that each of these outputs acquired by incentive stimuli may contribute to alcohol use in different but complementary pathways. Altogether, these theories posit that AB might play a major role in the development of SAUD for some individuals (and should thus be appropriately modified) but be far less crucial for others. In practical terms, implementing ABM in neuropsychological training programs would be more suitable for patients with SAUD presenting a strong AB towards alcohol at baseline, but also for patients presenting sufficient time and cognitive resources to perform multiple sessions of training during their detoxification stay and achieve therapeutic benefits (Rolland et al., 2019).

Nevertheless, some ABM studies found that modifying AB in the desirable direction was possible even when no AB directed towards alcohol-related cues was observed at baseline (Field & Eastwood, 2005; Field et al., 2007b; Schoenmakers et al., 2007; 2010). These findings challenge the presence of AB at baseline as a prerequisite for the effectiveness of ABM interventions (Heitmann et al., 2018), since they could not only learn to override and control a pre-existing AB towards alcohol but could also train a new avoidance AB for alcohol in patients who did not exhibit such AB directed towards alcohol. Importantly, teaching patients to avoid processing alcohol-related stimuli might play a protective role when exposed to these cues in real life. This could offer an interesting explanation to the positive impact of multi-sessions ABM interventions on symptoms of addiction (Heitmann et al., 2018). Yet, no straightforward association was found in the reviewed studies between these clinical outcomes (e.g., time until relapse, craving) and AB at baseline and/or AB changes after intervention, thus questioning the reliability of their AB measures and/or insinuating that other unspecified mechanisms might also explain the positive effect of ABM on clinical outcomes.

2.3.2. The usefulness of modifying an unstable AB

Beyond the avoidance AB observed in most detoxified patients with SAUD, findings from Chapter 8 also highlighted the key role of current craving at testing time in the direction and magnitude of AB. These findings suggested that patients with SAUD might present an AB strongly affected by their current motivational states, and that these fluctuations of AB would be found within individuals. The high intra-individual variability of AB might hamper the valid and reliable assessment of its modification through attentional training and partly explain the inconsistencies found in ABM studies regarding the association between baseline AB and post-test AB and/or between clinical outcomes and AB changes after training.

The present thesis provided empirical evidence that AB, subjective craving and mood are highly bonded, and emphasized the importance of considering them as intercorrelated to draw multiple clinical avenues regarding prevention and intervention of excessive alcohol use (i.e., binge drinking and SAUD). Indeed, detoxified patients with high craving and/or low abstinence motivation might exhibit stronger AB and would thus benefit more from attentional training (Rinck et al., 2018). Moreover, since AB is more easily triggered by specific motivational states (i.e., high craving, positive alcohol evaluation), ABM interventions could have stronger effects by being administrated when patients are currently experiencing these states, but also by combining them with other therapeutic strategies directly targeting these states (e.g., mindfulness, cognitive regulation of craving, visual cognitive interference; Gratz et al., 2015; Naqvi et al., 2015; Skorka-Brown et al., 2015).

2.3.3. The importance of modifying the right component of AB

In the present thesis, we constantly showed that, besides being highly dependent from internal and contextual transient factors, alcohol-related AB occurs during the later and more controlled processing stages of attention. Therefore, it appears crucial that the attentional training programs proposed to patients with SAUD target the disturbed attentional component operating in alcohol-related AB (i.e., difficulty to disengage from alcohol). Nevertheless, this aspect has been frequently overlooked in previous ABM studies in addiction. Indeed, most of them used the training version of the VPT whereas this behavioural task shows very low internal reliability (Ataya et al., 2012) and might reflect a large variety of attentional mechanisms since it does not differentiate between facilitated detection and difficulty with disengaging attention from alcohol-related stimuli (Jiang & Vartanian, 2018). Moreover, the absence of explicit instructions on how to process the presented stimuli might lead patients to completely ignore alcohol-related stimuli during the task and/or only initiate attentional shifts after probe onset (Notebaert et al., 2015).

There is therefore an urgent need to develop ABM paradigms that specifically target the critical processes of attentional disengagement from alcohol. To do so, future research should draw from the ABM literature in anxiety and depression. To modify AB for threat in social phobia, Heeren et al. (2011) used a modified probe discrimination task in which they included a disengagement training condition consisting of the presentation of a single threatening face followed by an arrow appearing in the location opposite to the threatening face in 95% of the trials. The arrow remained on the screen until patients indicated the direction of the arrow. Ferrari et al. (2016) developed a gaze contingency ABM task with eye-tracking measures consisting of pre-assessment, training and post-assessment of both disengagement from negative pictures and maintained attention to positive pictures in depression. They presented a fixation cross into one of the four quadrants of the screen (instead of the screen centre) and asked participants to fixate it for 500ms before it was replaced by a set of 4 pictures (2 negative, 2 positive) in each quadrant. In the disengagement condition, a negative picture replaced the fixation cross and participants had to disengage from it and shift their attention towards a positive picture for 1000ms. This latter ABM paradigm could be easily adapted to patients with SAUD (by replacing negative/positive pictures with alcohol/non-alcohol stimuli respectively) and offer promising avenues for ABM research (by offering reliable and innovative measures of the effectiveness of ABM).

3. General limitations of the thesis

Beyond the specific limits described in the first section regarding our experimental investigation of the five theoretical assumptions about AB, we will present the general limitations of our work in the following sections, and discuss their repercussions on the generalization of our findings.

3.1. Population studied

Half of the present thesis aimed to investigate the occurrence and nature of alcohol-related AB in the alcohol consumption pattern associated with the most intense neurocognitive consequences, namely SAUD (Le Berre et al., 2017; Stavro et al., 2013). Whereas our studies provided the first eye-tracking data on this clinical population, we exclusively tested recently detoxified patients in clinical settings, which limits the generalization of our findings to the different stages of SAUD that are better described by dominant models (e.g., currently drinking individuals with SAUD). This methodological choice was made (1) for practical reasons, as our scientific collaborations with several Belgian hospitals ensured an easier access to our targeted clinical population, and (2) to control the established effects of acute intoxication on alcohol-related AB (Maurage et al., 2020b) and focus on those related to their chronic and severe alcohol use after the acute withdrawal period. However, the inter-contextual and intra-individual variability of AB suggested by our findings implies that the direction and magnitude of AB might strongly vary with contexts (e.g., clinical *versus* naturalistic settings) and disease course (e.g., readiness to change; Le Berre et al., 2012; Prochaska & DiClemente, 1983). While detoxified patients under treatment are usually characterized by low craving and other negative motivational states regarding alcohol, we could expect currently drinking individuals with SAUD to show more appetitive motivational states (or at least less motivational conflict) for alcohol, and therefore a higher probability to exhibit an AB directed towards alcohol beyond the influence of acute intoxication. This assumption might however remain speculative as it appears difficult to dissociate the effects of acute intoxication from chronic drinking habits on alcohol-related AB in this population (although one potential solution might be to test them at the beginning of the day when they have no or very low blood alcohol level). In contrast, we applied much less control for potential acute intoxication during experiment in binge drinking studies, as we simply ask participants to restrain from alcohol consumption two or three days before the experiment. Controlling for alcohol intoxication should however be a priority, to check that the remaining consequences of recent intoxications do not contaminate the eye-tracking correlates of binge drinking (e.g., Roche and King, 2010; Schoenmakers et al., 2008). Such recent consumption could be controlled by confirming the absence of current intoxication (using a blood alcohol concentration measure) and by excluding people who consumed alcohol in the preceding days (as the cognitive effects of intoxication can last for several days, Stephens et al., 2014).

The validity of the population recruited for our control group might also be questioned, since we frequently observed the presence of an avoidance AB for alcohol-related cues in CTL (Chapters 4, 8 and 9). This finding was not expected, since alcohol-related cues are notably characterized by their appetitive nature which should facilitate attentional attraction towards those cues in every individual, and especially among excessive drinkers for whom the incentive salience of alcohol-related stimuli has been enhanced (Robinson & Berridge, 1993). This avoidance AB might be partly caused by the negative evaluations of alcohol as well as the negative alcohol expectancies (i.e., beliefs about the proximal or distal negative effects of alcohol use) usually observed among LD (Jones et al., 2001; Labbe & Maisto, 2011; Leigh & Stacy, 2004), potentially derived from the well-known deleterious consequences of alcohol on consumers and society (Nutt et al., 2010). Since we thoroughly demonstrated that AB would be more predicted by alcohol evaluations than the severity/frequency of alcohol use, the presence of neutral evaluations and expectancies regarding alcohol might also be considered as selection criteria of our CTL group, or should at least be assessed and controlled for in AB studies. Overall, this limitation provides further support to consider both between- and within-group comparisons when interpreting AB results, as discussed above (see section 2.2.2). Moreover, comparing binge drinkers with light drinkers did not allow us to determine the specific effect of binge drinking patterns on alcohol-related AB, as those groups differed on most alcohol consumption variables in our studies (e.g., higher AUDIT score, higher frequency and intensity of alcohol use) and not only on binge drinking ones (e.g., higher binge drinking score, repeated alternations between intoxication and withdrawal periods). Therefore, the differential processing of alcohol-related cues in binge drinkers might simply result from the severity of their alcohol use compared to controls, and not be caused by the specific deleterious effect of binge drinking habits. Although we used strict selection criteria in Chapters 5 and 6 to differentiate binge drinkers from heavy drinkers, adding the AUDIT score as covariate in statistical analyses or comparing binge drinkers with daily drinkers (who drink similar amount of alcohol per week but more sparsely) would have allowed to better determine the specific effect of binge drinking on alcohol-related AB.

Finally, the present thesis made a focus on AB in binge drinking and SAUD and did not explore its extent to other substance-related stimuli in other substance use disorders. As most theoretical assumptions about AB were made by dominant models in addiction which do not differentiate between different substance users (Field et al., 2016; Robinson & Berridge, 1993; Wiers et al., 2007), their empirical validity should also be explored in those populations. In parallel with alcohol-related AB studies, many researches have been conducted on AB towards smoking cues in smokers using various behavioural, eye-tracking and other neuroscience measures (e.g., Rehme et al., 2018; Schröder & Mühlberger, 2022; Wetherill et al., 2014). Unifying all these results would help us integrate their main conclusions in the theoretical conceptualizations of AB and craving in addiction.

3.2. Assessment of variables associated with AB

While the present thesis has endeavoured to use the most reliable measures of AB, our assessment of key variables such as current craving bare limitations that should be highlighted. First, subjective craving experience was evaluated through self-reported measures. Although known as the best and only available measure of explicit craving, these measures are affected by various biases that undermine the association between self-reported craving and the state that the participant was currently experiencing (Field et al., 2009). Moreover, some participants might show some difficulty in accurately assessing their own internal states (due to poor metacognitive abilities; Flaudias et al., 2019) and/or some patients with SAUD might not want to give a sincere answer to their desire to consume alcohol during their detoxification treatment. Even when accounting for the physiological dimension of craving (Flaudias et al., 2019; Naqvi et al., 2004), its assessment actually relies on proxy measures of the bodily/interoceptive manifestations of craving, such as the physiological arousal (e.g., cardiac or electrodermal activity; van Lier et al., 2020) induced by an exposure to substance-related cues. Therefore, we should keep in mind that no psychometric measure of craving could offer a pure readout of this subjective state.

Like many previous studies in addiction, we provide an assessment of momentary self-reported craving using the single-item VAS in all our studies. Although this assessment is short and easy to implement in clinical settings, it bares limitations regarding its reliability compared to multi-items scales (Sayette et al., 2000) and the choice of terminology (e.g., craving, urge or desire to consume alcohol might not have the same meaning for every individual). To address this issue, we also used well-validated multi-item questionnaires in our studies to offer a complementary assessment of subjective craving. However, we usually found stronger associations between AB and VAS than between AB and those multi-items scales (e.g., Alcohol Craving Questionnaire), which might be related to their specific limitations (i.e., anchoring all responses to items based on the initial item's response and/or participants' attempts to remain consistent across items; Field et al., 2009).

Moreover, exploring the influence of current craving on the magnitude of AB did not allow for a comprehensive testing of Field et al. (2016)'s model. Indeed, craving is defined as a subjectively experienced appetitive motivational state that fluctuates over time (Field et al., 2009). However, this definition does not extend to aversive or avoidant motivational states such as the desire to limit alcohol use. None of the current or previous studies explored the association between AB and self-reported measures of these aversive motivational states, such as the avoidance subscale of the Approach and Avoidance of Alcohol Questionnaire (McEvoy et al., 2004) or the negative expectancies subscale of the Alcohol Expectancy Questionnaire (Brown et al., 1987). The assessment of a larger range of fluctuant motivational states might provide a better understanding of the motivational conflict experienced by our clinical sample, as well as their general thoughts and evaluations of alcohol, and could therefore extend our experimental exploration of their influence on AB.

Finally, we did not follow-up the SAUD symptoms and relapse rates of our tested patients, which prevents us from exploring the association between the magnitude of AB at testing time (when assessed through reliable eye-tracking measures) and clinical outcomes a few months later. This lack of knowledge limited the clinical implications of the present thesis, since an unstable AB without any impact on SAUD symptoms would strongly question the clinical relevance of extending the exploration of the nature of AB. Nevertheless, findings from ABM studies showed that these interventions would have a modest positive effect on clinical outcomes (Heitmann et al., 2018; Boffo et al., 2019), thus suggesting that AB actually plays a causal role in SAUD persistence. To support this assumption, further research is needed to explore the relationship between AB and relapse risk through the use of reliable measures, for example by assessing whether reliable AB measures could predict the treatment outcomes (e.g., relapse rate) at 6-month follow-up.

3.3. Stimuli selection

The stimuli selection procedure is a recurrent methodological issue in the AB literature that could strongly reduce the validity of alcohol-related AB paradigms and measures. Several recommendations have been formulated to improve the methodological rigour of AB research (Pennington et al., 2021) and were mostly followed in our studies. Nevertheless, the specific needs of each study required the use of different set of stimuli, with their own advantages and criticisms.

Most of our studies used the openly available ABPS battery (Pronk et al., 2015) to present validated and well-matched stimuli regarding their perceptual properties (e.g., arousal, brightness, colour) and facilitate the replication of our findings. Nevertheless, this battery is composed of pictures of alcoholic and non-alcoholic beverages presented on a white background, which strongly reduces the ecological validity of the stimuli and mask potential AB towards alcohol in more naturalistic settings. In contrast, we used pictures depicting alcoholic beverages and flowers with context in Chapter 5, which on the one hand improved the ecological validity of our stimuli but on the other hand raised matching issues in terms of luminance or main object size. Another concern about those stimuli sets is the use of identical stimuli for all participants, while variations in preferred alcohol drinks might highly influenced AB magnitude. To address this issue, we recruited BD mostly drinking beer and only used Belgian beer pictures as alcohol-related stimuli in Chapter 6. However, while the use of more individualized stimuli has been shown to improve internal reliability (Christiansen et al., 2015b), they also decrease the comparability across participants and/or studies.

3.4. Eye-tracking indexes

In the present thesis, all our studies capitalized on the hypothesized link between eye-tracking indexes and attentional processes underlying AB, leading to potential over-interpretations. Indeed, despite the established usefulness of eye-tracking, the interpretative gap between the actual indexes measured and the processes estimated should always be kept in mind. Eye-tracking actually allows to measure gaze location, as well as eye movements' characteristics (e.g., fixation, saccade, pursuit, blink) or eye-related factors (e.g., pupillary diameter), but these measures are not purely reflecting attentional processing. Indeed, eye movements' patterns should be cautiously interpreted as they can be influenced by various bottom-up (e.g., stimuli brightness, color, movement) or top-down (e.g., previous experience, expectations, goals) sources. Moreover, eye-tracking only captures the foveal vision, yet visual stimuli can be processed by the peripheral retina and this processing is even likely to influence the subsequent analysis in foveal vision, in particular when peripheral stimuli have a high salience or are affectively-laden (D'Hondt et al., 2013).

Overall, it is therefore important to carefully choose the task administered to participants, as well as the eye-tracking measures to consider, in order to draw accurate conclusions on the basis of gaze behaviour, especially to infer the cognitive processes responsible for the eye movements.

This is particularly true for dwell time: Our basic assumption behind dwell time is that it reflected the time spent looking at specific stimuli, and thus the attentional resources or AB dedicated to these stimuli. However, increased dwell time could also be related to uncontrolled variables as cognitive processing difficulty (Rayner et al., 1978), drowsiness or low arousal (Chapman and Underwood, 1998). For example, the free viewing task combined with eye-tracking measures in Chapter 8 did not specifically request participants to pay attention to the cues, since they were neither presented as distractors nor goal-oriented stimuli. While being more ecological, this absence of goal-oriented instructions did not ensure that participants were actually paying attention to the cues when looking at the screen.

Moreover, we interpreted dwell time as the controlled processing of attention maintenance. However, some authors interpreted reduced dwell time as reflecting lower automatic attentional capture by the substance (Lee and Lee, 2015). Conversely, we considered initial fixation or saccadic latency as indexing automatic attentional capture, as they are fast and early. However, automatic processes are not always fast, as they can be triggered after a delay. Furthermore, we recruited participants from Western cultures, who usually have a left-to-right oriented visual scanning (Dickinson and Intraub, 2009; Foulsham et al., 2013; Zelinsky, 1996). In free exploration tasks such as the VPT and the free-viewing task, we can thus expect participants to typically start their exploration on the left (Nuthmann and Matthias, 2014). This left-to-right scanning probably lowered the potential effect of stimuli content on the first fixation orientation. As a whole, the present thesis bares limitations by implicitly taking for granted that each eye-tracking index used in our experimental studies was a quite direct reflect of specific AB processes.

Finally, we did not take advantage of all the measures offered by the use of eye-tracking to investigate AB. Indeed, most of our studies have been limited to the exploration of saccadic eye movements and gaze fixations, thus solely indexing the overt aspect of attentional processing. Nevertheless, the measure of covert attention, through pupil size and micro-saccades measures (Lv et al., 2022; Mathôt & Van der Stigchel, 2015), has been forsaken in the present thesis (except for fixational eye movements in our exploratory analyses from Chapter 9), which prevented us from offering a comprehensive assessment of the alcohol-related AB.

The reported limitations regarding the exploration of AB through eye-tracking indexes might partly be overcome by complementing this approach with innovative AB tasks and/or other cognitive biases measures. First, we should give more consideration to the use of alternative behavioural paradigms specifically designed to assess temporal dynamics of AB (e.g., early encoding stages using the attentional blink paradigm; DePalma et al., 2017; Elton et al., 2021) and/or components of AB (e.g., engagement *versus* disengagement AB using the odd-one-out task; Heitmann et al., 2020; 2021). Second, the assessment of other cognitive biases associated with AB (i.e., alcohol approach bias; Wiers et al., 2017) can also provide experimental insights on the overactivation of the reflexive/reward system, notably through the use of alcohol approach/avoidance task (e.g., Chen et al., 2022b).

4. Perspectives for future research

Among all the recommendations and proposals disseminated throughout this discussion, we will now emphasize the two avenues of investigation that should in our view be prioritized. First, we will provide recommendations to improve the methodological rigor of AB assessment and discuss the various opportunities offered by eye-tracking technology. Second, we will highlight the next steps to be taken by the field to determine the clinical relevance of exploring alcohol-related AB in alcohol use disorders.

4.1. Understanding the underlying processes of AB and improving eye-tracking measures

As most studies exploring alcohol-related AB did not report sample size justification or statistical power computation and were based on quite limited sample sizes, the first global advice for future work is to provide a priori power analyses and to capitalize on larger samples, ensuring the reliable detection of existing effects (Maurage et al., 2020b). This a priori power computation should even be included in a more systematic trend to pre-register the methods and hypotheses of the planned studies, a practice that has become common in several scientific domains but that remains marginal in AB studies. More specifically, regarding AB measures, a key recommendation is to evolve towards the standardization of the designs used. While the search for innovative paradigms has been initiated, the establishment of uniform and sound designs specifically evaluating each AB process, together with valid and reliable eye-tracking measures, would allow a valid comparison across studies.

Such homogenization has been started in the field by mostly using the VPT to explore AB. Keeping in mind the limits raised above about this task and the need to combine it with complementary AB measures, the eye-tracking measurements during this task are useful to provide a first insight on the attentional processes involved when drinkers face alcohol-related and non-alcohol-related stimuli. Nevertheless, there is a need to determine guidelines for exploring AB through the VPT. Indeed, despite the use of the same paradigm, some methodological choices differ across studies (e.g., using an arrow, a crosshair, or a dot as targets, leading to discrepancies in participant's task), which could decrease inter-studies comparability. More centrally, the eye-tracking indexes measured strongly vary across studies, AB having been assessed by: (1) averaging the mean fixation time on each stimulus (e.g., Monem & Fillmore, 2017); (2) calculating the proportion of fixation time or of numbers of fixations made on each stimuli category (e.g., Lee et al., 2014); (3) calculating a bias score by subtracting the average dwell time on neutral stimuli from the average dwell time on alcohol stimuli (e.g., Marks et al., 2015); and (4) counting the number of fixations made on each stimuli (e.g., Roy-Charland et al., 2017). These different methods for calculating a seemingly identical construct can explain incongruencies across results, and methodology could thus be optimized to unravel the mechanisms sustaining AB: first saccade direction or first saccade latency can inform on the initial capture of attention; first fixation duration on early attentional engagement; total dwell time on attentional maintenance; proportion of second fixation on attentional disengagement and reengagement. Future studies should therefore take advantage of the diversity of eye-tracking indexes to explore the different components of AB and not be restricted to dwell time measurements.

In addition to the diversity of AB components assessed within a single task, a surge of interest was recently found for the development of various AB paradigms tapping on different underlying processes (e.g., spontaneous processes *versus* inhibitory processes) and/or targeting specific sub-components of AB (e.g., facilitated capture, disengagement and reengagement of attention, attentional monitoring). As underlined by the absence of correlation in Chapter 9 between dwell time in the visual probe task and break frequency in the avoidance task, these paradigms explore AB under very different conditions (spontaneous exploration *versus* forced avoidance) and might thus assess distinct processes. In this vein, future research should define AB as a multidimensional concept and systematically specify which components and/or processes of AB they aimed to investigate with the different tasks and/or measures of their experimental design.

Furthermore, recent eye-tracking research opened up the field of possibilities by proposing pupil size as a robust marker of attentional processing (Laeng et al., 2012; Pietrock et al., 2019). This proposal was notably made in the field of addiction by a recent study exploring attentional capture by nicotine-related stimuli in smokers (Blini & Zorzi, 2022). After a traditional assessment of AB through the VPT combined with eye-tracking measures, they administered a passive viewing task requiring participants to simply fixate a scrambled and clear version of smoke-related or neutral stimuli for 1 and 3 seconds respectively. Pupil diameter was measured continuously to acquire indices of autonomic activation for smoke-related stimuli. Critically, patterns of pupil dilation and constriction for those stimuli better predicted the smoking status of participants than RT, first fixation direction and dwell times measures in the VPT. Indeed, they found group differences in the time course of pupil dilation to nicotine stimuli while these differences were not observed for behavioral and eye fixation measures. Although the passive viewing task with one single stimulus at a time might actually provide an assessment of cue reactivity rather than AB towards nicotine *per se* (because it does not allow the study of the preferential allocation of attention to one stimulus over another), the replication of these findings to alcohol-related AB in alcohol use disorders could challenge the main conclusions drawn in the present thesis.

More centrally, the exploration of eye movements through the use of an eye-tracker provided us a much more reliable assessment of AB than RT measures in the present thesis, but at the same time it restrained us to the investigation of a specific part of attentional processes, namely overt attention. Therefore, the experimental data provided here did not offer a complete and exhaustive answer to the main theoretical questions about AB. Although Chapter 9 offered preliminary insights on the covert aspects of AB (notably suggesting that they go in the same direction than overt dwell time measures), future works should deepen these exploratory results by using paradigms directly dedicated at covert attention measurements. First, future research could simultaneously explore overt and covert attention shifts towards alcohol-related stimuli by combining eye-tracking measures with EEG and AB paradigms requiring eye movements to be either executed or withheld (Kulke et al., 2016; 2021). Second, the eye-tracking technology also allows to measure covert shifts of attention through micro-saccadic movements and pupillometry (Mathôt & Van der Stigchel, 2015; Yuval-Greenberg et al., 2014). There is a recent surge of interest in developing AB paradigms exploring covert attention through these measures (e.g., Lv et al., 2022; Salvaggio et al., 2022). Capitalizing on this trend, future research should adapt these novel paradigms in order to apply them in the field of addiction.

4.2. Reappraising the clinical relevance of AB in alcohol use disorders

Once all methodological recommendations have been implemented to provide the most valid and comprehensive assessment of alcohol-related AB, the exploration of the intra-individual stability of AB should become the priority for future studies to determine its clinical relevance. To do so, researchers should conduct longitudinal studies exploring the consistency of AB at different time points (notably by using ecological momentary assessment designs) and/or studies exploring whether the induction of specific motivational states might condition the occurrence of AB (e.g., craving induction *versus* reduction procedures).

Two main possibilities might be considered regarding this stability. First, the intra-individual stability of AB is established, which means that AB towards alcohol would only occur in a subgroup of drinkers but would stay constant among those specific drinkers. In this case, a further step would be to determine the impact of this stable trait on relapse risk and other clinical outcomes compared to drinkers who are not affected by this preferential allocation of attentional resources towards alcohol. If AB appears as a causal factor for SAUD persistence among those individuals, clinicians should offer them individualized rehabilitation programs which prioritize the implementation of ABM during their detoxification treatment. Second, AB is rather characterized by intra-individual variability, as it occurs in most drinkers when expressing congruent motivational states (e.g., after craving induction). Therefore, the magnitude and direction of AB would highly fluctuate within individuals according to momentary motivational states. In this case, future research should be dedicated to the better understanding of the psychological mechanisms triggering these transient states, as they might constitute relevant therapeutic target in SAUD treatment. In this view, further research using reliable measures to investigate the reciprocal relationship between AB and craving would help to determine whether ABM remains a relevant tool to reduce appetitive motivational states such as craving, and therefore decrease the relapse risk. Although the clinical relevance of ABM is still debated (Cristea et al., 2016; Boffo et al., 2019), the intra-individual variability of AB might partly explain the frequent absence of association between AB at baseline and clinical outcomes at follow-up (Heitmann et al., 2018), since patients might not exhibit an AB at that specific testing time but would progressively learn to override this fluctuant AB following multi-sessions of ABM.

The present thesis provided some initial insights on the intra-individual stability of AB, notably through the MIP used in BD (Chapter 6) and the test-retest design used in patients with SAUD (Chapter 7). These findings suggest that AB strongly varies within individuals across time and could occur in the majority of BD or detoxified patients with SAUD only if they are currently expressing congruent motivational states (e.g., high craving). However, we are blind regarding the core determinants of the expression of craving. Indeed, our correlational and regression analyses did not bring out any psychological (e.g., depression, trait or state anxiety, impulsivity) or consumption (e.g., AUDIT, SAUD or abstinence duration, doses per day, number of previous treatment) factors that might trigger the occurrence of craving or AB. One lead was offered by findings from Chapter 6, which revealed that participants were more likely to report craving when they endorsed binge drinking habits and experienced negative mood. This is in line with meta-analyses revealing that negative mood was a relevant craving predictor (Bresin et al., 2018; Cyr et al., 2022), and with the affective processing model of negative reinforcement (Baker et al., 2004) suggesting that the desire to consume is predominantly motivated by the escape and avoidance of negative mood.

Overall, although the causal role of AB in addiction is still debated, the clinical value of its assessment and modification is twofold. First, it appears as a valid marker of motivational states which naturally fluctuates over time (Christiansen et al., 2015a). Even if considered as the behavioural expression of these states, it can still represent a useful proxy for clinically meaningful information such as current craving, momentary evaluations of alcohol and/or affective reaction to alcohol-related stimuli, as it would rely on objective and reliable eye-tracking measures rather than self-reported ones (Blini & Zoriz, 2022). Therefore, deepening our knowledge about the nature of AB might help in developing useful and objective indices of these internal states. Second, the clinical relevance of AB lies in its relationship with craving, a DSM-V criterion for alcohol use disorders that has been extensively associated with prospective alcohol use and relapse (Vafaie & Kober, 2022). Whether AB has a triggering and amplifying effect on craving, its effective modification could break the vicious circle of addiction by providing a crucial lever on craving and therefore relapse risk. In this view, alcohol-related AB would not be the key factor in relapse prevention. However, improving the effectiveness of ABM would provide a new neuropsychological tool for reducing craving, in conjunction with psychotherapeutic methods directly targeting craving (e.g., meditation, mindfulness).

Conclusion

This Ph.D. thesis contributed to a better understanding of AB in alcohol use disorders by experimentally testing the key theoretical assumptions commonly made about the nature of AB in a population of BD and detoxified patients with SAUD. We went beyond traditional paradigms assessing AB through behavioural RT measures, which continue to be used routinely in both research and clinical settings despite their poor reliability, to promote the use of direct and efficient eye-tracking measures. Our main findings casted doubts on several proposals made by dominant models in addiction regarding alcohol-related AB, and led to the proposal that AB should be reconsidered at both theoretical and clinical levels.

First, we challenged the common idea that the magnitude of AB towards alcohol-related stimuli increases with the severity or intensity of alcohol use, as patients with SAUD (recruited to investigate the psychological mechanisms of the most severe pattern of alcohol use disorder) were actually more likely to avoid than approach these cues. Second, the way individuals preferentially processed those cues was better predicted by their motivational states at testing time (i.e., reported subjective craving) than by their chronic drinking habits (e.g., binge drinking pattern or SAUD), hence questioning the stability of AB across transient internal or contextual states. Third, the differential processing (i.e., approach or avoidance tendencies) of alcohol-related stimuli was systematically observed by eye-tracking indexes related to later and more controlled stages of attentional processing, thus contesting the traditional conceptualization of AB as an automatic hijacking of attentional resources by alcohol-related cues, affecting the early stages of attentional processing. Fourth, although some uncertainties remain about the influence of high-level reflective functioning on the occurrence and magnitude of AB, our findings offer preliminary support to the theoretical assumption of an independence between the reflexive/reward system and the reflective/control one. Fifth and finally, the preferential allocation of attentional resources would generalize to various types of appetitive stimuli in BD (i.e., alcohol, but also soft drinks and high-calories food), and would become specific to alcohol-related stimuli in the more severe forms of excessive alcohol use.

Overall, our results called for a reappraisal of dominant models in addiction regarding the role attributed to AB in the development and maintenance of the disorder. They rather provided empirical support to more recent theoretical proposals that accounted for the inter- and intra-individual variations of AB in alcohol use disorders. After highlighting the main methodological limitations encountered in previous studies, we endeavoured to offer the most direct and reliable assessment of the different components of AB, while remaining cautious about how our statistical results can actually be interpreted as indexing alcohol-related AB. Our findings also present major clinical implications since they strongly question the relevance and usefulness of implementing ABM in clinical settings when AB actually appears to be highly unstable and frequently not oriented towards alcohol (but rather away from alcohol) in most recently-detoxified patients with SAUD. Therefore, we strongly encourage future research to further explore the intra-individual stability of AB through a more valid and comprehensive assessment of AB, in order to clarify the clinical relevance of AB and to identify the ideal conditions for implementing ABM to maximise its therapeutic benefits.

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Appendix A

Description of the results related to other constructs relevant to AB from the reviewed studies in Chapter 2

1. Clinical population

1.1. Behavioral data

Influence of psychopathological variables on the relationship between AB and alcohol use. Three studies focused on the potential effects of psychopathological comorbidities on alcohol AB in SAUD patients (Fridrici et al., 2014; Müller-Oehring et al., 2019; Sinclair et al., 2016). Sinclair et al. (2016) administered a visual probe task using disorder-specific words to a large sample of outpatients with one or more comorbid conditions (e.g. depression, hypomania, anxiety, other substance use disorder). Results showed the presence of an alcohol AB – regardless of the group sample. Moreover, this AB was not correlated with the number or severity of comorbid conditions. Fridrici et al. (2014) investigated alcohol AB in detoxified outpatients with or without major depression. They used a modified Stroop task with alcohol-related, negative and neutral words. The authors did not find a more pronounced alcohol AB in patients with or without depression. Findings from these two studies suggested that psychiatric comorbidities have no influence on the magnitude of alcohol AB among patients. Finally, Müller-Oehring et al. (2019) explored the effect of cannabis use disorder on AB in detoxified SAUD patients. They asked participants to perform a modified Stroop task with alcohol, cannabis and neutral words. Surprisingly, later onset of cannabis use disorder and lighter cannabis use per month contributed to a stronger alcohol AB. These findings suggest that cannabis use could have a protective role on alcohol AB. Another study (Garland, 2011) measured the association between alcohol AB and trait mindfulness (i.e. nonreactive and nonjudgmental awareness of moment-by-moment cognition, emotion and sensation) in detoxified patients. The author found that alcohol-related AB, assessed by a spatial cueing task, was negatively associated with trait mindfulness.

Effect of medical treatment on alcohol AB. As mentioned above, Beraha et al. (2018) explored the effect of Baclofen treatment on AB in detoxified inpatients with SAUD. They were assigned in either baclofen or placebo groups. They performed a visual probe task (T1) at baseline and four weeks after the baclofen or placebo treatment (T2). A negative mood induction took place before each task. At T1, patients showed an AB towards alcohol at 500ms and an avoidance AB away from alcohol at 1500ms. At T2, patients who received the baclofen treatment showed a change in their AB after four weeks of treatment, as their avoidance AB was also found for alcohol-related stimuli presented for 500ms. These findings therefore support the benefic effects of baclofen on alcohol AB. Nevertheless, it should be noted that the effect of negative mood induction on AB could not be determined as no control condition was performed. Moreover, the combination of medication with psychotherapy might have limited the additional effects of baclofen on AB.

1.2. Eye-tracking data

Influence of psychological variables on the relationship between AB and alcohol use. Bollen et al. (2021) found a positive correlation among SAUD patients between dwell times for alcohol-related cues and depressive symptoms. They also showed that higher impulsivity was associated with stronger AB scores in controls.

2. Subclinical populations

2.1. Behavioral data

Influence of psychological/cognitive variables on the relationship between AB and alcohol use. Fadardi & Cox (2008) specifically investigated the predictive role of alcohol AB and maladaptive motivational structure on alcohol consumption in social drinkers. Results showed that alcohol Stroop interference and maladaptive motivation were both positive predictors of alcohol consumption. Alcohol AB did not however mediate the effects of motivational structure. Four studies from the same laboratory explored the variation of alcohol AB according to the intensity of alcohol-related problems and intellectual disabilities. In van Duijvenbode et al. (2012), participants with borderline or mild intellectual quotient performed a visual probe task. Results showed no association between alcohol AB and intellectual impairments, as groups did not differ for reaction times. Groups were however composed of heterogeneous sample size (with only 9 participants in the mild IQ group). Similar findings were found in other studies from the same laboratory, recruiting participants with or without mild to borderline intellectual disability (van Duijvenbode et al., 2016, 2017a, 2017b). Emery and Simons (2015) measured the effects of positive and negative mood on alcohol AB in college drinkers, and whether these effects were moderated by drinking motives. Participants performed visual probe tasks before and after mood induction (positive, negative or neutral). Results showed that alcohol AB was neither predicted by the mood induced nor moderated by drinking motives. However, the split-half and test-retest reliability of the visual probe task was very low, which might explain the largely null findings reported. Another study investigated how social anxiety and drinking coping motives might influence alcohol AB (Carrigan et al., 2004). Participants with large range of social anxiety performed a modified Stroop task with alcohol-related, social threat and neutral words. Alcohol interference scores were associated with drinking to cope measures, but not with social anxiety. These interference scores were higher in participants reporting a frequent use of alcohol to reduce anxiety prior to social situations, underlying the link between social anxiety and alcohol consumption.

Influence of demographics and environment on the relationship between AB and alcohol use. Three studies investigated the role of gender and contextual variables on alcohol AB in subclinical populations (Albery et al., 2015; Emery & Simons, 2015; Groefsema et al., 2016). Albery et al. (2015) assessed participants levels of exposure to alcohol-related environment (high, low – whether or not working in a bar or pub). Light social drinkers showed alcohol Stroop interferences only when they were working in an alcohol-related environment. Heavy social drinkers showed alcohol interferences - regardless of their level of alcohol exposure. Alcohol AB appeared dependent on the exposure to alcohol-related environment only in light social drinkers. As described earlier, Groefsema et al. (2016) determined whether social drinkers showed cognitive biases specific to social alcohol-related stimuli and whether they were associated with alcohol use in social drinking contexts. Results showed that the alcohol AB specific to social pictures was positively correlated with alcohol use and the number of friends of opposite gender in drinking contexts. Alcohol AB in social drinkers thus appeared related to situation-specific drinking behavior. The authors also showed that women presented higher alcohol AB than men.

Influence of physiological variables on alcohol AB. Pieters et al. (2011) explored the moderating role of the OPRM1 (reflecting both liking and wanting processes) and DRD4 (reflecting wanting processes specifically) polymorphisms on the association between alcohol AB and alcohol consumption. In the first experiment, alcohol AB positively predicted alcohol frequency and intensity only in early adolescents with an OPRM1 risk profile. In the second experiment, alcohol AB was associated with problem drinking only in young adult men with DRD4 risk genotype. In early adolescence, the association between alcohol AB and alcohol consumption is related to both liking and wanting processes. This association is specifically related to wanting processes in young adult heavy drinkers. Elton et al. (2021) investigated the mediating role of the dopaminergic pathways on alcohol AB by using a dopamine precursor depletion procedure. During two sessions, participants underwent a placebo-controlled depletion procedure followed by a resting-state fMRI. They then completed two alcohol AB tasks (visual probe task and attentional blink task) and a reward task assessing AB towards reward-conditioned cues. For the visual probe task, individuals reporting greater current binge drinking showed higher alcohol AB following placebo. This AB effect was reduced when undergoing the dopamine precursor depletion procedure. For the attentional blink task, decrease of alcohol AB following depletion procedure was moderated by adolescent rather than current binge drinking. Therefore, such findings support the role of dopamine in alcohol AB, especially in individuals with greater past or present binge drinking. Finally, van den Wildenberg et al. (2006) investigated the correlation between alcohol induced heart rate acceleration (1.0mL/kg of alcohol) and implicit alcohol-related cognitions in male heavy drinkers. Results showed that alcohol Stroop interference was unrelated to ethanol-induced heart rate change. The authors concluded that alcohol implicit associations and alcohol AB were unrelated to individual variations in the sensitivity of alcohol's activating effects.

Effect of training interventions on alcohol AB. Three studies finally explored the effects of ABM training on alcohol-related AB in subclinical drinkers which were not seeking for treatment (Fadardi & Cox, 2009; Langbridge et al., 2019; Luehring-Jones et al., 2017). In Fadardi and Cox (2009), hazardous and harmful drinkers were trained to modify their alcohol AB with the Alcohol Attention-Control Training Program for two and four sessions respectively. After ABM, both hazardous and harmful drinkers showed a decrease in classic and alcohol interference scores and an increase in motivation to change after AB training. Moreover, harmful drinkers reduced alcohol consumption after AB training. The authors did not include randomized control trials with a control group, which did not allow for the evaluation of the training program. Similar findings were found in Luehring-Jones and al. (2017), who investigated the effectiveness of a single session of ABM in reducing craving and alcohol AB in young social drinkers. Participants were randomly assigned to active ABM training or sham training condition. Alcohol AB tasks (visual probe task and alcohol Stroop task), an implicit association task and a cue-induced craving task were administered at baseline and during the post-training assessment. At baseline, alcohol Stroop interference was only correlated with the number of drinks per occasion. Active ABM training reduced alcohol AB scores in visual probe and alcohol Stroop tasks, and indirectly reduced craving through a decrease in Stroop interference scores. Alcohol AB was therefore was reduced by a single session of ABM training. Nevertheless, Langbridge et al. (2019) did not observe any beneficial effect of ABM in binge drinking. In their study, binge drinkers received either ABM, sense of control training, both interventions, or no intervention. They were compared against non-binge drinkers who did not receive any intervention. After the intervention, the alcohol AB decreased over time in all participants, regardless of the intervention administered. Alcohol consumption in binge drinkers was reduced when receiving the combined interventions. While binge drinkers showed higher alcohol AB than non-binge drinkers at baseline, these findings showed the null effect of ABM on alcohol AB in binge drinking. The authors however underlined the insufficient power of their analyses to detect group differences.

2.2. Eye-tracking data

Influence of psychological variables on the relationship between AB and alcohol use. In van Duijvenbode et al. (2012), participants with long term abstinence were grouped according to intellectual impairments (none or mild to borderline). Results showed that participants did not present AB, independently of intellectual abilities. Similar findings were found in van Duijvenbode et al. (2017a), who showed that the intensity of alcohol AB did not differ according to participants' IQ. This study therefore confirmed that the intensity of intellectual disabilities did not influence alcohol AB.

Appendix B

Supplementary analyses from Chapter 4

1. First fixation laterality

A main LATERALITY effect was found in the drink [$F(1,83)=64.836$, $p<.001$], drink-food [$F(1,83)=112.357$, $p<.001$] and food [$F(1,83)=160.072$, $p<.001$] blocks, showing higher frequency of first fixations on the left than right side of the screen. No significant main GROUP effect nor significant interaction was found in any block ($p>.050$).

2. Time course analyses

For the T1 dwell time, no significant main GROUP or TYPE effect nor significant interaction were found in the drink block ($p>.050$). For the T2 dwell time, a main TYPE effect [$F(1,83)=10.037$, $p=.002$] was found in the drink block, showing longer fixation time on soft drinks compared to alcohol. An interaction between GROUP and TYPE [$F(1,83)=6.188$, $p=.015$] was found: CTL showed longer fixation time on soft drinks compared to alcohol [$t(42)=-3.252$, p=.002] and compared to BD [$t(83)=-2.220$, $p=.029$].

3. Gender effect on high-calorie food

In the drink-food block, we found the same effect of TYPE in the drink–food [$F(1,81)=31.860$, $p<.001$, $\eta^2=.282$] and food [$F(1,81)=4.042$, $p=.048$, $\eta^2=.048$] blocks, showing a longer dwell time on soft drinks and food compared to alcohol, and on healthy food compared to sugary food. We also found the same interaction between TYPE and GROUP in the drink–food [$F(1,81)=8.102$, $p=.006$, $\eta^2=.091$] and food [$F(1,81)=7.181$, $p=.009$, $\eta^2=.081$] blocks. We found no interaction between TYPE and GENDER, nor main effect of GROUP in any block ($p>.050$).

Appendix C

Supplementary analyses from Chapter 5

1. Alcohol vs flower Task (with CTL participants ≤ 4 on AUDIT score)

Accuracy. The 2x2 ANCOVA on mean error rates for the first saccade revealed no main effect of Target (p=.158), Group (p=.623) or interaction between these two factors (p=.802).

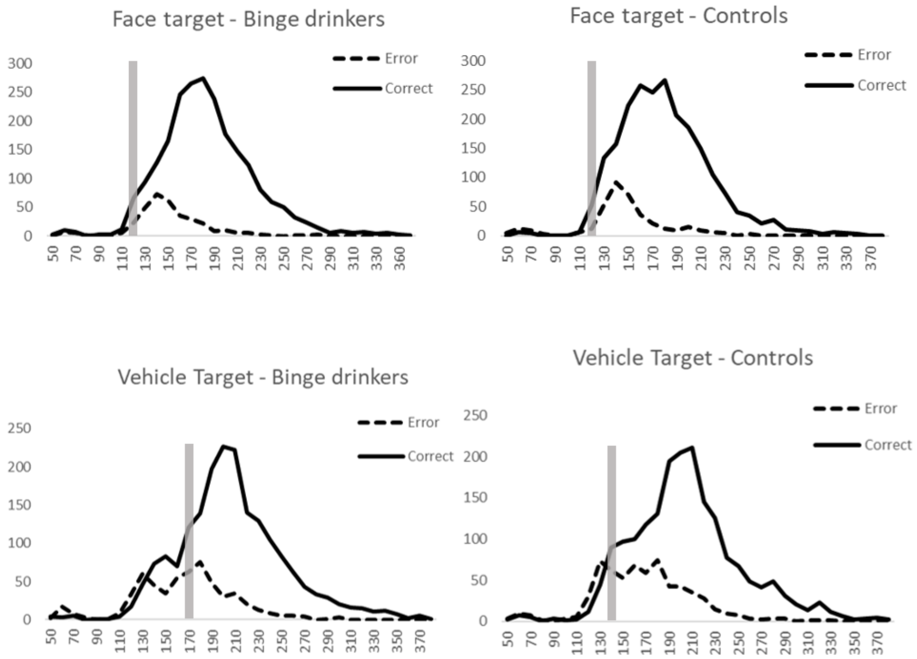
Latency and amplitude of the correct first saccade. The 2x2 ANCOVA on mean SRT for the correct first saccade showed a main effect of Target ($F_{1,73}$=7.99, p=.006, η_p^2=.099). Participants initiated their correct first saccade faster when the target stimulus was an alcoholic beverage (190±26ms) than when it was a flower (197±27ms). We observed neither Group effect (p=.432), nor interaction between Group and Target (p=.705). The 2x2 ANCOVA on mean amplitude for the correct first saccade showed no main effect of Target (p=.893), Group (p=.223) or interaction between these two factors (p=.148).

Proportion and latency of the corrective second saccade. The 2x2 ANCOVA performed on proportion of corrective saccade revealed a significant interaction between Target and Group ($F_{1,73}$=4.18, p=.045, η_p^2=.054). Post-Hoc independent sample t-tests showed that binge drinkers made fewer corrective saccades than controls when the target stimulus was a flower (BD: 63.15±22.22%; CTL: 74.88±16.42%; t_{74}=2.647, p=.010) but groups did not differ when the target stimulus was an alcoholic beverage (p=.556). We observed neither Target (p=.314) or Group (p=.153) effects. The 2x2 ANCOVA performed on mean SRT for the corrective saccade revealed no main effect of Target (p=.422), Group (p=.696) or interaction between these two factors (p=.842).

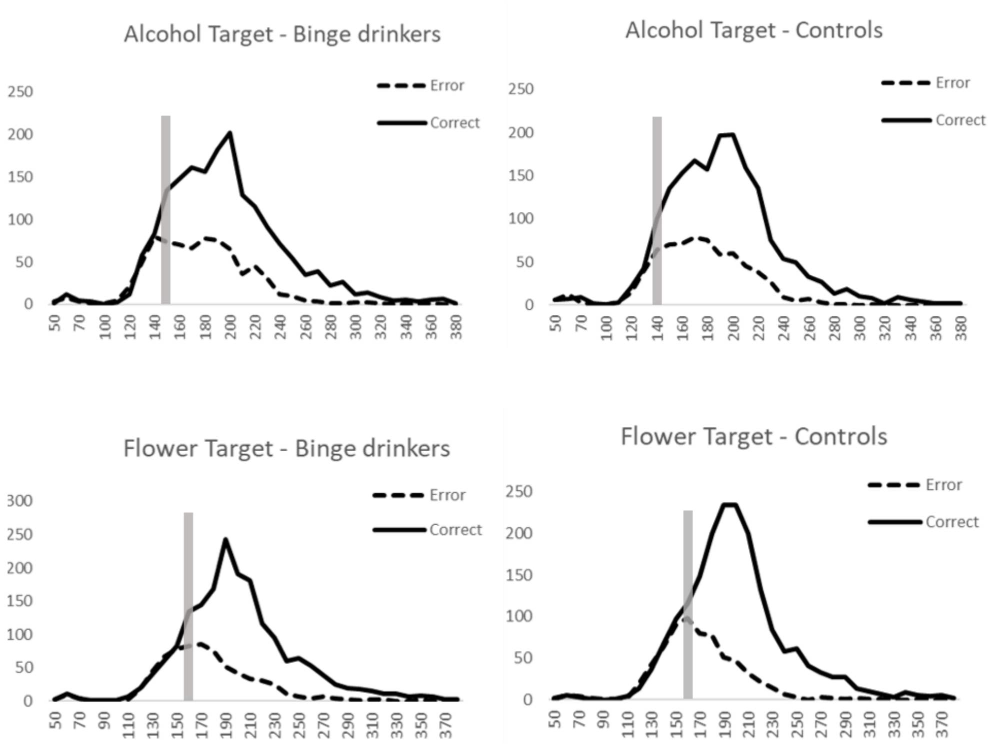
2. Minimum saccadic reaction time

We computed the minimum saccadic reaction times (minSRT) for each Target condition in each group. The minSRT corresponds to the minimum SRT leading to significantly more correct than error saccades. We computed the distributions of SRT separately for correct and error saccades, taking all saccades of participants from each group. We grouped SRTs into 10ms bins (e.g., the 120ms bin contained SRT comprised between 115 and 124ms). For each bin, the proportion of correct saccades was compared to the one of error saccades using a χ^2 test. If there was significantly more correct than error saccades in five consecutive bins, the first bin was then defined as the minSRT (for a similar procedure, see Crouzet et al., 2010; Guyader et al., 2017; Kauffman et al., 2021).

Face vs Vehicle Saccadic Choice Task. The analyses of minSRT showed that the fastest saccades correctly initiated towards face targets were comprised in the 120-ms bin (i.e. SRT between 115 and 124ms) in both groups, while those correctly initiated towards vehicle targets corresponded to the 140-ms bin in controls and the 170-ms bin in binge drinkers.



Alcohol vs flower Saccadic Choice Task. The analyses of minSRT showed that the fastest saccades correctly initiated towards alcohol targets were in the 150ms bin in binge drinkers and the 140ms bin in controls. The fastest saccades correctly initiated towards flower targets corresponded to the 160ms bin among binge drinkers and the 170ms bin among controls.



3. Correlations

We performed exploratory Pearson's correlations to investigate the influence of alcohol-related variables on the first and corrective saccades in the alcohol vs. flower saccadic choice task. To do so, we performed correlations on the difference score between blocks with alcohol as target and blocks with flower as target for accuracy and SRT of first saccades as well as the proportion of corrective saccades, leading to a positive score when alcohol was detected more correctly and faster than flower.

The difference score on the accuracy of first saccades did not correlate with AUDIT score (r=-.009, p=.933), binge drinking score (r=-.090, p=.406) or craving assessed through ACQ (r=.141, p=.195) or VAS (r=.023, p=.833).

The difference score on the SRT of first saccades did not correlate with AUDIT score (r=-.056, p=.605), binge drinking score (r=.156, p=.149) or craving assessed through ACQ (r=.001, p=.993) or VAS (r=.090, p=.412).

The difference score on the proportion of corrective second saccades significantly correlated with AUDIT score (r=.218, p=.043), binge drinking score (r=.300, p=.005) and craving assessed through ACQ (r=.243, p=.024) but not through VAS (r=.172, p=.112).

Appendix D

Instructions in French for the MIPs used in Chapter 6

1. Autobiographical recall task for the non-alcohol-related negative and positive MIP

« Prenez une dizaine de minutes pour répondre à cette tâche avec le plus d'honnêteté possible. Votre réponse restera bien évidemment confidentielle.

*Veuillez décrire, le plus précisément possible, une situation que vous avez vécue et où vous avez ressenti une émotion négative (tristesse, colère, etc.) * / positive (joie, amusement, etc.) * intense dans un contexte où vous n'avez pas consommé d'alcool ou toute autre substance addictive. Commencez par décrire les sentiments ressentis à ce moment-là. Ensuite, décrivez la situation.*

Il est important que vous utilisiez des phrases complètes afin d'être aussi précis que possible (minimum 1 page rédigée). Décrivez la situation comme si une autre personne devait la lire, et être capable de comprendre/éprouver les sentiments que vous avez ressentis. »

*depending on the mood condition.

2. Itinerary recall task for the neutral MIP

« Prenez une dizaine de minutes pour répondre à cette tâche. Votre réponse restera confidentielle.

Veuillez décrire, le plus précisément possible, le chemin que vous avez pris aujourd'hui, en partant de votre domicile/kot/auditoire, pour arriver jusqu'au laboratoire.

Décrivez votre chemin ainsi que ce que vous avez aperçu durant ce chemin (ex : bâtiments, parcs, magasins) comme si une autre personne devait lire cette description, et être capable d'imaginer et refaire lui-même ce chemin pour arriver jusqu'au laboratoire (minimum 1 page rédigée). »

3. Autobiographical recall task for the alcohol-related negative MIP

« Prenez une dizaine de minutes pour répondre à cette tâche avec le plus d'honnêteté possible. Votre réponse restera bien évidemment confidentielle.

Veuillez décrire, le plus précisément possible, une situation que vous avez vécue et où vous avez ressenti une émotion négative (tristesse, colère, etc.) intense dans un contexte où vous avez consommé une quantité importante d'alcool. Commencez par décrire les sentiments ressentis à ce moment-là. Ensuite, décrivez la situation.

Il est important que vous utilisiez des phrases complètes afin d'être aussi précis que possible (minimum 1 page rédigée). Décrivez la situation comme si une autre personne devait la lire, et être capable de comprendre/éprouver les sentiments que vous avez ressentis. »

Appendix E

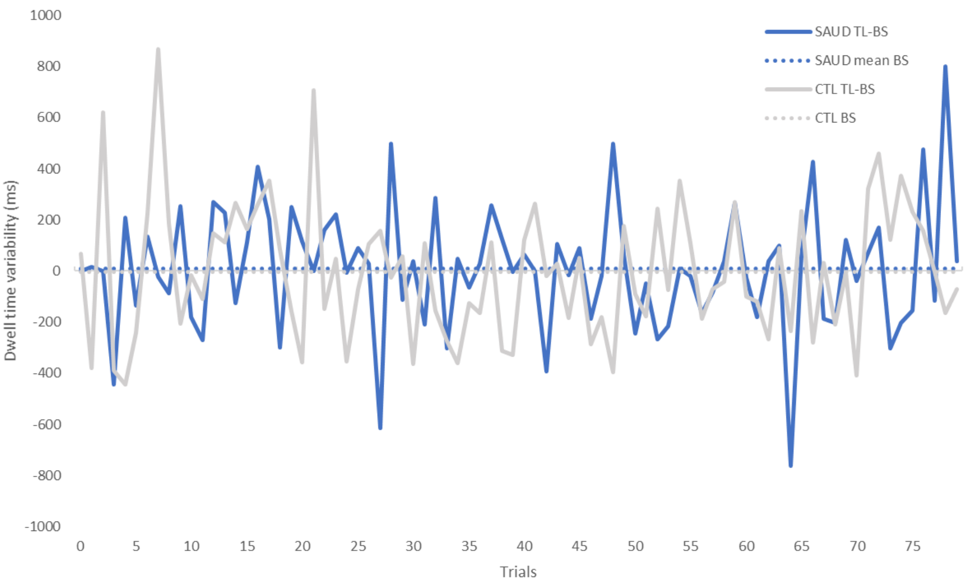
Supplementary analyses from Chapter 7

1. First fixation laterality

We performed a paired-samples t-test on first fixation laterality, which confirmed the left hemifield preference related to reading direction: more first fixations were directed leftwards (60%; SD=25) than rightwards [33%; SD=23; $t(50)=4.004$, $p<.001$].

2. Trial-by-trial variability

We explored the dynamic changes of AB through a new computational methodology (Liu et al., 2019; Zvielli et al., 2015) computing trial-level bias scores to capture dwell time variability. Its calculation is the sum of all absolute distances between sequential trial-by-trial dwell times (|dwell time BS trial x – dwell time BS trial x+1|) divided by the total number of dwell times. Independent-samples t-test indicated that patients with SAUD (431ms; SD=147) did not differ from CTL (493ms; SD=157) on dwell time variability [t(49)=1.443, p=.155].



Mean AB scores and trial-level bias scores for one patient with SAUD and one CTL participant. TL-BS = trial level bias scores; mean BS = mean attentional bias scores.