Alcohol use and cognition: Processing speed and subjective executive function deficits across the spectrum of drinking behaviours

Anna Claire Powell

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Glossary of Abbreviated Terms

5CSRTT – Five-Choice Serial Reaction Time Task (rodents)

ADHD – Attention Deficit Hyperactivity Disorder

AP – Anna Powell (Author)

APQ – Alcohol Problems Questionnaire

APQC – Alcohol Problems Questionnaire Common score

ARBI – Alcohol-Related Brain Injury

AUD – Alcohol Use Disorder

AUDIT – Alcohol Use Disorders Identification Test

AUDIT-C – Alcohol Use Disorders Identification Test-Consumption

BG – Brain Gauge

BIS – Barratt Impulsiveness Scale

BRIEF-A – Behaviour Rating Inventory Executive Function for Adults

CANTAB – Cambridge Neuropsychological Test Automated Battery

CEFI – Comprehensive Executive Functions Inventory

CFA – Confirmatory Factor Analysis

CI – Crossmodal Integration

COVID-19 – Coronavirus Disease 2019

DEX – Dysexecutive Questionnaire

DS – Digit Symbol Substitution

DSM – Diagnostic and Statistical Manual of Mental Disorders

EF – Executive Function

EFI – Executive Function Index

ERP – Event-Related Potential

fMRI – Functional Magnetic Resonance Imaging

GABA – Gamma-Aminobutyric Acid

HADS – Hospital Anxiety and Depression Scale

HCT – Halstead Category Test

HED – Heavy Episodic Drinking

ICD – International Classification of Diseases

IED – Intra-Extra Dimensional Set Shift

JBI – Joanna Briggs Institute

JS – Jessica Smith (assisted with screening and quality assessment for the systematic review)

LJMU – Liverpool John Moores University

LTM – Long-Term Memory

MANCOVA – Multivariate Analysis of Covariance

MANOVA – Multivariate Analysis of Variance

MCST – Modified Card Sorting Test

MMM – Multi-Store Memory Model

MMSE – Mini Mental State Exam

MoCA – Montreal Cognitive Assessment

MR – Matrix Reasoning task

NHS – National Health Service

NICE – National Institute for Health and Care Excellence

PFC – Prefrontal Cortex

RAVLT – Rey Auditory Verbal Learning Test

RK – Rebecca Kuiper (assisted with screening and quality assessment for the systematic review)

RT – Reaction Time

RVP – Rapid Visual Information Processing task

SADQ-C – Severity of Alcohol Dependence Questionnaire – Community version

Sx-5CRTT – Five-Choice Serial Reaction Time Task (humans)

SOPT – Self Ordered Pointing Test

SS – Symbol Search

SST – Stop Signal Task

STM – Short-Term Memory

SUD – Substance Use Disorder

TMT – Trail Making Test

UK – United Kingdom

WCST – Wisconsin Card Sorting Test

WHO – World Health Organisation

WMM – Working Memory Model

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Abstract

Previous research has demonstrated that multiple cognitive functions are impaired in alcohol use disorders, including executive functions and processing speed. Recovery of function may be possible, though to what extent is unclear. In non-dependent hazardous drinkers, executive function research is inconsistent (possibly due to a neurocompensatory mechanism of increased effort), as is processing speed literature. Self-report methods may provide a unique insight into executive functioning within different alcohol contexts, while differences in processing speed measurement may account for discrepancies. The purpose of this thesis was to investigate the relationship between alcohol use and cognitive function, in different contexts. A systematic review examined longitudinal recoverability of cognitive function during abstinence in individuals with an alcohol use disorder, followed by a series of studies that assessed subjective executive function and vibrotactile reaction time in a range of dependent and non-dependent drinkers. Overall, the results showed that 1) cognitive function in several areas can recover in individuals with an alcohol use disorder who maintain abstinence, 2) hazardous drinkers experience poorer subjective executive function, but 3) perform faster during choice reaction time, and 4) impaired choice reaction time is demonstrated during early abstinence in dependent drinkers compared to controls, as is worsening mental fatigue, specifically in outpatients. These results have implications for health providers and policymakers, as hazardous drinkers are subject to alcohol harms despite not being a clinically prioritised group, while outpatients, despite typically fewer complex needs, are experiencing potentially harmful effects of cognitive exertion, so may need more support within their treatment pathway.

Declaration

No portion of the work referred to in the thesis has been submitted in support of an application for another degree or qualification of this or any other university or other institute of learning.

Chapter 1 : An Overview of Cognitive Function and Alcohol Use

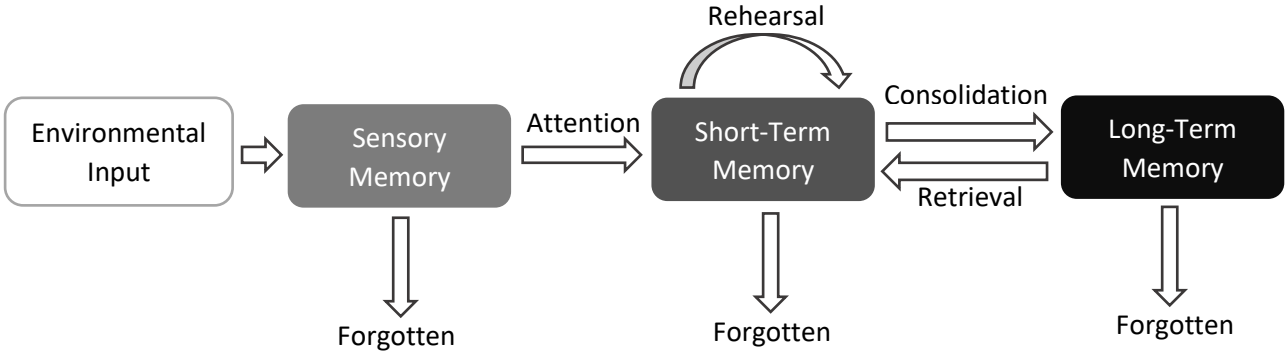
1.1 Chapter Overview

This chapter briefly provides a theoretical basis for executive functions and processing speed. Baddeley's model of working memory is referred to, followed by the Miyake and Friedman framework of fractionated executive components, and Salthouse's theory that these are underpinned by processing speed. The chapter then relates these functions to different patterns of alcohol use, including hazardous use, and alcohol use disorders, and gives an overview of the thesis.

1.2 Theoretical Models of Cognition

One of the earlier models of memory and cognition, is the Multi-Store Memory Model (MMM) by Atkinson and Shiffrin (1968), displayed in Figure 1. MMM posited that information passes in a linear fashion between three memory stores; a sensory register (brief store of sensory information), short-term memory (STM; where information moves if attended to), and long-term memory (LTM; information rehearsed in STM moves here to be stored indefinitely). While evidence supported the concept of separate stores for short- and long-term memory (Glanzer & Cunitz, 1966; Scoville & Milner, 1957; Warrington & Shallice, 1969), it became clear that both are more complex than previously thought, with separate stores for different types of information (Hitch & Baddeley, 1976; Paulesu et al., 1993; Shallice & Warrington, 1974), and that the model could not explain the ability of STM to allow for complex cognitive functions, such as problem solving.

Figure 1. *Multi-Store Memory Model (Atkinson & Shiffrin, 1968)*

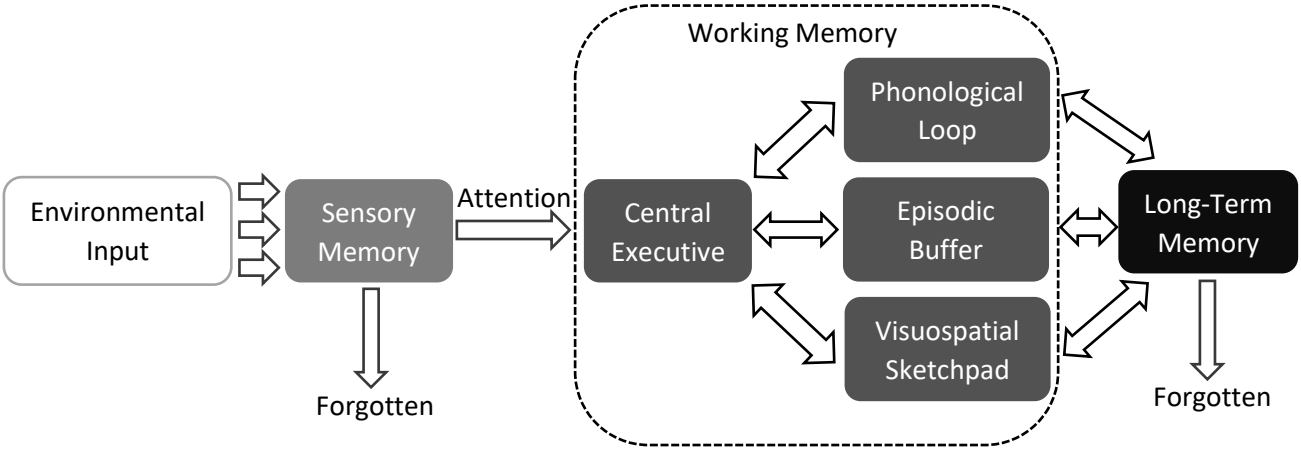


Therefore, Baddeley and Hitch (1974), introduced their Working Memory Model (WMM), displayed in Figure 2, to replace the construct of STM in the MMM. WMM introduced different types of STM; a phonological loop (including a store for phonological information, and an articulatory control process involved in speech production), and visuospatial sketchpad (stores and processes visual and spatial information, used for navigation). These are driven by the central executive, which allocates data to these subsystems, and relates them to LTM. The central executive also directs attention, and through a combination of its functions, leads complex cognitive tasks. The model was updated by Baddeley (2000) to include the episodic buffer, a backup store that communicates with the components of working and LTM. While there is support for the concept of a cognitive function which controls other processes (Baddeley, 1996), studies of this model have found disparate results, where participants showed differing results on different 'central executive' tasks, suggesting that this function is fractionated (Lehto, 1996; Miyake et al., 2000).

Furthermore, early research by various authors supported the notion of such higher order cognitive functions that are separable from more basic processes. For example, a patient with frontal lobe damage sustained during childhood scored normally on intelligence measures, but struggled with impulsivity and daily tasks (Ackerly & Benton, 1947). Similarly, patients with frontal lobe damage sustained during adulthood performed well in Shallice and Burgess (1991) on basic tests of intelligence, perception, and language, but poorly on two more complex working memory tests of multiple subgoal scheduling; the Six Element Test and the Multiple Errands Test (Shallice & Burgess, 1991), which both involve planning and completing multiple open-ended tasks in a set time-period, while adhering to certain rules. Issues with memory or motivation were unlikely, due to satisfactory performance on basic tasks, and so could not explain problems with more complex tasks. There are many other early examples where frontal lobe damage has been linked to impairments in higher order functions, such as sustained attention, reasoning, task organisation, and impulse control, but generally to low-average performance in more basic tasks such as global intelligence, language, memory and visual perception (Eslinger & Damasio, 1985; Grattan & Eslinger,

1992). Furthermore, more recently, in animal studies on mice, it has been possible for researchers to manipulate individual aspects of working memory (Kolata et al., 2007). These studies are further supported by lesion studies in non-human primates. Jacobsen (1936) found that bilateral frontal lesions associated with severe and long-lasting working memory deficits in delated-response performance, in which the monkey watches a food reward covered with two identical plates and after a delay must select the correct one. As the location changes randomly each trial, the spatial information must be remembered and used to inform decision making. Additionally, electrophysiological studies of awake monkeys show prefrontal neural correlates of delayed-response and delayed-alternation tasks (Fuster & Alexander, 1971; Kubota & Niki, 1971), the latter of which involves the monkey pressing two levers alternately with a delay between each press, to receive a fruit juice reward.

Figure 2. *Working Memory Model (Baddeley, 2000; Baddeley & Hitch, 1974)*



So, it was understood that there were 'basic' and 'higher order' cognitive processes, and that there was a fractionated control process coordinating higher processes and directing attention, allowing goal-oriented behaviour. Functions within this were coined "executive functions" (EF), high-level processes which control and coordinate sub processes, enabling individuals to regulate their thoughts and actions during goal-directed behaviour (Hughes, 2013; Miyake et al., 2000). Essentially,

EFs allow individuals to flexibly allocate mental resources (Wager et al., 2004), allowing for purposeful yet flexible behaviour (Miller & Cohen, 2001).

Miyake et al. (2000) used a latent variable approach to the variance shared on multiple relevant tasks, reducing the task impurity problem (whereby due to EFs operating on other functions, a proportion of variance on any one task is not necessarily due to the target EF (Friedman et al., 2008; Phillips, 1997)). Building on this, and additional previous research, Miyake and Friedman (2012) introduced their highly influential unity/diversity EF individual differences framework, which specifically focused on the cognitive and biological underpinnings of the unity and diversity of task-shifting, inhibition, and updating working memory. Conclusions were that functions are correlated yet separable, somewhat heritable, predict important phenomena, and show some developmental stability. This model is well-validated (Friedman & Miyake, 2017; Friedman et al., 2008), and has a strong neural basis in the prefrontal cortex (PFC), though the exact mapping of EFs onto the PFC as a unitary or multiple demand system is yet to be understood, and it is acknowledged that emotional motivation also plays a role on performance (Friedman & Robbins, 2022). Indeed, brain imaging in humans links EF to frontoparietal regions, particularly the PFC (Owen, 1997; Wager & Smith, 2003; Yuan & Raz, 2014), with EF tasks sometimes referred to as 'frontal lobe tasks' (Miyake et al., 2000).

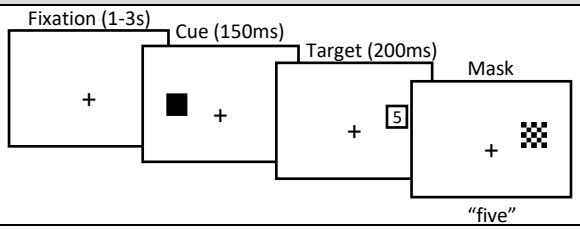
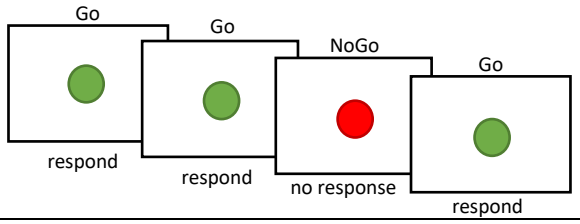
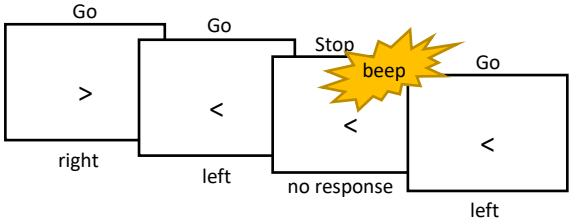
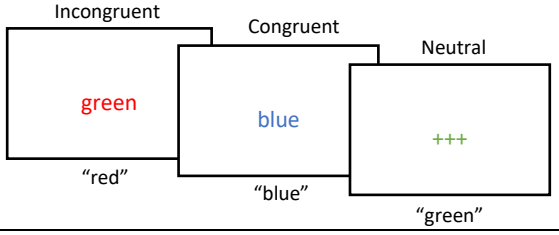
While the Miyake and Friedman (2012) framework is one of the most dominant theories of fractionated EF, there are others, such as the Supervisory Attention System (Norman & Shallice, 1986), controlled attention (Engle et al., 1999; Kane et al., 2001), and proactive versus reactive control (Braver et al., 2007). These are not necessarily mutually exclusive; Friedman and Miyake (2017) discuss these and others in relation to their framework, particularly how elements of these may correspond to variance shared by different EFs. Furthermore, Friedman and Miyake (2017) acknowledge they did not use an exhaustive set of EF measures. Indeed, although there is generally agreement on these core functions, there is not a single accepted definition of EF (Goldstein & Naglieri, 2014). Other components suggested include interference control, planning, fluency, access

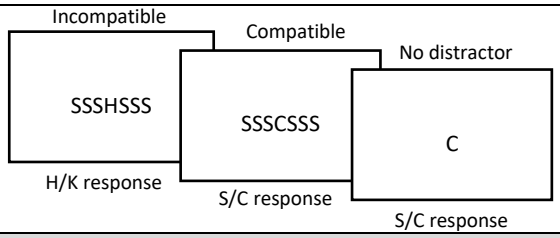
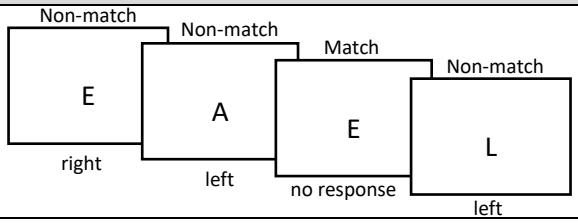
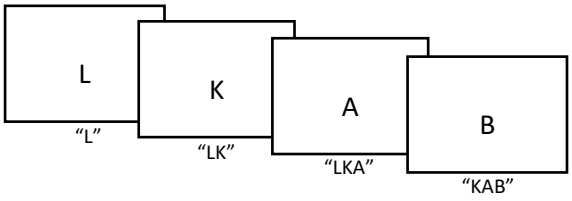
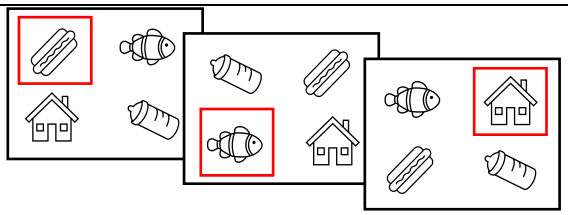
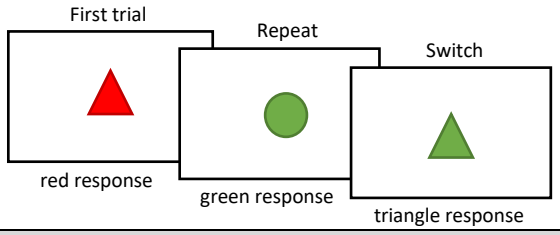
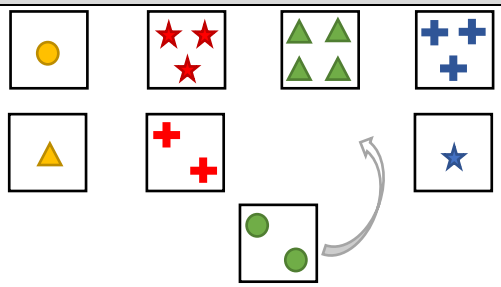
to semantic/long-term memory (Fisk & Sharp, 2004), and more (Diamond, 2013; Friedman & Miyake, 2017; Garon et al., 2008; Sharma et al., 2014). Ultimately, an in-depth discussion of these is beyond the scope of this thesis. However, the focused-on framework has good replicability, and the functions defined in it are consistently related to aspects of health and recovery, including in alcohol dependence (Brion et al., 2017; Snyder et al., 2015).

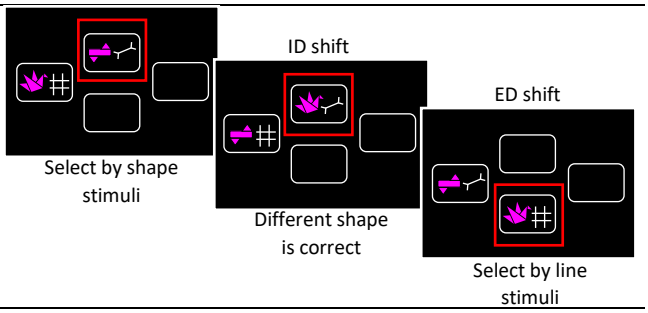
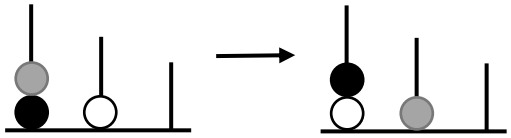
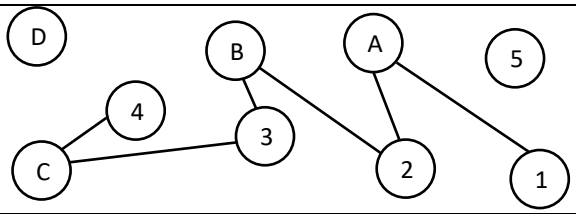
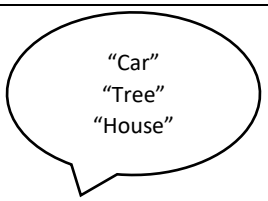
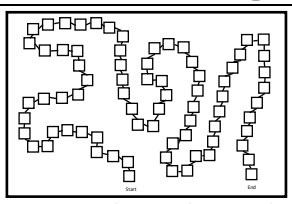
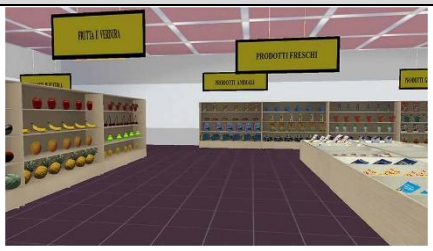
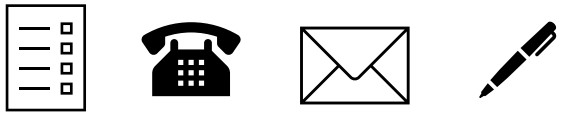
1.3 Assessment of executive function

These three components will now be defined in more detail, with some of the tasks used to assess them displayed in Table 1 (adapted from Friedman and Robbins (2022)).

Table 1. *Frequently used executive function tasks (adapted from Friedman and Robbins (2022), with references to the original task paradigms).*

Task	Task goal	Schematic
Response Inhibition and Interference Control Tasks		
Anti-saccade (Roberts et al., 1994)	Inhibit reflexive eye movement to a brief cue, looking instead to the other direction in time to identify a target stimulus.	
Go/No-Go (Donders, 1969)	Inhibit prepotent button pressing response on less frequent trials in which a no-go signal occurs at the start of the trial.	
Stop-signal (Logan, 1994)	Inhibit prepotent direction category response on the infrequent trials in which a stop signal occurs shortly after the start of the trial.	
Stroop (Stroop, 1935)	In the incongruent trials, avoid reading the word, instead, name the colour of the font.	

Flanker (Eriksen & Eriksen, 1974)	Assesses interference control. Indicate (e.g., using right/left keys) identity of central letter, resolving interference from flanking letters which may have been given a different (but not prepotent) response association. E.g., in example, H/K response = right, S/C response = left.	
Working Memory and Updating Tasks		
N-back (Kirchner, 1958)	Indicate whether each stimulus matches the one "n" back, e.g., two trials before in the 2-back task (modality may be verbal or visuospatial)	
Letter-Number Sequencing (Wechsler, 1997)	Listen to series of letters and digits, recite back digits in ascending numerical order and letters in alphabetical order, e.g., 5-G-2-B-7-A	"2-5-7-A-B-G"
Letter Memory (Morris & Jones, 1990)	Upon presentation of each new letter, say aloud the most recent three letters in order.	
Digits Backward (Wechsler, 1981)	Listen to and recite sequence backwards, e.g., 8-5-6-4-7-2-0-1-9	"9-1-0-2-7-4-6-5-8"
Brown-Peterson Technique (Brown, 1958; Peterson & Peterson, 1959)	Upon presentation of three consonants, count backwards from a two- or three-digit number till told to stop, and then report the consonant trigram, e.g., V-R-J, count back from 156.	"156, 155, 154, 153", then when stopped, "V-R-J"
Self-Ordered Pointing Test (Petrides & Milner, 1982)	Out of an array of stimuli, point to stimulus that has not been selected previously, despite positions shifting from trial to trial.	
Simple Set Shifting		
Cued switch tasks (Miyake et al., 2004)	Upon presentation of cue, shift between methods of categorising stimuli (e.g., based on shape, colour, letters, or numbers), using same response keys (e.g., left = green/circle, right = red/triangle). Switch cost is response time difference in switch vs repeat trials.	
More Complex Cognitive Flexibility		
Wisconsin Card Sorting Test (Grant & Berg, 1948; Kimberg et al., 1997)	Sort response cards into piles under four stimulus cards based on shape, colour, or number, discovering the rule based on feedback. After ten correct sorts, the rule changes.	

Intra-extra dimensional shifting and reversal learning (Downes et al., 1989)	Select correct stimuli (shape or line figure) based on feedback, after six correct, rule changes. Shifts can be either intra-dimensional (e.g., shape still relevant set, but different shape correct), or extra-dimensional (shape no longer relevant set, now one of the line stimuli is correct). Reversals require selecting the previously ignored stimuli within- or between-categories.	
Tower of London (Shallice, 1982)	Rearrange blocks according to a desired configuration, in as few moves as possible.	
Trail Making Test (Reitan, 1956)	Alternate between connecting visual array of letters in alphabetical order and digits in ascending numerical order (e.g., 1-A-2-B-3-C). Typically compared with baseline condition requiring connection of sequential numbers or letters (not alternating).	
Dual task paradigms (Baddeley et al., 1997; Miyake et al., 2000)	Simultaneously complete two tasks (such as classifying auditorily presented words as natural or man-made, whilst crossing out boxes on paper), compared to each task being completed separately.	 Classify words  Cross out boxes along trail
'Real-world' EF assessments with higher ecological validity		
Virtual Multiple Errands Test (Cipresso et al., 2014)	Within a virtual reality (VR) setting, participants given a list of tasks to complete in limited time, set in virtual supermarket (e.g., must buy items on a shopping list, buy a product on sale, remember the shopping list after the task, and remember details about the store such as closing time, all while following certain rules).	 *Note.* From "Virtual multiple errands test (VMET): a virtual reality-based tool to detect early executive functions deficit in Parkinson's disease", by Cipresso et al. (2014), Front. Behav. Neurosci, 8, 405 (https://doi.org/10.3389/fnbeh.2014.00405)
Multiple Errands (Shallice & Burgess, 1991)	Real-world tasks (e.g., arriving at specific location, purchasing certain items etc.), some with a deadline.	
Executive Secretarial (Lamberts et al., 2010)	Job assessment imitation, use supplies given to prioritise and complete secretarial tasks based on list, some which have a deadline. Involves self-initiation (e.g., deciding to use the phone to book travel). Similarly, the Hotel Task (Manly et al., 2002) is an imitation of running a hotel, while secretarial tasks occur in VR on the Jansari assessment of executive functions (Jansari et al., 2014).	

Working memory updating is the ability to monitor incoming information for task-relevance, and to update the contents of working memory, replacing material that is no longer relevant with that which is (Miyake et al., 2000; Morris & Jones, 1990). This allows resources (working memory capacity) to be used effectively (De Beni & Palladino, 2004). Working memory capacity is typically measured using complex span task variants (which involve items to be remembered, interspersed with an unrelated cognitive activity), and is a closely related construct to working memory updating at the level of individual differences (Ecker et al., 2010; Schmiedek et al., 2009).

Task-shifting (sometimes called set shifting, attention shifting, or attention switching, task switching, or cognitive flexibility) is the ability to switch attention flexibly between tasks or elements of the same task (Miyake et al., 2000; Monsell, 1996). This is often described as shifting between task sets; the cognitive parameters that are needed to complete the task at hand, an abstract version of the task, including the motor, mnemonic, attentional and perceptual processes required (Sakai, 2008).

'Inhibitory control' describes the multifaceted nature of control of stimuli, cognitive processes, and behavioural responses, that are irrelevant to the dominant goal (Tiego et al., 2018). Included within this umbrella is response inhibition, cognitive inhibition, and interference control. Response inhibition is the ability to suppress automatic motor responses when they are no longer appropriate to the situation (Logan, 1994). Cognitive inhibition refers to resisting memory intrusions of information that is now irrelevant (Friedman & Miyake, 2004; Nigg, 2000). Interference control involves resisting external distractors which are irrelevant to the current task, this is a cognitive process thought to occur at a perceptual, initial stage of processing (Friedman & Miyake, 2004; Nigg, 2000). Response inhibition and interference control are closely associated, but unrelated to cognitive inhibition, possibly as the latter may reflect a less active level of control (Friedman & Miyake, 2004), indicating that not all 'inhibition tasks' tap into the same ability (Friedman, 2016).

While it is important to clarify these aspects of control, cognitive inhibition is less frequently discussed in relation to alcohol use, and therefore will not be expanded further upon in this thesis.

While the tasks above have significant merit and may be less susceptible to bias, self-reported assessment of EF provides an interesting insight into subjective cognitive state and has been suggested to be more ecologically valid (Roth et al., 2013). Self-rated tools include the Behaviour Rating Inventory Executive Function for Adults (BRIEF-A, Roth et al. (2005)), the Dysexecutive Questionnaire (DEX, Wilson et al. (1998), Comprehensive Executive Functions Inventory (CEFI, Naglieri and Goldstein (2013), and the Executive Function Index (EFI, Spinella (2005)). Self-report EF assessment is used in this thesis to gain an understanding of the day-to-day experience of such functions.

1.4 Processing Speed

So, it is generally accepted that there are a variety of EF responsible for driving goal-related behaviour. But what happens when these functions lack efficiency? As far back as 1965, it was noted that processing rate increased with age (Birren, 1965), also observed in animal studies (Menich & Baron, 1984), and Salthouse and Babcock (1991) found that age-related differences in working memory performance were most attenuated when controlling for processing speed, concluding that this is a mediator for many of these differences. As a result, Salthouse (1996) proposed the 'Processing Speed Theory', which postulates that with increased age comes slowing of the speed at which cognitive processes can be performed, and that this causes the decline observed in more complex functions.

Specifically, the theory proposed by Salthouse (1996), suggests that older adults are impaired on two interconnected processing speed elements, a 'limited time' mechanism, and a 'simultaneity' mechanism. Limited time refers to time to perform later operations being constrained by more time taken in older adults for earlier operations, and simultaneity inferring that products of earlier processing may be lost by the time later processing is complete. Processing speed can be

considered a task-independent construct (Fry & Hale, 2000) which determines the efficiency of stimuli interpretation and response selection (Fisk & Warr, 1996; Gordon et al., 2018). It is dependent on both neural transmission speed (Volgushev, 2016), and white matter integrity (Magistro et al., 2015; Turken et al., 2008). Additionally, particularly in older adults, processing speed also associates with frontoparietal regions and the PFC, which has been interpreted as a compensation for the lower-order processing failures (Motes et al., 2011; Sims et al., 2021), proposed by Salthouse (1996) to deteriorate with age. Processing speed is sometimes divided further into simple psychomotor speed (time to complete rapid motor movements, e.g., in box completion), and higher-order 'perceptual' speed tasks additionally requiring executive control, e.g., in colour naming (Cepeda et al., 2013).

There are a variety of tasks that can be used to assess processing speed, with some being very simple (such as prosaccade latency - moving your eyes to look at a stimuli), and others increasing in executive control due to various levels/combinations of recruitment of working memory updating, decision-making, response selection, motor control, previous knowledge, and interference control (Cepeda et al., 2013). An assessment often used is 'reaction time' (RT; Woods et al. (2015)), generally either 'simple' (one stimulus and one response type) requiring motor control, or 'choice' (multiple potential stimuli each requiring a different response) additionally requiring executive interference control and a moderate amount of response selection and working memory updating (Cepeda et al., 2013). These tasks can generally be administered quite quickly, which gives them some advantage over the EF tasks displayed in Table 1, particularly when considering that some performance-related aspects on these tasks will be dependent on processing speed efficiency anyway.

1.5 Alcohol use context and effects on cognitive function

Alcohol is consumed by around one third of the global population (Griswold et al., 2018). Although most drinkers report pleasurable and positive effects of drinking and drinking contexts

(Peele & Grant, 2013; Sayette, 2017), alcohol is a leading risk factor for disease burden, and is the seventh leading risk for death and disability (Griswold et al., 2018; Rehm et al., 2003). Indeed, alcohol-related harm is estimated to cost the NHS £3.5 billion a year, and globally 5.1% of all individuals aged 15+ are estimated to have an alcohol use disorder (AUD), though this differs by WHO region; European (8.8%), Americas (8.2%), Western Pacific (4.7%), African (3.7), Eastern Mediterranean (0.8%) (Public Health England, 2014; WHO, 2019). AUD describes a clinical condition of continued alcohol use despite negative consequences (American Psychiatric Association, 2013; Friedmann, 2013).

Acutely, alcohol has sedative properties via its effect on Gamma-aminobutyric acid (GABA)-ergic and glutamatergic receptors, and induces a state of intoxication and lowered inhibition, due to potentiated GABA release and inhibited glutamate (Abrahao et al., 2017; Lovinger & Roberto, 2013; Zorumski et al., 2014). Furthermore, alcohol induced influence of the GABAergic system on the mesolimbic reward circuitry has been linked strongly to self-administration in animal models (Chester & Cunningham, 2002). While recreational alcohol use in many countries is normalised, any level of consumption increases risk via various means, with AUD emerging as the most prevalent substance use disorder (SUD) globally (Griswold et al., 2018). Among those who do not have AUD, many people are still classified as 'hazardous' (drinking that increases risk of harm) and 'harmful' drinkers (pattern of drinking that results in harm), as defined by the National Institute for Health Clinical Excellence (NICE, 2010). As a note, hazardous drinking definitions vary, though the current thesis defines it using the NICE guidelines, but it is often defined similarly to heavy drinking; relating to consumption that may increase risk and exceeds a specific threshold (Reid et al., 1999). Current United Kingdom (UK) weekly alcohol guidelines are ≤ 14 units per week, spread evenly over three or more days (Department of Health, 2016). Consequently, drinking patterns that identify increased risk include drinking over 14 units continuously across the week, or consuming large amounts during drinking sessions (heavy episodic drinking; HED, or "binge drinking"; Adan et al. (2017)). Acutely, alcohol use affects cognitive functions, likely via its effect on GABA and glutamate receptors

(Zorumski et al., 2014), including EF (Day et al., 2015), and processing speed (Maylor & Rabbitt, 1993; Tzambazis & Stough, 2000).

1.5.1 Function in Alcohol Use Disorders

1.5.1.1 Executive Function in Alcohol Use Disorders

EF are also impaired in chronic heavy use in AUD (Stavro et al., 2012), linked to PFC differences (Abernathy et al., 2010; Chanraud et al., 2006; Noel, 2002), though it is understood that this may be a somewhat cyclical relationship, with some elements of EF being heritable, and increasing risk of problematic drinking in humans (Benzerouk et al., 2013), found also in animals specifically bred for these characteristics (Dick et al., 2010). In AUD, the PFC shows atrophy, along with the parietal cortex, when measured using functional magnetic resonance imaging (fMRI) (Harris et al., 2008; Oscar-Berman & Marinković, 2007). Furthermore, fMRI shows that AUD is related to abnormal activation of these areas during working memory tasks (Desmond et al., 2003; Tapert et al., 2001). Additionally, low cognitive performance in AUD correlates with PFC and parietal degradation (Chanraud et al., 2006).

Studies of laboratory animals indicate that compulsive substance use is associated with loss of control (Wolffgramm & Heyne, 1995), which alongside motivational aspects of substance use, associate with mesolimbic and mesocortical dopamine systems including the PFC, orbitofrontal cortex, and anterior cingulate, all implicated in craving and compulsive administration in animal models (Jentsch & Taylor, 1999). Furthermore, in humans, AUD is associated with a loss of top-down prefrontal cortical control (Goldstein & Volkow, 2002; Miller & Cohen, 2001), which increases relapse risk (Duka & Stephens, 2014). Indeed, fMRI indicates that the medial PFC plays a large role in relapse (Charlet et al., 2013), and overcoming craving (Goldstein & Volkow, 2011). PFC dysfunction is therefore assumed to have a significant impact on the cognitive deficits observed in AUD (Moselhy et al., 2001), and consequently on treatment outcomes. EF impairment in AUD decreases quality of

life (Brion et al., 2017), and also an individual's ability to plan and maintain recovery behaviours (Dawson & Grant, 2000; Pitel et al., 2007; Wilkinson & Sanchez-Craig, 1981).

Indeed, EF predict SUD treatment outcomes (Domínguez-Salas et al., 2016). Response inhibition in particular has been highlighted as impaired in AUD and involved in its development (Rubio et al., 2008), and important as a predictor of craving (Bernard et al., 2021), relapse (Czapla, Simon, Richter, et al., 2015), and treatment adherence (Rupp et al., 2016). Similarly, task shifting is associated with relapse (Morrison, 2011) and treatment adherence (Desfosses et al., 2014), and memory updating predicts relapse (Noel, 2002), and in methamphetamine recovery predicts treatment adherence (Dean et al., 2009).

Various hypotheses have been put forward regarding the vulnerability of the brain to AUD damage (Oscar-Berman & Marinkovic, 2003). The 'whole brain hypothesis' suggests that the entirety of the cerebral cortex is vulnerable, while the 'frontal lobe hypothesis' proposes that this lobe is more vulnerable than other regions (Oscar-Berman & Marinkovic, 2003), indicating that while the cerebral regions are vulnerable, the frontal lobes are most vulnerable (Oscar-Berman & Marinković, 2007). The 'right brain hypothesis', which posits that the right hemisphere is more vulnerable than the left (Ellis & Oscar-Berman, 1989; Oscar-Berman & Marinkovic, 2003) has received less consistent support (Oscar-Berman & Marinković, 2007). Interestingly, the 'premature aging hypothesis' suggests that alcohol either ages the brain prematurely, or that older brains are more vulnerable to alcohol damage (Ellis & Oscar-Berman, 1989; Oscar-Berman & Marinkovic, 2003), the latter of which has received more support (Oscar-Berman & Marinković, 2007), as has a combination of both interpretations (Guggenmos et al., 2017).

It appears that cognitive impairment in AUD may be partially reversible with long-term abstinence (Moselhy et al., 2001). This suggests that if an individual can be supported appropriately through the initial treatment stages, their cognitive function may improve to a point at which relapse is less likely. However, the extent to which functional recovery may occur is unclear, as

reviews on the topic have found inconsistent results (Crowe, 2019; Schulte et al., 2014; Stavro et al., 2012). Much of this research has been cross-sectional (Crowe, 2019; Stavro et al., 2012), which reduces the ability to assess causality regarding abstinence and function change. Furthermore, while longitudinal review measures would not allow for understanding if functional differences were pre-existing, within-subjects recovery would indicate that at least some impairment was due to alcohol use. However, Schulte et al. (2014), who included longitudinal studies only, still found multiple inconsistencies regarding recovery of functions. Therefore, an up-to-date systematic reviewing of literature on cognitive recovery upon abstinence in AUD may be beneficial, to further the understanding of alcohol's impact on function, and whether this can be reversed.

1.5.1.2 Processing Speed in Alcohol Use Disorders

As worsening EF has been linked to declined processing speed previously (e.g., in older adults, Salthouse (1996)), it is possible that it may be a factor contributing to the impaired EF in AUD (Glass et al., 1999). Indeed, along with atrophy and functional alterations of the PFC (Desmond et al., 2003; Oscar-Berman & Marinković, 2007; Tapert et al., 2001), white matter in AUD displays widespread reductions, particularly in the frontal lobes, cerebellum, and limbic system (Bühler & Mann, 2011). Furthermore, in addition to PFC dysfunction being linked to relapse and craving (Charlet et al., 2013; Goldstein & Volkow, 2011), white matter integrity predicted relapse in Y. Zou et al. (2018) and correlated significantly with composite z-scores of processing speed in future abstainers, but not relapsers. Significantly, as a critical component underpinning EF, processing speed has also been highlighted as a predictor of relapse in AUD alongside post-treatment self-efficacy (Allsop et al., 2000), coping style (Susan F. Tapert et al., 2004), and comorbid unipolar mood disorder (Durazzo et al., 2008). The contribution of processing speed to poor EF may even occur via the increased vulnerability interpretation of the premature aging hypothesis, particularly given that AUD appears to exacerbate age-related reduction in white matter integrity, and that this lower integrity associates with poorer processing speed (Sorg et al., 2015). Furthermore, correlations are

reported in AUD between age, neural measures, and performance on working memory tasks (Pfefferbaum et al., 2006).

Processing speed shows possible improvement across long-term abstinence from AUD (Crowe, 2019; Stavro et al., 2012), but again, results have been inconsistent (Crowe, 2019; Schulte et al., 2014; Stavro et al., 2012). However, it has been suggested that deficits in processing speed and EF are more likely to characterise the early stage of abstinence (up to a month), rather than the middle and later stages, which appear related to verbal and visuospatial processing and memory deficits, and residual memory deficits respectively (Crowe, 2019). Therefore, given that 50-80% of people with AUD relapse, and that this often occurs during early abstinence, such as in the first few days/weeks following detox (Manning et al., 2016), it is clearly important to examine potentially relevant functions to understand treatment outcomes that occur during this early stage.

1.5.2 Function in Hazardous Drinking

1.5.2.1 Executive Function in Hazardous Drinking

Although acute and dependent use is associated with impaired EF, less is known about the longer-lasting impact of non-dependent drinking on EF, though the literature does generally suggest it is associated with deficits, particularly task shifting and response inhibition, on the Wisconsin Card Sorting Test (WCST) and GoStop Task (Houston et al., 2014), and on the Number-letter task and Random letter generation task (Montgomery et al., 2012). Access to semantic memory on the Chicago Word Fluency Test appears also impaired, but not updating on the Computation Span task (Montgomery et al., 2012). A recent meta-analysis found that young HED were significantly impaired relative to controls in EF (inhibitory control, decision making) (Lees et al., 2019). Similar results have been observed across broader age ranges of HED adults with impairments in tasks assessing response inhibition and cognitive flexibility after controlling for age and gender effects (Houston et al., 2014); increased Stroop RT and decreased accuracy associated with HED, with corresponding decreases in brain activity in regions mediating these functions (Affan et al., 2018). Carbia, López-

Caneda, et al. (2018) also highlight the effects of HED on response inhibition and to a lesser extent attentional switching and memory updating in their systematic review. Interestingly, Boelema et al. (2015) found no difference in EF maturation between six levels of alcohol consumption over four years, starting in childhood (but noted such deficits could manifest later in life).

Indeed, Carbia, Corral, et al. (2018) followed 63 young adults (from age 18, older than the baseline for Boelema et al. (2015)) for 11 years and found continuous HED associated with poor inhibition (Stroop Test) and updating (Self-Ordered Pointing Test; SOPT), but not shifting on the Trail Making Test (TMT). Carbia's results were not supported by a cross-sectional study of EF, drinking motives, alcohol use, heavy drinking, and related problems (e.g., regretted sexual activity), assessed in a large sample of young adults (Martins et al., 2018). They found no association between heavy drinking and inhibition or updating, and no EF components predicted alcohol-related problems. Interestingly, better shifting-specific abilities associated with heavy drinking. While this appears counterintuitive, strong shifting-specific abilities differ from other EF by undermining self-control (Friedman & Miyake, 2017; Herd et al., 2014). Known as the "stability-flexibility trade-off", high shifting enables moving attention to appealing alternatives, but impairs maintenance/shielding of long-term goals (Hofmann et al., 2012). However, differences between these two studies are likely due to methodological differences such as cross-sectional versus longitudinal design, general population versus undergraduate university students, HED versus 'heavy drinking' (frequency and quantity), or single-task versus latent variable approach.

There are multiple other examples of studies finding impaired EF, particularly response inhibition in HED, on the Go/NoGo task (Ames et al., 2014; Czapla, Simon, Friederich, et al., 2015; Lannoy et al., 2020), and on the Flanker task (Kim & Kim, 2019; Lannoy et al., 2019), but also of studies finding the opposite, on the Go/NoGo task (Blanco-Ramos et al., 2019; Lannoy et al., 2017; López-Caneda et al., 2012; López-Caneda et al., 2014), and on tasks assessing updating such as the N-back (Park & Kim, 2018; Schroder et al., 2019) and Letter Memory task (Lannoy et al., 2019), and

on the Number-letter task assessing shifting (Lannoy et al., 2019). A possible explanation for these discrepancies is a 'neurocompensatory mechanism' in young drinkers, whereby increased cognitive effort enables maintenance of behavioural task performance, which loses efficiency over time and continued hazardous drinking (Almeida-Antunes et al., 2021; Gil-Hernandez et al., 2017; Susan F Tapert et al., 2004). Indeed, many of the studies in this paragraph that did not find performance differences did find electrophysiological differences in hazardous drinkers, including delayed latencies and/or higher amplitudes of event-related potentials (ERP) indexing executive control (Blanco-Ramos et al., 2019; Lannoy et al., 2017; López-Caneda et al., 2012; López-Caneda et al., 2014; Park & Kim, 2018; Schroder et al., 2019) . Additionally, functional neuroimaging reveals that while decreased activity in frontoparietal areas during EF tasks may be a precursor for hazardous drinking, these areas often display hyperactivation during EF tasks after the onset of this (Lees et al., 2019; Spear, 2018).

Additionally, as stated previously, EF are associated with the PFC, and neuroimaging indicates that HED is associated with degradations in whole-brain white matter and prefrontal grey matter anomalies, which is linked to poor updating on the Cambridge Neuropsychological Test Automated Battery (CANTAB) Spatial Working Memory test, and the non-computerised version, the SOPT (Doallo et al., 2014; K. W. Smith et al., 2017), but not inhibition assessed by CANTAB Stop Signal Task (SST) (K. W. Smith et al., 2017). Again, there is some discrepancy. Therefore, it is important for further investigation to examine what type of 'frontal lobe functions' may be impaired with hazardous/harmful drinking, and what the individual cost of this may be. While objective assessments of EF are important in identifying component processes of EF that may be affected by HED, self-reported problems with EF function provide an interesting insight into the subjective experience of such deficits. This may be more indicative of the effects of HED on cognitive effort required in performing these EF in real-world settings, possibly a result of neurocompensatory action. Indeed, heavy drinking is related to higher subjective ratings of dysexecutive function (Houston et al., 2014), though further study is needed.

1.5.2.2 Processing Speed in Hazardous Drinking

While there are generally consistent links between hazardous alcohol use and EF deficits (Carbia, Corral, et al., 2018; Houston et al., 2014; Lees et al., 2019; Montgomery et al., 2012), the relationship between hazardous use and processing speed is unclear. Some studies have shown no difference between hazardous and non-hazardous drinkers. For example, studies using Digit Symbol Substitution (DS) and pattern comparison tasks (requiring identification and copying of symbols into a matrix over a set time period) have found no difference in the number of correct substitutions made between HED and controls (Affan et al., 2018; Winward et al. 2014a; Winward et al., 2014b) in addition to absence of effects of age and age x drinking level interactions (Woods et al., 2016). Similarly, tasks requiring letter or number sequencing like the TMT-A and Delis-Kaplan Executive Function System letter/number sequencing have demonstrated no HED-related differences in overall time to complete (Winward et al., 2014a; Winward et al., 2014b; Nguyen-Louie et al., 2015), with one study demonstrating that heavier drinkers aged 70 showed no effects of binge drinking (ranging from 0 – 3+ drinks daily) on TMT-A, and that performance did not decline over the seven years from age 70 to age 77 (Hogenkamp et al., 2014). Congruent Stroop RT has been shown to be comparable between moderate drinkers and HED on a spatial Stroop task (Kashfi et al., 2017). Rodgers et al., (2005) have also reported that light drinkers were superior to abstainers and occasional drinkers in a simple and choice RT task composite score (requiring pressing a response box when a specified light appeared), though hazardous and harmful drinkers did not differ significantly from any of the other groups.

However, there is also evidence that heavier non-dependent drinkers have faster processing speed than their lighter drinking counterparts. For example, Townshend and Duka (2005) demonstrated that HED were faster in eight-pattern matching to sample choice RT, with no increase in errors indicating this was not due to a speed-accuracy trade-off. In a longitudinal study, Zanjani et al. (2013) utilised a task requiring finding and matching of figures, finding that overall males showed consistent decline across drinking status (abstainer, moderate drinker, at risk drinker) while female

abstainers showed the greatest decline relative to moderate and at-risk drinkers. These effects of heavier drinking on processing speed were supported in a recent systematic review including 18 studies assessing processing speed in HED, where HED was found to be associated with significantly faster processing speed in the meta-analysis (Lees et al., 2019). In addition, Piumatti et al. (2018) conducted a longitudinal analysis and found that RT was faster (improved) with every 1g/day of alcohol but slowed as this increased beyond 10g/day, with increasing age also identified as a factor in cognitive decline.

Whilst the evidence above suggests little negative effect of heavy alcohol consumption on processing speed, some studies have identified processing speed deficits in heavy drinkers. For example, using the Paced Auditory Serial Addition Task requiring addition of pairs of 2-digit numbers at different presentation speeds, HED were found to make fewer correct responses at faster presentation rates of 1.2 and 1.6 seconds (Hartley et al., 2004). Moreover, in a study that controlled for effects of age, sex, physical activity, age of onset of HED and other demographic variables, performance in TMT-A was found to be impaired in HED; there was also a significant effect in females only when stratifying the sample indicating female HED, but not male HED performed worse on TMT-A (Salas-Gomez et al., 2016). This was supported by Houston et al., (2014) who found heavier alcohol consumption was associated with slower TMT-A completion. It is clear from the preceding two paragraphs that there are mixed findings regarding the effects of heavy drinking on processing speed and RT, and that gender, age, and classification of drinking status could be potential confounds. For example, methods used to classify drinking behaviours (e.g., interview versus questionnaire, using frequency/quantity of consumption versus broader elements such as grouping into hazardous/non-hazardous versus assessing alcohol use as a continuum, and in studying hazardous drinkers generally versus specific consumption patterns e.g., HED) varied between individual studies and could result in differential classification of a participant as at risk/hazardous or not. In addition, the method of processing speed assessment, and the response modality could also affect the results. Further investigation, with an acknowledgement of potential

discrepancies between previous methodologies, is required, with the consideration of stimulus/response modality being discussed later in section 3.6.1.

1.6 Thesis Overview

With this chapter having provided a brief introduction to cognitive function in alcohol use, an overview of the theoretical models upon which this thesis is based, and a rationale for examining processing speed in alcohol use in both dependent and non-dependent drinkers, this section now provides a brief overview of the rest of the thesis. Chapter 2 describes the methodological approach of this thesis and discusses the methods used in the systematic review of function recovery from AUD, the self-report survey of executive function in hazardous and non-hazardous drinkers, and the use of vibrotactile perception to assess processing speed in different alcohol contexts.

Chapter 3 is a systematic review chapter, which examines impairment and recovery of neuropsychological functions in alcohol use disorders during abstinence. A narrative review found that sub-domains within attention, executive function, perception, and memory, demonstrate recovery, generally between 6-12 months, with basic processing speed recovering within a month, supporting their use as tools to track cognitive dysfunction and recovery in alcohol users.

Chapters 4, 5, and 6 are empirical chapters. Chapter 4 assesses self-reported executive function between hazardous and non-hazardous drinkers and considers the how the relationship between alcohol use and alcohol-related problems may be mediated by self-reported function. Chapter 5 assesses processing speed between hazardous and non-hazardous drinkers, using vibrotactile perception as the stimulus modality. The results from these two chapters revealed that subjective EF is impaired in hazardous drinkers, but that processing speed is faster in this group, which associates with poorer subjective executive function. Chapter 6 then assesses processing speed using the same method as in Chapter 5, between controls and individuals with a diagnosis of alcohol use disorder, the latter of whom were assessed twice during their early treatment. The results from this chapter revealed that processing speed (specifically the task requiring more

executive control) is impaired in alcohol use disorders at early treatment, and that mental fatigue becomes impaired, driven by increasing fatigue in outpatients.

The final chapter is a general discussion of the results, evaluating the results in terms of the implications for non-dependent and dependent alcohol users, and directions for future research.

1.6.1 Thesis Prologue

This work took place during the Coronavirus Disease 2019 (COVID-19) pandemic, starting in October 2019. As a result, the intended programme of work had to be significantly amended. Originally, the project intended to examine the recovery of function from alcohol dependence, starting during detoxification, with multiple follow-ups until around 5-7 months of abstinence, in comparison to a control group, with the entirety of recruitment and follow-up for the project intended to run for two years, from June 2020 to June 2022. It was also intended to examine the predictability of initial function assessment, regarding later relapse. Unfortunately, despite HRA ethical approval being granted in March 2020, the start of the first lockdown in the same month and the multiple subsequent lockdowns/restrictions, meant all procedures were put on hold, and the research was delayed at one National Health Service (NHS) site by around 15 months (starting in September 2021), and at the other by 18 (starting in December 2021), ending in October 2022. This meant that despite an extension to the PhD, study processes operated for around half the time initially intended.

Furthermore, once access to the sites were gained, there were still lasting impacts of the pandemic, including busier outpatient clinics (reducing access to testing rooms) and fewer clinical staff, resulting in delayed clinics making recruitment less consistent (patients were less willing to participate after already having waited a long time for their routine appointment). Additionally, the clinic largely moved to post-detox appointments via telephone as standard practice, rather than face-to-face, which was not compatible with the study follow-up procedures, and greatly impacted retention. The residential setting was similarly impacted, as new patients were required to isolate,

meaning that it took on fewer patients. Follow-up testing here was also difficult, as for a considerable time many suitable public spaces were not open or would not enable individuals who were not from the same 'bubble' to attend, and the University did not allow visitors. All these factors contributed to what is already a high attrition rate in samples of dependent drinkers.

To adapt to these circumstances, the nature of the project changed significantly, with a survey study in non-clinical drinkers and systematic review added to contribute to our understanding of alcohol use on cognitive function, maximising output while face-to-face testing was unfeasible. Regarding the clinical study, there were fewer participants with alcohol use disorders recruited than intended, and with only one well-populated follow-up occurring in very early abstinence, this significantly reduced the conclusions that can be made about recovery of function. The study therefore added a consideration of the context in which recovery occurs in this very early stage, comparing between treatment settings (inpatient versus outpatient). Study recruitment was not high enough to appropriately use the intended analysis (binomial logistic regression) to use initial function to predict relapse, but given that relapse rates between the treatment settings were similarly high, this indicates that consideration should be given to what represents the best provision model for services.

1.7 Chapter Summary

In summary, EF are the related yet separable higher-order components of working memory, which promote goal-directed behaviour. EF are impaired in AUD, which reduces quality of life and the ability to maintain recovery strategies, and indeed are predictive regarding relapse and other recovery indicators, such as treatment adherence and craving. AUD deficits in cognitive functions, including EF, appear to have the ability to recover with abstinence from alcohol, though the extent and timescale of this is not clear. This forms the basis of the first study of this thesis, a systematic review of recovery of cognitive functions in abstinence from AUD. In hazardous drinkers, EFs also appear to be impaired, though discrepancies may be due to a neurocompensatory mechanism,

particularly in younger drinkers, allowing for normal task performance, but requiring more cognitive effort. Self-report methods of EF measurement also show sensitivity to alcohol use, and may theoretically provide insight into heightened cognitive effort, though further insight is needed regarding which EF measured subjectively display impairment. Processing speed is the efficiency of cognitive processes, and underpins higher order processes, such as EF. Processing speed is also impaired in AUD and predicts relapse, and this deficit is a characteristic of early abstinence, which is a vulnerable time for many individuals, so may be useful to study during this early period to give insight into outcomes. Research into processing speed in hazardous drinking is inconsistent, which may be due to methodological differences, including in measurement of speed.

Chapter 2 : Research Aims and Methodology

2.1 Chapter Overview

In the previous chapter, an overview of the theoretical cognitive models underpinning this thesis were discussed, as was how the relevant functions (EF and processing speed) relate to alcohol use. This chapter presents the justification for the chosen methodological approaches used in this thesis to examine cognitive function in alcohol use, alongside the aims. As a summary of methods, in a systematic review, the recovery of cognitive functions upon cessation of alcohol use in AUD was examined. A survey study then assessed subjective EF in non-dependent drinkers, to discern whether this differed between drinkers categorised as hazardous or non-hazardous, and if the relationship between alcohol use and related problems could be mediated by subjective function. These studies both gave insight into cognitive function in different levels of alcohol use (and change in function upon maintenance of abstinence), to be built on by the third and fourth studies, which examined processing speed and subjective EF between hazardous and non-hazardous drinkers, and then between controls and individuals with AUD (in early abstinence), and within the AUD subjects to examine change in function in early abstinence between inpatient and outpatient settings.

2.2 Research Aims

The principal aim of this thesis is to investigate the relationship between alcohol use and cognitive function, in different contexts. To accomplish this, multiple aims must first be described.

1) In a systematic review, to investigate the impairment and recovery potential of neuropsychological function in AUD. This question is explored in Study 1 of the thesis, found in Chapter 3.
2) To explore subjectively reported EF in non-dependent drinkers, and how this relates to real-life problems experienced because of alcohol use. This question is examined in Study 2, found in Chapter 4.

3) To assess processing speed alongside subjective EF in non-dependent drinkers, this is Study 3, in Chapter 5.
4) To examine processing speed change in early recovery in drinkers with AUD, consider how this relates to change in subjective EF, and to compare speed to matched controls without AUD, which is Study 4, described in Chapter 6.

Individual study hypotheses have been formulated to address these aims, which can be found in the respective empirical chapters.

2.3 Study 1 – Systematic Review

Rather than conduct an in-depth literature review of the topic, it was determined that a systematic review (Chapter 3) on neuropsychological function recovery in AUD would be more valuable. This is because a systematic approach to the literature considers a greater breadth of sources, is more objective and transparent, reduces researcher bias, and encourages more criticality of evidence quality (Mallett et al., 2012). Bias in literature reviews can be introduced by frequent citing of the same sources (due to familiarity or likelihood of return in a quick literature search), focus on results rather than methods, and lack of transparency (Mallett et al., 2012). Systematic reviews reduce this due to broad and predefined search strategies, assessment of evidence quality (and bearing on robustness of review), and pre-registration and/or peer-review of the protocol (Mallett et al., 2012), all of which were observed in the systematic review presented as part of this thesis. Therefore, compared to a literature review, it is able to give a more comprehensive overview of the available evidence, the methodological concerns, and the gaps in the current field, all of which can inform future work (Poklepovic & Tanveer, 2019). Ultimately, in comparison to literature reviews, systematic reviews do not just describe the literature, they use primary research to generate new knowledge (Higgins et al., 2022).

2.4 Study 2 – Subjective Executive Function in Hazardous Drinkers

A between-groups design assessed subjective EF between hazardous and non-hazardous drinkers, and then used regression to assess whether this subjective function mediated the relationship between alcohol and alcohol-related problems. All measures used in Chapter 4 were self-report tools, and although the demographics measure was designed for this study, the other measures (EFI, Hospital Anxiety and Depression Scale, HADS; Zigmond and Snaith (1983), Alcohol Use Disorders Identification Test, AUDIT; Saunders et al. (1993), and Alcohol Problems Questionnaire, APQ; Drummond (1990)) are well validated and demonstrate good reliability (Aalto et al., 2009; Bjelland et al., 2002; Donovan et al., 2006; Drummond, 1990; Miley & Spinella, 2006; Williams & Drummond, 1994). While self-report assessments lack the ability to establish clear cause-and-effect relationships by manipulating predictor variables, this type of manipulation would not be possible or ethical when examining the relationship between alcohol use and EF. Non-experimental methods are therefore necessary. Self-reporting is such a method, and within the assessment of alcohol-use, self-report techniques demonstrate validity (Del Boca & Darkes, 2003) and are reliable when compared with other non-experimental methods (such as observation), though it is acknowledged that heavier drinkers may be more likely to underestimate their consumption, perhaps due to social desirability bias (Northcote & Livingston, 2011). Qualitative research by Muggli et al. (2015) have shown that with regards to alcohol-related 'socially undesirable behaviours', such as those investigated in the APQ, participants prefer confidential methods, including those which are not face-to-face. The authors concluded that such methods may reduce social desirability bias, highlighting the usefulness of remote survey methods.

Furthermore, the ability of self-report EF methods to investigate an individual's lived experience should not be overlooked. While to researchers, a person's ability to complete laboratory tasks (e.g., N-back or Stroop), is interesting, it likely lacks meaning to the individual, perhaps indicating that studies purely relying purely on these measures run the risk of overstating the importance of their findings. Similarly, these tasks are designed to try to isolate specific aspects of EF

as much as possible, but day-to-day scenarios are less likely to fractionate this integrated system (Burgess, 2004), real life decision making is multidimensional, integrated, subjective, and priority-based (Goldberg & Podell, 2000). These issues limit the ecological validity of experimental EF tasks (Isquith et al., 2013; Jansari et al., 2014). Interestingly, Caswell et al. (2015) found that multiple behavioural inhibitory control measures (Go/NoGo task, Immediate Memory Task, Information Sampling Task, Matching Familiar Figures Task, Single Key Impulsivity Paradigm, Two Choice Impulsivity Paradigm, Delay Discounting Task, Monetary Choice Questionnaire, and the SST) did not correlate with subscales of the Barratt Impulsiveness Scale (BIS; Patton et al. (1995)) (though SST correlated with the BIS motor subscale), which lends support to the notion that experimental EF tasks do not reflect real-world experience of goal-directed behaviour. Furthermore, while there are some tasks designed to improve ecological validity (e.g., by involving potentially real-world scenarios with multiple tasks which need prioritising etc.), such as the Executive Secretarial Task and Multiple Errands Task, these still do not necessarily tap into what is important to the individual. Additionally, many studies rely on comparison of self-reported alcohol use and alcohol-related day-to-day problems to experimental tasks, however these involve totally different data collection paradigms, and so may not be as compatible as they are treated. Therefore, this thesis compared self-reported EF to self-reported alcohol and -related problem measures.

While surveys do not allow for in-depth exploration of a topic, they benefit from the ability to reach a large and diverse sample in a cost-effective manner (Ponto, 2015) compared to other non-experimental methods (such as interview or observation), the logistics of which make larger and more varied samples less practical. Surveys can be delivered face-to-face, paper-and-pencil, over telephone, or online. Internet surveys in particular allow low-cost sampling of a large number of the population (Ponto, 2015), and alongside their other benefits, enable researchers to study the target population with no face-to-face contact. This was particularly crucial as the current study was conducted during the COVID-19 pandemic, and therefore was required to operate outside of face-to-face parameters, using self-selection sampling to further avoid this issue. It is therefore

acknowledged that the selection technique could cause the sample to be more at risk of self-selection bias, which could create a less representative sample, or exaggerated findings (Bethlehem, 2010).

While there are some concerns over the use of online surveys versus other survey methods, Gosling et al. (2004) investigated and found that they are a reliable and valid measure compared to traditional methods, with a good level of diversity in many domains (including gender, age, socioeconomic status, and geographical location). Research shows that completion rates and self-rated enjoyment decreases with survey length, and that the average attention span is between 15-20 minutes for an online survey (Brace, 2018). It was therefore crucial that the current study be kept as short as possible, to maintain completion rates and reliability (which could be affected by boredom). Questionnaires that were considered but eventually not included were the BRIEF-A self-report EF tool (which at 75 items is considerably longer than the EFI) and the Severity of Alcohol Dependence Questionnaire – Community version (SADQ-C; designed to measure the presence and severity of alcohol dependence), as it was decided that while the data from these would have been useful, the chosen tools covered enough information to examine the research question, without unnecessarily lengthening the time to complete.

2.5 Studies 3 & 4 – Vibrotactile Assessment of Processing Speed

In Chapter 5 (Study 3), processing speed was compared between non-dependent hazardous and non-hazardous drinkers, and a subset of this cohort was age-and-gender matched to participants with AUD for use in Chapter 6 (Study 4). This fourth and final study compared processing speed between participants with AUD in early abstinence and controls, from around 3 days of abstinence to around 7 days (further follow-ups occurred, but due to high attrition were not included in analyses), and examined within-group changes in subjective EF and processing speed between inpatients (Mersey Care NHS Foundation Trust) and outpatients (Royal Liverpool and Broadgreen University Hospitals NHS Trust). As the research with AUD participants was intended to

be longitudinal, and as a population AUD patients may have less stable personal circumstances, strategies to improve participant retention were considered.

The study was designed through collaboration between the researcher, supervisory team, and NHS gatekeepers. L. J. Smith et al. (2017) suggested three key strategy types for optimising retention in longitudinal alcohol research: a) mind-set, b) modalities of the study, and c) mitigating non-responsive participants. These were all considered. With regards to mind-set, L. J. Smith et al. (2017) highlight the importance of study identity, positive alliance, and regular communications. Study identity was promoted using a 'logo' (a friendly brain character), which was included on the study advertising material. Positive alliance was fostered through friendly and engaging interactions with participants. The researcher had previously worked with people in recovery from substance use and mental health problems, and so had experience in developing appropriate and positive relationships with service users. Positive feedback from participants regarding their experience in the study indicated that this was successful. Compensation for participant burden was provided in the form of a £10 Love2Shop voucher. This was chosen carefully in discussions with NHS gatekeepers, with consideration given to time spent by participants, realistic economic limitations, and potential uses of this compensation.

With regards to communication, the study incorporated in-depth informing about the expectations for follow-up (for AUD participants only) and why this is important. Study candidates were not recruited if they were unwilling to be contacted for follow-up (by either the research team, or the NHS gatekeepers). Furthermore, each participant that the researcher could contact directly (inpatients only), was reminded of their follow-up a few days in advance, and given the opportunity to reschedule. If participants did not respond, they were contacted again twice. In theory, as the outpatient AUD participants were tested after their routine clinic appointments, this should have helped with retention, however, as discussed in section 1.6.1, this was not as simple as originally intended, due to COVID-19. L. J. Smith et al. (2017) suggest that modality can be utilised by using

technology, which can reduce cost and staff/participant burden. Due to the nature of the processing speed tasks used, it was not possible to design a study without face-to-face requirements. However, the questionnaires were upgraded to a computerised format for ease of completion, and burden was also reduced by NHS gatekeepers providing pseudonymised information relating to alcohol use and demographics. Mitigating non-responsive and difficult to reach participants has already been touched on with regards to the communications and reminders of the study, however the study design also attempted to reduce participant follow-up burden where possible. Participants who were not tested on-site after their routine treatment appointments (such as inpatients followed up after discharge, and controls), had the option to meet the researcher at an appropriate public space near them, rather than having to travel to take part in the study, though again, issues with this due to COVID-19 are described in section 1.6.1.

Each of the exclusion criteria in Chapter 6 (Study 4) were chosen due to either a practical testing reason, or due to potential confounding effects on cognitive function. As the study is investigating alcohol use, confounding effects of other substances needed to be avoided, therefore other SUD (many of which are associated with EF; (Hagen et al., 2016)), were excluded. Similarly, pregnancy is associated with mild-severe cognitive impairment (Davies et al., 2018), so was also excluded. Finally, participants needed full sensation in their dominant arm and hand, due to the method of assessing processing speed that was used, which will be discussed shortly.

While it is recommended by NICE (2011) for individuals in AUD treatment to be routinely screened for cognitive problems, there are issues with the suggested tool, the Mini Mental State Exam (MMSE), not being sensitive to frontal lobe dysfunction, and other tools show an educational bias (Carnero-Pardo, 2014). Therefore, this study aimed to use a relatively novel technique to assess processing speed (as a requirement of higher-level function), in early recovery, via simple and choice RT. The Brain Gauge (BG; Cortical Metrics , Chapel Hill, NC, USA, www.corticalmetrics.com) is a relatively cheap high precision 2-point vibrotactile biofeedback interface (using perception of

vibration through touch) which plugs into any computer or laptop via USB, and can be used to assess several cognitive abilities, including that of processing speed (Tommerdahl et al., 2019). See Figure 3 for an image of the BG, which participants place their dominant hand upon, with their index and middle fingers over the cylinders, to receive the stimuli, and to respond by pressing down on the appropriate cylinder. See Table 2 for a description of the vibrotactile tasks and related composite scores, that were used in this thesis. Due to the nature of the stimuli (tactile as opposed to words, numbers, or letters), it is possible that the risk of educational bias is reduced, and while instructions are presented on-screen, the facilitator can additionally explain the task verbally.

Figure 3. *Brain Gauge device (from "The Brain Gauge: A Novel Tool for Assessing Brain Health", by Tommerdahl et al. (2019), J Sci Med, 1(1), (https://doi.org/10.3389/fnbeh.2014.00405))*

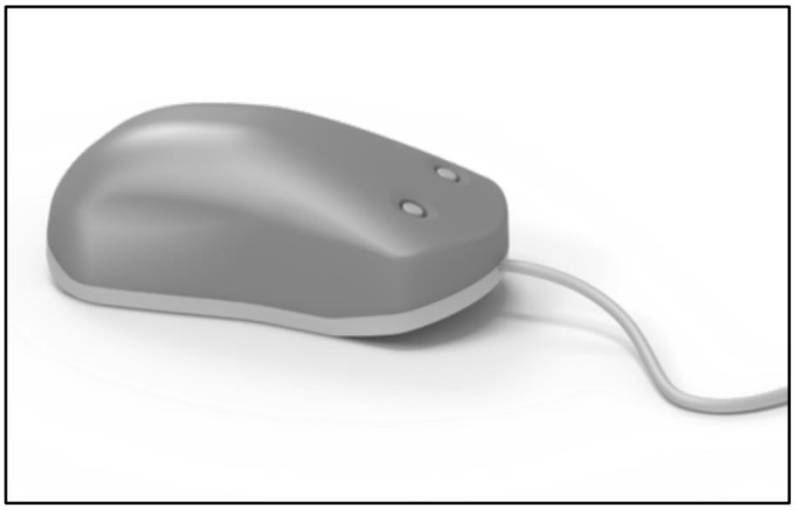


Table 2. *Brain Gauge tasks (and related composite scores) used to assess processing speed*

Tasks/*scores*	Description
Simple RT	Subject must press the tip under their index finger as soon as a pulse is felt at their middle finger
RT Variability	Standard deviation of the simple RT trials
Choice RT	Pulse may occur at either tip, as soon as it is felt, subject must press the opposite tip
Fatigue	Simple RT is repeated, and the first simple RT score is subtracted from this second score, to create a composite measure comparing the two.

Note: for all measures, higher scores = worse performance.

2.5.1 Development of the Brain Gauge

The BG was developed on the basis of many years of research into the dynamic neural representations of somatosensory events in the somatosensory cortex (see Tommerdahl et al. (2010) for review), to assess perceptual correlates of interactions between groups of neurons

(Tommerdahl, 2017). In conducting experiments in humans and non-human primates, parallels were found between the sensory percept in humans, and patterns of brain activity in non-human primates (Tommerdahl et al., 2010). Additionally, it was demonstrated that alterations in these perceptual metrics ("cortical metrics") could be related to specific underlying neural correlates (Tommerdahl et al., 2019). These cortical interactions react in predictable patterns that affect perception of the stimuli, inferring the state of the relevant neural mechanisms (Favorov et al., 2019), which underpin both higher-level and more basic cognitive functions (Tommerdahl et al., 2019). One early example of discoveries around the cortical-cortical underpinning of sensory perception was lateral inhibition (the ability of an excited cortical area to inhibit surrounding areas, Cohen (2011); Nguyen, Kirsch, et al. (2013)), initially proposed by von Békésy (1967) based on sensory perceptual experiments, later confirmed using neurophysiological techniques (Tommerdahl et al., 2010).

This contrast enhancement can be measured in animals by these invasive neurophysiological paradigms (Mountcastle, 1957; Simons et al., 2007; Simons et al., 2005; Tommerdahl et al., 2002; Tommerdahl et al., 1993), but is also reflected in perception of tactile stimuli amplitude discrimination in humans, as increased stimulus amplitude and duration causes more intense lateral inhibition, allowing an individual to discriminate between two amplitudes, despite stimulation projecting to adjacent regions of the cortex (Zhang et al., 2008). When there is neurological damage, individuals are impaired in their ability to determine difference in amplitude between two simultaneously applied stimuli, compared to ability to discriminate the amplitudes of sequential stimuli, implying impaired lateral inhibition, whilst in healthy controls, task performances are similar (Tommerdahl et al., 2019).

Regarding comparison of the BG sensitivity to other brain measures, amplitude discrimination is typically possible between 10-20% stimulus intensity on adjacent fingers, but the corresponding difference in cortical response would unlikely be visible in medical imaging (Francisco et al., 2008). Whilst lateral inhibition is relevant to the understanding of the development of the BG

and will occur with any tactile stimulation of a fingertip, it is not directly assessed by processing speed, and so will not be discussed further. Additionally, the BG also uses several other paradigms to assess other neural correlates (Tommerdahl et al., 2019), however like lateral inhibition, these are not directly relevant to the assessment of processing speed, and therefore will not be discussed.

Cognitive functions are often objectively assessed using tasks that involve stimulus perception, for example a RT assessment may rely on the pressing of a button upon seeing or hearing certain stimuli. Moreover, previous research also suggests that impairments may be domain specific, with Woods et al. (2016) finding no difference for perceptual speed, but an impairment in psychomotor speed. Consequently, modality of presentation and response may impact results. Previous research using inhibitory control tasks has identified that inhibition assessed using an auditory Go/NoGo task is more consistent in finding impairment when alcohol is administered than when visual stimuli are used (Christiansen et al., 2013; Guillot et al., 2010). Vibrotactile perception may be a useful method of assessing cognitive functions for a number of reasons. Firstly, the organisation of the somatosensory system is somatotopic (adjacent regions of the body represented adjacently), and is therefore ideal for inducing cortical-cortical interactions in adjacent or near-adjacent cortical regions (Nelson & Chen, 2008). Secondly, compared to auditory or visual input, it is also easier to limit competing same-sense distractions (Holden et al., 2020; Tommerdahl et al., 2016). With regards to RT assessment specifically, noise can be added by computer systems, core processors, screen refresh rates, and other hardware/software processing latencies (Holden et al., 2020). Holden et al. (2019) suggest that tactile stimulation using dedicated hardware is the most accurate method for RT assessment compared to visual stimuli with various response methods, and the one with the least RT variability.

Cortical metrics have been validated across 50 years of research (Tommerdahl et al., 2019), including validation with other neuroscience techniques, such as fMRI (Maeda et al., 2014), magnetic resonance imaging (Cassady et al., 2020), magnetoencephalography (Khan et al., 2015), transcranial

magnetic stimulation (Rai et al., 2012), and magnetic resonance spectroscopy (Puts et al., 2015; Puts et al., 2017). BG has successfully tracked recovery in mild brain injury (Favorov et al., 2019), and highlighted alcohol-related effects in binge drinking students (Nguyen, Gillen, et al., 2013). It is cheap, portable, and easy to use, making it a potential alternative for measuring cortical function in AD, and for tracking changes during recovery. During the MSc of the author of this thesis, a small pilot based on this principle (N = 28 alcohol dependent patients; measured at the start/end of initial inpatient detox, Powell, Tommerdahl, et al. (2021)) was undertaken. This provided preliminary support for BG as a cognitive function assessment tool, as it highlighted certain changes across early treatment. However, a larger study across different recruitment settings was intended to give further insight.

2.6 Chapter Summary

This chapter discussed the aims and methodology implemented in the four studies which make up this thesis. Regarding Study 1 in Chapter 3, it was determined that systematic review methods would allow the researcher to generate new knowledge around cognitive function recovery in AUD, and that this would be less biased than a literature review. Survey methods were a necessity in Chapter 4 (Study 2) due to COVID-19, but also presented an opportunity to recruit a wide range of participants from around the globe, with potentially less motivation for individuals to present socially desirable results. Finally, for Chapters 5 and 6 (Studies 3 and 4), vibrotactile perception provided a novel method of examining processing speed in non-dependent and dependent alcohol users, potentially with more accuracy than other modalities, whilst methods used to try and facilitate study retention in Chapter 6 were also described.

Chapter 3 : Systematic Review of Neuropsychological Function Recovery in AUD

The protocol for the review in this chapter is published open access in PLOS ONE, and is cited in this thesis as Powell et al. (2022), and available in Appendix 3.

3.1 Chapter Overview

The previous chapter justified the methods used in this thesis, including the use of a systematic review to assess recovery of neuropsychological function from AUD (of which the literature is not consistent, as discussed in Chapter 1), which will provide new knowledge and a reduced risk of bias compared to a literature review. Bias can occur due frequent citation of the same sources, lack of transparency, and focus on results not methods, which systematic reviews limit due to broad search strategies, pre-registration/publication of the protocol, and assessment of evidence quality. This chapter therefore describes a systematic review of longitudinal studies that assess neuropsychological function recovery in abstinence from alcohol in AUD. The secondary objective was to assess predictors of neuropsychological recovery in AUD. APA PsycInfo, EBSCO MEDLINE, CINAHL, and Web of Science Core Collection were searched between 1999–2022. Study reporting follows the Joanna Briggs Institute (JBI) Manual for Evidence Synthesis, study quality was assessed using the JBI Checklist for Cohort Studies. Eligible studies were those with a longitudinal design that assessed neuropsychological recovery following abstinence from alcohol in adults with a clinical diagnosis of AUD. Studies were excluded if participant group was defined by another or co-morbid condition/injury, or by relapse. Recovery was defined as function reaching 'normal' performance. Fifteen studies were selected for narrative synthesis. Most functions demonstrated recovery within 6-12 months, including sub-domains within attention, EF, perception, and memory, though basic processing speed and working memory updating/tracking recovered earlier. Additionally, verbal fluency was not impaired at baseline (while verbal function was not assessed compared to normal levels), and concept formation and reasoning recovery was inconsistent. These

results provide evidence that recovery of most functions is possible, though methodological limitations of the literature available, and of the review itself, are discussed.

3.2 Introduction

Alcohol-related brain injury (ARBI) affects an estimated 35% of dependent drinkers, though not all will be diagnosed (Wilson et al., 2014) and is an umbrella term for major neurocognitive disorders caused by drinking (Thompson et al., 2020). There is a lack of consensus on which conditions are ARBI, though it generally includes Wernicke's encephalopathy, Korsakoff's Syndrome (usually preceded by Wernicke's (Arts et al., 2017), together Wernicke-Korsakoff's Syndrome), and alcohol related dementia (Thompson et al., 2020). While not everyone with an AUD is diagnosed with an ARBI, there is review level research linking uncomplicated AUD with brain differences, though this seems more pronounced in diagnosed ARBI (Bühler & Mann, 2011). Brain differences in AUD occur across structure and function, including within neurotransmitter and metabolic systems (Bühler & Mann, 2011), grey and white matter (Bühler & Mann, 2011; Klaming et al., 2019; Monnig et al., 2013; Spindler et al., 2021; Xiao et al., 2015; Yang et al., 2016), and ERP markers of attentional capacity (Hamidovic & Wang, 2019).

Furthermore, a variety of neuropsychological functions are impaired in AUD, including memory, processing speed, and higher level cognitive processes such as EF and decision making (Crowe, 2019; Stavro et al., 2012; Stephan et al., 2017), social cognition (Bora & Zorlu, 2017; Onuoha et al., 2016), and facial emotion recognition (Bora & Zorlu, 2017; Castellano et al., 2015). Previous research has also sought to assess recovery of these functions over time. A prospective review (Schulte et al., 2014) found consistent improvement of sustained attention, but inconsistencies for attention, memory, working memory, EF, and processing speed. Poorer baseline performance, number of detoxifications, family history, and smoking were all moderating factors for neurocognitive recovery. Two methodologically similar meta-analyses across varying levels of abstinence by Stavro et al. (2012) and Crowe (2019), found conflicting results. While both indicated

impairment across all functions tested (except IQ in Stavro et al. (2012)), one found recovery of all domains (inhibition not included as too few papers) by a year of abstinence (Stavro et al., 2012), while Crowe (2019) found a wide variety of persisting impairments at all three time periods, including after a year (particularly visual/verbal memory, EF, processing speed, and verbal learning, and except working memory). Therefore, while there is support for recovery of neuropsychological functions with abstinence, evidence is inconsistent, and there are methodological issues. Firstly, the studies included in Crowe (2019); Stavro et al. (2012) were largely cross-sectional, limiting conclusions about causality (Barnett & Hyman, 2006). Secondly, the most suitable review is Schulte et al. (2014), as it included only longitudinal studies with controls (with many papers having tested controls at least twice, reducing impact of AUD practice effects), however this still found inconsistent results.

The current systematic review specifically aimed to investigate recovery of neuropsychological function following abstinence in AUD, addressing the limitations discussed above.

3.2.1 Objective(s)

To assess neuropsychological function recovery following abstinence in individuals with a clinical AUD diagnosis. The secondary objective was to assess predictors of neuropsychological recovery in AUD.

3.3 Method

3.3.1 Protocol

The protocol (Powell et al. (2022), see Appendix 3 for published version) used the JBI Manual for Evidence Synthesis (Moola et al., 2020), and PRESS (McGowan et al., 2016)/ PRISMA-P checklists (Shamseer et al., 2015).

3.3.2 Eligibility Criteria

3.3.2.1 Population

Adults with a clinical diagnosis of AUD and in recovery (abstinent at least two weeks (Schulte et al., 2014)) for at least the first recovery time point). Overall mean age for inclusion was 18-64 years at baseline, as alcohol use, related risk, and brain structure/function change across lifespan, but this is likely most pronounced in young people and older adults thus reducing comparability (Barry & Blow, 2016; Lövdén et al., 2020). It is likely that many people (indeed likely the majority) in a clinical sample being treated for AUD will also use other substances (Moss et al., 2015), alcohol must have been the primary substance reported in the study for inclusion. If a study included groups of individuals with different types of SUD including AUD, it could be included so long as the study clearly reported AUD subgroup results.

3.3.2.2 Exposure

Abstinence from alcohol in recovery from an AUD, defined as either a clinical diagnosis of AUD (mild, moderate, or severe) as per Diagnostic and Statistical Manual of Mental Disorders (DSM)-5 (2013), alcohol dependence/abuse as per DSM-IV (1994), or alcohol dependence/harmful use, as per International Classification of Diseases (ICD)-10 (1994) or ICD-11 (2019), for diagnostic consistency.

3.3.2.3 Control/comparator

i) adults without AUD; ii) adults with a different severity of AUD; iii) abstinence duration assessed by regression (including analysis of variance), as in Schulte et al. (2014).

3.3.2.4 Outcome

Primary outcome was change in neuropsychological function from baseline (which may have been recorded before/during active AUD, or in early recovery) to last available follow-up. This must have been assessed at least twice using a validated self-report/task measure or analogous measure, or as clinical diagnoses/progression of neuropsychological impairment.

3.3.2.5 Study Design

Longitudinal (cohort: prospective or retrospective), published since the year 1999 to account for the introduction of various contemporary neuroscientific theories of addiction (Fernández-Serrano et al., 2011), such as (Everitt & Robbins, 2005; Goldstein & Volkow, 2002; Koob & Le Moal, 2001).

3.3.2.6 Exclusion Criteria

Grey literature; animal studies; studies not published in English; population defined by another or co-morbid condition (such as a major psychiatric condition, head trauma, ARBI diagnosis, or co-morbid or secondary other SUD, or alcohol relapse).

3.3.3 Search Strategy

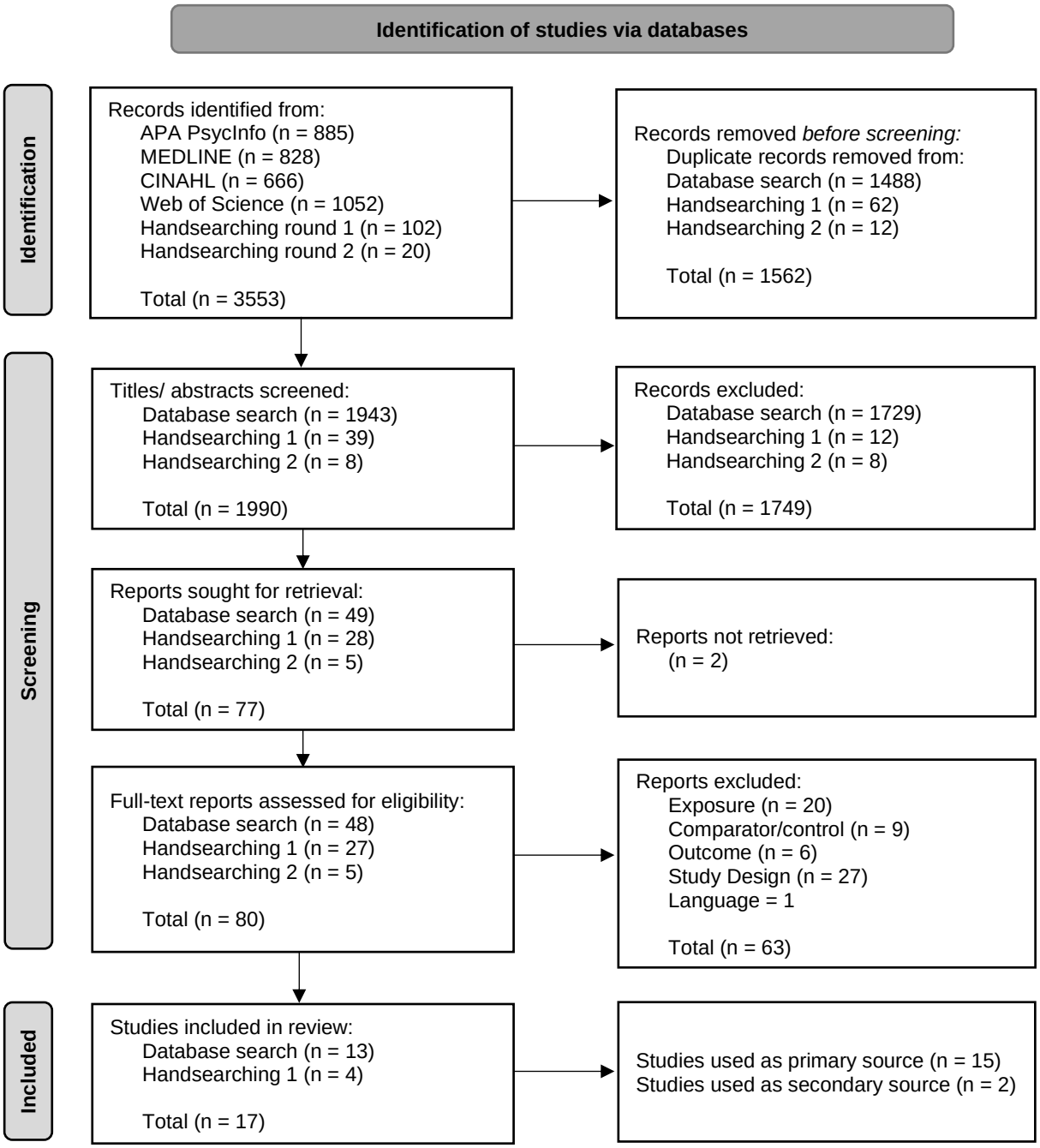
A four-stage search strategy was used: 1) an initial search of databases (CINAHL, APA PsycInfo, EBSCO MEDLINE, Web of Science Core Collection) using pre-specified keywords (alcohol dependence, alcohol use disorder, cognitive function) identified other keywords and subject headings, and was followed by: 2) full strategy searching across all sources, 3) handsearching reference lists of included papers, 4) forward searching, with articles citing included studies screened for relevance. Search filters were used where possible. Clinical trials registers were not searched, as these were judged likely to bring up papers on intervention efficacy, rather than neuropsychological assessment/recovery. Searches were re-run prior to final analysis. See Appendix 1 for search strategies for each source.

3.3.4 Data Management and Selection Process

Search strategy results (references, abstracts, and full texts where available) were transferred into EndNote for duplicate checking, into Rayyan for title/abstract screening, and then into Microsoft Excel to manage full-text screening between assessors. Pre-screening exclusion was documented (see Figure 4 for PRISMA flowchart). Papers were screened (first via titles/abstracts) using review criteria. Initial screening was against two preliminary criteria: a) study participants are

human adults aged 18+, and b) study appears to longitudinally assess recovery of neuropsychological function from AUD.

Figure 4. *PRISMA chart of study process*



When studies met above initial criteria, attempts were made to obtain full texts and key information for full criteria screening, and data extraction. If necessary, full texts were obtained via inter-library loan, and/or contacting authors. If key information was not received within a month of contact, the study was excluded. Rationale for exclusion at this full-text screening stage was documented in the PRISMA chart. Screening was conducted independently by three assessors, one of whom (Anna Powell, AP, thesis author) screened all data, and the other two (Jessica Smith, JS & Rebecca Kuiper, RK) each screened half, for fidelity. Inter-reviewer consistency was determined prior to screening and determined to be *good* (AP and RK [κ = .747, *p* <.001]; AP and JS [κ = .641, p <.001]), after which a discussion was held to benchmark criteria. Following the completion of full-text screening, uncertainties were discussed between the research team, allowing final decisions to be made.

Duplicates were identified, including identical records and papers describing different outcomes or time-points of the same study. If multiple articles described the same study, a primary paper was chosen as the main source of results. This was decided via discussion between reviewers. Papers reporting different relevant outcomes but not chosen as the primary paper were considered secondary sources of study information.

3.3.5 Data Extraction

A data extraction form based on the JBI manual was created (Appendix 2), including definitions of each element for consistency. The following details were extracted: authors; title; year; funding; conflicts of interest; design; setting; location; participant characteristics (age, sex, gender, sample size, exact diagnosis, diagnosis length, age of onset, no. treatment attempts, comorbidities, substance use, details of comparison groups, attrition details); recruitment/follow-up procedures; data relating to change in neuropsychological function (measurement, analysis, results, statistical significance, and confound adjustments); data relating to secondary aims (characteristics reported as predictors of neuropsychological recovery) including measurement and results.

Data extraction and quality appraisal were piloted by AP on a sample of five full-text papers (selected for wide-ranging outcome measures and time-points). This method informed refinement of data extraction and quality appraisal (Centre for Reviews and Dissemination, 2009).

3.3.6 Quality Assessment

The JBI Checklist for Cohort studies (Moola et al., 2020) was applied at the primary outcome level to provide appraisal of study methods, risk of bias, and validity of results. Scoring was rated as 'yes', 'no', 'unclear' or 'not applicable'. Responses of 'yes' (1) were summed against the maximum total and scores transformed into percentages and ratings (poor = 49%, moderate = 50-69%, good = 70% onwards), as in Hall et al. (2021). Scores were not used to exclude studies but to inform appraisal. 10% of this screening was independently conducted for accuracy.

3.3.7 Data Synthesis

Due to the expected heterogenous nature of methodologies, a narrative synthesis was produced, and meta-bias was not assessed. Popay et al. (2006) and the University of York's Centre for Reviews and Dissemination (2009) suggest four key elements of a narrative synthesis; 1) developing a theory of how the intervention works, 2) developing a preliminary synthesis of results, 3) exploring relationships in the data, 4) assessing robustness of the synthesis. This review was not evaluating an intervention, therefore did not use the first feature.

The synthesis has grouped, described and discussed data according to functions assessed, and neuropsychological measures used, using Lezak et al. (2012) for guidance. Some studies are therefore represented multiple times. Tables and figures have been used to support the synthesis, including a table of study characteristics, and a table summarising the measures used in each study, domains assessed, and outcomes. As a preliminary synthesis, a recovery matrix was created, in a similar fashion to that created by Pask et al. (2020). Finally, robustness of findings was discussed using JBI Quality Appraisal Checklist results and limitations of the synthesis process itself.

3.4 Results

Searches were initially run on 10/03/2022 and were re-ran on the 17/03/2023 prior to finalising the synthesis (see Figure 4 for PRISMA chart of screening process). Seventeen studies longitudinally measured neuropsychological recovery from AUD, with follow-ups ranging from 14-18 days of abstinence to 24 months. Three studies were described as using mostly the same cohort (Durazzo et al., 2015; Durazzo et al., 2014; Pennington et al., 2013), so the study with the longest follow-up duration at eight months (Durazzo et al., 2014) was selected to be the primary source for this cohort. The details of the fifteen studies included in the synthesis can be found in Table 3. Of these, ten studies compared neuropsychological function to controls (though three of these only tested controls once, and one of these only compared AUD baseline performance to controls), while two compared to test-provided normative data. The remaining three studies did not compare AUD function to 'normal' performance but did assess the impact of abstinence duration using regression analyses. As a result of these methodologies, it is not possible to exclude the confounding impact of practice effects on neuropsychological improvement.

Table 3. *Study characteristics, tasks measured, and outcomes, grouped by study quality (good, moderate, poor)*

Author, Year	Country, Economic status at time	Setting	Diagnostic tool	% Male	Average age (years)	Timepoints	Sample size at each time	Comparator	Tasks	Function **Impaired vs controls or normative data at T0**/not impaired or not compared at T0	**Improvement/** no change or not reached normal performance if compared/ *worsened.* Significance level $p \leq .05$.
Alhassoon et al., 2012	USA High	Inpatient	DSM-IV, AD	100	51.4 ± 6.0	T0 = 2w T1 = 12m	T0 = 19 T1 = 15	15 controls (51.8 ± 7.4 years, 100% Male), assessed twice in same interval. Matched age/education.	TMT-B DB HCT	DA, F **WMU/T** **F, VCF**	DA, F **WMU/T** F, VCF
Bartels et al., 2007	Germany High	Outpatient	DSM-IV, AD	71.9	44.7 ± 6.2	T0 = 2-3w T1 = 3m T2 = 6m T3 = 12m T4 = 24m	T0 = 50 T4 = 32	Normative data. Three groups; hippocampal dysfunction (HC group) implied by related tasks, no HC dysfunction, additional brain damage, indicated by clinical diagnostics).	CI Alt VLT NVLT CMT	PS, RI, FA PS **Ver LTM** (HC group) **Vis STM** (HC group) **Vis LTM** (HC group)	PS, RI, **FA** in HC group by T4 PS **Ver LTM** by T3 & T4 (HC group) **Vis STM** by T3 & T4 (HC group) **Vis LTM** by T4 (HC group)
Czapla et al., 2016	Germany High	Inpatient	DSM-IV, AD	81	48.05 ± 9.26	T0 = 2-4w T1 = 6m	T0 = 94 T1= 44 (32 of whom relapsed)	71 healthy controls (46.00 ± 12.02 years, 76% Male), assessed once. Controls only compared at baseline. Regression methods assessed impact of abstinence duration.	RVP CRT CGT AGnG IED	**FA, PS, RI, WMU/T** PS, RI **DM** **RI** F, **S**	FA, PS, RI, WMU/T PS, RI **DM***** **RI***** F, S
Durazzo et al., 2014	USA High	2+ Outpatient	DSM-IV, AD	84 ns 85 fs 96 as	ns = 50 ± 10 fs = 55 ± 13 as = 50 ± 9	T0 = 1w T1 = 1m T2 = 8m	T0 = 93 T1 = 133 (58 added)	38 never smoking controls from local community (47 ± 9 years, 89% Male), assessed twice in similar interval. Regression methods assessed impact of abstinence duration. Within AD, never smokers = ns, former smokers = fs, active smokers = as.	SS DS DSp CVLT BVMT	**PS** (fs & as) **PS** **AC** **Ver STM** (as) Ver LTM **Vis STM, Vis LTM** (fs & as)	**PS** by T1 & T2 **PS** by T1 & T2 (fs & ns, not as) **AC** by T1 (ns & as) & T2 *Ver STM (fs & as), Ver LTM (as) by T1,* Ver STM, Ver LTM by T2 **Vis STM, Vis LTM** by T2 (fs, not as)
Foisy et al., 2007	Belgium High	Residential post-detox centre	DSM-IV, AD	57.1	42.44 ± 8.05	T0 = 3-4w T1 = 3m	T0 = 49 T1 = 22	22 controls (44.86 ± 9.31 years, 54.5% Males), tested twice over same interval. Matched age (± 5 years)/ gender/ education. Regression methods assessed impact of abstinence duration.	EFERp	**EFE**	EFE
Ioime et al., 2018	Italy High	2 Outpatient	DSM-IV-TR, AD	75	46.63 ± 8.5	T0 = 12-17d T1 = 6m T2 = 12m	T0 = 41 T1 = 37 T2 = 27	40 controls (46.60 ± 6.2 years, 70% Males), tested once. Regression methods assessed impact of abstinence duration.	ST TMT-B TMT B-A MCST RPM RAVLT ROCF CoF	**FA, RI** **DA, F** **F** **F, S** **VCF** **Ver STM, Ver LTM** **FM, FD, Vis STM, Vis LTM FD, FD** **FM, FD** by T1 & T2	**FA, RI** by T1 & T2 **DA, F** by T1 & T2 **F** by T1 & T2 **F, S** by T1 & T2 VCF Ver STM, *Ver LTM by T1,* Ver LTM by T2 Fm, FD, Vis STM, **Vis LTM** by T2
Loeber et al., 2010	Germany High	Inpatient	DSM-IV, AD	60.4	HD = 47.4 ± 8.4 LD = 44.9 ± 7.7	T0 = ≥ 5d after end of medication T1 = 3m	T0 = 48 T1 = 35 T2 = 28	36 controls (44.4 ± 9.1 years, 56.3% Male), assessed twice in three months. Matched age/ gender/ premorbid intelligence. Grouped by	IGT TMT-B + WCST	M **DA, F** Ver STM, Vis STM	M DA, F by T1, **DA, F** by T2*** Ver STM, Vis STM

						T2 = 6m		previous detoxes; 2+ detoxes, High-detox = HD, others Low-detox = LD.	RAVLT + BVRT		
Petit et al., 2017	Belgium High	2 Inpatient	DSM-IV, AD	73.2	49.54 ± 11.58	T0 = 1d T1 = 18d	T0 = 41* T1 = 41*	41 healthy controls (43.80 ± 11.34 years, 41.5% Male), assessed twice in same interval. Matched age/gender.	ST DF B-P	**FA,** PS, **RI** AC **WMU/T, Vis STM** (10 & 20 sec delays, not 0 or 5 sec)	FA, PS, RI AC **WMU/T, Vis STM** (10 & 20 sec delays)
Pitel et al., 2009	France High	Inpatient	DSM-IV, AD	**	47.31 ± 7.42	T0 = 9.58 ± 4.42d T1 = 6 m	T0 = 54 T1 = 21 (9 of whom relapsed)	54 controls (47.27 ± 6.80 years, ** % Male), tested once. Matched age /education.	ST N-b Flx FCSRT	FA **WMU/T, U** F **Ver STM, Ver LTM**	FA **WMU/T** F **Ver STM, Ver LTM**
Wegner et al., 2001	Germany High	Inpatient	ICD-10 & DSM-IV, AD/ misuse	84.2	44.6 ± 2.14 (SEM)	T0 = 0-4d T1 = 14-18d	T0 = 19 T1 = 19	19 controls (42.2 ± 1.75 years (SEM), 47.4% Males), tested twice in 3-week span. Matched age/ education. Regression methods assessed impact of abstinence duration.	G/L DVD	**DA** Vis STM	**DA** Vis STM
De Sousa et al., 2010	Belgium High	Residential	DSM-IV, AD	48.5	48.40 ± 8.2	T0 = 1-2d T1 = 14-18d	T0 = 35* T1 = 35*	22 controls (44.36 ± 9.64 years, 63.6% Male), assessed twice. Matched age/ gender/ education. IGT performed on split sample, each half did IGT at T0 or T1.	ST D2 TMT-A TMT-B TMT B-A IGT	**FA, PS, RI** **FA, PS** **PS** **DA, F** **F** **DM**	FA, PS, RI FA, PS PS DA, F F DM
McCutcheon et al., 2016	USA High	3 likely Outpatient	DSM-5, AUD (28 severe, 1 mild)	0	42.3 ± 9.5	T0 = 27.7 ± 10.2d T1 = 4 m	T0 = 28 T1 = 18	No comparison group. Regression methods assessed impact of abstinence duration.	CPT	FA	**FA**
Yeh et al., 2007	USA High	2+ Outpatient	DSM-IV, AD/ abuse	93.3	ns = 51.5 ± 9.6 s = 47.2 ± 9.8	T0 = 1w T1 = 1m T2 = 7m	T0 = 50 T1 = 46 T2 = 17	Controls not in statistical model of function recovery. Regression methods assessed impact of abstinence duration. Within AD, non-smokers = ns, smokers =s.	BVMT	Vis STM, Vis LTM	**Vis STM** by T1, **Vis LTM** by T1 (s) & by T2 (ns)
Kaur et al., 2020	India Lower-middle	Outpatient and Inpatient	ICD-10, AD	100	41.83 ± 9.16	T0 = 0d T1 = 1m T2 = 3m	T0 = 60 T1 = **	No comparison group. Regression methods assessed impact of abstinence duration.	SSp L-N COWA ANT WCST B-G	AC WMU/T VF (phonemic) VF (category) F, S FD, FM	**AC** by T1 & T2 **WMU/T** by T1 & T2 **VF** by T1 & T2 **VF** by T1 & T2 **F, S** by T1 & T2 **FD, FM** by T2
Manning et al., 2008	UK High	Inpatient	ICD-10, AD	63	44.0 ± 7.6	T0 = 3.8 ± 0.9d T1 = 12m	T0 = 30 T1 = 30	Scores scaled according to age-matched test-provided normative data. Regression methods assessed impact of abstinence duration.	MST SOC L-N COWA ANT IED MR VPA PRM Vc	PS, FM **P** WMU/T VF (phonemic) VF (category) **F, S** VCF Ver STM, **Ver LTM** **Vis LTM** V	PS, FM P **WMU/T** **VF** **VF** F, S **VCF** Ver STM**, Ver LTM** Vis LTM **V**

*Stated that relapsers were excluded from study, but these were not described in numbers or characteristics; ** data unknown; *** impaired vs controls at baseline, but not compared to controls at indicated time

Impaired function in this review is understood to be that which is significantly worse than control or normative level, while recovery is when function reaches this. Therefore, studies that did not assess controls or normative performance have been used to provide an indication of improvement rather than full recovery. Classification of functional domains and sub-domains are displayed in Table 4. A preliminary synthesis was conducted, which involved creating a recovery matrix of all function domains over time (see Figure 5). This informed the narrative synthesis reported below.

Table 4. *Grouping of cognitive functions and tasks*

Domain	Sub-domain	Abbreviation	Task (& if pertinent, specific task outcome)
Attention	Focused Attention	**FA**	CI, ST, D2, CPT, RVP
	Divided Attention	**DA**	TMT-B, G/L
	Processing Speed	**PS**	Alt, ST (congruent RT), TMT-A, MST, D2, CRT, DD, DS, RVP (RT correct, RVP-B), CI (RT)
	Attentional Capacity	**AC**	DF, SSp, DSp
Executive Functions	Planning	**P**	SOC
	Decision Making	**DM**	IGT, CGT
	Working Memory Updating/ Tracking	**WMU/T**	DB, B-P, L-N, N-b, RVP
	Response Inhibition	**RI**	ST (incongruent), commission errors on AGnG, RVP, CI & CRT
	Verbal Fluency	**VF**	COWA, ANT
	Flexibility	**F**	WCST (perseverative errors), MCST (perseverative errors), IED (extra dimensional errors), Flx, TMT-B, TMT B-A, HCT
Concept Formation & Reasoning	Visual Concept Formation	**VCF**	HCT, MR, RPM
	Sort and Shift	**S**	WCST (perseverative errors, categories achieved), MCST (perseverative errors, categories achieved), IED (extra dimensional errors, stages completed)
Learning & Memory	Short-term memory	**STM**	MF
	Verbal short-term memory	**Ver STM**	VPA (immediate recall), FCSRT (immediate free recall), RAVLT (immediate recall), CVLT (total recall)
	Verbal long-term memory	**Ver LTM**	VPA (delayed recall), FCSRT (delayed free recall), RAVLT (delayed recall), CVLT (delayed recall), VLT
	Visual short-term memory	**Vis STM**	B-P, ROCF (immediate recall), BVMT (total recall), BVRT, DVD
	Visual long-term memory	**Vis LTM**	CMT, NVLT, ROCF (delayed recall), BVMT (delayed recall), PRM
Perception	Figure & Design	**FD**	B-G, CoF, ROCF (immediate recall)
	Emotional Facial Expression	**EFE**	EFERp
Verbal Functions	Vocabulary	**V**	Vc
Motor Performance	Fine Motor Function	**FM**	B-G, MST, CoF, ROCF (immediate recall)

Tasks: **AGnG,** Alcohol Go/No-Go Task; **Alt,** Alertness subtest of Test of Attentional Performance; **ANT,** Animal Names Test; **B-G,** Bender-Gestalt Test; **B-P,** Brown-Peterson Technique; **BVMT,** Brief Visuospatial Memory Test revised; **BVRT,** Benton Visual Retention Test; **CGT,** Cambridge Gambling Task; **CI,** Crossmodal Integration subtest of Test of Attentional Performance; **CMT,** City Map Test; **CoF,** Copy of Figures; **COWA,** Controlled Word Association (F-A-S); **CPT,** Continuous Performance Test – 2nd Edition; **CRT,** Choice Reaction Time subtest of CANTAB; **CVLT,** California Verbal Learning Test revised; **D2,** D2 Cancellation Test; **DB,** Digit Span backward; **DF,** Digit Span forward; **DS,** Digit Symbol subtest of Wechsler Adult Intelligence Scale – 3rd Edition; **DSp,** Digit Span unspecified (likely composite score of Forwards and Backwards); **DVD,** Delayed Vernier Discrimination; **EFERp,** Emotional Facial Expression Recognition paradigm; **FCSRT,** Free and Cued Selective Reminding Test; **Flx,** Flexibility subtest of Test of Attentional Performance; **FSIQ,** Full-Scale-IQ-2 of Wechsler Abbreviated Scale of Intelligence – 2nd Edition; **G/L,** Global/Local paradigm; **HCT,** Halstead Category Test; **IED,** Intra-Extra Dimensional Set Shift subtest of CANTAB; **IGT,** Iowa Gambling Task; **L-N,** Letter-Number Sequencing; **MCST,** Modified Card Sorting Test; **MR,** Matrix Reasoning subtest of Wechsler Abbreviated Scale of Intelligence – 2nd Edition; **MST,** Motor Screening Test subtest of CANTAB; **N-b,** N-back (2-back); **NVLT,** Nonverbal Learning Test (German version of Kimura

Recurring Figures Test); **PRM,** Pattern Recognition Memory subtest of CANTAB; **RAVLT,** Rey Auditory Verbal Learning Test; **ROCF,** Rey-Osterrieth Complex Figure Test; **RPM,** Raven's Progressive Matrices; **RVP,** Rapid Visual Information Processing subtest of CANTAB; **SOC,** Stockings of Cambridge subtest of CANTAB; **SS,** Symbol Search subtest of Wechsler Adult Intelligence Scale – 3rd Edition; **SSp,** Spatial Span composite Forwards and Backwards; **ST,** Stroop Colour and Word Test; **TMT B-A,** Trail Making Task part B minus part A; **TMT-B,** Trail Making Task part A; **TMT-B,** Trail Making Task part B; **Vc,** Vocabulary subtest of Wechsler Abbreviated Scale of Intelligence – 2nd Edition; **VLT,** Verbal Learning Test (German version of Recurring Words Test); **VPA,** Verbal Paired Associates subtest of Wechsler Memory Scale – 3rd Edition; **WCST,** Wisconsin Card Sorting Test.

Figure 5. *Recovery matrix of function over time*

Domain	Sub-domain	Study follow-ups, increasing in abstinence duration →																					
		Cor10 14-18d	Weg01 14-18d	Pet17 18d	Kau20 1m	Yeh 1m	Dur14 1m	Kau20 3m	Loe10 3m	Bar07 3m	Foi07 3m	Mc16 4m	Pit09 6m	Loe10 6m	Ioi18 6m	Bar07 6m	Cza15 6m	Yeh07 7m	Dur14 8m	Man08 12m	Alh12 12m	Ioi18 12m	Bar07 12m	Bar07 24m
Attention	Focused Attention	ST, D2	---	ST	---	---	---	---	---	CI	---	***CPT***	ST	---	ST	CI	RVP	---	---	---	---	ST	CI	***CI***
	Divided Attention	TMT-B	G/L	---	---	---	---	---	TMT-B$	---	---	---	---	***TMT-B**$***	TMT-B	---	---	---	---	---	TMT-B	TMT-B	---	---
	Processing Speed	ST, D2, TMT-A	---	ST	---	---	SS, DS	---	---	Alt, CI	---	---	---	---	---	Alt, CI	CRT, RVP	---	SS, DS	MST	---	---	Alt, CI	Alt, CI
	Attentional Capacity	---	---	DF	***SSp***	---	DSp	***SSp***	---	---	---	---	---	---	---	---	---	---	DSp	---	---	---	---	---
Executive Functions	Planning	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	SOC	---	---	---	---
	Decision Making	IGT	---	---	---	---	---	---	IGT	---	---	---	---	IGT	---	---	***CGT****	---	---	---	---	---	---	---
	Working Memory Updating/Tracking	---	---	B-P	***L-N***	---	---	***L-N***	---	---	---	---	N-b	---	---	---	RVP	---	---	***L-N***	DB	---	---	---
	Response Inhibition	ST	---	ST	---	---	---	---	---	CI	---	---	ST	---	ST	CI	***AGnG**** CRT, RVP	---	---	---	---	ST	CI	CI
	Verbal Fluency	---	---	---	***COWA, ANT***	---	---	***COWA, ANT***	---	---	---	---	---	---	---	---	---	---	---	***COWA, ANT***	---	---	---	---
	Flexibility	TMT-B, TMT B-A	---	---	***WCST***	---	---	***WCST***	TMT-B$, WCST$	---	---	---	Flx	***TMT-B**$, WCST**$***	TMT-B, TMT B-A, MCST	---	IED	---	---	IED	TMT-B, HCT	TMT-B, TMT B-A, MCST	---	---
Concept Formation & Reasoning	Visual Concept Formation	---	---	---	---	---	---	---	---	---	---	---	---	---	RPM	---	---	---	---	***MR***	HCT	RPM	---	---
	Sort and Shift	---	---	---	***WCST***	---	---	***WCST***	---	---	---	---	---	---	MCST	---	IED	---	---	IED	---	MCST	---	---
Learning & Memory	Verbal short-term memory	---	---	---	---	---	CVLT	---	RAVLT&	---	---	---	FCSRT	RAVLT*&	RAVLT	---	---	---	CVLT	***VPA***	---	RAVLT	---	---
	Verbal long-term memory	---	---	---	---	---	CVLT	---	---	VLT	---	---	FCSRT	---	RAVLT	VLT	---	---	CVLT	VPA	---	RAVLT	VLT	VLT
	Visual short-term memory	---	DVD	B-P	---	***BVMT***	BVMT	---	BVRT&	NVLT	---	---	---	BVRT*&	ROCF	NVLT	---	***BVMT***	BVMT	---	---	ROCF	NVLT	NVLT
	Visual long-term memory	---	---	---	---	***BVMT***	BVMT	---	---	CMT	---	---	---	---	ROCF	CMT	---	***BVMT***	BVMT	PRM	---	ROCF	CMT	CMT
Perception	Figure & Design	---	---	---	B-G	---	---	***B-G***	---	---	---	---	---	---	ROCF, CoF	---	---	---	---	---	---	ROCF, CoF	---	---
	Emotional Facial Expression	---	---	---	---	---	---	---	---	---	EFERp	---	---	---	---	---	---	---	---	---	---	---	---	---
Verbal Functions	Vocabulary	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	***Vc***	---		---	---
Motor Performance	Fine Motor Function	---	---	---	B-G	---	---	***B-G***	---	---	---	---	---	---	ROCF, CoF	---	---	---	---	MST	---	ROCF, CoF	---	---

* Impaired vs controls at baseline, but not compared to controls at indicated time; & Composite of verbal/visual STM, individual tests not reported separately; $Composite of attention/executive function, individual tests not reported separately

--- Not measured | Initially impaired vs controls/ normative, no longer impaired | No initial impairment vs controls/ normative (or not compared to this), ***italics/bold*** = improved regardless | Initially impaired vs controls/ normative, still impaired | Performance worsened (and is now impaired if it was not initially)

3.4.1 Attention

Thirteen studies assessed attention. Of those comparing to 'normal' performance, complete attentional recovery was indicated by twelve months of abstinence at the latest, though there were indications of recovery earlier than this for the sub-domains.

3.4.1.1 Processing speed

Five studies assessed processing speed. Initial impairment was inconsistent, but this may be due to some studies conducting baseline testing too late to capture this. Basic processing speed recovers by one month, but not when other task and goal related elements are involved, such as accuracy on more complex tasks.

Half of the studies which did not find an initial impairment had generally not conducted baseline testing until at least two weeks of abstinence had already passed (Bartels et al., 2007; Czapla, Simon, Richter, et al., 2015), except for Manning et al. (2008); Petit et al. (2017). Of those that did find an initial impairment, two conducted baseline assessment within a week of abstinence (Cordovil De Sousa Uva et al., 2010; Durazzo et al., 2014), whilst the third was later at 18 days of abstinence but used a more complex attentional assessment (Rapid Visual Information Processing task, RVP) and recorded RT for correct responses only (Czapla, Simon, Richter, et al., 2015). Recovery was indicated to occur by a month of abstinence onwards for two basic processing speed tasks (Durazzo et al., 2014), DS and Symbol Search (SS), but processing speed of correct responses on RVP was still impaired by six months (Czapla, Simon, Richter, et al., 2015).

Only Durazzo et al. (2014) assessed predictors of processing speed recovery. Independently, age and premorbid verbal intelligence predicted change on both tasks in Durazzo et al. (2014) across the whole sample. Additionally, differential recovery was indicated as a result of smoking status, with active smokers demonstrating the poorest outcomes in both DS and SS (indeed, not recovering to control performance on DS). Furthermore, as a supplementary finding in the same cohort from a secondary source, processing speed recovery in non-smokers was associated with increasing

volumes in lobar grey and white matter regions and subcortical regions during 7.5 months of abstinence, though volume increase was similar between smokers and non-smokers, so this is unlikely to explain functional recovery differences between the two groups (Durazzo et al., 2015).

3.4.1.2 Attentional capacity

Attentional capacity was assessed by three studies only, and initial impairment and recovery was inconsistent. It is likely that attentional capacity is not impaired in AD, and that impairments and improvements in the other studies are more likely working memory performance related.

Petit et al. (2017) used Digits Forward, a more specific test of capacity (Gerton et al., 2004), finding no impairment or change up to 18 days of abstinence. In contrast, Durazzo et al. (2014) appeared to use a composite of Digits Forward and Backward, finding impairment, and Kaur et al. (2020) used a composite of Forwards and Backwards Spatial Span. Composite span measures may be confounded by impairments of working memory (Lezak et al., 2012)), and both indicated improvement, but it is hard to separate this from possible working memory changes. Furthermore, differences may also be confounded by the modality of span used, as visuospatial and verbal tasks may involve modality-specific processes (Donolato et al., 2017).

Again, age and premorbid intelligence were independent predictors of recovery across AUD (Durazzo et al., 2014), and although only never smokers were impaired versus controls at one week of abstinence, only former smokers were at one month. This may indicate a co-occurring impact of smoking and AUD on attentional capacity (or indeed, working memory) in some patients.

3.4.1.3 Focused attention

Seven studies assessed focused attention. This was generally initially impaired, which was consistent in early abstinence. Recovery was inconsistent but indicated to occur by 6-12 months in some cases, with discrepancies across baseline and recovery possibly driven by task and methodology differences.

Of the six studies that compared function to normal performance, two found no initial impairment (Bartels et al., 2007; Pitel et al., 2009), whilst four did (Cordovil De Sousa Uva et al., 2010; Czapla, Simon, Richter, et al., 2015; Ioime et al., 2018; Petit et al., 2017), one of which (Cordovil De Sousa Uva et al., 2010), used two measures. By 14-18 days of abstinence there was continued impairment (Cordovil De Sousa Uva et al., 2010; Petit et al., 2017), while in McCutcheon et al. (2016), who did not recruit controls, performance improved by three months. Performance at six months was inconsistent, with Ioime et al. (2018) finding recovery to control levels on the Stroop, but Czapla, Simon, Richter, et al. (2015) still finding impairment on the RVP. Recovery in Ioime et al. (2018) was maintained at 12 months.

While Pitel et al. (2009) used the Stroop test, the main outcome was the number of colours named in the interference condition, but other Stroop studies used a combination of incongruent trial RT, and/or isolated incongruent performance from neutral trial performance in some way. These measures may have been more able to comprehensively assess focused attention, as they would be more sensitive to problems with efficiency and executive inhibitory control deficits (Scarpina & Tagini, 2017), which are required for focused attention (Diamond, 2013). Indeed, other studies finding impairment in focused attention may have done so due to its reliance on efficiency and inhibitory control, as Continuous Performance Test score in McCutcheon et al. (2016) is a combination of commission errors (response inhibition), and RT correct, while D2 Cancellation Test (used in Cordovil De Sousa Uva et al. (2010)) assesses speed concurrently with focus, as it is time limited (Bates & Lemay, 2004). Furthermore, in Czapla, Simon, Richter, et al. (2015), RVP commission errors (response inhibition) and RT correct (processing speed) were impaired, indicating that there were issues with efficiency and response inhibition, which could possibly have contributed to poor performance on the task overall. This is not supported however by Bartels et al. (2007), who found no processing speed or inhibitory deficits or change on the task used, but with the latest attention baseline assessment at 2-3 weeks, this finding is less reliable.

When considering the conflicting findings at six months, the RVP task used by Czapla, Simon, Richter, et al. (2015) may arguably involve another layer of functional ability compared to the Stroop (alongside inhibition and efficiency), as it requires a participant to detect target digit sequences by witnessing one digit at a time, so the individual must remember the previous one or two digits (dependent on trial difficulty) to state whether the overall sequence matches that of the target sequence. This involves working memory updating/tracking, which is not required by the Stroop task, perhaps explaining why performance on this task was still impaired.

Regarding predictability, McCutcheon et al. (2016) found that in their women only sample, increases in network drinking scores (drinking behaviour of people important to the individual) between 1-4 months of abstinence, was associated with worsening focused attention, whilst the opposite was true for those whose network drinking decreased.

3.4.1.4 Divided attention

Five studies assessed divided attention, which was generally impaired at baseline, and demonstrated recovery by around six months. Of the five studies, four found initial impairment at baseline (Cordovil De Sousa Uva et al., 2010; Ioime et al., 2018; Loeber et al., 2010; Wegner et al., 2020), while one did not (Alhassoon et al., 2012). This impairment improved by six months (Ioime et al., 2018; Loeber et al., 2010), to the same level as controls (Ioime et al., 2018), which was maintained at 12 months (Ioime et al., 2018). Improvement to control level was observed very early in Wegner et al. (2001), by 14-18 days of abstinence, however compared to the other measures, they used a much simpler divided attention task (a Global/Local paradigm), with current findings suggesting this may not be able to capture continued impairment in AUD.

Alhassoon et al. (2012), was the exception, finding no impairment vs controls on TMT-B, and no change by 12 months of abstinence, which could be related to the late baseline assessment in this study. Furthermore, the sample in Alhassoon et al. (2012) were all male, and previous research has demonstrated gender differences on the TMT tasks (Płotek et al., 2014). Although the exact

nature of this relationship is not consistent throughout the literature, at least one study has found that men demonstrate better performance on TMT-B (Foroozandeh, 2014).

Predictability was not generally assessed. However, Loeber et al. (2010) found that individuals with two or more previous detoxes performed poorer than those with fewer previous treatments by six months of abstinence on a composite EF/attention score, indicating that repeated cycles of withdrawal and relapse have a damaging influence regarding recovery of divided attention and cognitive flexibility.

3.4.2 Executive Functions

Ten studies assessed aspects of EF, one of which assessed planning, three decision-making, six working memory updating/tracking, six response inhibition, two verbal fluency, and eight cognitive flexibility. Despite these abilities being related, the studies demonstrated differential recovery of sub domains.

3.4.2.1 Planning

Planning, assessed using the Stockings of Cambridge task (total score and problem-solving speed), was initially impaired and continued to be so at 12 months of abstinence (Manning et al., 2008). Further research is needed to confirm this.

3.4.2.2 Decision Making

Decision making was generally impaired at baseline and demonstrated some improvement by six months of abstinence. Interestingly, while Cordovil De Sousa Uva et al. (2010) and Czapla, Simon, Richter, et al. (2015) found initial impairment, which persisted at 14-18 days of abstinence, Loeber et al. (2010) did not, and found no change by three or six months. Czapla, Simon, Richter, et al. (2015) did not compare to controls beyond baseline but did find some improvement by six months, indicating that when decision making is impaired, improvement can take up to six months.

It is unclear why Loeber et al. (2010) did not find impairment at baseline or change in performance, given that the initial baseline assessments occurred at an abstinence duration comparable to the other two. Loeber et al. (2010) controlled for premorbid intelligence (Vocabulary Test; Schmidt and Metzler (1992)) in their analysis, but both Cordovil De Sousa Uva et al. (2010) and Czapla, Simon, Richter, et al. (2015) reported that controls and AUD participants did not differ regarding educational level, so this is less likely to be the cause of discrepancy, and all three either matched controls on age and gender, or reported no differences in these between the groups. It is possible that another confounding factor that was not assessed or controlled for contributed to the inconsistency.

3.4.2.3 Working Memory Updating/Tracking

Working memory updating/tracking was typically impaired at baseline and demonstrated recovery from as early as 18 days into abstinence, which was generally maintained up to a year of abstinence. The majority of studies found initial impairment (except Manning et al. (2008)), which typically demonstrated full recovery across studies, including at 18 days (Petit et al., 2017), six months (Pitel et al., 2009), and 12 months (Alhassoon et al., 2012), with continued improvement not compared to controls at one and three months (Kaur et al., 2020). However, Czapla, Simon, Richter, et al. (2015) found continued impairment at six months.

Despite Manning et al. (2008) not finding initial impairment compared to normative data, their participants did demonstrate improvement by 12 months, though it is unclear why the initial discrepancy occurred.

3.4.2.4 Response Inhibition

Response inhibition was generally impaired at baseline, and in the majority, demonstrated improvement and in some cases, full recovery between 6-12 months. Five of the studies found initial impairment (except for Crossmodal Integration (CI) commission errors in Bartels et al. (2007), words recalled in incongruent Stroop in Pitel et al. (2009), and choice RT in Czapla, Simon, Richter, et al.

(2015)). Cordovil De Sousa Uva et al. (2010) and Petit et al. (2017) both found that inhibitory control on the Stroop was still impaired around 18 days into abstinence. This recovered to control levels in Ioime et al. (2018) by six months, which was maintained at 12 months. However, while Czapla, Simon, Richter, et al. (2015) found, like Ioime et al. (2018), that response inhibition on an alcohol Go/No-Go (AGnG) task improved at six months, commission errors on the CANTAB RVP were still impaired.

As discussed before, as the RVP involves response inhibition and working memory updating/tracking, both of which alone typically demonstrated recovery from six months onwards, this may indicate that when a participant with AUD must perform multiple executive processes at once, performance still suffers compared to controls at this stage. Future research could examine the effect of combined executive processes on performance, as this may be closer to demonstrating real-world executive deficits. Additionally, of the EF, inhibitory control in particular has been identified as being heritable and predisposing individuals to developing AUD. Indeed, the IMAGEN study, a multidimensional longitudinal study of adolescent development, has identified genetic polymorphisms associated with functional brain activity, inhibitory control, and alcohol use (Mascarell Maričić et al., 2020). Furthermore, translational work by Sanchez-Roige et al. (2014), identified similarities in performance on homologous versions of the Five-Choice Serial Reaction Time Task (5CSRTT, and Sx-5CSRTT, the human version) between young social HED and alcohol-naïve mice bred to prefer alcohol, who were both more prone to premature responding (waiting impulsivity) when compared to non-HED and mice bred to be alcohol-averse. Similarly, Sanchez-Roige et al. (2016) found that young adults with a first-degree family history of AUD (a risk factor for development of AUD) had higher waiting impulsivity on the Sx-5CSRTT. Given that these particular choice RT tasks are relatively complex, perhaps more difficult inhibitory control tasks can identify inhibitory deficits that were pre-existing, which would be less likely to demonstrate recovery upon abstinence. Alternatively, the RVP finding may indicate a difference in the cohort measured by Czapla, Simon, Richter, et al. (2015), but as there was improvement on the AGnG this seems less

likely (no initial inhibitory deficit on choice RT may be explained by task simplicity (Scaife & Duka, 2009) relative to the other two examined in this study). Furthermore, the lack of inhibitory deficit on the CI in Bartels et al. (2007), may relate to research showing that crossmodal stop signals are more effective at prompting response inhibition (Friehs et al., 2023), perhaps due to higher salience (Carrillo-de-la-Peña et al., 2019), so possibly making this task type less able to capture inhibitory impairment in AUD. Finally, issues with using words recalled in the Stroop incongruent condition (as in Pitel et al. (2009)) have already been discussed in the focused attention section.

3.4.2.5 Verbal Fluency

Whilst verbal fluency was not impaired at baseline (Manning et al., 2008), it did demonstrate improvement consistently across the two studies, at one, three, (Kaur et al., 2020) and 12 months (Manning et al., 2008). Verbal fluency is often considered an EF (Diamond, 2013), but less consistently than the other measures (Gustavson et al., 2019), and it may be more driven by language processing (Whiteside et al., 2016), possibly explaining why this did not demonstrate impairment.

3.4.2.6 Flexibility

Flexibility was generally impaired at baseline, though recovery was inconsistent. The majority found an initial flexibility deficit, except for Czapla, Simon, Richter, et al. (2015) and Alhassoon et al. (2012), who found impairment on the Halstead Category Test (HCT), but not TMT-B. Impairment continued consistently across studies during early recovery (between 18 days and three months) but was inconsistent beyond six months. Loeber et al. (2010), who did not compare to controls beyond baseline, and Ioime et al. (2018) found improvement, even recovery (Ioime et al., 2018) by this stage. However, at 12 months, two studies found continued impairment (Alhassoon et al., 2012; Manning et al., 2008), while individuals in Ioime et al. (2018) maintained their recovery from six months.

Perhaps this suggests that flexibility in some individuals will recover by six months, and that there are predictors of the discrepancies that were not assessed but may also indicate that there is a risk that performance can improve and deteriorate again by 12 months. However, without more studies with multiple follow-ups, this trajectory remains unclear. Interestingly, Alhassoon et al. (2012), who found maintained impairment at 12 months on the HCT, did not find initial impairment on the TMT-B (which has been discussed previously in relation to gender, in the divided attention section) perhaps indicating that at least in this cohort, the added element of concept formation and reasoning in HCT contributed to initial deficit on this executive measure.

It is unclear why Czapla, Simon, Richter, et al. (2015) found no impairment on Intra-Extra Dimensional Set Shift (IED) extradimensional shift errors, given that this task is essentially analogous to the WCST and therefore similar to the Modified Card Sorting Test (MCST), and that all other studies using either of these, or even the IED itself, did find impairment (Ioime et al., 2018; Loeber et al., 2010; Manning et al., 2008), however, this was the latest baseline assessment of these, at 2-4 weeks of abstinence, which may have reduced the reliability of the assessment.

As mentioned previously, Loeber et al. (2010), who used a composite TMT-B/WCST measure, found that repeated cycles of abstinence/relapse, worsened outcomes in divided attention and cognitive flexibility by six months. Similarly, while Pitel et al. (2009) found no initial impairment on the Flexibility task, they did find that individuals who relapsed before the six-month follow-up, then demonstrated worsened performance.

3.4.3 Concept Formation & Reasoning

Five studies assessed concept formation and reasoning abilities, three of which assessed visual concept formation, and four the ability to form a concept by which to sort stimuli, and then to switch and form/sort by a new concept. General concept formation and reasoning skills demonstrated consistent impairment, whilst recovery of sorting and shifting ability was inconsistent.

3.4.3.1 Visual Concept Formation

Visual concept formation and reasoning was both initially and consistently impaired, even up to 12 months. This is logical given that reasoning abilities are often considered a good indicator of premorbid intelligence (Lezak et al., 2012). The exception was Manning et al. (2008), who used Matrix Reasoning (MR) combined with Vocabulary to create a Full-Scale IQ score and reported that the IQ score was in the normal range at baseline (but did not describe the range of MR itself), and that MR improved by 12 months. This conflicts with the findings of both Alhassoon et al. (2012) and Ioime et al. (2018), who found continued impairment on HCT, and Raven's Progressive Matrices, at this abstinence period.

Interestingly, Ioime et al. (2018) did find some improvement by both six and 12 months, but not recovery to control level. Furthermore, grouping of this construct should be considered, as despite it being considered a premorbid ability, some reviews on this topic have grouped it with functions that would be expected to improve, such as EF (Crowe, 2019; Stavro et al., 2012). This may reduce the validity of the synthesis/analysis. Finally, while Schulte et al. (2014) concluded that 'Performance IQ' as the function of MR, improved with abstinence in AD, a closer examination indicates that the only study to find this was Manning et al. (2008). Therefore, when additional studies are considered, this seems to be a consistently impaired ability in abstinence from AUD.

3.4.3.2 Sort and Shift

The ability to sort and shift was impaired at baseline, and recovery was inconsistent. Kaur et al. (2020), who did not compare to controls, indicated that there was some improvement of function on WCST by both one and three months, whilst Ioime et al. (2018) found that MCST performance was fully recovered by both six and 12 months. In contrast, both Czapla, Simon, Richter, et al. (2015) and Manning et al. (2008) found consistent impairment, at six and 12 months respectively, using IED. It seems that there may be some improvement, but it is unclear if this reaches control performance.

Perhaps the modified form of the WCST is less able to monitor continued impairment in AD, particularly as it simplifies the concept formation (Nelson, 1976).

3.4.4 Learning & Memory

Memory was assessed by nine studies, four of which assessed verbal STM, five assessed verbal LTM, six assessed visual STM, and five assessed visual LTM. One study only assessed STM as a composite score of visual and verbal ability, which will be discussed separately at the end of this section. Typically, STM for both modalities demonstrated faster recovery than LTM, and despite verbal memory being indicated as recovering faster overall, it was more inclined to worsen during the first six months of abstinence, compared to visual. Visual LTM recovery was the slowest, generally not recovering until two years.

3.4.4.1 Verbal short-term memory

Verbal STM was generally impaired (except in Manning et al. (2008)), with recovery occurring from six months onwards in the majority. Durazzo et al. (2014) indicated that performance worsened by one month in former and active smokers, but recovered fully by eight, which complements Pitel et al. (2009) who found full recovery by six months. However, Ioime et al. (2018) found that deficits persisted at both six and 12 months, despite Manning et al. (2008) finding improvement at 12.

3.4.4.2 Verbal long-term memory

Verbal LTM was consistently impaired at baseline (except in Durazzo) but recovered in the majority by eight months. Durazzo et al. (2014) and Ioime et al. (2018) both found worsening of performance, at one and six months respectively, and only in active smokers in the former. There was inconsistency at six months, as alongside Ioime et al. (2018) finding worsening, the cohort in Pitel et al. (2009) had fully recovered, while Bartels et al. (2007) found continued impairment, suggesting that impairment is still likely at this stage. Beyond this, full recovery was consistent at

eight (Durazzo et al., 2014), 12 (Bartels et al., 2007; Manning et al., 2008), and 24 months (Bartels et al., 2007), except for Ioime et al. (2018) who still found impairment at 12 months.

It is worth noting that Ioime et al. (2018) was the only study that found impairment in both verbal short- and long-term memory at 12 months, using the Rey Auditory Verbal Learning Test (RAVLT) indicating perhaps that this was specific to their cohort. Indeed, it is possible that verbal memory recovery slope/extent is driven by confounding factors. Durazzo et al. (2014) again found that age and premorbid verbal intelligence independently predicted change across the whole sample, as did education. Additionally, differential rates of impairment and change were found regarding smoking status, with active/former smokers (and greater lifetime years of smoking) driving initial impairment and showing poorer recovery. Additionally, both active/former smokers recovered more poorly with increasing age, further highlighting the importance of age as a predictor.

3.4.4.3 Visual short-term memory

Visual STM was consistently impaired at baseline, recovered by eight months onwards (Bartels et al., 2007; Durazzo et al., 2014; Ioime et al., 2018) and maintained at 24 months (Bartels et al., 2007). Exceptions were Wegner et al. (2001), who used a simple delayed vernier discrimination task and may therefore have been unable to capture group differences, and Petit et al. (2017), who found recovery on the Brown-Peterson technique by 14-18 days. It is unclear why function was recovered so early in Petit et al. (2017), however as they also tested controls twice during the same interval, it is unlikely due to practice effects.

3.4.4.4 Visual long-term memory

Visual LTM was consistently impaired at baseline, with recall also consistently impaired at 12 months (Alhassoon et al., 2012; Bartels et al., 2007; Ioime et al., 2018), and signs of complete recovery not evident until 24 months (Bartels et al., 2007). However Durazzo et al. (2014), found recovery at eight months (though not in active smokers), and Yeh et al. (2007), found improvement at one and seven months.

Once again, age and premorbid verbal intelligence independently predicted change across the whole sample (Durazzo et al., 2014). Both Durazzo et al. (2014) and Yeh et al. (2007) found differential recovery as a result of smoking status, with poorest initial performance and outcomes in former and active smokers, the latter of which did not recover to the level of controls (Durazzo et al., 2014). Furthermore, again, both smoking groups demonstrated poorer recovery with increasing age. Yeh et al. (2007) also investigated brain volume, finding that gains in STM correlated negatively in smokers with brain volume increases during one month of abstinence, which they suggested may indicate that these structural brain changes are pathological.

One extra study that assessed memory did not report memory task outcomes individually. Loeber et al. (2010) created a composite measure of visual and verbal STM (number of pictures remembered on Benton Visual Retention Test, and words remembered on RAVLT). This study was an outlier, as it did not find initial impairment, or change of this memory function across three or six months, perhaps indicating that a composite measure is less valid.

3.4.5 Perception & Motor Performance

Only four studies assessed visual perception, three of which also assessed figure and design reproduction (drawing, an indicator of fine motor function). One further study assessed fine motor function alone, which is synthesised here also. It seems that perception of simple designs, along with fine motor function, generally responds well to abstinence, recovering by at least 6-7 months, but perception of more complex designs requires up to 12 months to recover.

Indeed, recognition and reproduction of complex figures was still impaired by six months but did recover by 12 (Ioime et al., 2018). All other tasks involved copying much simpler designs, which showed recovery by six and 12 months (Ioime et al., 2018), or demonstrated improvement consistently at one and three months (Kaur et al., 2020). Furthermore, Motor Screening Test performance was not impaired at a baseline assessment of two weeks (Manning et al., 2008). Emotional expression recognition was impaired in both accuracy of emotion judgement, and

judgement of emotion intensity, in AUD versus controls (Foisy et al., 2007), which did not recover by three months of abstinence. Due to the lack of studies assessing emotional decoding, it is difficult to synthesise this finding, and it is unclear how long recovery would take.

3.4.6 Verbal Function

Only one study assessed verbal knowledge (Manning et al., 2008), finding an improvement by one month of abstinence. While this was not directly compared to normal performance, it was combined with MR to form an IQ measure, which was in the normal range at baseline. It is not possible to synthesise much from this given the single study, however these results show that at least in this cohort, vocabulary was likely unimpaired in early abstinence, but demonstrated improvement regardless.

3.5 Discussion

The aim of this review was to examine recovery of neuropsychological function following abstinence in AUD, with the expectation being that every domain assessed would likely be impaired upon baseline testing, but that recovery would differ between domains and even sub-domains. These expectations were generally met. Of the domains assessed, attention, specific sub-domains of EF, memory, and perception (for figures) demonstrated the ability to recover, and verbal function demonstrated improvement.

That most of the domains and sub-domains assessed were generally initially impaired (with the exception of verbal fluency and attentional capacity) supports previous research that has found the same (Crowe, 2019; Schulte et al., 2014; Stavro et al., 2012; Stephan et al., 2017). When compared to Schulte et al. (2014), the current review similarly found recovery of verbal memory, response inhibition, and continued impairment of emotional facial expression recognition and planning. In contrast, Schulte et al. (2014) found no improvement in decision making, focused attention, or verbal functions, but did find improvement in reasoning ability.

In relation to neural correlates, inhibitory control, flexibility, working memory, planning, decision making, attention, reasoning, processing speed, verbal short- and long-term memory, are all arguably functions depending heavily on frontoparietal regions, particularly the PFC (Andreasen et al., 1995; Emch et al., 2019; Kim et al., 2017; Rottschy et al., 2012; Wagner et al., 2014). Exceptions include fine motor function which associates with frontal and cerebellar regions (Diamond, 2000), perception which is frontoparietal and occipital (Dijkstra et al., 2019), verbal fluency which is largely frontal (Wagner et al., 2014), visual STM which is occipito-parietal, visual LTM which associates with the medial temporal lobe and hippocampus (Schurgin, 2018), vocabulary which involves frontal, temporal, thalamic, and cerebellar regions (Indefrey, 2011), and emotion recognition which associates with visual and limbic systems, prefrontal, temporoparietal, and subcortical areas such as the cerebellum (Fusar-Poli et al., 2009).

The current findings of initial impairment therefore are in line with grey matter alterations in AUD which have been found consistently in parts of the PFC, anterior cingulate cortex, and insulae in AUD (Bühler & Mann, 2011; Klaming et al., 2019; Li et al., 2021; Spindler et al., 2021; Xiao et al., 2015; Yang et al., 2016), in various frontal and parietal areas (Bühler & Mann, 2011; Spindler et al., 2021; Yang et al., 2016) and subcortical regions such as the thalamus, hippocampus and cerebellum (Bühler & Mann, 2011; Yang et al., 2016), along with widespread white matter reductions (Bühler & Mann, 2011; Monnig et al., 2013) which are most pronounced in the frontal lobes, cerebellum, and limbic system (Bühler & Mann, 2011). Furthermore, that there were relatively consistent improvements, even to the point of recovery, of various sub-domains within attention, EF, memory, and perception, supports findings of X. Zou et al. (2018) that the volumes of the anterior cingulate cortex, dorsolateral PFC, orbitofrontal cortex, and insula reached equivalent volume to controls by seven months of abstinence, while the hippocampal volume increased but still remained smaller than controls, perhaps explaining the slower recovery of visual LTM compared to other types of memory in this review. However, Durazzo et al. (2015) found that lobar and cerebellar brain volume increases associated with processing speed recovery only, not that of verbal or visual memory.

Relating to the impact of alcohol on the brain, impairment and recovery of many of these functions upon abstinence appears to support that the frontal lobe and cerebral cortex are particularly vulnerable to damage by active AUD (the frontal lobe vulnerability, and whole brain hypotheses; Oscar-Berman and Marinkovic (2003)), though it is likely that elements of cognitive function may be heritable and have a cyclical relationship with alcohol (Benzerouk et al., 2013). Given that the frontal lobes have rich connections with other brain regions, and that prefrontal functions are required for cognitive control, damage to this area may therefore influence performance on tests used for assessing functions of other brain regions (Kamarajan et al., 2004). Furthermore, given that Durazzo et al. (2014) found that age independently predicted recovery on processing speed, attentional capacity, and memory, this supports the 'premature aging hypothesis', which posits that alcohol either ages the brain prematurely, or that age increases the vulnerability of the brain to alcohol (Ellis & Oscar-Berman, 1989; Oscar-Berman & Marinkovic, 2003; Oscar-Berman et al., 2000).

With regards to the second aim of this review, various predictors were indicated for several domains/sub-domains. A consistent predictor of recovery was age, which predicted recovery of processing speed, attentional capacity, and memory (Durazzo et al., 2014), as did smoking status, and premorbid verbal intelligence (Vocabulary Test; Schmidt and Metzler (1992)), while verbal memory was also predicted by education. Additionally, in smokers, visual short term memory recovery negatively associated with potentially pathological increases in brain volume (Yeh et al., 2007). Finally, a reduction of drinking behaviour in people important to the individual supported recovery of focused attention (McCutcheon et al., 2016), while divided attention recovered more poorly with repeated cycles of withdrawal and relapse (Loeber et al., 2010). Future research and intervention should consider these elements to ensure that best outcomes can be achieved for everyone.

3.6 Robustness of Synthesis

Study quality was assessed using the JBI Checklist for Cohort Studies (Moola et al. (2020), see Table 5). The majority (ten) of studies were classed as 'good', allowing for relative trustworthiness of the current review, while three were considered 'moderate', and two were 'poor'. The most frequent issues throughout the literature reviewed were not including controls, confirming abstinence using self-report only, assessing function up to less than six months of abstinence (given that previous research suggested function may take up to a year to recover (Stavro et al., 2012)), limited description of the characteristics of those lost to attrition, lack of strategies to reduce attrition bias, and not controlling for potential confounds in the statistical analysis. Furthermore, ultimately, as Schulte et al. (2014) stated, without studies that assess neuropsychological functioning before, during, and after AUD, there is less certainty about the findings with regards to the relationship of alcohol use to function at each of these stages.

Two of the 'moderate' quality studies (McCutcheon et al., 2016; Yeh et al., 2007), and one of the 'poor' (Kaur et al., 2020) , did not compare to controls or normative data, and so were only considered as information on improvement within the review, not as direct assessment of recovery. Furthermore, as a safeguard to the quality of the review, despite Kaur et al. (2020) reporting on predictors of cognitive recovery, these were not included, as the nature of statistical analyses and findings were unclear and contradictory throughout this source. Manning et al. (2008) (poor) and Cordovil De Sousa Uva et al. (2010) (moderate) however did include performance comparisons, and so any conclusions drawn because of their inclusion may need caution in interpretation. In particular, those relating to Manning et al. (2008), such as within planning, verbal fluency, and verbal function, for which this was the only study at all to assess comparative to normative data. This study was also at odds with other papers regarding absence of initial impairment for processing speed, working memory updating/tracking, visual concept formation, verbal STM, and fine motor function; however as multiple studies opposed this, these findings were considered the exception. Similarly, most sub-domains and domains were assessed by three or more studies, except for planning, verbal

fluency, and verbal function (which are also those contributed to most significantly by Manning et al. (2008)), suggesting that all functions except these, the synthesis results are trustworthy regarding the quantity and quality of evidence.

Table 5. *Quality assessment using JBI Checklist for Cohort Studies*

Author	1. Were the two groups similar and recruited from the same population?	2. Were the exposures measured similarly to assign people to both exposed and unexposed groups?	3. Was the exposure measured in a valid and reliable way?	4. Were confounding factors identified?	5. Were strategies to deal with confounding factors stated?	6. Were the groups/ participants free of the outcome at the start of the study (or at the moment of exposure)?	7. Were the outcomes measured in a valid and reliable way?	8. Was the follow up time reported and sufficient to be long enough for outcomes to occur?	9. Was follow up complete, and if not, were the reasons for loss to follow up described and explored?	10. Were strategies to address incomplete follow up utilized?	11. Was appropriate statistical analysis used?	Quality Score (%) Poor ≤ 49. Moderate = 50-69 Good ≥ 70
Alhassoon et al., 2012	Yes	Yes	Yes	Yes	Yes		Yes	Yes	Yes	Yes	Yes	100
Bartels et al., 2007	Not Applicable	Not Applicable	Yes	Yes	Yes		Yes	Yes	Yes	Yes	No	70
Czapla et al., 2016	Yes	Yes	Yes	Yes	Yes		Yes	Yes	Yes	Yes	Yes	100
Cordovil De Sousa Uva et al., 2010	Yes	Yes	Yes	Yes	Yes		Yes	Unclear	No	No	Yes	70
Durazzo et al., 2014	Not applicable	Not applicable	Yes	Yes	Yes		Yes	Yes	Yes	Yes	Yes	80
Foisy et al., 2007	Yes	Yes	Yes	Yes	Yes		Yes	Unclear	Yes	No	Yes	80
Ioime et al., 2018	Yes	Yes	Yes	Yes	Yes		Yes	Yes	Yes	Yes	No	90
Kaur et al., 2020	Not applicable	Not applicable	No	Yes	Yes		Yes	Unclear	Unclear	Unclear	Unclear	30
Loeber et al., 2010	Yes	Yes	Yes	Yes	Yes		Yes	Yes	Yes	No	Yes	90
Manning et al., 2008	Not applicable	Not applicable	Yes	Yes	Unclear		Yes	Unclear	Unclear	Unclear	Yes	40
McCutcheon et al., 2016	Not applicable	Not applicable	No	Yes	Yes		Yes	Unclear	Yes	Yes	Yes	60
Petit et al., 2017	Yes	Yes	Yes	Yes	Yes		Yes	Unclear	Unclear	No	Yes	70
Pitel et al., 2009	Yes	Yes	No	Yes	Yes		Yes	Yes	Yes	Yes	No	80
Wegner et al., 2001	Yes	Yes	Yes	Yes	Yes		Yes	Unclear	Unclear	Unclear	Yes	70
Yeh et al., 2007	Not applicable	Not applicable	No	Yes	Yes		Yes	Yes	No	Yes	Yes	60

Note: due to the nature of this review, some checklist questions were not directly applicable. Therefore, question one was answered "Yes" if a control and AUD group were matched or described as similar on age, gender, or education. Question two was answered "Yes" if it was made clear that controls did not have a diagnosis of AUD. Question three was answered "Yes" if abstinence from alcohol was confirmed in AUD participants at each time, using additional methods to self-report (except for follow-ups conducted in inpatient settings where abstinence would be assured). Question six was not relevant as the outcome was neuropsychological change upon maintenance of abstinence in AUD rather than an incidence of illness, so this question was not used to assess study quality. Based on previous literature, question eight was answered "Yes" if the study followed up to six months of abstinence or longer. Question ten in the checklist suggested methods such as calculating person-years at risk, which again is not suitable for studies in this review, therefore this question was answered "Yes" if studies used statistical methods such as linear mixed modelling, multiple imputation, dummy variables, or sample weights. Alternatively, complete case analysis was deemed acceptable when characteristics of those lost to follow-up were like those who remained. Finally, question 11 was answered "Yes" if the statistical analysis used adjusted in some way for covariates/ confounds, or multiple dependent variables (if appropriate considering outcomes measured) including use of multivariate analysis or Bonferroni correction.

A strength of this is review is the grouping of tasks under multiple functions (as opposed to Crowe (2019); Stavro et al. (2012)), as it is recognised that multiple tasks span various domains and sub-domains (Schulte et al., 2014), and indeed that specific elements of each task may measure different abilities (as described in Table 4). Additionally, the review considers the predictive features contributing to the variance in recovery, though a limitation is the inability to control for confounds such as practice effects, medication, and comorbid health problems. However, the reality is that in populations recovering from AUD, medication and comorbid health problems are likely to be the norm (Kieres-Salomoński & Wojnar, 2015), suggesting that these are less isolated contributions to variance.

The authors used various methods to strengthen the quality of this narrative synthesis by reducing bias, including pre-registering the protocol with PROSPERO (CRD42022308686), publishing the protocol so as to gain valuable feedback prior to conducting the review (Powell et al., 2022), limiting to only DSM-IV/5 and ICD-10/11 to try to ensure comparative cohorts (Saunders et al., 2019), full-text screening being checked by multiple reviewers, and 10% of quality assessment being independently conducted.

3.7 Chapter Summary

This chapter investigated neuropsychological recovery in abstinence from AUD using a narrative systematic review. Overall robustness of results was deemed good, though not for planning, verbal fluency, and verbal function, for which further research addressing previous methodological limitations is required, which include lack of control groups, additional methods to self-report to confirm abstinence, description/control for attrition, statistical control of confounds, and of long enough study durations to capture change. Results supported the whole brain, frontal vulnerability, and premature aging hypotheses. That EF demonstrated impairment and recovery, and that processing speed recovered so quickly, support that these are of particular interest in relation

to alcohol use, as both appear sensitive. The following chapter therefore describes a study subjectively assessing EF in hazardous drinkers.

Chapter 4 Subjective Executive Function Deficits in Hazardous Drinkers

The study in this chapter is published open access in the Journal of Psychopharmacology, and is cited in this thesis as Powell, Sumnall, et al. (2021), and available in Appendix 4.

4.1 Chapter Overview

The previous chapter systematically presented the current literature regarding impairment of neuropsychological function in AUD and the possibility for its recovery in abstinence, while this chapter describes a study which uses an online survey to examine subjective EF, which as described in Chapter 1 may provide a unique insight into function in hazardous drinking, of which the literature is less consistent than that of AUD. A between-groups cross-sectional design assessed EF across hazardous (AUDIT score of ≥8) and non-hazardous drinkers. Alcohol drinkers (n = 666; 136 m; 524 f; 6 not disclosed; aged 28.02 ± 10.40 years) completed validated questionnaires online assessing subjective EF, alcohol use, and alcohol-related problems. Subjectively, Organisation, Strategic Planning, Impulse Control and overall function were significantly impaired in hazardous drinkers. Furthermore, the effect of alcohol on subjective EF partially mediated the relationship between alcohol use and alcohol-related problems. This indicates a need to objectively assess function in this group and consider the implications of any impairment, such as via the task-independent construct of processing speed.

4.2 Introduction

As described in section 1.5.2.1, hazardous drinking is generally associated with EF deficits (Carbia, Corral, et al., 2018; Houston et al., 2014; Lees et al., 2019; Montgomery et al., 2012), though with some younger individuals able to perform at similar levels to controls due to neurocompensatory action (Hatchard et al., 2017), which may explain some discrepancies within the literature. However, few studies have addressed the daily life experience of individuals with regards

to EF, by using subjective assessments. This becomes especially interesting when one considers that increased cognitive effort to achieve satisfactory performance (as in the neurocompensation hypothesis), may be better reflected in self-report assessment of difficulties. Research using subjective measures is conflicting, with Heffernan et al. (2004) finding that "excessive" drinkers experienced more problems related to the executive component of memory. Similarly, Houston et al. (2014) found greater alcohol use associated with poorer EF measured by subjective EF (DEX), and behavioural task performance (TMT, Go/NoGo, WCST). However, Czapla, Simon, Friederich, et al. (2015) found that HED and controls did not differ in overall response inhibition on a Go/NoGo task, or self-reported impulsiveness, though there was an impairment on the task for alcohol-related stimuli.

Hazardous drinking has a considerable effect on overall function and quality of life, including on interpersonal relationships, finances, and employment (WHO, 2004). The relationship between alcohol use and EF may contribute to this, as EF controls behaviour in everyday life (Snyder et al., 2015), and EF dysfunction in AUD decreases quality of life (Brion et al., 2017). However, there is limited research investigating this relationship in non-dependent hazardous drinking. One study of 62 college students found EF mediated the relationship between alcohol use and overall life functioning (assessed by the Barkley Functional Impairment Scale), however this was in people with attention deficit hyperactivity disorder (ADHD) who may be predisposed to EF deficits (Langberg et al., 2015). Furthermore, an older study found a small dose-effect, with the heaviest drinkers (10+ drinks a week) demonstrating lower general cognitive function and poor reported daily life functioning (Hendrie et al., 1996). While this supports a relationship between daily functioning and the effect of hazardous drinking on cognitive function, it did not specifically examine EF. In contrast, Martins et al. (2018) found no relationship between EF and alcohol-related problems.

Clearly, EF is affected by hazardous drinking to some extent, but the aetiology is not always consistent. This could be due to neurocompensation in individuals, which may be better reflected in

subjective judgement of EF. Furthermore, whilst EFs are predictive of clinical outcomes in AUD, less is known about the relationship between EF and daily-life outcomes in the general population. The current study investigated subjective EF deficits in adult non-dependent hazardous drinkers using an online survey, and explored the relationship between subjective deficits and self-reported alcohol-related problems (Powell, Sumnall, et al. (2021), see Appendix 4 for published version). Based on the literature above, we hypothesised that 1) hazardous drinkers would have significantly poorer subjective EF than non-hazardous drinkers, and 2) the relationship between alcohol use and alcohol-related problems would be mediated by the effect of alcohol on subjective EF.

4.3 Method

4.3.1 Design

A between-groups design assessed EF between hazardous and non-hazardous drinkers. The independent variable was alcohol use, with two levels; non-hazardous and hazardous drinking (determined by AUDIT cut-off score; ≥8 deemed hazardous drinking; WHO (2001)). The main dependent variable was EF.

4.3.2 Participants

Eight hundred and three individuals took part. Upon initial screening, 128 incomplete datasets were removed (15.9%), and nine more were removed as outliers[1]. Thus, the study comprised of 666 participants (136 male; 524 female; 6 gender not disclosed; aged 28.02 ± 10.40 years). Participants were recruited globally (73.6% UK, 9.6% Ireland, 6.2% United States of America, 2.6% Australia, 7.7% rest of world). Participants were categorised into non-hazardous (*n* = 323, 48.50%; 56 male, 264 female; 3 gender not disclosed, aged 29.73 ± 10.68 years; mean AUDIT total

[1] Inspection of Mahalanobis Distance and Standardized Residuals during the main analysis (Factorial MANCOVA) identified nine outliers (3 male; 6 female; 3 non-hazardous; 6 hazardous), which when removed from the analysis, changed Box's M test from being violated (*p* = .038) to being met (*p* = .116), and had no other impact on the results or assumptions. These were therefore removed from all final analyses and descriptives.

score = 4.72 *SD* = 1.77) and hazardous (*n* = 343, 51.50%; 80 male, 260 female; 3 gender not disclosed, aged 26.40 ± 9.85 years; mean AUDIT total score = 13.04, *SD* = 4.80) drinkers, using AUDIT score (≥8 deemed hazardous).

Recruitment channels included an advert on the Liverpool John Moores University (LJMU) website and personal/professional social media, referrals from previous participants, asking research team acquaintances, and an email to LJMU students. Each advert contained a link to the Qualtrics survey. Potential participants self-identified as eligible if they were alcohol drinkers aged 18+. There were no exclusion criteria. The original recruitment target was 282 participants, based on a multivariate analysis of variance (MANOVA) sample size calculation with a 95% confidence level ($f^2 \geq .02$, a small effect size (Cohen, 2013)) using GPower version 3.1.94 (Faul et al., 2009), adjusted for multivariate analysis of covariance (MANCOVA) by adding number of covariates to number of cells (Dattalo, 2008).

4.3.3 Materials

4.3.3.1 Demographics

Participants answered questions on age, gender, and country of residence.

4.3.3.2 Executive Function

This study uses the EFI, which is a 27-item, five-point Likert-scale questionnaire assessing five EF components derived from factor analysis; Motivational Drive, Strategic Planning, Organisation, Impulse Control, and Empathy. Motivational Drive items assess interest in novelty, activity level, and behavioural drive. Strategic Planning items measure ability to use strategies, plan, and think ahead. Organisation assesses sequencing, multitasking, and holding information in the working memory to inform decisions. Impulse Control measures self-inhibition, social conduct, and risk taking. Empathy items assess prosocial behaviours, a cooperative attitude, and concern for others' wellbeing.

Higher total (global measure) and subscale scores indicate better EF. Scoring occurs through summing relevant items (some reverse scored). The EFI corresponds well with neuroanatomical findings, as the items factor logically regarding prefrontal system abilities (Spinella, 2005), and also into a three-factor model, in which Impulse Control and Empathy form one factor, Strategic Planning and Organisation another, and Motivational Drive a third. These are proposed to correspond to a model of functional organisation of orbitofrontal, dorsolateral, and medial prefrontal circuits (Cummings, 1993; Miller & Cummings, 2017). Note, whilst this grouping is interesting, and is discussed in relation to the results of this study, we did not use group the EFI scores in this three-factor manner because current models of EF do not follow the related suggested functional divisions of the frontal lobe (Miyake & Friedman, 2012), and studies attempting to identify this factor structure have found limited support (Janssen et al., 2009). We therefore decided that the more widely accepted five-factor model (Janssen et al., 2009; Miley & Spinella, 2006; Smithmyer, 2013; Spinella, 2005) would be more useful for this thesis. In initial development, EFI had a Cronbach's α ranging between 0.69 to 0.76 for the five subscales, with a total α of 0.82, an acceptable internal consistency (Spinella, 2005). In this study, Cronbach's α ranged from 0.76-0.80 across the items, and a total α of 0.77. It was lower for the subscales: Motivational Drive = .59, Impulse Control = .55, Strategic Planning = .44, Organisation = .72, Empathy = .68.

4.3.3.3 Mood State

The HADS was used to assess state anxiety and depression, this is a four-point, 14-item Likert-scale, scored 0-3 by separately summing subscales (some items require reverse scoring). Higher scores indicate worse symptoms. A general population review of 747 studies found HADS demonstrates good validity and reliability (Bjelland et al., 2002). In this study, Cronbach's α ranged from 0.84-0.87 across the items, and a total α of 0.86, while for the subscales, anxiety = .81, depression = .67.

4.3.3.4 Alcohol Use

The AUDIT is a 10-item five-point Likert-scale assessing harmful/hazardous drinking developed by the WHO. A cut-off score of 8+ is recommended as an indicator of hazardous/harmful alcohol use, and possible alcohol dependence (WHO, 2001), and so in this study, participants were grouped as scoring < 8 non-hazardous) or ≥8 (hazardous). Furthermore, the median AUDIT score was 8, so even if the data was divided using a median split (as in Montgomery et al. (2012)), it would have still provided the same groups. A further use of the AUDIT is to isolate the first three questions about consumption only, classed as the AUDIT-Consumption (AUDIT-C) scale (Bradley et al., 2007). The AUDIT is reliable (Donovan et al., 2006; Fiellin et al., 2000), and validated within primary health care in six countries (WHO, 2001) and the general population (Aalto et al., 2009). Indeed, a systematic review by Fiellin et al. (2000) concluded that the well-used cut-off of 8 for the AUDIT is more sensitive for identifying hazardous and harmful drinkers than two other measures - CAGE (Ewing, 1984) and Short Michigan Alcoholism Screening Test (Selzer et al., 1975). In this study, Cronbach's α ranged from 0.74-0.78 across the items, and a total α of 0.77, with AUDIT-C = .51.

4.3.3.5 Alcohol-Related Problems

The APQ by is a 44-item tool rated yes(1)/no(0), contributing to a common score, and eight separately summed subscales. Five subscales apply to all participants: the perceived drinking impact on Financial, Legal, Physical, Social, and Psychological issues. The "Alcohol Problems Questionnaire Common" score (APQC), is comprised of total scores of these five subscales, and demonstrates high reliability coefficients, internal consistency, and stability over time (Drummond, 1991; Williams & Drummond, 1994). Where relevant, subscales of impact on Work, relationships with Children, and Spouse are also assessed. Lower scores within each subscale indicate fewer alcohol-related problems. APQ demonstrates high test-retest reliability (Williams & Drummond, 1994), has been validated within a clinical population (Drummond, 1990; Williams & Drummond, 1994) and a sample of college students (Drummond, 1991), and is the UK measure of choice for alcohol-related problems (Raistrick et al., 2019). In this study, Cronbach's α ranged from 0.75-0.78 across the items,

and a total α of 0.77 with APQC also at .77, but with lower scores for the financial = .46, legal = zero variance (could not be calculated), psychological = .66, physical = .60, work = .60, children = .82, spouse = .66, social = .48.

4.3.4 Procedure

Potential participants read the online study information and confirmed eligibility. They were reminded of confidentiality, right to withdraw, or omit questions, and provided consent through a tick-box. When finished, participants were provided with a full debrief, with no reward for completion, but could enter a prize draw for one of three shopping vouchers. This study was approved by LJMU Research Ethics Committee.

4.3.5 Statistical Analysis

All analyses were completed using SPSS v26 (IBM Corp., Armonk, N.Y., USA). MANOVA assessed mood state (HADS anxiety and depression scores) across gender and drinking level. A 2x2 Factorial MANCOVA was then performed on EFI subscales (dependent variables assessing EF), with drinking category (non-hazardous and hazardous) and gender (male and female) as the between-groups independent variables. Mood state and age were included in the model as continuous covariates, chosen due to their associations with EF (Best & Miller, 2010; Grissom & Reyes, 2019; Gulpers et al., 2016; Snyder, 2013; Zaninotto et al., 2018) and alcohol use (Jane-Llopis & Matytsina, 2006; Mooney et al., 1987; Wilsnack et al., 2009).

Finally, a hierarchical multiple regression was conducted with alcohol use (AUDIT-C) and EF (EFI subscales) as predictors of alcohol-related problems, with a subsequent mediation analysis, using the PROCESS plugin version 3.5, as in (Hayes, 2017), examining the mediation of EF (EFI total score) on the relationship between alcohol use (AUDIT-C) and related problems (APQC). Mood state, age, and gender were included in the mediation as covariates, which was further supported by their significant contributions in the Factorial MANCOVA.

4.4 Results

Table 6 shows descriptive statistics for mood state and alcohol problems.

Table 6. *MANOVA estimates comparing mood state across gender and drinking level, and also the unadjusted alcohol problems descriptives across gender and drinking level*

Hospital Anxiety and Depression Scale (MANOVA)	Anxiety		Depression	
	M	*SE*	*M*	*SE*
Drinking Level				
Non-Hazardous	7.94	.31	3.87	.24
Hazardous	8.80	.27	4.24	.21
Gender				
Male	7.46*	.37	3.92	.28
Female	9.28	.19	4.19	.14

Alcohol Problems Questionnaire (unadjusted)	Friendships		Partner		Children		Work		Money		Legal		Physical		Psychological	
	M	SD	M	SD	M	SD	M	SD	M	SD	M	SD	M	SD	M	SD
Drinking Level																
Non-Hazardous	.09	.29	.11	.41	.02	.13	.16	.37	.20	.40	0	0	.84	1.07	.29	.78
Hazardous	.71	.80	1.12	1.63	.24	.78	.44	.86	.36	.79	.03	.17	1.74	1.38	.41	.78
Gender																
Male	.50	.66	.67	1.01	.04	.20	.38	.88	.25	.53	.04	.20	1.17	1.31	.42	.83
Female	.26	.59	.42	1.20	.12	.57	.32	.65	.26	.56	0	0	1.18	1.26	.30	.76

Note: **p* = .000012. Mood State = Hospital Anxiety and Depression Scale anxiety and depression scores; Alcohol Problems = Alcohol Problems Questionnaire scores; Hazardous Drinking = Alcohol Use Disorders Identification score of ≥8.

MANOVA assessed differences in state anxiety and depression (HADS) across gender and drinking level (see Table 6).[2] Levene's and Box's tests were acceptable (*ps* <.05). There was a significant main effect of gender [$F(2, 651) = 11.50$, $p < .001$, Wilks' $\Lambda = .97$, $\eta_p^2 = .03$], but not drinking level [$F(2, 651) = 2.14$, $p = .119$, Wilks' $\Lambda = .99$, $\eta_p^2 = .01$], and no significant interaction between the two factors [$F(2, 651) = .07$, $p = .935$, Wilks' $\Lambda = 1.0$, $\eta_p^2 < .001$]. Pairwise comparisons revealed that females had significantly higher state anxiety than males [$F(1, 652) = 19.47$, $p < .001$, $\eta_p^2 = .03$], but that there was no gender difference for state depression ($p = .398$).

4.4.1 Subjective Executive Function

Factorial MANCOVA assumptions were assessed. Scatterplots indicated approximately linear relationships between each pair of dependent variables, and between the covariates and each dependent variable. Homogeneity of regression was achieved at $p > .05$ for covariate by drinking level interaction, covariate by gender interaction, and covariate by drinking level by gender interaction, in all cases. Levene's test indicated the homogeneity of variance assumption was met for all EFI subscales between groups ($p > .05$). Shapiro-Wilk tests with a Bonferroni correction indicated residual normality was met for 18 out of 20 conditions ($p > .003$), which was deemed acceptable. Box's test of equality of covariance matrices was met ($p = .116$).

The 2x2 Factorial MANCOVA (see Table 7) found a significant effect of each covariate on EFI scores; age [$F(5, 615) = 11.34$, $p < .001$, Wilks' $\Lambda = .92$, $\eta_p^2 = .08$] depression [$F(5, 615) = 38.97$, $p < .001$, Wilks' $\Lambda = .76$, $\eta_p^2 = .24$] and anxiety [$F(5, 615) = 11.70$, $p < .001$, Wilks' $\Lambda = .91$, $\eta_p^2 = .09$]. After controlling for these, there was a significant difference between drinking level groups on EFI scores [$F(5, 615) = 12.90$, $p < .001$, Wilks' $\Lambda = .91$, $\eta_p^2 = .10$]. Gender was also included in the model as a fixed factor, displaying a significant effect on EFI scores [$F(5, 615) = 4.50$, $p < .001$, Wilks' Λ

[2] Multple Shapiro-Wilk tests using a Bonferroni correction indicated normality of mood state across gender and drinking level was violated for 6 out of 8 tests ($p < .006$). While this suggests the results should be interpreted with caution, due to there being no non-parametric MANOVA equivalent, and due to MANOVA being fairly robust with regards to normality violations, it was decided to continue with this analysis.

= .96, η_p^2 = .04], however there was no significant interaction between gender and drinking level [F(5, 615) = .336, Wilks' Λ = .10, p = .891, η_p^2 <.01].

Hazardous drinkers had lower scores on all EFI subscales (with the exception of Empathy; see Table 7), but this difference was significant for EFI subscales Organisation [F(1, 619) = 5.44, p = .020, η_p^2 = .01], Strategic Planning [F(1, 619) = 27.53, p <.001, η_p^2 = .04], and Impulse Control [F(1, 619) = 41.91 p <.001, η_p^2 = .06]. There was no significant difference between drinking level groups on the Motivational Drive and Empathy subscales (p = .932 and .695 respectively). Therefore, hazardous drinking was associated with worse subjective EF compared to non-hazardous drinking.

Males had lower scores on all EFI subscales (see Table 7), but this difference was significant for EFI subscales Impulse Control [F(1, 619) = 16.77, p <.001, η_p^2 = .03], and Empathy [F(1, 619) = 9.57, p = .002, η_p^2 = .02]. There were no differences between males and females on the Motivational Drive, Organisation, and Strategic Planning subscales (p = .123, .855 and .086 respectively). Therefore, males had worse subjective EF compared to females.

Table 7. *Estimates of factorial MANCOVA comparing subjective executive function across hazardous and non-hazardous drinking, and across males and females, controlling for age and mood state*

	Motivational Drive		Organisation		Strategic Planning		Impulse Control		Empathy	
	M	*SE*	*M*	*SE*	*M*	*SE*	*M*	*SE*	*M*	*SE*
Drinking Level										
Non-Hazardous	14.05	.17	16.87***	.23	25.54*	.24	16.43*	.21	26.01	.18
Hazardous	14.03	.15	16.15	.20	23.90	.21	14.62	.19	26.11	.16
Gender										
Male	13.86	.21	16.48	.28	24.44	.28	14.94*	.25	25.68**	.22
Female	14.22	.10	16.54	.14	24.99	.14	16.11	.13	26.43	.11

Note: from smallest, *p <.001, **, p=.002, ***p=.020. Subjective Executive Function = Executive Function Index subscales (Motivational Drive, Organisation, Strategic Planning, Impulse Control, Empathy); Hazardous Drinking = Alcohol Use Disorders Identification score of ≥8; Mood State = Hospital Anxiety and Depression Scale Anxiety and Depression scores.

4.4.2 Relationship Between Subjective Executive Function and Alcohol-Related Problems

A hierarchical regression modelled the relationship between EF and alcohol-related problems, with continuous APQC score as the dependent variable. Variables were entered simultaneously in successive model blocks; demographic variables (age, gender) in model one, alcohol use (AUDIT-C scores, expected to account for the most variance) in model two, mood state (HADS depression and anxiety scores) in model three, and EFI subscales (Motivational Drive, Impulse Control, Organisation, Strategic Planning, and Empathy) in model four, thereby ensuring that cognitive factors were added successively. Model parameters are shown in Table 8.

Model one significantly predicted alcohol-related problems $F(2,608) = 16.38$, $p < .001$, as did model two $F(3,607) = 56.85$, $p < .001$, and model three $F(5,605) = 78.13$, $p < .001$. For these three models, gender was not a significant predictor (see Table 8). Finally, model four also significantly predicted alcohol-related problems $F(10,600) = 47.92$, $p < .001$ (though gender, Motivational Drive, Strategic Planning, and Empathy were not significant predictors, see Table 8). The addition of EFI subscales explained an additional 44% of the variance, taking overall explained variance in alcohol-related problems to 44.4%. Beta coefficients and partial correlations indicated that model four, predictor order of importance was as follows; alcohol use, state depression, Impulse Control, Organisation, state anxiety, and age (β = .33, .22, -.20, -.12, .10, -.08, respectively, $ps < .05$). The final model effect size was calculated as $f^2 = .80$, a large effect (Cohen, 1988), and the local effect size of the EFI subscales was calculated at $f^2 = .09$ (using local effect size calculation proposed by Selya et al. (2012)), a small effect.

Table 8. *Results for each independent variable in the hierarchical multiple linear regression analysis with Alcohol Problems Questionnaire Common Score as the dependent variable*

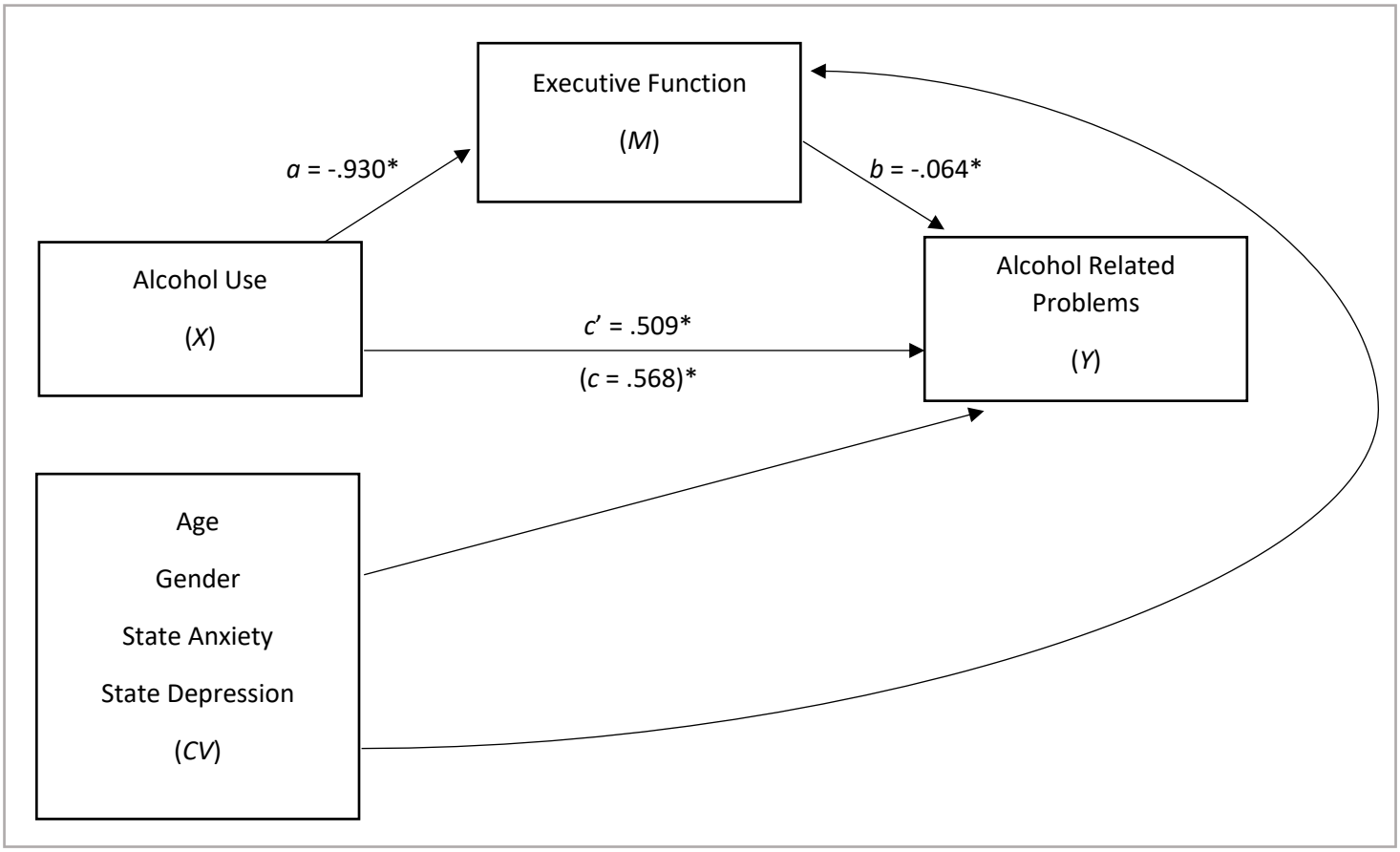
	Unstandardized and standardized coefficients			*Squared semi-partial correlation coefficients*	*Obtained t and p values*		*Obtained R values*			
	B	*SE* B	β	sr^2	t^a	*p*	*R*	R^2	ΔR^2	*p*
Model 1							.23	.05	.05	<.001
Constant	6.23	.71			8.73	<.001				
Age	-.07	.01	-.23	.05	-5.72	<.001				
Gender	-.35	.31	-.05	.002	-1.12	.262				
Model 2							.47	.22	.17	<.001
Constant	1.87	.75			2.49	.013				
Age	-.05	.01	-.18	.03	-4.95	<.001				
Gender	.17	.28	.02	<.001	.61	.543				
AUDIT-C	.60	.05	.42	.17	11.447	<.001				
Model 3							.63	.39	.17	<.001
Constant	-.05	.69			-.07	.944				
Age	-.05	.01	-.16	.02	-4.72	<.001				
Gender	-.03	.25	.004	<.001	-.12	.908				
AUDIT-C	.57	.05	.40	.15	12.25	<.001				
Anxiety	.11	.03	.16	.02	3.96	<.001				
Depression	.30	.04	.31	.07	8.21	<.001				
Model 4							.67	.44	.05	<.001
Constant	3.99	1.43			2.79	.005				
Age	-.03	.01	-.08	.01	-2.52	.012				
Gender	.14	.25	.02	<.001	.56	.574				
AUDIT-C	.47	.05	.33	.09	9.74	<.001				
Anxiety	.07	.03	.10	.01	2.56	.011				
Depression	.22	.04	.22	.03	5.31	<.001				
Motivational Drive	-.06	.04	-.05	.002	-1.42	.158				
Organisation	-.11	.03	-.12	.01	-3.28	.001				
Strategic Planning	-.01	.03	-.01	<.001	-.33	.742				
Impulse Control	-.19	.04	-.20	.03	-5.22	<.001				
Empathy	.08	.04	.07	.004	2.00	.046				

[a]Model 1: *df* = 608; model 2: *df* = 607; model 3: *df* = 605, model 4: *df* = 600
Notes: AUDIT-C = Alcohol Use Disorders Identification Test-Consumption; Depression and Anxiety = Hospital Anxiety and Depression Scale subscales; Motivational Drive, Organisation, Strategic Planning, Impulse Control, Empathy = Executive Function Index subscales.

Mediation analysis was then performed, which indicated alcohol use (AUDIT-C) was indirectly related to alcohol-related problems (APQC) through its relationship with EF (EFI total score), after controlling for covariates. As shown in Figure 6, EF mediated the relationship between alcohol use and alcohol-related problems. Higher consumption was associated with poorer EF (*a* = -.930, *p* <.001; standardized *a* = -.205), which was subsequently related to more alcohol-related

problems (*b* = -.064, *p* = .001; standardized *b* = -.203). A 95% bias-corrected confidence interval based on 10,000 bootstrap samples indicated the indirect effect, *ab* = .060, BCa CI [.033, .091] was statistically significant. However, the direct effect of alcohol use on alcohol-related problems was also significant *c'* = .509, *p* <.001, indicating partial mediation of EF. The completely standardized indirect effect was ab_{cs} = .042, BCa CI [.024, .063].

Figure 6. *The mediating effect of executive function on the relationship between alcohol Use and alcohol related problems, while controlling for age, gender, and state anxiety and depression*



Note: All presented effects are unstandardized; *a* is effect of alcohol use (Alcohol Use Disorders Identification Test-Consumption) on executive function; *b* is effect of executive function (Executive Function Index total score) on alcohol related problems (Alcohol Problems Questionnaire Common); *c'* is direct effect of alcohol use on alcohol related problems; *c* is total effect of alcohol use on alcohol related problems. State anxiety and depression = Hospital Anxiety and Depression Scale subscales. **p* <.001.

4.5 Discussion

This Chapter examined drinking behaviour and EF. Hypothesis one was partially supported as some EFI subscales (Strategic Planning, Impulse Control, and Organisation) were significantly lower in hazardous drinkers, indicating poorer performance. Hypothesis two was also supported, as EF partially mediated the relationship between alcohol use and alcohol-related problems. After controlling for covariates, hazardous drinking was associated with worse EFI Strategic Planning, Impulse Control, and Organisation, but not Empathy and Motivational Drive. This suggests hazardous drinkers in this study struggle with planning/using strategies, self-inhibition, risk taking, and holding information in mind or multitasking, but not prosocial behaviours or motivation. This supports research showing EF deficits in hazardous drinkers (Doallo et al., 2014; Montgomery et al., 2012; K. W. Smith et al., 2017), particularly in inhibition (Ames et al., 2014; Carbia, Corral, et al., 2018; Carbia, López-Caneda, et al., 2018; Czapla, Simon, Friederich, et al., 2015; Kim & Kim, 2019; Lannoy et al., 2020; Lannoy et al., 2019; Montgomery et al., 2012), as Impulse Control was the largest subscale deficit found.

This highlights potential similarities between EF in hazardous drinking, and AUD such as in Smith et al. (2014). Furthermore, these results may contrast with those showing no inhibitory deficit in hazardous drinking (Blanco-Ramos et al., 2019; Czapla, Simon, Friederich, et al., 2015; Lannoy et al., 2017; López-Caneda et al., 2012; López-Caneda et al., 2014; Martins et al., 2018; K. W. Smith et al., 2017) due to the varied age range; 48.4% of participants were above 24 years old, which has been proposed as a more appropriate 'end of adolescence' in relation to various biological and social factors, including neurodevelopment (Sawyer et al., 2018). It is therefore possible to infer that the current sample was diverse with regards to neurological development (and years of continuous hazardous drinking), which may have reduced the ability of neurocompensation to preserve inhibition, contrasting with studies focusing on young adults. These results also support a possible distinction from AUD as in Kim and Kim (2019), as not every EFI subscale was significantly poorer in hazardous drinkers. Importantly, poor EF (particularly inhibition) appears to be involved in the

development and maintenance of addictions, including AUD (Hester et al., 2010). This chapter therefore indicates a potentially vulnerable cohort, which should be further assessed. However, it is likely the relationship between EF and alcohol use is cyclical, with elements of EF being heritable and increasing risk of problematic drinking (Benzerouk et al., 2013).

The current findings may result from anomalies in prefrontal structures, and can be considered against the suggested groupings of prefrontal EF systems (Cummings, 1993; Miller & Cummings, 2017) previously indicated to associate with EFI subscales; Impulse Control and Empathy with orbitofrontal, Strategic Planning and Organisation with dorsolateral, and Motivational Drive with medial (Miley & Spinella, 2006). These areas are disrupted in AUD, associated with decreased EF (Abernathy et al., 2010). Less is known about hazardous drinking and neural function, though as discussed, there is evidence HED leads to prefrontal anomalies associated with impaired EF (Doallo et al., 2014; K. W. Smith et al., 2017). Specific subscale impairments indicate more potential damage to orbitofrontal and dorsolateral regions, which may differentiate hazardous and dependent drinkers. However, as described in the materials section, this interpretation is restricted due to limited support for a three-factor model of the EFI (Janssen et al., 2009), and because the most used models of EF do not follow these frontal lobe divisions. There is evidence to suggest hazardous drinking cessation leads to partial cognitive and neural recovery, though not to the same performance as controls (Lees et al., 2019). Future research could use additional means (neuroimaging, ERP, objective EF assessments) to investigate brain structure/function of hazardous drinkers, the cause/effect, reversibility or chronic nature of any changes, and predictability of assessments to indicate risk of progression from hazardous drinking to AUD.

Our second prediction was supported as hazardous drinking predicted alcohol-related problems, and this was partially mediated by EF. Although the APQC score does not indicate specific issues, its high internal consistency upon conception indicates problems assessed within it may co-occur, indicating general problematic tendencies (Drummond, 1991). It is understandable how

problems planning/using strategies, self-inhibiting, managing risk taking, and holding information in mind or multitasking, could contribute to items included in APQC. Indeed, hazardous drinkers (≥8 AUDIT score) experience more mental health problems, hospital admissions, and social issues (Conigrave et al., 1995), and alcohol use contributes to financial, legal and workplace problems (Rehm, 2011). EF is associated with all of these domains (Allan et al., 2016; Gulpers et al., 2016; Snyder, 2013; Spinella et al., 2004; Wolf, 2010; Yeh, 2013), so it is possible alcohol-related EF impairments may partially underlie the disruptive impact of problematic drinking for some people, even before considering whether hazardous drinking/poor EF increases risk of AUD. That self-reported EF predicted hazardous drinking and mediated the relationship between alcohol use and -related problems, is supported by other studies of self-reported emotional or interoception processing and alcohol use. Specifically, self-reported emotional dysregulation (specifically, decreased trait empathy) was found to moderate the effect of self-efficacy on resisting peer pressure to drink (Laghi et al., 2019), while self-reported interoception (specifically, difficulty in identifying feelings) mediates the relationship between sensitivity to bodily sensations and alcohol use (Betka et al., 2018). This again highlights that self-report methods capturing lived experience of day-to-day cognitive function is important to consider in relation to drinking behaviour and related experiences.

This study had a number of limitations. Conducted during the first 2020 COVID-19 lockdown, this may have induced drinking pattern changes due to stress/boredom (Institute of Alcohol Studies, 2020). Indeed, a general population survey suggested 21% of UK adults reported drinking more than normal, while 35% reduced/abstained (Alcohol Change UK, 2020). Another large self-selecting online survey (n= 40,000) found 44% of respondents reported an increase in drinking (Global Drugs Survey, 2020), and 23.8% reported an increase in HED (though 30.5% of these said this increase was slight). However, the Alcohol Change survey found people whose drinking increased were those who already drank heavily prior to the lockdown. Furthermore, while lockdown drinking may be somewhat different, the AUDIT asks questions in relation to the previous 12 months, so classification

of drinking group should have remained stable. We also aimed to keep the survey short to increase engagement, thus, no data was collected on abstinence period from alcohol. It is possible participants experienced alcohol acute/sub-acute effects (such as residual intoxication) which may have impacted their responses. However, as hazardous drinkers had higher overall alcohol consumption, and were the group demonstrating poorer EF, the effects found are unlikely related to sub-acute intoxication, even if this occurred for some people. Statistical limitations include the lower Cronbach's α coefficients for subscales of the EFI, indicating potential internal inconsistencies and future research should seek to use additional methods of EF assessment. Additionally, as this was a cross-sectional survey it was not possible to discern whether lower EF was a cause or effect of hazardous drinking in this cohort.

Despite limitations, this study gives insight into the under-explored area of subjective EF in hazardous drinking, and the mediating effect of EF on the impact of such drinking on real-world functioning, suggesting hazardous drinkers may be more vulnerable.

4.6 Chapter Summary

This chapter examined hazardous drinking and subjective EF in a large online survey. Hazardous drinkers reported significantly lower subjective EF, specifically of Strategic Planning, Impulse Control, and Organisation. Additionally, the relationship between alcohol use and alcohol-related problems was partially mediated by effect of alcohol use on subjective EF, indicating the importance of understanding and addressing poorer EF in hazardous drinkers. The following chapter builds from this, by examining vibrotactile processing speed alongside subjective EF, in hazardous drinkers.

Chapter 5 : Vibrotactile Reaction Time in Hazardous Drinkers

The study in this chapter is published open access in the Journal of Psychopharmacology, and is cited as Powell et al. (2023), and available in Appendix 5.

5.1 Chapter Overview

The previous chapter found poorer subjective EF in hazardous drinkers, and indicated that this has an impact on their wellbeing, suggesting that subjective assessment has utility in this context. Consequently, this chapter presents a study examining the relationship between hazardous alcohol use and cognitive function further, by assessing subjective EF, vibrotactile choice and simple RT, and the relationship between these higher-level and more basic functions in this drinking behaviour. Participants (n = 86) completed vibrotactile tasks and alcohol, mood, and subjective function (EFI) questionnaires. Hazardous drinkers exhibited significantly faster choice RT. With regards to subjective EF, Strategic Planning and Impulse Control were significantly better in non-hazardous drinkers. Finally, Organisation and Impulse Control both significantly positively correlated with choice and simple RT, indicating that as subjective function improved, RT increased (a decline in performance). These results further indicate that hazardous drinkers subjectively experience harm, but also indicates, somewhat counterintuitively, that this harm does not correspond to impaired processing speed at this level of drinking. It is important therefore to consider these functions and their relationships in a clinical, AUD group.

5.2 Introduction

As described in section 1.5.2.2, there is mixed evidence regarding hazardous drinking and processing speed. Some studies have shown no speed difference between hazardous and non-hazardous drinkers (Affan et al., 2018; Cohen-Gilbert et al., 2017; Hogenkamp et al., 2014; Nguyen, Gillen, et al., 2013; Rodgers et al., 2005; Winward, Hanson, Bekman, et al., 2014; Winward, Hanson, Tapert, et al., 2014; Woods et al., 2016), whilst others have found slower processing (Hartley et al., 2004; Houston et al., 2014; Nguyen-Louie et al., 2015; Salas-Gomez et al., 2016; Woods et al., 2016).

However, other studies have found faster processing in hazardous drinkers (Bø et al., 2016; Hartley et al., 2004; Kashfi et al., 2017; Mazumder et al., 2021; Townshend & Duka, 2005; Zanjani et al., 2013), including one systematic review and meta-analysis of HED, (Lees et al., 2019), though this review highlighted a high risk of bias, and significant heterogeneity. Additionally, as discussed in section 1.5.2.2, variation in findings may be partially accounted for by confounds, such as age, gender, and classification of drinking status method. Finally, as described in section 2.5.1, the method of processing speed assessment may also impact findings.

There were a range of tasks used in previous research that include pencil and paper, manual responding to visual or auditory presentation, and manual responding to vibrotactile presentation. Indeed, most studies used visual presentation and manual responding (Hogenkamp et al., 2014; Houston et al., 2014; Nguyen-Louie et al., 2015; Winward, Hanson, Bekman, et al., 2014; Winward, Hanson, Tapert, et al., 2014; Woods et al., 2016; Zanjani et al., 2013). Two studies used dedicated hardware, with Rodgers et al. (2005) using a 'box' that displayed lights and had response buttons, and Nguyen, Gillen, et al. (2013) using the dedicated vibrotactile device mentioned previously in Chapter 2. These methodological variations could account for some of the variability in findings.

In an earlier study, we used vibrotactile presentation with response via computer mouse to identify alcohol-related changes in processing speed during early inpatient detox in individuals with an AUD (Powell, Tommerdahl, et al., 2021). This approach also identified differences in ability to discriminate between different amplitudes in heavy and light drinkers (Nguyen, Gillen, et al., 2013) in young (aged 18-26) drinkers, and therefore appears sensitive to alcohol-related cognitive changes. In the previous chapter (Study 2), differences in subjective EF were captured in a large sample of hazardous drinkers. The current study aimed to assess simple and choice vibrotactile RT and subjective EF between hazardous and non-hazardous drinkers. We hypothesised that (1) hazardous drinkers would have slower RTs than non-hazardous drinkers, (2) hazardous drinkers would report poorer subjective EF than non-hazardous drinkers, and (3) there would be a negative correlation

between objective and subjective measures, with slower RT scores (worse performance) correlating with poorer subjective function.

5.3 Method

5.3.1 Design

A between-groups cross-sectional design assessed cognitive function via vibrotactile perception tasks and subjectively rated questionnaires between hazardous and non-hazardous drinkers. The independent variable was alcohol use, with two levels; non-hazardous and hazardous (AUDIT ≥8 categorised as hazardous drinking). The dependent variables were simple RT, RT variability, choice RT and RT Fatigue, and subscales of the EFI. Age, gender, and mood state were covariates in all main analyses.

5.3.2 Participants

Potential participants self-identified as eligible if they were aged 18+ and were fluent in English. Exclusion criteria which could affect RT were history of AUD or SUD, learning disabilities, neurological impairment, pregnancy, use of cocaine within the last month, or a condition impacting sensation in dominant hand. Ninety individuals took part. Four participants were removed from the main analyses[3]. Therefore, the study comprised of 86 participants. All individuals lived in the UK and were recruited from the Northwest of England. Participants were categorised into hazardous (*n* = 36) and non-hazardous drinkers (*n* = 50) drinkers using AUDIT score (≥8 classed as hazardous drinking). Age was significantly higher in the non-hazardous group $t(83.65) = 2.621$, $p = .010$. See Table 9 for participant characteristics.

[3] One participant was removed from all analyses due to nerve damage in their dominant hand that was not disclosed until testing was complete. Three participants were removed due to initial boxplot outlier inspection revealing that they had invalid scores due to not meeting the choice reaction time response threshold required.

Table 9. *Characteristics of participants*

	Non-Hazardous (n=50)				Hazardous (n=36)				Independent t-test		
	Min	**Max**	**M**	**SD**	**Min**	**Max**	**M**	**SD**	***t***	***df***	***p***
Age	18	80	37.40	18.83	18	70	28.00	14.41	2.62	83.65	.010
AUDIT Total	0	6	3.44	1.96	8	22	12.06	3.76	-12.58	48.73	<.001
HADS Anxiety	0	17	6.78	4.07	3	15	8.61	3.50	-2.18	84	.028
HADS Depression	0	13	3.02	2.63	0	10	3.08	2.27	-0.12	84	.91
	Count		**Percentage**		**Count**		**Percentage**				
Female	36		72.0		21		58.3		-	-	-
Male	14		28.0		15		41.7		-	-	-
Educational Level											
Level 1 – 5 (Secondary school – Cert/HNC/HND or equivalent)	19		38.0		21		58.3		-	-	-
Level 6 (BSc, BA, or equivalent)	10		20.0		4		11.1		-	-	-
Level 7 & 8 (MSc, MA, Doctoral or equivalent)	16		32.0		6		16.7		-	-	-
Trade, technical, or vocational training (level unknown)	4		8.0		5		13.9		-	-	-
Employment Status											
Full-time work	10		20.0		8		22.2		-	-	-
Part-time work	13		26.0		14		38.9		-	-	-
Student	8		16.0		5		13.9		-	-	-
Retired	7		14.0		2		5.6		-	-	-
Unemployed	12		24.0		7		19.4		-	-	-
Mental Health Disorders											
None	43		86.0		30		83.3		-	-	-
Reported mental health condition (e.g., anxiety, personality, eating, neurodevelopmental)	7		14.0		6		16.7		-	-	-
Cognition Impacting Medication*											
No medication	34		68.0		27		75.0		-	-	-
Medication which could impact cognition (including contraceptive pill, antidepressants, PPI or H1/H2 antagonist)	14		28		8		22.2		-	-	-
Other medication not affecting cognition	2		4.0		1		2.8		-	-	-

*No participants took antiparkinsonian, antibiotic, antipsychotic, pain relief (opioid or NSAID), anticonvulsant, anxiolytic, alcohol-related, or high dose vitamin medications.

5.3.3 Materials

5.3.3.1 Demographics

Participants answered questions on age, gender, employment status, housing status, education level, mental health diagnoses, medication, and country of residence.

5.3.3.2 Subjective Executive Function

Once again, the EFI was used to assess the integrity of subjective EF. In this study, Cronbach's α totalled 0.80, and ranged from 0.78-0.80 across the items. It was lower for the subscales, which were as follows: Motivational Drive = .42, Impulse Control = .49, Strategic Planning = .67, Organisation = .74, Empathy = .78.

5.3.3.3 Mood State

HADS assessed state anxiety and depression. In this study, Cronbach's α totalled 0.80, and ranged from 0.77-0.80 across the items. For the subscales it was 0.77 (anxiety) and 0.66 (depression).

5.3.3.4 Alcohol Use

Assessed by the AUDIT, for which Cronbach's α totalled 0.80 and ranged from 0.74-0.81 across the items (though item six, "How often during the last year have you needed a drink first thing in the morning to get yourself going after a heavy drinking session?" was removed from this internal consistency assessment due to there being no variance as every participant scored 0, "Never").

5.3.3.5 Reaction Time

This was assessed using dedicated hardware with an inbuilt microprocessor (the BG Pro), which is the same size/shape as a computer mouse. A customised test battery was used to target prefrontal function, with two cylinders (5mm diameter) delivering vibrotactile stimulation to the middle and index finger of the dominant hand. The device software provides participants with instructions on the computer screen. For simple RT, participants were instructed to press the

opposing tip (index finger) as soon as they felt a tap (25Hz, 300µm, 40ms) on their middle finger. For choice RT, participants were instructed to press the opposing tip as soon as they feel a vibration to the other finger. In this condition, either index or middle finger may be tapped each time, so responding involves choice. For both simple and choice RT, participants first completed a series of practice trials for which they had to correctly respond three consecutive times to proceed, and ten successive trials, which were separated by a randomised intertrial interval of 2-7 seconds (Kim et al., 2020; Zhang et al., 2011). All participants in the present study were able to proceed past the practice trials to the main tasks. In addition to the simple and choice RT scores a *RT variability* score (the standard deviation of the ten trials) and a *Fatigue* score (comparing the first and last tasks) are also generated. Averaged scores of simple RT, RT variability, and choice RT were used in all analyses (milliseconds), as was the composite score of Fatigue. Lower scores in all measures indicate better function.

5.3.4 Procedure

Potential participants were recruited using opportunity sampling via various methods. Student participants were recruited via an internal recruitment database, posters in university buildings, Listserv emails, and the LJMU research participation website. Members of the public were recruited via social media adverts (Twitter) and the LJMU Psychology Research Participation Panel. Recruited participants were invited to LJMU for an individual testing session in a psychology laboratory. After giving informed consent, participants completed the vibrotactile tasks (simple, choice, and then a repetition of simple to create the Fatigue score). After completion of the RT tasks, the questionnaires were completed in a counterbalanced fashion. Overall, the testing session lasted between 45 – 60 minutes per participant and participants were given a debrief sheet explaining the purpose of the study with information about where they can seek help for their/others' drinking, and given a £10 shopping voucher as a thank you for their participation. The study was approved by LJMU Research Ethics Committee (19LJMUSPONSOR0037).

5.3.5 Statistical Analysis

Analyses were conducted using SPSS v28 (IBM Corp., Armonk, N.Y., USA). To assess differences in mood state between the groups, we used MANOVA with drinking level (hazardous vs. non-hazardous) as the between groups independent variable and HADS anxiety and depression as the dependent variables. Shapiro–Wilk tests using a Bonferroni correction indicated normality of mood state across drinking level was violated for two out of four tests. Due to there being no non-parametric MANOVA equivalent, and due to MANOVA being robust regarding normality violations, this analysis was considered most appropriate. Two MANCOVAs were performed on average RT scores, and on EFI scores, using drinking level (non-hazardous and hazardous) as the between-groups independent variable. In both analyses, mood state, age, and gender were included as covariates, due to their associations with both alcohol use/consequences (Novier et al., 2015; Tovmasyan et al., 2022; White, 2020) and EF ((Best & Miller, 2010; Ferguson et al., 2021; Grissom & Reyes, 2019; Mitchell & Phillips, 2007; Zaninotto et al., 2018). MANCOVA assumptions were assessed, linearity and residual normality were acceptable. For the RT MANCOVA, Box's test was violated ($p = .01$) so Pillai's Trace statistics are reported. Homogeneity of regression slopes were achieved in all cases except drinking level*gender ($p = .05$). Therefore, this violation indicates that a moderator approach would be more appropriate, so the drinking level*gender interaction term is subsequently included in the model. As age was significantly higher in the non-hazardous group, and the RT MANCOVA indicated faster choice RT in hazardous drinkers (which has previously been found in younger drinkers (Scaife & Duka, 2009; Townshend & Duka, 2005)), we also created age-related drinking groups and repeated the RT MANCOVA, to assess the effects of age-related drinking level on RT measures. This was conducted with age-related drinking level (four levels: 'older' (30+ years) hazardous; older non-hazardous; 'younger' (18-29 years) hazardous; younger non-hazardous) as the between groups independent variable, average RT scores as the dependent variables and gender and mood state as covariates. Finally, to investigate relationships between subjective and objective function, a bivariate correlation was conducted.

5.4 Results

Descriptive statistics for mood state, subjective EF and RT in hazardous and non-hazardous drinkers, and RT in age-grouped drinking levels are displayed in Table 10.

Table 10. *Descriptive statistics for mood, reaction time and EFI for hazardous and non-hazardous drinkers*

	Non-Hazardous		Hazardous	
	M	**SE**	**M**	**SE**
HADS Anxiety	6.78*	.54	8.61	.64
HADS Depression	3.02	.35	3.08	.41
MANCOVA adjusted RT scores				
Simple RT	310.97	9.46	301.01	11.27
RT Variability	28.78	2.89	28.78	3.44
Choice RT	462.07*	11.84	442.64	14.10
Fatigue	-9.04	9.39	-12.83	11.19
MANCOVA adjusted EFI mean scores				
Motivational Drive	15.36	.33	14.49	.39
Organisation	16.97	.43	15.88	.51
Strategic Planning	26.75***	.54	23.48	.63
Impulse Control	17.40***	.32	14.93	.38
Empathy	25.70	.44	26.11	.52

	Younger Non-Hazardous		Younger Hazardous		Older non-Hazardous		Older Hazardous	
MANCOVA adjusted RT scores for age grouped drinking levels								
Simple RT	295.06	14.96	267.19****	14.27	345.73**	14.88	357.18*	25.96
RT Variability	22.19	4.26	26.00	4.06	38.84	4.26	26.59	7.39
Choice RT	421.47**	18.99	401.28****	18.11	520.61****	18.88	489.95	32.94
Fatigue	-1.97	13.15	1.64	12.55	-22.27	13.08	-43.85	22.82

Denotes differences significant at: * p<.05; **p<.01; *** p<.001; **** p<.0001

Inspection of Table 10 shows that while self-reported state depression scores were comparable between the groups, the hazardous drinking group had higher mean scores for state anxiety indicating higher subjective levels of anxiety. Using MANOVA, the multivariate main effect of drinking level on mood approached significance $F(2,83) = 2.86$, $p = .06$, with univariate analyses demonstrating that anxiety [$F(1,84) = 4.75$, $p = .03$], but not depression [$F(1,84) = .01$, $p = .91$], differed significantly between the groups.

5.4.1 Reaction Time

Table 10 shows that there was little difference between the groups in covariate adjusted means for simple RT, RT variability and Fatigue. There were no significant differences in percentage correct on choice RT between hazardous (93.33%) and non-hazardous (93.80%) drinkers [$F(1,83) = .06$, $p = .81$]. However, the hazardous drinkers had lower scores for choice RT indicating that they were faster (better) than the non-hazardous drinkers. We used MANCOVA to assess between group differences in RT measures; for brevity, only multivariate effects are reported in full below (see Table 11 for full MANCOVA statistics). There was a significant multivariate main effect of drinking level on overall RT performance [$F(4,76) = 2.80$ $p = .03$, $\eta_p^2 = .13$]. Age [$F(4, 76) = 14.56$, $p < .001$, $\eta_p^2 = .43$] and gender [$F(4, 76) = 3.09$, $p = .02$, $\eta_p^2 = .14$] were also significant as covariates, as was the gender*drinking level interaction [$F(4.76) = 2.70$, $p = .04$, $\eta_p^2 = .12$). State depression [$F(4,76) = .19$, $p = .12$] and state anxiety [$F(4,76) = .19$, $p = .12$] were not significant as covariates. Table 11 reveals that age (RT, RT variability, choice RT) and gender (RT variability, choice RT) were both significant covariates for differing RT scores in the MANOVA, while the effects of drinking level on choice RT was the only significant difference after controlling for the effects of age, gender, and state mood.

Table 11. *MANCOVA between-subjects effects for i) drinking level on RT controlling for mood state, age, and gender with a gender*drinking level interaction term and ii) age-related drinking level on RT controlling for gender and mood state*

		i) Drinking level (hazardous vs. non)			**ii) Age-related drinking group**		
		F	*p*	η_p^2	*F*	*p*	η_p^2
Drinking Level * Gender [F(1,79)]	RT	0.08	0.78	0.00	-	-	-
	RT variability	0.09	0.76	0.00	-	-	-
	Choice RT	4.69	0.03	0.06	-	-	-
	Fatigue	0.04	0.84	0.00	-	-	-
HADS Anxiety [F(1,79)]	RT	0.09	0.77	0.00	.05	.83	.01
	RT variability	0.37	0.54	0.00	.34	.56	.01
	Choice RT	1.15	0.29	0.01	.68	.41	.01
	Fatigue	1.66	0.20	0.02	2.02	.16	.03
HADS Depression [F(1,79)]	RT	0.61	0.44	0.01	1.72	.19	.02
	RT variability	3.81	0.05	0.05	3.21	.08	.04
	Choice RT	1.17	0.28	0.01	1.93	.17	.02
	Fatigue	0.27	0.61	0.00	.02	.89	.01
Age [F(1,79)]	RT	39.68	0.01	0.33	-	-	-
	RT variability	16.53	0.01	0.17	-	-	-
	Choice RT	43.88	0.01	0.36	-	-	-
	Fatigue	3.62	0.06	0.04	-	-	-
Gender [F(1,79)]	RT	3.68	0.06	0.04	2.94	.09	.04
	RT variability	4.25	0.04	0.05	4.52	.04	.05
	Choice RT	7.48	0.01	0.09	5.86	.02	.07
	Fatigue	3.06	0.08	0.04	3.11	.08	.04
Drinking Level [F(1,79)] or Age-related drinking level [F(3,79)]	RT	0.01	0.94	0.00	6.04	.001	.19
	RT variability	0.08	0.77	0.00	2.77	.05	.10
	Choice RT	5.61	0.02	0.07	7.91	.001	.23
	Fatigue	0.07	0.79	0.00	1.41	.25	.05

Due to the significant covariate effect of age in all analyses, we categorised participants as 'older' (30+ years) hazardous (*n* = 8) and non-hazardous (*n* = 25) drinkers and 'younger' (18-29 years) hazardous (*n* = 28) and non-hazardous (*n* = 24) drinkers, and repeated MANCOVA. The mean scores for these groups in Table 10 demonstrate that the two younger groups have lower (faster) RT scores than the older groups, and that the younger hazardous drinkers are faster than the other groups. There was a significant multivariate main effect of age-related drinking group [F(12,234) =2.77, *p* <.001, η_p^2 = .12] and significant covariate effects of gender [F(4,76) = 2.79, *p* = .03, η_p^2 = .13], and state depression [F(4,76) = 2.68, *p* = .04, η_p^2 = .12] but not anxiety [F(4,76) = 1.87, *p* = .12]. Pairwise

comparisons (Table 12) indicated that young hazardous drinkers performed better than both older groups on simple RT; non-hazardous older drinkers had significantly worse RT variability than non-hazardous younger drinkers; and non-hazardous older drinkers performed worse than both young groups on choice RT.

Table 12. *Mean differences in pairwise comparisons in MANCOVA of age-related drinking groups*

		Hazardous Older	Non-Hazardous Younger	Non-Hazardous Older
RT	Hazardous Younger	-89.99*	-27.88	-78.54*
	Hazardous Older		62.11	11.45
	Non-Hazardous Younger			-50.67
RT Variability	Hazardous Younger	-.58	3.91	-12.84
	Hazardous Older		4.40	-12.26
	Non-Hazardous Younger			-16.65*
Choice RT	Hazardous Younger	-88.67	-20.18	119.32*
	Hazardous Older		68.49	-30.65
	Non-Hazardous Younger			-99.14*
Fatigue	Hazardous Younger	45.48	3.61	23.90
	Hazardous Older		-41.88	-21.58
	Non-Hazardous Younger			20.30

*Note: For the raw means, see Table 10. * Denotes mean difference significant at p<.01 after Bonferroni correction*

5.4.2 Subjective Executive Function

Table 10 displays the MANCOVA adjusted means for the EFI subscales, indicating that for all subscales except Empathy, non-hazardous drinkers scores higher (better subjective EF). MANCOVA found significant covariate effects of age [$F(5, 75) = 5.94$, $p < .001$, $\eta_p^2 = .28$], state depression [$F(5, 75) = 6.45$, $p < .001$, $\eta_p^2 = .30$], and anxiety [$F(5, 75) = 6.34$, $p < .001$, $\eta_p^2 = .30$], but not of gender [$F(5,75) = .75$, $p = .60$). After covariates were controlled for, there was a significant multivariate main effect of drinking group on subjective EF [$F(5, 75) = 7.56$, $p < .001$, $\eta_p^2 = .34$]. Follow-up univariate ANCOVAs found that while non-hazardous drinkers reported better subjective EF on all measures

(except for Empathy), this difference was only significant for Strategic Planning [$F(1, 79) = 14.38$, $p < .001$, $\eta_p^2 = .15$], and Impulse Control [$F(1, 79) = 22.81$, $p < .001$, $\eta_p^2 = .22$]. There were no significant differences between hazardous and non-hazardous drinkers for Motivational Drive, Organisation, or Empathy ($p = .11$, .12, and .57 respectively).

5.4.3 Subjective and Objective Function

To assess the relationships between subjective and objective function, bivariate correlations (Kendall's Tau) were run on average RT scores and EFI subscale scores (see Table 13). There were significant positive associations between Organisation and simple [$\tau_b = .20$, $p = .01$] and between Impulse Control and simple [$\tau_b = .25$, $p = .001$] and choice RT [$\tau_b = .25$, $p = .001$]. This suggests that as subjective function improved, RT performance worsened (response latency increased).

Table 13. *Kendall's Tau correlation matrix for reaction time and subjective executive function*

	Simple RT	RT Variability	Choice RT	Fatigue	EFI -MD	EFI-ORG	EFI-SP	EFI-IC
RT Variability	.393*	-						
Choice RT	.451*	.280*	-					
Fatigue	-.173	-.082	.120	-				
Motivational Drive	.091	.069	.077	.043	-			
Organisation	.198*	.093	.161	-.002	.214*	-		
Strategic Planning	.084	.041	.116	.125	.255*	.249*	-	
Impulse Control	.252*	.103	.251*	.032	.218*	.452*	.200	-
Empathy	-.030	-.115	-.019	-.028	.113	.042	.161	.398

* $p \leq .01$ (2-tailed)

5.5 Discussion

This chapter assessed hazardous drinking-related differences in vibrotactile simple and choice RT. In contrast to hypothesis one, hazardous drinkers were faster than non-hazardous drinkers at choice RT, though they reported poorer subjective EF. There was a positive correlation between objective and subjective measures, slower simple or choice RT scores (worse performance) correlated with better self-reported EF on certain EFI subscales (Organisation and simple RT, and Impulse Control and simple and choice RT). After controlling for covariates, hazardous drinking was associated with faster choice RT, but not with simple RT, RT variability, or Fatigue. This suggests

hazardous drinkers in this study were better at responding quickly on the more executive-oriented task, but that this advantage did not extend to simple RT, the variability between simple RT trials (an indicator of attention), or the Fatigue score.

Research with clinical populations of people with AUD consistently shows impaired processing speed (Crowe, 2019; Stavro et al., 2012). It has been assumed that hazardous drinking can be considered a precursor stage to developing an AUD, and therefore that many of the impairments observed at the dependent stage would be seen in hazardous drinkers, albeit to a lesser extent (Lees et al., 2019). However, the current results challenge this assumption, and are more consistent with other studies showing faster RT in hazardous drinkers (Bø et al., 2016; Hartley et al., 2004; Kashfi et al., 2017; Lees et al., 2019; Mazumder et al., 2021; Townshend & Duka, 2005; Zanjani et al., 2013), and even somewhat with those that show no relationship between alcohol use and processing speed (Affan et al., 2018; Cohen-Gilbert et al., 2017; Hogenkamp et al., 2014; Nguyen, Gillen, et al., 2013; Rodgers et al., 2005; Winward, Hanson, Bekman, et al., 2014; Winward, Hanson, Tapert, et al., 2014; Woods et al., 2016). This finding is of interest and suggests that perhaps hazardous drinkers require less time to make a choice in a choice RT task than non-hazardous drinkers (as proposed by Townshend & Duka, 2005), while the lack of difference on simple RT indicates that non-hazardous drinkers may be more likely to slow down when considering the choice RT, as hazardous drinkers are not always faster. There are a number of possible tentative explanations for this. Firstly, in animal models, acute alcohol administration reduces longer RTs on the 5 Choice Serial Reaction Time task, with longer RT emerging during abstinence, and peaking 30 days after last acute administration (Wright et al., 2013). Consequently, it is possible that in the present study, the hazardous drinkers were faster due to recent heavier alcohol use, and that slower RT might have become apparent under longer periods of abstinence. Higher levels of GABA due to recent heavy alcohol consumption could lend support to this explanation. GABA increases cortical inhibition and thus higher GABA may be beneficial for tasks involving response selection, as it limits

neuronal noise, enabling selective neural activity (de la Vega et al., 2014; Munakata et al., 2011; Snyder et al., 2010).

Secondly, while in the present study it is unlikely that the increased RT reflects a speed-accuracy trade-off as there were no significant between group differences in percentage correct in choice RT, it is possible that the choice RT task was too simple to elicit errors, with only two possible choices. Other studies that have found a speed-accuracy trade-off have used more complex choice RT tasks, or those that require adaptive learning after responding, for example Bø et al's (2016) adaptive go/no-go where HED were faster but failed to adapt to incorrect responses in line with controls. Such speed-accuracy trade-offs are often seen in EF tasks measuring response inhibition, though tasks assessing this EF do not solely measure response inhibition, and include elements of processing speed; such as average RT in the Go/NoGo task, mean RT in Go trials of the SST, and prosaccade latency in the Antisaccade task (Weiss & Luciana, 2022). As described in the introduction, in one previous study that found faster processing, there was a speed-accuracy trade-off (quicker responses but fewer correct choices), interpreted as indicating an inhibitory control deficit (Kashfi et al., 2017), which may in part explain the initiation of hazardous alcohol use (Blakemore & Robbins, 2012; Gullo & Dawe, 2008). However, in Cohen-Gilbert et al. (2017); Townshend and Duka (2005), several of the studies assessed in Lees et al. (2019), and in the current study, there was no evidence of such a trade-off, even though individuals who responded faster were those who scored lower on the subjective Impulse Control subscale of the EFI. While impulsivity is often viewed negatively, perhaps in some circumstances (particularly those with low capacity for risk) it can lead to favourable outcomes (Gullo & Dawe, 2008). This perhaps indicates an ecological issue with examining processing speed in a standard task paradigm and considering its implications valid in stress- or risk-involved scenarios, compared to e.g., virtual reality assessment of performance in a work environment complete with harsh managerial feedback, such as in Donahue and Shrestha (2019). Alternatively, as suggested by Scaife and Duka (2009), the choice RT task may not be complex enough to produce errors in performance at this level of alcohol use, regardless of

impulsivity. Another consideration is that young adult drinkers may be faster due to better response monitoring (slowing down following errors, allowing success/failure to guide performance) (Bø et al. (2016), which was not assessed in the current study.

In the age-related drinking group analysis, the participants demonstrating fastest processing speed on simple RT were younger hazardous drinkers, whilst those with the poorest speed on choice RT were non-hazardous older drinkers. Considered against the 'premature aging hypothesis', where AUD in clinical populations may either accelerate ageing of the brain in individuals of any age, or brains of older drinkers with AUD may be more vulnerable to the effects of alcohol (Ellis & Oscar-Berman, 1989; Oscar-Berman & Marinkovic, 2003; Oscar-Berman et al., 2000), this finding in non-clinical hazardous drinkers suggests the phenomena may not be so clear cut. One study comparing whole-brain contrasts of patients with AUD and controls, provided support for the premature ageing hypothesis, suggesting that increased age increases vulnerability to the cognitive effects of alcohol, and that youth provides protection (Guggenmos et al., 2017). Therefore, considering the current finding that young hazardous drinkers performed better than all older drinkers at simple RT, perhaps the performance difference is pre-existing, but alcohol use eventually negates this, just not to the extent of clinical cases of AUD, as hazardous older drinkers were no worse than the other groups. As processing speed is a task-independent construct (Fry & Hale, 2000), it is unlike other functions examined in the literature. Indeed, the findings regarding higher-order EF in hazardous drinkers are more inconsistent in younger drinkers, while older drinkers generally display impairment compared to controls, likely due to a neurocompensatory mechanism of increased cognitive effort/neuronal labour in younger subjects (Gil-Hernandez et al., 2017). Furthermore, some of the processing speed studies previously mentioned found higher brain activation in areas supporting cognitive processes during tasks, which was interpreted as possible neurocompensation (Affan et al., 2018; Kashfi et al., 2017). The systematic review by Lees et al. (2019) also found greater brain activity during tasks involving attention, inhibition, and working memory in HED. It is worth considering whether perhaps an initial processing speed advantage in younger hazardous drinkers could contribute to their ability

to perform executive tasks at a comparable level to non-hazardous drinkers, and future research should seek to clarify this.

The finding of poorer subjective function in hazardous drinkers initially appears to contrast with the result of better processing speed but is consistent with the previous chapter and highlights the ability of self-report methods to identify deficits. Additionally, the finding of a positive correlation between objective and subjective function is intriguing, as those who were fastest, reported worse day-to-day subjective function. However, given that the strongest relationship was found between Impulse Control and the RT scores, this suggests that slower individuals may have been more prone to thinking before acting, and importantly indicates a relationship between self-reported inhibitory control and behavioural processing speed. This is supported by (Gorlyn et al., 2005), who found an association between RT and the BIS subscales Motor Impulsiveness and Non-Planning Impulsiveness. That there was no speed-accuracy trade-off limits this theory, but again, may be due beneficial elements of impulsivity (Gullo & Dawe, 2008), or the relatively easy choice RT task (Scaife & Duka, 2009). Alternatively, this finding may be due to other alcohol effects, such as on metacognition (Le Berre et al., 2017), increased cognitive effort required for tasks (neurocompensation, as described), or methodological issues with vibrotactile perception as an assessment in this cohort.

It is important to note that while this study found faster processing in hazardous drinkers, particularly in younger hazardous drinkers, the literature is obviously still inconsistent, and the study in this chapter is not without its limitations. Firstly, while this chapter used two versions of the RT task, neither were particularly complex, which as mentioned, may have disguised any speed-accuracy disadvantages of quick responding (Scaife & Duka, 2009). Secondly, while it is interesting to speculate about causes for the current findings, this study did not use direct brain measurements relevant to processing speed. A further limitation of the current study is that it did not assess across patterns of hazardous drinking (e.g., daily drinking versus HED). Maurage et al. (2012) found ERP

deficits associated with specific drinking patterns, indicating that researchers should consider how these different patterns affect function. Finally, the lower Cronbach's α across certain EFI subscales, relatively small sample size (particularly in the groups in the age-related drinking group analysis), and lack of a priori power calculation reduces dependability of the findings.

5.6 Chapter Summary

This chapter found that hazardous drinkers were significantly faster at choice RT, and when examined in age-groups, younger hazardous drinkers were fastest at simple RT, while older non-hazardous drinkers were poorest at choice RT. Like the previous chapter, subjective function was still poorer in hazardous drinkers, specifically in young hazardous drinkers. These findings are tentatively considered against a number of possible explanations, including lingering effects of recent hazardous alcohol use on GABA, or a pre-existing performance difference that fades with alcohol use and age, though not to the extent of older adults with AUD, who display deficits. They may otherwise be due to lower inhibitory control, given that poor subjective Impulse Control was associated with faster responses on the choice RT task. However, the lack of speed-accuracy trade-off complicates this, possibly indicating increased cognitive effort to maintain task performance (neurocompensation), an advantageous aspect of lower inhibitory control in low-risk scenarios, a metacognitive deficit, an issue with using vibrotactile perception to assess alcohol-related processing speed differences, or that the choice task was not complex enough to introduce mistakes. The following chapter considers subjective EF and vibrotactile processing speed in individuals with AUD, against whom a subset of the current participants was compared.

Chapter 6 : Vibrotactile Reaction Time Recovery in Abstinence from Alcohol in AUD

6.1 Chapter Overview

The previous two chapters found poorer subjective EF in hazardous drinkers, indicating that they experience cognitive harm from alcohol use. Contrastingly, processing speed in the more executive choice RT task was better in hazardous drinkers, with no inclination for mistakes because of this speed. This chapter utilises the same set of tasks, in individuals with an AUD, in early abstinence. The chapter compares function in AUD to age-and-gender matched 35 once-tested controls (19 female; 41.00 ± 13.60) from the previous chapter, and assesses change in function during early abstinence (from day 3 to day 7 of treatment) in 67 individuals with AUD (26 female; aged 19-74, 44.50 ± 10.50 years), with a consideration of treatment setting. Group (AUD vs control) significantly predicted choice RT at baseline and follow-up as expected, but did not significantly predict simple RT or RT variability. At follow-up, Fatigue was also predicted by group, and further investigation indicated that this had worsened in outpatients but improved in inpatients. Change in Fatigue correlated negatively with change in subjective Impulse Control, indicating that as Fatigue increased, subjective control decreased. Persisting choice RT deficit is consistent with previous research, though no impairment of simple RT or RT variability is not, indicating that in this cohort, only the more executive task captured impairment. The interaction between setting and timepoint indicates that despite being typically less medically complex, outpatients require ongoing support and monitoring during their recovery.

6.2 Introduction

Recent reviews identify grey matter reductions in the cortex (particularly the PFC and anterior cingulate cortex) and insulae in AUD (Griswold et al., 2018). In dependent drinkers, this can lead to cognitive deficits, ARBI, major neurocognitive disorders such as alcohol-related dementia or Wernicke-Korsakoff syndrome (Thompson et al., 2020). ARBI is estimated to affect 35% of those with AUD (Wilson et al., 2014). Even in the absence of ARBI, cognitive impairments have been shown to reduce quality of life (Balthazar et al., 2010; Binder et al., 2009; Kapur et al., 1996) and negatively impact treatment outcomes (Domínguez-Salas et al., 2016).

As described in sections 1.5.1.1 and 1.5.1.2, one way in which damage to the brain can negatively affect treatment outcomes is via disruption to cognitive function, including EF, and processing speed (Crowe, 2019; Stavro et al., 2012). EF are critical for maintenance of recovery-directed behaviour (Kravitz et al., 2011; Kravitz et al., 2013). EF is predictive of relapse (Czapla, Simon, Richter, et al., 2015; Desfosses et al., 2014; Morrison, 2011; Noel, 2002; Petit et al., 2014), and as a construct critical to EF, inefficient processing speed has also been linked to relapse (Allsop et al., 2000; Durazzo et al., 2008). Processing speed and EF deficits have been suggested as characterising the first month of recovery (Crowe, 2019), and given that 50-80% of people with AUD relapse, often during early abstinence (Manning et al., 2016), it seems that further research into processing speed and its progression during early abstinence, may be useful, to further understanding of outcomes during this crucial stage.

Currently, UK clinical guidelines recommend routine cognitive screening of individuals receiving alcohol treatment. However, more formal assessments are only advised if an obvious impairment persists after abstention or reduction in alcohol use (NICE, 2011), despite lower-level impairments being widespread and affecting treatment outcomes. Additionally, the suggested initial assessment tool, the MMSE, may not be sensitive to frontal lobe dysfunction (Carnero-Pardo, 2014). Suggested alternatives (Heirene et al., 2021), including the Montreal Cognitive Assessment (MoCA;

Nasreddine et al. (2005); Thompson et al. (2020)) or the Addenbrooke's Cognitive Examination (Hsieh et al., 2013), show an educational bias (Carnero-Pardo, 2014), possibly less likely to occur with vibrotactile perception.

Understanding RT change during early recovery and how this compares to 'normal' function (of controls) will contribute to understandings of treatment outcomes. Treatment setting should also be considered, as those referred for inpatient support are likely to have more severe alcohol dependence, more complex comorbidities, and more prior episodes of relapse following treatment/abstinence (NICE, 2011), all of which may impair cognitive function further (Deepak et al., 2019; Duka & Stephens, 2014; Gudayol-Ferré et al., 2022). Therefore, given that early recovery is such a vulnerable time, it is important to consider treatment setting, particularly at this stage because the groups are still very distinct, however once inpatients leave the facility, differences in type of treatment received between the groups reduce. Previous research using the BG has highlighted alcohol-related difference and changes in cognitive function (Nguyen, Gillen, et al., 2013; Powell, Tommerdahl, et al., 2021), indicating that this technology has potential use in this field. Indeed, a pilot study by Powell, Tommerdahl, et al. (2021) found that the BG composite scores most sensitive to early treatment were largely those using RT tasks.

The current study therefore aimed to assess changes in RT from baseline (at the start of a detoxification programme) across early abstinence. We hypothesised that 1) compared to 35 controls, the AUD group would perform more poorly (greater scores) on all RT scores at both timepoints, 2) in the AUD participants, outpatients would demonstrate greater processing speed recovery by T1 than those in the inpatient setting, and 3) that within the AUD group, worsening RT performance between T0 and T1 would associate with worsening subjective EF.

6.3 Method

6.3.1 Design

While a longitudinal design assessed the relationship between processing speed and length of abstinence (N = 4 timepoints), lower initial recruitment than expected and high attrition (both largely due to COVID-19) meant that only the first two timepoints had enough data to analyse, so this became a repeated-measures study. Additionally, while treatment setting was always going to be examined, this became more of a focus in the current study due to the lack of longitudinal data. The first timepoints occurred during early treatment, and there was some overlap regarding abstinence length. This was due to various factors, including changing outpatient appointment dates, treatment duration differences, and study postponement resulting from participant illness/availability. Testing occurred i) T0 at 3.27 ± 1.77 (range = 0-7) days post admission; and ii) T1 at 7.42 ± 2.69 (3-17) days. Despite the overlap, the two timepoints were significantly different regarding abstinence length when assessed by paired t-test [$t(44) = -13.81$, $p < .001$]. The final two timepoints occurred between 1-2.5 months, and 3-4 months post detox, however these are not included in statistical analyses, due to high attrition.

6.3.2 Participants

Potential participants with alcohol dependence were identified by clinicians at either an inpatient or outpatient hospital clinic in Liverpool, UK using convenience sampling. Participants were eligible to take part if they were aged 18+, had an ICD-10 diagnosis of alcohol dependence, were currently undergoing detoxification from alcohol, and were fluent in English. Exclusion criteria were pregnancy or a condition affecting sensation in their dominant hand. Sixty-seven individuals with AUD were recruited into the study (26 female; aged 19-74, 44.50 ± 10.50 years; AUDIT total 22-44, 32.90 ± 4.93; SADQ-C total 18-59, 33.40 ± 11.10). Participants were grouped based on treatment setting (inpatient, n = 41 vs. outpatient, n = 26). See Table 14 for characteristics of participants. Typically, both treatment pathways involved a medically assisted detox, with Librium

(chlordiazepoxide) prescribed to treat withdrawal syndrome, after which patients were offered anti-craving medication. Librium was prescribed to 97.6% (n=40) of inpatients and 96.2% (n=25) of outpatients at T0, and to 55.9% (n=19) of inpatients and 81.8% (n=9) of outpatients at T1. By T2 onwards it was no longer prescribed for this purpose. There was a high attrition rate due to: relapse, unexplained loss of contact, changes to clinical appointment date and COVID-19 related issues. Therefore, at T1 there were only 11 outpatients, and 34 inpatients remaining in the study; 4 outpatients, 7 inpatients at T2; and 4 outpatients and 2 inpatients at T3.

Control participant data was obtained from the cohort recruited in the previous chapter, a general population sample. In the current study, individuals from the previous cohort were age-and-gender-matched against the AUD patients using the SPSS (v 28; IBM Corp (2021)) case-control matching function, by age ± 5 years, which selected thirty-five controls (19 female; aged 41.00 ± 13.60).

Table 14. *Characteristics of Participants at Timepoint 0*

	Controls (n=35)				Outpatient					Inpatient				
	Min	Max	M	SD	Min	Max	M	SD	n	Min	Max	M	SD	n
AUDIT Total*	0	19	6.69	4.72	22	44	29.50	4.14	26	24	40	35.60	3.66	33
SADQ-C Total*	0	21	4.56	5.03	18	30	24.70	3.25	26	21	59	41.60	9.88	31
Units Per Day	-	-	-	-	5	45	22.10	11.30	26	5	75	34.50	13.20	41
Age of initiation of problem drinking	-	-	-	-	20	63	38.50	13.00	17	13	72	29.90	12.60	40
Duration of problem drinking (in years)	-	-	-	-	2	37	7.35	8.19	17	0	42	13.60	12.00	40
Age of first drink	-	-	-	-	12	26	15.80	3.48	23	10	18	14.60	2.33	28
Mood State*														
Anxiety	0	17	7.4	4.28	4	21	14.90	4.70	26	5	21	13.40	4.74	40
Depression	0	13	3.69	2.82	0	18	9.65	4.73	26	2	19	10.40	4.26	40
	Count		Percentage		Count		Percentage		n	Count		Percentage		n
Substance Use														
None	-		-		13		50.0		26	3		7.32		41
Smoker	-		-		9		34.6		26	6		14.6		41
Use of cannabis	-		-		3		11.5		26	3		7.32		41
User of other illicit substances	-		-		1		3.85		26	29		70.7		41

**N varies according to complete/missing data. See method below for categorisation of missing data.*

6.3.3 Materials

6.3.3.1 Demographics

Data was collected on age and gender using questionnaires and patient records.

6.3.3.2 Alcohol use

Assessed using total scores on the AUDIT, SADQ-C (Stockwell et al., 1994) and total mean daily alcohol use prior to detox initiation (UK standard alcohol units). However, due to this information being passed to the research team via gatekeepers, AUDIT and SADQ-C were not available for some patients (see Table 14). Additionally, it was not possible to calculate Cronbach's α for AUDIT and SADQ-C, as only total scores had been recorded. One participant (female, aged 36) was missing mood state data at T0, due to fatigue after the BG tasks.

6.3.3.3 Subjective Executive Function

Assessed using EFI, Cronbach's α totalled 0.87 at T0, and .88 at T1 and ranged from 0.85-0.87 at T0 and .87-.88 at T1 across the items. It was lower for the subscales at both times, which were as follows: Motivational Drive = .72 at T0, .70 at T1, Impulse Control = .54, .59, Strategic Planning = .77, .75, Organisation = .83, .86, Empathy = .75, .82.

6.3.3.4 Clinical information

Data on substance use other than alcohol (including cigarette smoking, cannabis use, or other illicit substances), and relapse or abstinence, were provided by clinical staff. Additionally, in the instance that a follow-up session was attended, clinical records of current alcohol use status were supplemented via self-report).

6.3.3.5 Mood state

The HADS, was used to assess state anxiety and depression. In the current study, Cronbach's α totalled 0.92 at T0 and 0.91 at T1 and ranged from 0.91-0.92 at T0 and 0.90-0.91 at T1 across the items. Regarding Cronbach's for the subscales, anxiety scored 0.89 at T0, 0.87 at T1, and depression was 0.81 at T0, and again at T1.

6.3.3.6 Reaction Time

Again, this was assessed using the BG Pro. As in Chapter 5, mean scores (milliseconds) of simple RT, RT variability, and choice RT were used in all analyses, as was the composite score of Fatigue, with lower scores indicating better function.

6.3.4 Procedure

Potential participants with AUD were informed of the study by clinical staff at either an outpatient or inpatient detox setting. If interested, they were introduced to the researcher, who gave more details. After giving informed consent, participants completed the vibrotactile tasks and the questionnaires (all of which were administered on a Lenovo V14-IIL 14-inch Laptop, with questionnaires via Qualtrics). AUD data collection was conducted over multiple sessions, with the initial testing session occurring near the start of patients' detox. Where possible, further testing sessions were conducted on around day seven. For the testing itself, participants who were recruited at the outpatient service were always assessed in a room by the clinic (after their attendance at a routine clinic appointment), whilst those in the inpatient setting were assessed initially at this setting, but with any follow-ups on completion of detox assessed in either residential rehabilitation providers or public libraries. Participants were given a £10 shopping voucher for their time, and the study was approved by both the Health Research Authority (IRAS ID: 274928, R&D ID SP0565) and LJMU Research Ethics Committee (REC ID: 19LJMUSPONSOR0037). Control participants were recruited via the methods described in section 5.3.4.

6.3.5 Statistical Analysis

Analyses were conducted using R and RStudio (R version 4.2.2; R Core Team (2022), RStudio version 2022.07.2+576; RStudio Team (2022)). To investigate processing speed recovery compared to control scores, multivariate multiple regressions were conducted for timepoints T0 and T1. The predictors were age, gender, mood state, and group (control versus AD), and the dependent variables were simple RT, RT variability, choice RT, and Fatigue. Cross-sectional methods were used,

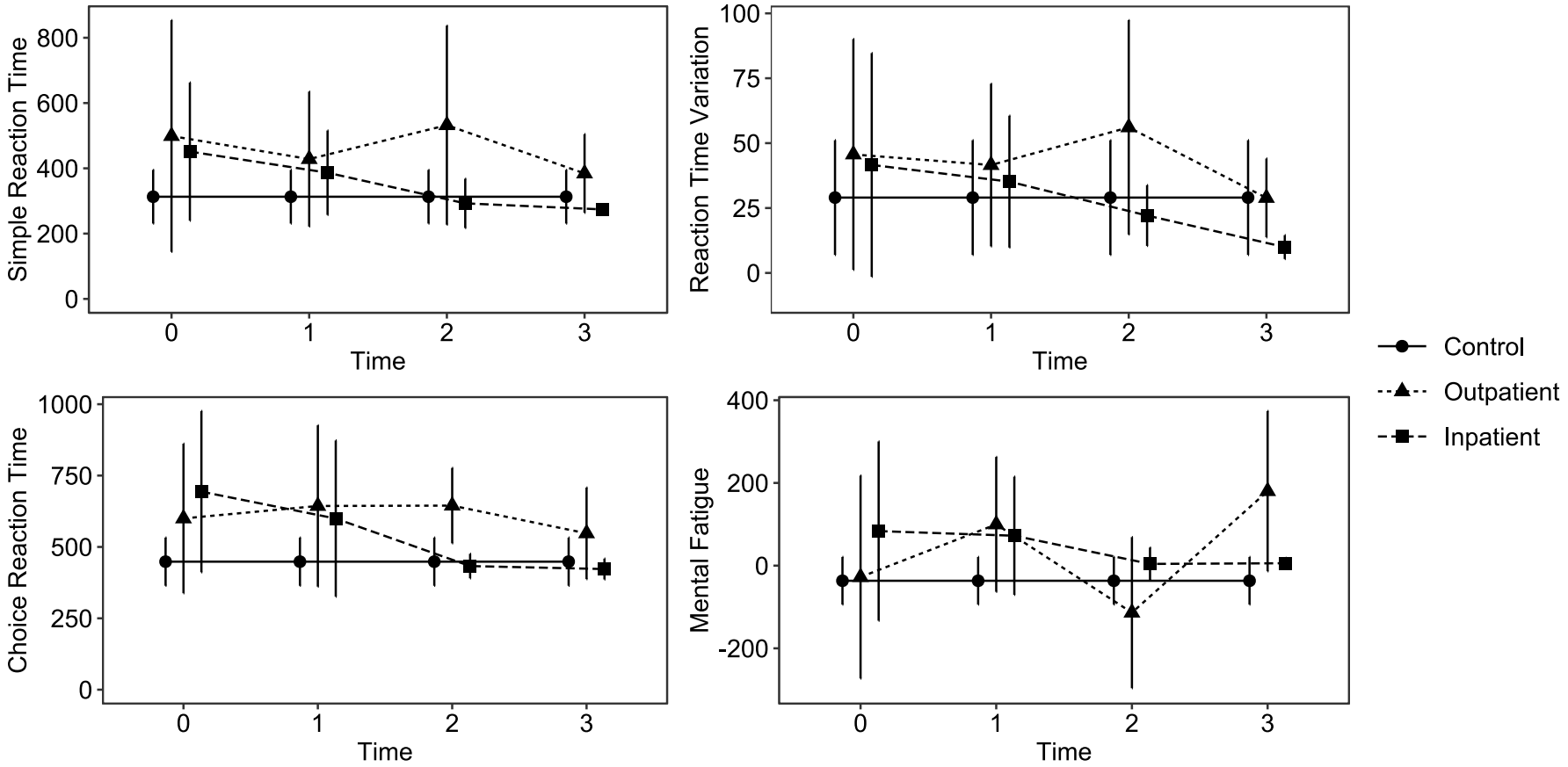
as controls in the previously recruited study were tested only once but were compared to AUD at both abstinence duration points. For regression assumptions, independence of errors and multicollinearity were met. Violations included homogeneity of variance-covariance matrices, and a minority of plots (37.5%) of residuals displaying possible non-linear relationships and heteroskedasticity, with Q-Q plots indicating somewhat non-normal distributions of residuals. However, regression is often robust to this (Schmidt & Finan, 2018), particularly when the sample size is not small (Pek et al., 2018).

A mixed 2x2 MANOVA of AUD data assessed difference between T0 and T1, with group (outpatient vs. inpatient) as the between-groups factor, time as the within-groups factor, and RT measures as the dependent variables. Homogeneity of variance was met for each dependent variable, and normality was met for most variables (75% of Shapiro-Wilk tests). Violations included homogeneity of variance-covariance matrices, some data correlations indicating multicollinearity (29.2%), and some non-linearity between scatterplots of dependent variables (33.3%), so Pillai's Trace values are reported. Several outliers were identified using studentised residuals, however none were influential or high leverage, so these were kept in the analyses. Finally, a Pearson's correlation of AUD data assessed the relationship between RT change scores from T0 and T1 and EFI change scores.

6.4 Results

Figure 7 displays the unadjusted RT descriptives for controls, outpatients, and inpatients.

Figure 7. *Unadjusted reaction time means and standard deviations across group and time*



Note: Reaction Time (RT) variables assessed using vibrotactile perception with tactile response. Mental Fatigue is a composite measure comparing simple RT at the start and end of the testing session. Timepoints include T0 at around 3 days of treatment, T1 at around 7 days, T2 at around 1-2.5 months post-detox, and T3 around 3-4 months post-detox. Controls were tested only once, but their scores are included across each timepoint for comparison. In all cases, higher scores = poorer performance. T0: outpatients (n = 26); inpatients (n = 41), T1: outpatients (n = 11); inpatients (n = 34), T2: outpatients (n = 4); inpatients (n = 7), T3: outpatients (n = 4); inpatients (n = 2).

6.4.1 Recovery of RT compared to controls

6.4.1.1 Timepoint 0

A multivariate assessment at T0 (see Table 15) indicated that overall, group was a significant predictor, while age, gender, and mood state were not. Individually, multiple regressions for simple RT, RT variability, and choice RT, were significant, while Fatigue was not. Overall explained variance for each of these significantly predicted RT measures was 19.9%, 15.3%, and 19.3%, respectively. Individually, group was a significant predictor of choice RT. Regression coefficients and standard errors can be found in Table 15.

Effect sizes were calculated for each individual regression, globally for each RT variable model (Cohen, 1988), and also locally for the variable of interest (group), as per Selya et al. (2012). The global model effect size of the individual RT variable regressions was medium f^2s = .248, .180, .239, when predicting simple RT, RT variability, choice RT, respectively, and small for Fatigue f^2 = .103. The local effect size of group was small in all models f^2s = .006, .002, .101, .038. However, multivariate model effect sizes indicated an overall large effect size for group, η_p^2 = .136. Due to the impact of group on choice RT, Pearson's correlation was used to investigate the relationship between group and the number of correct responses to assess the speed-accuracy trade-off for all three groups (control, outpatient, and inpatient). There was a strong negative correlation only for inpatients (r(39) = -.62, *p* <.001), but no other group (*ps* > .05) indicating that in this group at baseline, as speed increased, accuracy decreased.

Table 15. *Timepoint 0 multivariate multiple regression predicting RT variables based on age, gender, mood state (HADS anxiety and depression scores), and group (control versus alcohol dependent)*

Multivariate Analysis of the Multiple Regressions					
	Pillai's T	*F*	*df*	*p*	η_p^2
Model					
Constant	.07	1.59	4, 92	.183	
Age	.08	2.09	4, 92	.089	.08
Gender	.03	0.64	4, 92	.638	.03
Anxiety	.02	0.55	4, 92	.701	.02
Depression	.09	2.26	4, 92	.070	.09
Group	.146	3.61	4, 92	.009	.14

Individual Multiple Regressions												
Dependent Variable	Unstandardized and standardized coefficients			*Squared semi-partial correlation coefficients*	*Obtained t and p values*		*Obtained R values*			*Obtained F values*		
	B	*SE B*	*β*	sr^2	*t*	*p*	R^2	*R*	*adj.* R^2	*F*	*df*	*p*
Simple Reaction Time							.20	.45	.16	4.71	5, 95	.001
Constant	98.73	96.59			1.02	.309						
Age	4.59	1.81	.24	.23	2.53	.013						
Gender	-24.33	42.69	-.05	-.05	-0.57	.570						
Anxiety	-1.54	5.81	-.04	-.02	-0.27	.791						
Depression	13.78	6.56	.31	.19	2.10	.038						
Group	44.87	58.75	.10	.07	0.76	.447						
Reaction Time Variability							.15	.39	.11	3.42	5, 95	.007
Constant	1.88	13.19			0.14	.887						
Age	0.60	0.25	.24	.23	2.42	.017						
Gender	-0.45	5.83	.01	-.01	-0.08	.939						
Anxiety	-0.76	0.79	-.14	-.09	-0.96	.340						
Depression	2.30	0. 90	.39	.24	2.57	.012						
Group	-1.39	8.02	-.02	-.02	-0.17	.863						
Choice Reaction Time							.19	.44	.15	4.53	5, 95	.001

Constant	274.38	108.62			2.53	.013						
Age	4.03	2.04	.19	.18	1.98	.051						
Gender	20.82	48.01	.04	.04	0.43	.666						
Anxiety	1.27	6.53	.03	.02	0.19	.847						
Depression	-3.17	7.38	-.06	-.04	-0.43	.669						
Group	204.58	66.07	.40	.29	3.10	.003						
Fatigue							.09	.31	.05	1.92	5, 95	.093
Constant	-5.57	90.80			-0.06	.951						
Age	-1.90	1.70	-.12	-.11	-1.12	.267						
Gender	55.37	40.13	.14	.14	1.38	.171						
Anxiety	6.16	5.46	.18	.11	1.13	.262						
Depression	-7.81	6.17	-.20	-.12	-1.27	.209						
Group	104.68	55.23	.26	.19	1.90	.061						

Note: N = 102 (35 controls, 67 AD). RT variables assessed using vibrotactile perception with tactile response. Fatigue is a composite measure comparing simple RT at the start and end of the testing session. B = unstandardised regression coefficient; *SE B* = standard error of the coefficient; *β* = beta coefficient; *adj.* R^2 = adjusted R^2.

6.4.1.2 Timepoint 1

A multivariate assessment at T1 (see Table 16) indicated that overall, group and age were significant predictors, while gender and mood state were not. Individually, all four RT variable multiple regressions were significant. Overall explained variance for simple RT, RT variability, choice RT, and Fatigue was 23.4%, 15.0%, 25.3%, and 24.7%, respectively. Individually, group significantly predicted choice RT and Fatigue, while age predicted all measures. Regression coefficients and standard errors can be found in Table 16.

The global model effect size of all individual RT variable regressions was medium, f^2s = .305, .177, .339, .328, while the local effect size of group was small in all four models, f^2s = .018, .002, .054, .134. Again, multivariate effect sizes indicated that the overall effect of group was large η_p^2 = .148, as was the effect of age η_p^2 = .158. Again, regarding speed-accuracy, there was a strong negative correlation for inpatients (r(33) = -.69, p <.001), but no other group (*ps* > .05) indicating that in this group, increased speed still associated with poorer accuracy.

Table 16. *Timepoint 1 multivariate multiple regression predicting RT variables based on age, gender, mood state (HADS anxiety and depression scores), and group (control versus alcohol dependent)*

Multivariate Analysis of the Multiple Regressions					
	Pillai's T	*F*	*df*	*p*	η_p^2
Model					
Constant	.19	4.27	4, 71	.004	
Age	.16	3.34	4, 71	.015	.16
Gender	.01	0.23	4, 71	.924	.01
Anxiety	.02	0.41	4, 71	.799	.02
Depression	.05	0.98	4, 71	.426	.05
Group	.15	3.08	4, 71	.021	.15

Individual Multiple Regressions												
Dependent Variable	Unstandardized and standardized coefficients			*Squared semi-partial correlation coefficients*	*Obtained t and p values*		*Obtained R values*			*Obtained F values*		
	B	*SE B*	*β*	sr^2	*t*	*p*	R^2	*R*	*adj.* R^2	*F*	*df*	*p*
Simple Reaction Time												
Constant	183.66	63.21			2.91	.005	.23	.48	.18	4.52	5, 74	.001
Age	2.70	1.19	.25	.23	2.26	.027						
Gender	-5.34	28.88	-.02	-.02	-0.19	.854						
Anxiety	-1.91	4.43	-.07	-.04	-0.43	.668						
Depression	9.66	4.99	.33	.20	1.93	.057						
Group	37.41	32.30	.14	.12	1.16	.251						
Reaction Time Variability							.15	.39	.09	2.62	5, 74	.031
Constant	4.35	12.66			0.34	.732						
Age	0.54	0.24	.26	.24	2.25	.028						
Gender	3.79	5.78	.08	.07	0.66	.515						
Anxiety	-0.68	0.89	-.13	-.08	-0.76	.448						
Depression	1.51	1.00	.27	.16	1.60	.136						
Group	2.18	6.47	.04	.04	0.34	.737						

Choice Reaction Time							.25	.50	.20	5.01	5, 74	.001
Constant	193.56	107.54			1.80	.076						
Age	5.94	2.04	.32	.29	2.92	.005						
Gender	-3.72	49.13	-.01	-.01	-0.08	.940						
Anxiety	-2.52	7.54	-.06	-.03	-0.33	.740						
Depression	8.63	8.49	.17	.10	1.02	.313						
Group	109.44	54.95	.24	.20	1.99	.050						
Fatigue							.25	.50	.20	4.86	5, 74	.001
Constant	-161.58	61.75			-2.62	.011						
Age	2.30	1.17	.22	.20	1.96	.054						
Gender	7.17	28.21	.03	.03	0.25	.800						
Anxiety	4.44	4.33	.17	.10	1.03	.308						
Depression	-1.59	4.88	-.05	-.03	-0.33	.746						
Group	99.48	31.56	.38	.32	3.15	.002						

Note: N = 80 (35 controls, 45 AD). RT variables assessed using vibrotactile perception with tactile response. Fatigue is a composite measure comparing simple RT at the start and end of the testing session. B = unstandardised regression coefficient; *SE B* = standard error of the coefficient; *β* = beta coefficient; *adj.* R^2 = adjusted R^2.

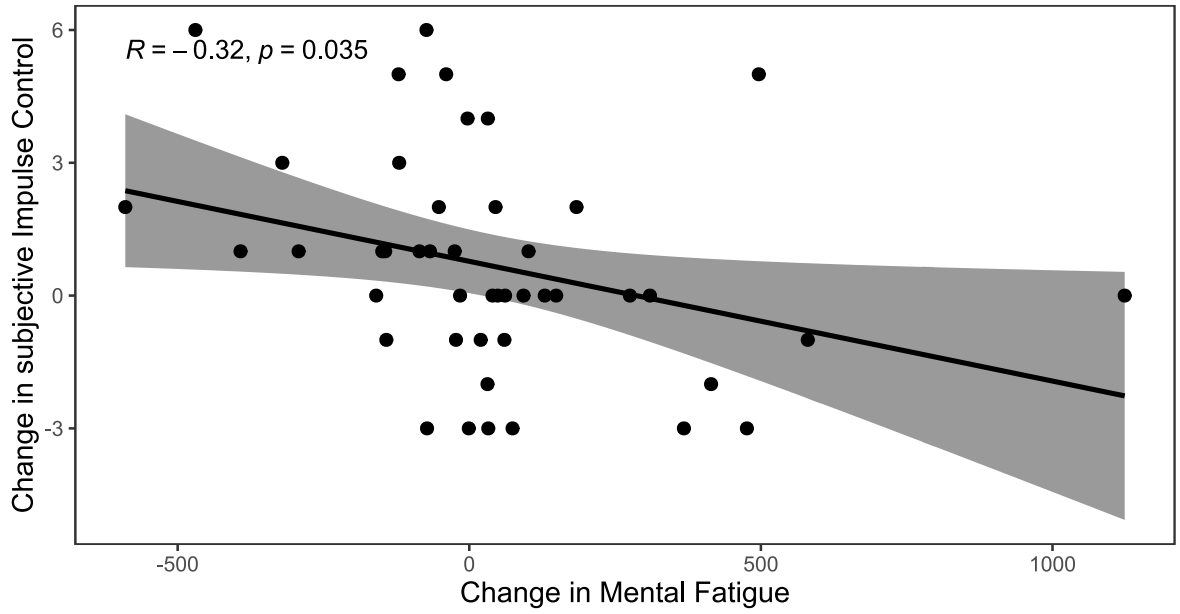
6.4.2 Recovery of RT between treatment settings

See Figure 7 to assist with understanding this mixed 2x2 MANOVA, only T0 and T1 were statistically compared. There was a significant interaction effect between time and treatment setting on the combined dependent variables, $F(4, 40) = 2.55$, $p = .053$. However, the main effects of time $F(4, 40) = 1.35$, $p = .270$, and treatment setting $F(4, 40) = 1.43$, $p = .241$ were non-significant. Univariate ANOVAs revealed that there was a significant interaction of medium effect between the two factors on Fatigue $F(1, 43) = 5.05$, $p = .030$, $\eta p^2 = .11$, due to outpatient participants scoring worse (higher) at T1 than at T0, while inpatients improved (scored lower) by T1. There were no significant interaction effects across the other outcome measures in the univariate ANOVAs (*ps* > .05).

6.4.3 Relationship between change in RT and change in subjective executive function

There was a significant negative correlation indicating that in the AUD group, when Fatigue increased between T0 and T1, subjective Impulse Control worsened (see Figure 8). No other objective vs subjective change score correlations were significant (*ps* > .05).

Figure 8. *Pearson's correlation of change in Mental Fatigue and change in subjective Impulse Control between T0 and T1*



Note: Mental Fatigue is a composite measure comparing simple vibrotactile RT at the start and end of the testing session. Timepoints include T0 at 3 days of treatment, and T1 at around 7 days. Higher Mental Fatigue = poorer performance, while higher subjective Impulse Control = better performance.

6.5 Discussion

We investigated recovery of processing speed in people with AUD undergoing outpatient and inpatient based alcohol treatment. We hypothesised that 1) compared to matched controls, AUD would perform more poorly (higher scores) on all RT scores at both timepoints, but 2) in the AUD participants, outpatients would demonstrate greater processing speed recovery by T1 than those in the inpatient setting, and 3) that within the AUD group, worsening RT performance between T0 and T1 would associate with worsening subjective function. Hypothesis one was partially supported, as AUD performance was poorer than controls at T0 regarding choice RT, but not the other measures, and was poorer in both choice RT and Fatigue at T1. Hypothesis two was not supported; whilst there was an interaction between time and treatment setting, this indicated that outpatients performed more poorly on the Fatigue measure at T1 than baseline, while inpatients had improved. Finally, hypothesis three was partially supported, as there was a negative correlation between change scores in Fatigue and subjective Impulse Control, indicating that as mental fatigue increased, subjective control worsened.

Impairment in choice RT at baseline, is supportive of previous research showing processing speed deficits in AUD (Crowe, 2019; Stavro et al., 2012), and persisting slower choice RT at T1 in addition to higher Fatigue is also consistent with expectations. Continued impairment of choice RT indicates that early AUD recovery is characterised by impaired performance on RT tasks requiring more executive control (and at least in inpatients, any speed came at a cost of reduced accuracy). However, the absence of impairment in simple RT and RT variability compared to controls contrasts with previous research indicating that such impairments persist up to and over a year of recovery (Crowe, 2019; Stavro et al., 2012). This is further contrasted by the absence of a difference in recovery of these functions between outpatients and the more clinically complex inpatients from baseline to T1. The reason for this is unclear, and perhaps indicates a difference between the current

cohort, and those studied previously. Indeed, the range of AUDIT and SADQ-C scores indicate that some control participants were engaging in possibly harmful alcohol use, as the highest AUDIT score was 19, while for SADQ-C it was 21, with scores of eight or above on the AUDIT representing hazardous or harmful use (WHO, 2001), and scores between 15-30 on the SADQ-C indicating possible moderate physical dependence (NICE, 2011)). This may have to some extent reduced the difference in alcohol-related impact on processing speed between controls and patients assessed in this study, though the group means indicate that overall, alcohol use in the control group was likely to be low risk (non-hazardous on the AUDIT, and none or low-dependence on the SADQ-C).

Fatigue worsened in AUD participants compared to controls by T1. The mixed MANOVA found that outpatients had worsened by T1, but that inpatients had improved. Indeed, while sample sizes at T2 and T3 were too small to include in this analysis, the unadjusted means (see Figure 7) for all participants indicate that the outpatients' initial Fatigue scores were similar to controls (with inpatients scoring far higher), but that inpatients then gradually improved, while outpatients scores did not change linearly, and were poorest at T3. Mental fatigue is a decrease in cognitive and neural resources due to persistent cognitive demand (Borragán et al., 2017; Qi et al., 2019), and is experienced as feelings of low energy, or as an increase in effort required to maintain performance (Van Cutsem et al., 2022). The subjective experience can be mitigated by having a break or changing to a less demanding task, and is independent from sleepiness (Trejo et al., 2015), which is mitigated by undisturbed sleep (Kumar, 2008). Fatigue can reduce wellbeing (Smith, 2018), physical endurance (Van Cutsem et al., 2017), academic attainment (Smith, 2018), work performance (McCormick et al., 2012), and leads to changes in motivation, emotion regulation, and cognitive function, including EF (Boksem & Tops, 2008; Grillon et al., 2015; Plukaard et al., 2015). Mental fatigue does not always impair performance, as increased effort, and individual differences in interest/motivation/personality may moderate its effects (Ackerman & Kanfer, 2009), however it is still subjectively experienced. The presence of mental fatigue in the absence of simple RT and RT variability deficits indicates that there are alternative measures of cognitive function which should

be considered to reduce risk of negative outcomes. These results also highlight the possibility that current cognitive assessments used in clinical alcohol treatment settings may not capture this, despite being considered when determining treatment setting (NICE, 2011).

Specifically, with regards to EF, mental fatigue is problematic as it reduces an individual's ability to inhibit a dominant response (Guo et al., 2018), efficiently shift resources between cognitive tasks (van der Linden et al., 2003), plan (van der Linden et al., 2003), replace outdated information in working memory (Pergher et al., 2019), and selectively attend (Faber et al., 2012). This shift in executive control increases the likelihood that decisions will be guided by autonomic 'bottom-up' regulatory processes, rather than 'top-down' cortical control (van der Linden et al., 2003), a shift which increases relapse risk (Duka & Stephens, 2014). Crucially, mental fatigue has also been associated with an increased risk of alcohol problems (Obeid et al., 2020). Furthermore, in the current study, AUD participants whose Fatigue increased by T1 also experienced a reduction in subjective Impulse Control, which may link to the risk of increased 'bottom-up' regulatory processes and the potential consequences (though this interpretation is constrained by the limited reliability of the subscale), and like the previous chapter, highlights the relationship between self-reported experience of inhibitory control and behavioural processing speed measures. That speed-related measurement (choice RT) improved in inpatients during early abstinence is consistent with the previous pilot study (Powell, Tommerdahl, et al., 2021). Perhaps the expectation for those in outpatient settings to continue their daily lives alongside treatment, means they are more likely to cognitively tire during recovery. This may, over time, leave the outpatient group at a higher risk for relapse than they should be, considering their fewer complex needs. At least 50% of the outpatients relapsed, which despite their apparent lower need for support, is similar to the 57% relapse rate in the inpatient sample. Additionally, some of those who relapsed from the outpatient group are likely to eventually develop more complex needs and so might require inpatient treatment in the future. It is also possible that treatment differences (such as higher benzodiazepine dose in the inpatient sample) may explain some of the observed effects. However, this is congruent with the current

conclusions, as the dose was more markedly higher in inpatients than outpatients at T1, which would be expected to continue to impair function in this group, not improve it, as benzodiazepines have similar pharmacological properties to alcohol (Kreuzer et al., 2019) and have also been linked to cognitive deficits (Crowe & Stranks, 2018; Lader, 2014). Future research should seek to examine this relationship further, over a longer time-period, using validated tasks to assess both recovery and predictability (regarding relapse and other relevant outcomes) of function between treatment settings. Results of such work could enable further study into how best to support individuals in each treatment pathway.

There were a number of limitations to the present study. Recruitment and follow-up numbers were lower than planned and anticipated, which meant that using RT to predict relapse, and within-subjects test of RT change across all timepoints, were not possible. The COVID-19 pandemic resulted in busier outpatient clinics (reducing access to testing rooms) and fewer clinical staff resulting in delayed clinics making recruitment less consistent. Furthermore, post-detox appointments were mostly via telephone as standard practice, rather than face-to-face, which was not compatible with the study follow-up procedures. We cannot know how RT would be impaired or improved in those individuals lost to follow-up which limits the scope of the study. Additionally, despite the use of Pillai's Trace to report regression and MANOVA results, the presence of violations is likely to reduce the statistical power of the models. Both poor reliability indicated for the EFI, and lack of a priori sample size calculation limits the strength of the findings. There were also several possible confounding variables that could not be controlled for, such as comorbidities/related medication (Gudayol-Ferré et al., 2022; Marraccini et al., 2016; Nigg et al., 2017). However, controlling these would be difficult, as patients with AUD generally have higher rates of comorbid conditions, particularly mental health conditions (Keaney et al., 2011; Kieres-Salomoński & Wojnar, 2015). Finally, controls were only assessed once meaning that the study could not control for potential practice effects in the AUD group.

6.6 Chapter Summary

This chapter found that choice RT and mental fatigue showed AD-related deficits during early abstinence, the latter of which worsened during early abstinence, driven by change in outpatients rather than inpatients. This increase in mental fatigue related to worsening of subjective inhibitory control. Therefore, individuals in this study performed normally on simple RT and RT variability, whilst still experiencing potentially unpleasant and harmful repercussions of cognitive exertion. This is noteworthy, as someone performing normatively on e.g., the MoCA, might be deemed to lack cognitive impairment and thus not need support. Additionally, that this increase in fatigue was driven by outpatients, indicates that these individuals may be more at risk of experiencing these negative repercussions, perhaps as a result of receiving less support and facing more day-to-day challenges on their treatment pathway.

Chapter 7 : General Discussion

7.1 Thesis Summary

The aim of this thesis was to investigate the relationship between alcohol use and cognitive function, across different levels of use. Three papers have been published so far based on this work. Specifically, this thesis aimed to 1) investigate the impairment and recovery potential of neuropsychological function in AUD, 2) explore the subjective experience of higher-order EF in non-dependent drinkers, and how this relates to real-life problems experienced because of alcohol use, 3) assess processing speed alongside subjective EF in non-dependent drinkers, and 4) examine processing speed change in early recovery in drinkers with AUD, and to compare this to matched controls without AUD.

To achieve this, Chapter 3 (Study 1) systematically reviewed longitudinal studies of neuropsychological recovery upon abstinence in AUD. It was concluded that sub-domains within attention, EF, perception, and memory, generally demonstrate recovery between 6-12 months, though basic processing speed recovers within a month, and working memory updating/tracking as early as 18 days. That EF has such strong connections with outcomes, and that processing speed is a relatively quick and easy function to measure, underpins EF, and demonstrates the ability to change in early recovery (when individuals are at high risk of relapse), supported the use of these as the experimental focus of this thesis. Three empirical studies then followed using various methods to explore cognitive function. Chapter 4 (Study 2) described a survey of alcohol use, related problems, and subjective EF. Subjectively, Organisation, Strategic Planning, Impulse Control and overall function were significantly impaired in hazardous drinkers compared to non-hazardous. Additionally, the effect of alcohol on EF partially mediated the relationship between alcohol use and alcohol-related problems.

Chapter 5 (Study 3) built on these findings by examining vibrotactile processing speed and subjective EF between hazardous and non-hazardous drinkers. Hazardous drinkers were found to be

faster on choice RT, though did again demonstrate poorer subjective Strategic Planning and Impulse Control (like the survey findings). Additionally, an analysis of age-grouped data found that younger hazardous drinkers demonstrated the best simple RT, whilst the poorest choice RT was demonstrated by older non-hazardous drinkers. In the whole sample, subjective Organisation and Impulse Control both positively correlated with choice and simple RT, indicating that as subjective function improved, RT increased (a decline in performance), which was unexpected. Finally, Chapter 6 (Study 4) assessed processing speed within patients with AUD measured at two time-points compared to matched controls. This was originally intended as a longitudinal study, but high attrition meant that a repeated-measures analysis was more suitable. Group (AUD vs control) predicted choice RT at around three days of abstinence and at around seven days, with Fatigue also predicted at seven days, though group did not predict simple RT or RT variability at either time. Fatigue worsened in inpatients between the two times but improved in outpatients. In the whole AUD sample, change in Fatigue negatively correlated with change in subjective Impulse Control, so as mental fatigue increased, subjective control worsened.

7.2 General Discussion of Findings

The systematic review of longitudinal neuropsychological function recovery during abstinence in AUD (Chapter 3) supports previous research regarding impairment (Crowe, 2019; Stavro et al., 2012) and displays some similarities to the Schulte et al. (2014) review of longitudinal recovery. Differential recovery of EFs supports that these are separable abilities (Miyake & Friedman, 2012). Specific findings of impairment and recovery support the 'whole brain' and 'frontal lobe' hypotheses of regional alcohol vulnerability (Oscar-Berman & Marinkovic, 2003). Additionally, with age being a consistent predictor for several functions, this also supports the 'premature aging hypothesis' of age increasing the brain's vulnerability to alcohol (Oscar-Berman & Marinkovic, 2003).

Deficits found in the survey of subjective EF (Chapter 4) support previous findings of EF impairments in hazardous drinkers (Doallo et al., 2014; Houston et al., 2014; Montgomery et al.,

2012; K. W. Smith et al., 2017), and as Impulse Control displayed the largest deficit, supports that there are particular issues with inhibition in individuals who engage in this drinking behaviour (e.g., Lees et al. (2019)). Contrasts with some of the previous literature may be due to the varied age range of this study reducing the impact of possible neurocompensation. Despite limitations of a three factor-grouping of the EFI and of associated suggested functional divisions of the frontal cortex, these findings may indicate particular damage to orbitofrontal and dorsolateral regions of the brain (Spinella, 2005), possibly differentiating from AUD, which typically associates with more widespread damage. Partial mediation of EF on alcohol-related problems indicates that subjective EF impairments associated with alcohol use may somewhat underlie the impact of alcohol on an individual's life.

Following on from this, while findings of subjective deficits in hazardous drinkers in the smaller laboratory study (Chapter 5) were similar to those in Chapter 4, findings of faster processing speed do not support that if hazardous drinking is a precursor to AUD in some cases, the same functional deficits should be seen at a lesser extent (Lees et al., 2019). Although it is unclear why hazardous drinkers were faster, it is possible that recent alcohol use may have lingering effects. Interestingly, there was no speed-accuracy trade-off, indicating perhaps that the task was too easy to elicit this (Scaife & Duka, 2009), or that impulsivity may be adaptive in low-risk scenarios (see Gullo and Dawe (2008)). This study was unclear regarding the premature aging hypothesis; it does not suggest that older adults are most vulnerable to alcohol effects on the brain. This may be due to the young hazardous group experiencing neurocompensation, pre-existing lower inhibitory control, or an adaptive effect of alcohol, which may fade to some extent over time. That better subjective function associated with worse processing speed may imply issues with the subjective EF measure, impaired metacognition, or again a relatively easy task or adaptive aspects of impulsivity.

In Chapter 6, that choice RT and Fatigue demonstrated impairment is consistent with previous processing speed literature (Crowe, 2019; Stavro et al., 2012), and that in the inpatient

sample there was a speed-accuracy trade-off, similarly highlights poorer performance in AUD. However, that simple RT and RT variability were not impaired possibly indicates a uniqueness of this cohort or of the controls. It was unexpected that inpatients would show more of a reduction in mental fatigue compared to outpatients, who worsened between the two times. Indeed, inpatients had higher SADQ-C scores (see Table 14), indicating a higher severity of alcohol dependence, which would be expected to hinder cognitive recovery. Mental fatigue is associated with reduced executive control (Guo et al., 2018; Pergher et al., 2019; van der Linden et al., 2003). A switch to more 'bottom-up' regulatory control does seem possible here, given that AUD participants whose Fatigue increased between the two times, also experienced a reduction in subjective Impulse Control. This indicates that outpatients (who may have higher mental load compared to inpatients) may require more support than currently provided, particularly given that this group had a comparable relapse rate to the more clinically complex inpatients.

One of the consistent threads throughout this thesis is that processing speed tasks requiring more executive control (such as choice RT which requires response inhibition) may be better at highlighting alcohol-related processing speed differences. This suggests that there may be a stronger impact of alcohol on processing speed tasks that also require executive control (and/or, that pre-disposed differences in executive speed tasks may increase an individual's likelihood of riskier alcohol use). Interestingly, in the systematic review, the only processing speed task that still demonstrated impairment compared to 'normal' performance at six months of abstinence was the RVP, arguably a more executive task than simple or choice RT, as it involves aspects of working memory updating/tracking alongside response inhibition. However, it must be noted that in the same sample, a 2-choice RT task (more executive than simple RT, but less so than RVP) did not demonstrate impairment at any time, though the baseline assessment was fairly late at 2-4 weeks of abstinence and so may have been too late to capture impairment.

Taken together, the systematic review and processing speed studies of this thesis seem to indicate that there is some level of executive complexity impact on the recovery duration of processing speed tasks, and that in tasks requiring multiple types of EF (such as RVP in the systematic review), their impact may be additive, which is perhaps more relatable to real-life. Indeed, in the development of their virtual reality 'Jansari assessment of Executive Functions', Jansari et al. (2014) suggested that assessing individual EF is like a conductor listening to individual instruments of an orchestra to decide if they work together, when listening to them in harmony would give a more ecologically sound understanding of ability. Additionally, in their study of a dual working memory updating (N-back) and response inhibition (Flanker) task, Kim et al. (2017) found that increasing the working memory load led to a decrease in both working memory and response inhibition performance, indicating an interaction effect of the two EFs on individual task performance. Furthermore, Finn et al. (1999) suggest that individuals with low working memory capacity are more susceptible to a reduction in inhibitory control due to alcohol.

Relating back to the choice RT results in the two experimental studies, that hazardous drinkers performed better, but dependent drinkers performed worse (slower, and with inpatients demonstrating a speed-accuracy trade-off) is interesting. It implies that any pre-existing speed advantage (or any unexpected effect of hazardous alcohol use), dissipates by the time an individual is drinking at levels requiring treatment for an AUD, including when matched for age and with age as a predictor in the regression model. Furthermore, better choice RT associated with poorer subjective Impulse Control in the general population study, but there was no association between the two measures in the AUD group of the final study, perhaps indicating that lower inhibitory control can be advantageous to performance on speed tasks in low-risk scenarios, but no longer at when a person is drinking at dependent levels.

While choice RT was implicated in hazardous and dependent drinkers as being related to alcohol use, the finding of poor mental fatigue was specific to AUD, indicating that after the initial

few days of treatment, availability of cognitive and neural resources in the face of persistent demand (Borragán et al., 2017; Qi et al., 2019) becomes an issue, particularly in outpatients. That this finding was specific to AUD is not ultimately surprising, given that the process of both developing and being treated from an AUD is likely to be cognitively, physically, and emotionally taxing (Gooden et al., 2023). These individuals therefore likely have a large cognitive demand alongside the tasks, though it should be noted that their lack of difference in RT variability indicates similar attentiveness to controls, so this mental fatigue is unlikely due to distraction. Furthermore, compared to the non-clinical sample in Chapter 5, that Fatigue (rather than choice RT) in AUD associated with Impulse Control, indicates that while subjective inhibition did not link to response inhibitory performance, it is possible that a subjective experience of lowered control may reflect a reduction in mental resources available for cognitive tasks.

Another consistent finding throughout this thesis, is that out of the EFI subscales, Impulse Control was implicated in each assessment as being most sensitive to alcohol. This is consistent with previous research which suggests that of the EF, inhibitory control is particularly likely to be both damaged by alcohol use, and a risk factor for problematic drinking, with the relationship suggested to be cyclical (Koob, 2013; López-Caneda et al., 2013). It also supports the notion that self-reported function is important to measure and captures impairment that is possibly more meaningful to the individual, particularly given that they are aware of it, and that it relates to self-reported drinking. Indeed, a recent study by Satyal et al. (2023) found that self-reported EF (measured by the Executive Skills Questionnaire; Dawson and Guare (2010)) positively associates with self-reported engagement in health behaviours in AUD and other SUD, strengthening the argument that self-report is an ecologically valid method of EF assessment, as it reflects and relates to various aspects day-to-day experience, and may be a method via which to support recovery and wellbeing across related domains. That self-reported inhibitory control consistently related to behavioural processing speed measures (Chapters 5 and 6), but has previously demonstrated low association with behavioural inhibitory control tasks (Caswell et al., 2015), is interesting. Perhaps indicating that as a basic, task-

independent construct, processing speed is a more ecologically valid comparator for subjective function, compared to the fractionated EF tasks which may have little relationship to day-to-day experience of integrated function (Burgess, 2004).

Regarding covariates across the studies, of all that were measured, age was the most consistently implicated, with it highlighted as a predictor of several functions (including processing speed) in the systematic review of neuropsychological recovery in AUD (alongside smoking status and premorbid verbal intelligence), a covariate of subjective function in the Chapter 4 study of non-clinical drinkers (together with gender and mood state) as well as a predictor of alcohol-related problems (along with mood state, and subjective Impulse Control and Organisation), a covariate of processing speed (alongside gender) and subjective function (alongside mood state) in non-clinical drinkers in Chapter 5, and a predictor of processing speed (all measures) in the whole sample of controls and AUD at T1 in Chapter 6.

Whilst the implications of these findings are not obviously consistent (specifically that older non-hazardous drinkers performed the poorest on choice RT in Chapter 5), and the thesis was not designed to examine them, they are interesting, particularly in relation to both the premature aging hypothesis (Ellis & Oscar-Berman, 1989; Oscar-Berman & Marinkovic, 2003), and the Salthouse (1996) theory that age-related decline processing speed underpins decline in EF in older adults. This is especially important when it is considered that this decline may be a mechanism leading to EF deficits in AUD (Glass et al., 1999), perhaps even via increased vulnerability of the brain to age in AUD. The current thesis did not directly assess this, though it did find that age was related to poorer subjective EF in hazardous drinkers, in the expected direction (in Chapters 4 and 5). However, that in Chapter 6 increased age predicted poorer performance in all speed measures across the whole sample, does imply at least the right direction for such a possibility (and supports the vulnerability element of the premature aging hypothesis), though comments on how this seeming age-related decline in processing speed relates to EF, or how this may be more pronounced in AUD, cannot be

made here as these possibilities were not assessed/analysed. Future research could be designed more specifically to examine this, as it may shed light on potential treatment or support routes.

7.3 Methodological Strengths and Limitations

There are several strengths of the methods employed in this thesis. Regarding the systematic review (Chapter 3) reliability of screening and quality assessment was checked with co-authors, and most studies included were judged to be of good quality, while of those that were moderate or poor, most were only used as supplementary data on improvement (rather than recovery) due to not comparing AUD performance to that of controls or normative data. Furthermore, the review grouped tasks under multiple functions, allowing for the consideration that many tasks involve more than one (Schulte et al., 2014). In addition, the review protocol was both pre-registered on PROSPERO and published prior to commencement, enabling for the incorporation of peer-review into its process. Therefore, the review considered and limited bias where possible, and in comparison to a literature review, has the ability to assess a broader array of literature, and to contribute new knowledge to it (Higgins et al., 2022; Mallett et al., 2012).

In Chapter 4, the survey of subjective EF in hazardous and non-hazardous drinkers, a large number of participants (n = 666) from multiple countries increases the generalisability of the findings (though most participants were from the 'Western World', limiting this somewhat), while the use of online, self-report tools, may have limited the likelihood that participants would display social desirability bias (Chang & Krosnick, 2009; Kiesler & Sproull, 1986; Richman et al., 1999; Turner et al., 1998), particularly given that the questions in the APQ involve socially 'undesirable' behaviours. Additionally, the survey duration was purposefully kept relatively short (around 15-20 minutes), increasing the likelihood that individuals would remain attentive throughout, and therefore the reliability of their responses.

The methods in Chapters 5 and 6 were relatively novel, in that they used vibrotactile perception to assess processing speed, rather than the more frequently used visual or auditory

stimuli, because of previous findings that this increases RT accuracy and reduces variability (Holden et al., 2019). Furthermore, relating to Chapter 6, the recommended tool (MMSE) for routine cognitive screening in AUD is not sensitive to frontal lobe dysfunction, while other suggested tools show an educational bias (Carnero-Pardo, 2014), which may be less likely due to the nature of the BG stimuli (not being verbal or written letters, numbers, or words).

However, no piece of research is without limitations, and this is true of the current thesis. In Chapter 3, synthesis conclusions regarding planning, verbal fluency, and verbal function, must all be interpreted with caution, due to fewer studies and poor study quality, though synthesis of the other functions remains relatively robust. Furthermore, due to methodologies of the studies included, it was not possible to rule out practice effects regarding improvement in functions. In Chapters 4, 5, and 6, that individuals were recruited by self-selection increases the risk of self-selection bias, possibly creating less representative samples (offset somewhat by the large sample size in Chapter 4) or exaggerated findings (Bethlehem, 2010), while alcohol-related questions such as on the AUDIT or SADQ-C may have introduced social desirability bias (Northcote & Livingston, 2011). Additionally, in all of these studies, time of testing was not controlled for, which may have impacted cognitive function (Valdez, 2019). Appointment time and treatment activities dictated when testing could occur in Chapter 6, and although roughly equal numbers of hazardous (26%) and non-hazardous (29%) drinkers were tested in the morning vs. afternoon in Chapter 5, individual circadian rhythms may still have impacted results (perhaps less likely in Chapter 4, when individuals would have been able to complete the questionnaire at whatever time they wanted). Furthermore, in Chapter 4, cognitive function was assessed using self-report only, which may reduce validity, for a variety of reasons, including alcohol-induced deficits in metacognition (Le Berre et al., 2017), or other uncontrolled confounds, though the author still believes it is important to examine the subjective experience of such functions, even if it is not reflected in performance. Additionally, in Chapter 5, the choice RT task may have been too simple to induce speed-accuracy deficits (Scaife & Duka, 2009) at that level of alcohol use, reducing the validity of the conclusions, and though speculation about

the neurotransmitters and pre-existing lower inhibitory control in hazardous drinkers is interesting, neither were actually measured, and so cannot be relied upon as explanations for the findings. Chapters 4 and 5 also did not assess different patterns of hazardous drinking, which may affect results (Maurage et al., 2012).

Additionally, that the study in Chapter 4 was conducted at the height of the COVID-19 pandemic (during the first UK lockdown), may have induced changes in participant drinking behaviours (Alcohol Change UK, 2020; Global Drugs Survey, 2020; Institute of Alcohol Studies, 2020). However, Alcohol Change UK (2020) found that an increase in alcohol consumption occurred primarily in those who already drank heavily, and this combined with the AUDIT questions relating to the prior 12 months, should have increased the stability of the alcohol groups created. The studies in Chapters 4 and 5 were also both purely cross-sectional, which means that they were unable to assess causal relationships between alcohol and cognitive function (Barnett & Hyman, 2006), and without the examination of certain confounding variables in Chapters 4, 5, and 6 (such as smoking or premorbid intelligence, as highlighted in Durazzo et al. (2014), or benzodiazepine dose during detox), this relationship again becomes less clear. However, regarding benzodiazepines, these are used in the majority of alcohol detoxes, and so to avoid testing during this time, in the author's opinion, misses a legitimate and important shared aspect of alcohol treatment. Furthermore Petit et al. (2017) found that benzodiazepine dose did not impact their results on cognitive recovery at day one or day 18 of treatment. We did not include an a priori power analysis in Chapters 5 and 6 which reduces the dependability of the findings reported.

Unfortunately, while the research in Chapter 6 was designed to measure longitudinal relationships up to around seven months of abstinence, methodological issues resulting from the COVID-19 pandemic meant that this became impossible (see section 1.6.1), largely due to high attrition beyond the first follow-up in very early abstinence. As a result, the intended analyses of cognitive function recovery in abstinence from AUD, and of the predictive ability of initial

performance regarding relapse risk, were not feasible, weakening the study design. Furthermore, largely because of COVID-19, but also due to limited resources, despite having used the systematic review to ascertain the limitations of the current literature, this study has not managed to address several of these, including objective confirmation of abstinence, a short duration of follow-up (rather than six months or more), and control for attrition (due to such high rates). This sadly increases the risk of bias with regards to individual results.

Additionally, despite consideration having been given during the design of research in Chapter 6 to the compensation given to AUD participants (£10 vouchers, which was limited due to financial restraints), with hindsight, this may also have affected attrition, as it is a relatively small amount, given that participants were asked to attend multiple testing sessions (even with the researcher meeting them after their clinical appointment or at locations local to the participant). Indeed, during the PhD process, the author went to a session at the Society for the Study of Addiction 2022 PhD Symposium titled "Impact, inclusivity, and involvement in addictions research", in which Dr Magdalena Harris made the impassioned argument that substance users should be paid more for their participation in research. She highlighted that unfair payment could be seen as exploiting a vulnerable group (who are more likely to struggle financially), even though their willingness to participate is crucial to the sector, so their compensation should reflect this. She also argued that payments should be made in cash, as vouchers have more restrictions and so are worth less than their face value, and that it is disempowering to participants to imagine that not giving fair compensation in cash somehow protects them from the harms of substances/alcohol, or that it is the researcher's decision what they spend that money on. Therefore, in future, the author intends to give fairer compensation to participants, and if possible (depending on institutional restrictions), in cash.

Throughout all three experimental studies, the EFI was used as a self-report measure of EF, with Impulse Control in particular being highlighted as relating to alcohol use. However, despite this

consistency, and the EFI being a validated measure (Miley & Spinella, 2006; Spinella, 2005), in this thesis the Cronbach's α for the subscales were consistently low, limiting the validity of the analyses and conclusions that included these. This is unfortunate, as the consistency of the findings suggest that something measured by this scale is related to alcohol use, but the low reliability makes it hard to ascertain with certainty that this is impulse control. Indeed, despite claims of ecological validity, and research showing predictability of self-report EF tools (Roth et al., 2013), there is also the suggestion that such tools measure entirely different constructs to objective behavioural tasks (Allom et al., 2016), which further complicates the interpretation of this thesis.

Additionally, that simple RT and RT variability were not impaired in AUD reduces certainty that the BG is able to capture alcohol-related differences, which is interesting as it has a favourable evidence base regarding discrimination of other types of injury, such as mild traumatic brain injury (mTBI) (Favorov et al., 2019; Tommerdahl et al., 2022). However, an independent study by Ivins et al. (2022), did not find expected results regarding classification of acute mTBI, and presented some important criticisms of the tool. These were namely that normative data is not published, and neither is a clear description of task scoring or procedure for researchers to follow, particularly regarding BG outliers and invalid performance, all of which are important to ensure valid use and interpretation of the tool within research. The authors concluded that the BG may attain a good level of clinical utility if these issues are addressed, so it is hoped by the current author that they will be, as this will also improve its research utility.

7.4 Future Research Implications

There are various directions for future research that arise from this thesis. Findings of Chapter 3 suggest that future research into neuropsychological recovery from AUD should consider the impacts of age, premorbid intelligence, smoking, education, brain volume, number of previous treatments, and drinking behaviour of those close to the individual, as all were identified as predictors (Durazzo et al., 2014; Loeber et al., 2010; McCutcheon et al., 2016), so could explain some

of the variance identified across the literature. Large scale prospective studies are also needed to understand what functional differences compared to controls may be pre-existing, and how this may be cyclical, as some are likely to have causal relationships with AUD (Koob, 2013; López-Caneda et al., 2013). Interestingly, in the RVP task, which required a combination of multiple executive or executive and reasoning abilities, initial and continued impairment was more likely than tasks that were more function specific. This indicates that to capture impairment, the additive nature of task requirements should be considered in future research, particularly as day-to-day demands are likely to be competing for cognitive resource in this way. This also relates to findings in Chapter 6 that choice RT was better able to capture impairment than simple RT in AUD. Future research using a range of tasks in AUD recovery could assess the impact of task difficulty on recovery of function, and directly compare the utility of tactile (such as BG) versus visual or auditory stimuli in measuring impairment and recovery of processing speed in AUD, as previous findings of higher accuracy for tactile stimuli (Holden et al., 2019) may be less replicable in alcohol use contexts, e.g., due to nerve damage in the extremities (though this is not typical of all AUD patients, and usually occurs in the feet, Chopra and Tiwari (2012)). Differences in cognitive deficit and recovery in AUD between inpatient and outpatient settings should also be further explored, as should the most appropriate way to capture this, the implications of disparities, and methods to address these. Furthermore, as stated in the systematic review, to reduce bias in the literature on cognitive recovery from AUD, future studies should use control groups, use additional methods to self-report to confirm abstinence, assess function for over six months of abstinence, describe and control for attrition, and statistically control for confounds.

The finding that subjective EF is impaired in hazardous drinkers and AUD is relatively novel, and therefore should be examined further, perhaps using a different tool (such as BRIEF-A; Roth et al. (2005)) alongside task-based EF and processing speed methods to validate findings, due to the low Cronbach's α in the current thesis. The relationships between self-reported EF, behavioural EF, and processing speed could additionally be examined. This would give further insight into whether a

task-independent construct such as processing speed has more relevance to day-to-day experience than a fractionated assessment of an integrated EF system, which has been a previous criticism of behavioural EF measures (Burgess, 2004). Scale reliability of the EFI could also be re-examined and improved, as it is a relatively short tool so could have utility in the general and AUD population. It would also be interesting to consider whether there are methods that could be used to assess whether subjective EF provides an indication of neurocompensation, where more effort may be used to ensure task performance is 'normal' (Almeida-Antunes et al., 2021; Gil-Hernandez et al., 2017; Susan F Tapert et al., 2004), and to observe whether the impairments observed, which according to Spinella (2005), indicate possible damage to the orbitofrontal and dorsolateral regions, actually relate to these areas. Additionally, the use of neuroimaging during processing speed assessment, would help clarify whether fast performance in hazardous drinkers could be due to neurocompensation. Longitudinal research examining subjective EF, task-based EF, and processing speed would be useful in clarifying the predictive nature of the current findings in hazardous drinkers regarding the development of AUD, and also the recovery of subjective function if alcohol use is reduced.

Regarding the finding in Chapter 4 that alcohol-related problems were mediated by subjective EF in hazardous drinkers, it would be interesting for future research to examine which specific EF (subjective and/or task-based) show stronger relationships with these problems, and if there are certain problem areas (e.g., legal, financial, physical, psychological, or social) that are implicated. Researchers could then go on to consider whether EF training or other interventions could utilise this relationship to improve wellbeing, as research has shown EFs can be improved via intervention (Diamond & Ling, 2016), and EF training has successfully reduced alcohol consumption in hazardous drinkers (Houben et al., 2012; Houben, Nederkoorn, et al., 2011; Houben, Wiers, et al., 2011). Furthermore, all future research that investigates cognitive function in hazardous drinking could consider different patterns of drinking that fall into this category, such as HED versus daily

drinking, as Maurage et al. (2012) found that there may be differences in the way the brain responds to these.

Hazardous drinkers were faster on the choice RT task in Chapter 5, which could be further investigated using a range of processing speed tasks to ascertain whether performance is worsened by a speed-accuracy trade-off when requirements are more executive (Scaife & Duka, 2009). Both subjective EF and processing speed should also be compared to validated EF tasks, to further knowledge of these relationships in this context, and to assess the possibility of metacognitive deficits. Additionally, using structural methods linked to neural transmission speed, such as those assessing myelination (via recent myelin magnetic resonance imaging techniques (van der Weijden et al., 2021) or indirectly through diffusion tensor imaging (Aung et al., 2013; Song et al., 2002)), or functional methods that assess temporal information about neural processes, such as ERP, or neurotransmitter activity, such as positron emission tomography, may ascertain if any speeded processing effects of hazardous drinkers can be explained as a result of these. Likewise, results relating to age across the studies indicate that examination of the relationship between age-related processing speed decline and performance on validated EF tasks, comparing this across patterns of drinking behaviour in non-clinical groups, and also to individuals with AUD, would be useful.

Finally, alongside those already discussed, future research suggestions resulting specifically from Chapter 6, include further assessment of recovery of function (subjective and objective EF, alongside processing speed) between treatment settings, the implications of this (relating to both relapse and other wellbeing indicators), over a longer period, and consider methods to support those who demonstrate poorer recovery, and to facilitate positive outcomes in each treatment pathway.

7.4.1 Implications for Policy and Practice

The current findings have implications beyond academia. Indeed, government bodies must consider additional strategies to address alcohol harm. Chapter 4 found that even in non-clinical

hazardous drinkers, subjective EF was poorer (specifically in ability to plan/use strategies, self-inhibit, and to hold information in mind or multitask), implying that alcohol-related harm is still subjectively experienced at this level. Additionally, this subjective experience partially mediated alcohol-related harm indicating that these deficits decrease quality of life in several domains. Furthermore, in Chapter 5 these subjective deficits were again observed, even when processing speed was not poorer, suggesting that subjective experience is not always reflected outwardly in task performance (even if it may impact day-to-day life quality).

Current NICE guidelines, which are mentioned in the UK government alcohol policy aimed at health professionals (Office for Health Improvement and Disparities, 2022) recommend assessing cognitive function in AUD (NICE, 2011) but this is not recommended in individuals indicated to be hazardous alcohol users (in their AUD prevention guide, NICE (2010)). This seems counterproductive given the body of evidence that not only may function be harmed by alcohol at this level but may also contribute to drinking behaviour (and ultimately to overall wellbeing), thereby missing the chance to give advice and support on these areas depending on individual need.

Regarding AUD, the current findings indicate that individuals not diagnosed with an ARBI still experience both subjective and objective performance differences compared to controls, which have previously indicated to enhance relapse risk, even though these individuals may not have been indicated to require further cognitive testing beyond admission, according to NICE (2011). This finding indicates that more extensive and ongoing cognitive assessment should be the norm during treatment, as it seems that certain elements of functional deficits are not currently being identified, despite the possible implications of these deficits. While this thesis is not conclusive regarding the utility of the BG within this setting, consideration should be given to whether current cognitive testing is adequate, or whether another tool, or combination of tools, should be used to capture potentially outcome-relevant impairment.

Furthermore, outpatients' worsening mental fatigue during early treatment is concerning, as it indicates that policymakers and healthcare providers should consider whether the level of support received by these individuals is adequate, given the additional day-to-day stressors they may experience alongside treatment, and that this could theoretically increase relapse risk. Additionally, while this was not a qualitative investigation, most individuals who took part in the research, both inpatient and outpatient, described their distress at a lack of integrated mental health support alongside AUD treatment, which could contribute to cognitive demand, and ultimately to relapse risk. Clearly, reductions in local authority funding for substance and alcohol treatment services across England and Wales since the Health and Social Care Act 2012 transferred the budget from the NHS to these local authorities (Roscoe et al., 2021) will have reduced the ability of healthcare providers to address these problems. However, given that a recent government press release promises an extra £421 million in government funding through to 2025 for this sector, with local authority funding set to increase 40% (Department of Health and Social Care, 2023), the author hopes this will change.

Finally, the author experienced significant difficulty whilst accessing and then combining data received from the two NHS trusts accessed in Chapter 6, indicating a need for standardised reporting of important characteristics within and across trusts (comorbidities, AUDIT/SADQ-C scores, withdrawal symptoms, number of previous treatments, relapse etc.), which ideally need to be easily accessible without requiring staff to read back through the entirety of a patient's relevant history at the trust. Additionally, both trusts typically only had access to information recorded while under their care, surely reducing the ability of clinical staff to adequately assess their relapse (or even mortality) risk and undermining the research data collection process.

7.5 Conclusions

This thesis aimed to explore alcohol use and cognitive function, in both general population drinkers and in AUD. Systematic review results revealed that several functions indicate recovery

within the first year of abstinence, but that there are methodological issues within the literature that limit the certainty of these findings. Of particular interest to this thesis was the finding that EF recovered differentially, supporting their being separable functions, and that basic processing speed recovered within a month, suggesting that it is a useful function to study regarding individual differences and relapse risk during this vulnerable stage. Subjective EF was found to be impaired in hazardous drinkers (in both Chapter 4 and 6), despite their quicker processing speed in Chapter 4. This suggests that even if task performance is not impaired, there are still subjective harms being experienced, which need addressing and further examination. Furthermore, it suggests that 'poor impulse control' may not always be outwardly disadvantageous, particularly in low-risk scenarios. Finally, in individuals receiving treatment for AUD, performance on the more executive choice RT task remained impaired versus controls at around 3 and 7 days of abstinence, while simple RT and RT variability displayed no impairment at either time, suggesting that the more executive task is more able to capture impairment in this group. Fatigue was indicated at 7 days of abstinence, suggesting a toll of treatment on cognitive resources, which was driven by worsening mental fatigue in outpatients, implying a need for greater support for these individuals. Consequently, these results are relatively hopeful regarding recovery of function over long-term abstinence in AUD but suggest that more needs to be done to protect hazardous drinkers from experiencing cognitive harm, and to support individuals treated via outpatient clinics, who must maintain their day-to-day behaviours alongside treatment. Regarding assessment of processing speed via vibrotactile methods, more work needs undertaking to compare this to other modalities when examining alcohol-related differences.

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Appendices

Appendix 1: Systematic Review Search Strategy

Recovery of neuropsychological function following abstinence from alcohol in adults diagnosed with an Alcohol Use Disorder: Protocol for a systematic review of longitudinal studies

Anna Powell, Harry Sumnall, Jessica Smith, Rebecca Kuiper, Catharine Montgomery

Systematic search strategies for APA PsycInfo, EBSCO MEDLINE, CINAHL, and Web of Science

Source(s)	**Search Strategy**
APA PsycInfo, accessed via https://www.proquest.com/	i #1 ab(alcoholism OR alcoholic*) ii #2 ab(alcohol OR drinking) AND ab(abus* OR addict* OR dependen* OR disorder* OR harmful) iii #3 #1 OR #2 iv #4 ab(recover* OR abstinen* OR sober OR treatment) v #5 #3 AND #4 vi #6 (cogniti* OR neuropsycholog*OR executive) vii #7 ti(learning OR attention OR orientation OR switching OR shifting OR updating OR flexibility OR initiating OR motor OR planning OR “problem solving” OR “functional ability” OR “decision making” OR “time manag*” OR inhibit* OR monitor* OR “goal directed” OR “mental process*” OR memory OR dysexecutive OR intelligence OR IQ OR gait OR posture OR balance OR propriocept* OR “emotional function*” OR “emotion recognition” OR “emotional processing” OR language OR sensory OR perception OR vibrotactile OR visuospatial OR spatial OR "reaction time" OR "processing speed" OR "temporal order judgement" OR "amplitude discrimination" OR "duration discrimination" OR coordination) viii #8 #6 OR #7 ix #9 #5 AND #8 x #10 ab(cohort OR prospective OR longitudinal OR “follow up*” OR retrospective OR “repeated measures” or timepoin* or “time poin*”)) xi #11 #9 AND #10 xii Filters – 1999-2022

MEDLINE (EBSCO) and **CINAHL**, accessed separately via https://web.a.ebscohost.com	i S1 (MH “Alcohol-Related Disorders+”) ii S2 (MH “Alcoholism”) iii S3 AB (alcohol OR drinking) iv S4 AB (abus* OR addict* OR dependen* OR disorder* OR harmful) v S5 S3 AND S4 vi S6 S1 OR S2 OR S5 vii S7 AB recover* OR abstinen* OR sober OR treatment viii S8 S6 AND S7 ix S9 (MH “Cognition Disorders+”) x S10 (MH “Cognition+”) xi S11 TX (cogniti* OR neuropsycholog*OR executive) xii S12 TI learning OR attention OR orientation OR switching OR shifting OR updating OR flexibility OR initiating OR motor OR planning OR “problem solving” OR “functional ability” OR “decision making” OR “time manag*” OR inhibit* OR monitor* OR “goal directed” OR “mental process*” OR memory OR dysexecutive OR intelligence OR IQ OR gait OR posture OR balance OR propriocept* OR “emotional function*” OR “emotion recognition” OR “emotional processing” OR language OR sensory OR perception OR vibrotactile OR visuospatial OR spatial OR "reaction time" OR "processing speed" OR "temporal order judgement" OR "amplitude discrimination" OR "duration discrimination" OR coordination xiii S13 (MH “Task Performance and Analysis+”) xiv S14 (MH “Psychological Tests+”) xv S15 S9 OR S10 OR S11 OR S12 OR S13 OR S14 xvi S16 S8 AND S15 xvii S17 AB cohort OR prospective OR longitudinal OR “follow up*” OR retrospective OR “repeated measures” OR 2timepoint* OR “time poin*” xviii S18 S16 AND S17 xix Filters – 1999-2022, middle aged: 45-64 years, adult: 19-44 years, adult: 19+ years, adolescent: 13-18 years, young adult: 19-24 years
Web of Science Core Collection; accessed via https://www.webofscience.com/wos/	i #1 AB=(alcoholism OR alcoholic*) ii #2 AB=(alcohol OR drinking) iii #3 AB=(abus* OR addict* OR dependen* OR disorder* OR harmful) iv #4 #2 AND #3 v #5 #1 OR #4 vi #6 AB=(recover* OR abstinen* OR sober OR treatment)

	vii #7 #5 AND #6 viii #8 ALL=(cogniti* OR neuropsycholog*OR executive) ix #9 TI=(learning OR attention OR orientation OR switching OR shifting OR updating OR flexibility OR initiating OR motor OR planning OR “problem solving” OR “functional ability” OR “decision making” OR “time manag*” OR inhibit* OR monitor* OR “goal directed” OR “mental process*” OR memory OR dysexecutive OR intelligence OR IQ OR gait OR posture OR balance OR propriocept* OR “emotional function*” OR “emotion recognition” OR “emotional processing” OR language OR sensory OR perception OR vibrotactile OR visuospatial OR spatial OR "reaction time" OR "processing speed" OR "temporal order judgement" OR "amplitude discrimination" OR "duration discrimination" OR coordination) x #10 #8 OR #9 xi #11 #7 AND #10 xii #12 AB=(cohort OR prospective OR longitudinal OR “follow up*” OR retrospective OR “repeated measures” or timepoin* “time poin*”) xiii #13 #10 AND #12 xiv Filters – 2022 OR 2021 OR 2020 OR 2019 OR 2018 OR 2017 OR 2016 OR 2015 OR 2014 OR 2012 OR 2011 OR 2009 OR 2010 OR 2008 OR 2007 OR 2006 OR 2005 OR 2004 OR 2003 OR 2002 OR 2001 OR 2000 OR 1999

Appendix 2: Systematic Review Data Extraction Form

Recovery of neuropsychological function following abstinence from alcohol in adults diagnosed with an Alcohol Use Disorder: Protocol for a systematic review of longitudinal studies

Anna Powell, Harry Sumnall, Jessica Smith, Rebecca Kuiper, Catharine Montgomery

Data extraction form

Note: where information is not available, highlight form description (e.g., age range) for clarity in deciding if correspondence with author required.

1. General Information	
Record title *First few characters of primary study author's name*	
Person extracting	
Date *Of study publication*	
Study Title	
Authors *Including lead author contact details*	
Study funding source	
Possible conflicts of interest	

2. Study method/characteristics	
Design *Cohort – prospective or retrospective*	
Setting *May refer to hospital/community, inpatient/outpatient, rural/urban etc.*	
Location *Country and region* *AP to check WHO region and related economic status at the time of study*	
Participants *Sample size (and how calculated/justified), age (range; mean), gender (male n, %; female n, %), sample size (at each time point), any other relevant characteristics*	

Exposure(s) *Exact alcohol diagnosis and tool used: DSM-5 AUD (mild/moderate/severe) DSM-4 alcohol dependence vs abuse ICD-10/11 dependence vs harmful use. If available - length of diagnosis, no. treatment attempts, age of first drink, details of alcohol use (type/frequency/intensity/duration), and length of abstinence at each time point*	
Co-morbidities *Study cannot be defined by co-morbidities (e.g., all patients have both AUD and ADHD), but if any co-morbidities are reported in the sample, state these*	
Other reported substance use *Again, study cannot be defined by this, but note if any reported in the sample, and whether current or past*	
Comparison group *Are these non-AUD controls, individuals with different AUD severity, or with different lengths of abstinence? Age, gender, country/location, sample size (at each time point), diagnosis, other relevant characteristics, how many times tested, how chosen, were they matched?*	
Recruitment procedures *Including inclusion/exclusion criteria*	
Details of administration *Any details on the duration of the study, timeline of assessment (initial assessment, follow-ups), follow-up methods and any other details of them. Specify whether each follow-up before, during, or after active AUD, and any relapse details.*	
Details of participants leaving study at each time-point *Characteristics of those who left via attrition, or exclusion by the research team/clinical staff (and details given)*	

3. Primary Outcome (dependent variable)	

4. Secondary Aims	
Did paper assess predictors of neuropsychological function recovery?	
If so what, and how measured/classified? *Some possible predictors might be AUD severity/duration, treatment attempts/adherence, age of first drink, mood disorders etc.*	
What were the findings? *Description for result at each available time point, effect sizes, p values, confidence intervals, statistical techniques used, describe adjustments for confounding factors and attrition.*	

5. Quality Assessment	
JBI Cohort Study Checklist score	

6. Extra Information	
Does the study directly address the review objective?	
Reviewer comments *Any extra details. If uncertain about any elements and want discussion, mention here, and highlight*	
Is correspondence needed for further study information? *What and from whom?* *Give date requested*	
Correspondence received? *What/when/from whom* *If not received within a month, and the details are key, exclude.*	

PLOS ONE

STUDY PROTOCOL

Recovery of neuropsychological function following abstinence from alcohol in adults diagnosed with an alcohol use disorder: Protocol for a systematic review of longitudinal studies

Anna Powell[1,2☯*], **Harry Sumnall**[2,3☯], **Jessica Smith**[2,3‡], **Rebecca Kuiper**[1,2‡], **Catharine Montgomery**[1,2☯]

1 Faculty of Health, School of Psychology, Liverpool John Moores University, Liverpool, United Kingdom, **2** Liverpool Centre for Alcohol Research, University of Liverpool, Liverpool, United Kingdom, **3** Faculty of Health, Public Health Institute, Liverpool John Moores University, Liverpool, United Kingdom

☯ These authors contributed equally to this work.
‡ These authors also contributed equally to this work.
* a.powell@2019.ljmu.ac.uk

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Abstract

Background

Alcohol use disorders (AUD) associate with structural and functional brain differences, including impairments in neuropsychological functions; however, review level research (largely cross-sectional) is inconsistent with regards to recovery of such functions following abstinence. Such recovery is important, as these impairments associate with treatment outcomes and quality of life.

Objective(s)

To assess neuropsychological function recovery following abstinence in individuals with a clinical AUD diagnosis. The secondary objective is to assess predictors of neuropsychological recovery in AUD.

Methods

Four electronic databases (APA PsycInfo, EBSCO MEDLINE, CINAHL, Web of Science Core Collection) will be searched between 1999–2022, with search strategies adapted for each source. Study reporting will follow the Joanna Briggs Institute (JBI) Manual for Evidence Synthesis, study quality will be assessed using the JBI Checklist for Cohort Studies. Eligible studies are those with a longitudinal design that assessed neuropsychological recovery following abstinence from alcohol in adults with a clinical diagnosis of AUD. Studies will be excluded if participant group is defined by another or co-morbid condition/injury, or by relapse.

relevant data from this study will be made available upon study completion.

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Competing interests: The authors have declared that no competing interests exist.

Results

This is an ongoing review. As of July 2022, the review protocol is registered on PROSPERO (CRD42022308686), searches have been conducted, and screening is in progress. Results are predicted to be complete by October 2022.

Conclusions

Comparing data on neuropsychological recovery from AUD will improve understanding of the impact of alcohol on the brain, and the relationship between AUD recovery and quality of life/treatment outcomes. It may provide information that could one day inform aspects of treatment and aftercare (e.g., options for cognitive training of functions that do not improve on their own).

Introduction

Globally, alcohol is the seventh leading risk for death and disability, with all-cause mortality risk rising with consumption [1]. Adult per-capita alcohol consumption has been increasing since 1990, and trends are predicted to rise until 2030 [2]. Furthermore, 5.1% of all individuals aged 15+ are estimated to have an alcohol use disorder (AUD), though this differs by WHO region (European (8.8%), Americas (8.2%), Western Pacific (4.7%), African (3.7), Eastern Mediterranean (0.8%)) [3]. AUD describes continued alcohol use despite negative consequences [4,5]. Prolonged use can be neurotoxic, possibly via neuronal loss through disrupting neurogenesis, oxidative stress, or glutamate excitotoxicity [6]. Thiamine deficiency causes indirect damage [7]. A diagnosis occurring more in AUD than the general population is alcohol-related brain injury (ARBI), affecting an estimated 35%, though not all will be diagnosed [8]. ARBI is an umbrella term for major neurocognitive disorders caused by drinking [9]. There is a lack of consensus on which conditions are ARBI, though it generally includes Wernicke's encephalopathy, Korsakoff's Syndrome (usually preceded by Wernicke's [10], together Wernicke-Korsakoff's Syndrome), and alcohol related dementia [9].

While not everyone with an AUD is diagnosed with an ARBI, there is review level research linking uncomplicated AUD with brain differences, though this seems more pronounced in diagnosed ARBI [11]. Brain differences in AUD occur across structure and function, including within neurotransmitter and metabolic systems [11], grey and white matter [11–16], and event-related potential markers of attentional capacity [17].

Furthermore, a variety of neuropsychological functions are impaired in AUD, including inhibition, set-shifting, working memory, problem solving, planning, attention, reasoning/abstraction, processing speed, visuospatial abilities, verbal memory, verbal learning, verbal fluency, visual memory, visual learning, intelligence [18–20]. Other deficits include social cognition, such as Theory of Mind [21,22], and facial emotion recognition [21,23]. The severity of the latter associates with alcohol use duration and depressive symptoms [21]. Fauth-Bühler and Kiefer [24] found reduced brain response to emotional stimuli (particularly in limbic regions).

Consequently, AUD is associated with multiple neuropsychological impairments (though most of this literature is cross-sectional, so cannot exclude pre-existing differences), it is important to understand whether these can recover with abstinence. A prospective review [25] consistent improved sustained attention, but inconsistencies for attention, memory, working

memory, executive functions, and processing speed. Poorer baseline performance, number of detoxifications, family history, and smoking were all moderating factors for neurocognitive recovery.

Two methodologically similar meta-analyses across varying levels of abstinence by Stavro, Pelletier [19] and Crowe [18], found conflicting results. While both indicated impairment across all functions tested (except IQ in Stavro, Pelletier [19]), one found recovery of all domains (inhibition not included as too few papers) by a year of abstinence [19], while Crowe [18] found a wide variety of persisting impairments at all three time periods, including after a year (particularly visual/verbal memory, executive functioning, processing speed, and verbal learning, and except working memory).

Therefore, while there is support for recovery of neuropsychological functions with abstinence, evidence is inconsistent, and there are methodological issues. Firstly, the studies included in Crowe [18], Stavro, Pelletier [19] were largely cross-sectional, limiting conclusions about causality [26]. Secondly, the most suitable review is Schulte, Cousijn [25], as it included only longitudinal studies with controls (with many papers having tested controls at least twice, reducing impact of AUD practice effects), however this still found inconsistent results.

The proposed systematic review specifically aims to investigate recovery of neuropsychological function following abstinence in AUD, addressing the limitations discussed above. This research is important, because a) functional impairments in AUD can reduce a person's quality of life [27], and b) these impairments are linked to treatment outcomes [28], so how they recover may inform methods to support individuals through AUD recovery.

Objective(s)

To assess neuropsychological function recovery following abstinence in individuals with a clinical AUD diagnosis. The secondary objective is to assess predictors of neuropsychological recovery in AUD.

Methods

Protocol

The protocol used the Joanna Briggs Institute (JBI; [29]) Manual for Evidence Synthesis, and PRESS [30]/ PRISMA-P checklists ([31]).

Eligibility criteria

Population

Adults with a clinical diagnosis of AUD and in recovery (abstinent at least two weeks [25]) for at least the first recovery time point). Overall mean age shall be 18–64 years at baseline, as alcohol use, related risk, and brain structure/function change across lifespan, but this is likely most pronounced in young people (aged < 18) and older adults (aged >64) thus reducing comparability [32–35]. It is likely that many people (indeed likely the majority) in a clinical sample being treated for AUD will also use other substances [36,37], therefore if participants are reported as consuming other substances, to be included, a study cannot be defined by this and alcohol must be the primary (a study will not be included if it specifically recruits individuals with AUD who also use other substances). An SUD that is particularly highly comorbid with AUD is tobacco use disorders [38,39], and therefore if a study reports some participants as having a comorbid tobacco use disorder (but does not specifically recruit individuals with AUD who use tobacco), then it can be included. If a study includes groups of individuals with

different types of SUD including AUD, it can be included so long as the study clearly reports AUD subgroup results.

Exposure. Abstinence from alcohol in recovery from an AUD, defined as either a clinical diagnosis of AUD (mild, moderate, or severe) as per DSM-5 (2013), alcohol dependence/abuse as per DSM-IV (1994), or alcohol dependence/harmful use, as per ICD-10 (1994) or ICD-11 (2019), for diagnostic consistency.

Comparators

i) adults without AUD; ii) adults with a different severity of AUD; iii) abstinence duration assessed by regression (including analysis of variance), as in Schulte, Cousijn [25].

Outcome. Primary outcome is change in neuropsychological function from baseline (which may occur before/during active AUD, or in early recovery) to last available follow-up. This must have been assessed at least twice using a validated self-report/task measure or analogous measure, or as clinical diagnoses/progression of neuropsychological impairment.

Study design. Longitudinal (cohort: prospective or retrospective), published since the year 1999 to account for the introduction of various contemporary neuroscientific theories of addiction [40], such as [41–43].

Exclusion criteria. Grey literature; animal studies; studies not published in English (as this is an unfunded review, though these shall be described and excluded at the full-text stage; Centre for Reviews and Dissemination [44], with language listed as reason for exclusion); population defined by another or co-morbid condition (such as a major psychiatric condition, head trauma, ARBI diagnosis, or co-morbid or secondary other substance use disorder, or alcohol relapse).

Search strategy

A four-stage search strategy will be used: 1) an initial search of databases (CINAHL, APA PsycInfo, EBSCO MEDLINE, Web of Science Core Collection) using pre-specified keywords (alcohol dependence, alcohol use disorder, cognitive function) has identified other keywords and subject headings, to be followed by: 2) full strategy searching across all sources, 3) hand-searching reference lists of included papers, 4) forward searching, with articles citing included studies screened for relevance. Search filters will be used where possible. Clinical trials registers will not be searched, as these are likely to bring up papers on intervention efficacy, rather than neuropsychological assessment/recovery. The study list will be circulated amongst all authors to enable identification of any missing studies. Searches will be re-run prior to final analysis. See S1 File for search strategies for each source.

Data management and selection process

Search strategy results (references, abstracts, and full texts where available) will be transferred into EndNote, for storage and grouping by decision. Pre-screening exclusion (e.g., duplicates identified by Endnote, or records removed via search source filters such as participant age/species or publication date) shall be documented. Papers will be screened (first via titles/abstracts) using review criteria. Initial screening will be against two preliminary criteria: a) study participants are human adults aged 18+, and b) study appears to longitudinally assess recovery of neuropsychological function from AUD.

When studies meet above initial criteria, an attempt will be made to obtain full texts and key information for full criteria screening, and data extraction. If necessary, full texts will be obtained via inter-library loan, and/or contacting authors. If key information is not received within a month of contact, the text will be excluded. Rationale for exclusion at this full-text

screening stage shall be documented in a table. Screening shall be conducted independently by three assessors, one of whom (AP) will screen all data, and the other two (JS & RK) shall each screen half, for fidelity. Any uncertainties shall be discussed between the research team. Inter-reviewer consistency shall be determined prior to screening, by the three assessors all screening 25 randomly selected sources and establishing a kappa statistic.

Duplicates will be identified, including identical records and papers describing different outcomes or time-points of the same study. Identifiers will be used, including paper and author name, description of methods, participant numbers, baseline data, study dates/durations. If necessary, authors will be contacted. If multiple articles describe the same study, a primary paper will be chosen as the main source of results. This shall be decided via discussion between reviewers. Papers reporting different relevant outcomes but not chosen as the primary paper will be considered secondary sources of study information. Management of the selection process will be supported via EndNote and Microsoft Excel. Study selection will be presented in a PRISMA 2020 flow diagram.

Data extraction

A data extraction from based on the JBI manual has been created (S2 File), including definitions of each element for consistency. Data extraction will be undertaken by AP, and the spreadsheet shared with other team members, so 10% of articles can be checked for fidelity. The following details will be extracted: authors; title; year; funding; conflicts of interest; design; setting; location; participant characteristics (age, sex, gender, sample size, exact diagnosis, diagnosis length, age of onset, no. treatment attempts, comorbidities, substance use, details of comparison groups, attrition details); recruitment/follow-up procedures; data relating to change in neuropsychological function (measurement, analysis, results, statistical significance, and confound adjustments); data relating to secondary aims (characteristics reported as predictors of neuropsychological recovery) including measurement and results.

Data extraction and quality appraisal will be piloted by AP on a sample of five full-text papers (selected for wide-ranging outcome measures and time-points). This method will inform refinement of data extraction and quality appraisal [44].

Quality assessment

The JBI Checklist for Cohort studies [29] will be applied at the primary outcome level to provide appraisal of study methods, risk of bias, and validity of results. Scoring is rated as 'yes', 'no', 'unclear' or 'not applicable'. Responses of 'yes' (1) will be summed against the maximum total (11) and scores transformed into percentages and ratings (poor = 49%, moderate = 50–69%, good = 70% onwards), as in Hall, Le [45]. Scores will not be used to exclude studies [44] but displayed in a table to inform appraisal. At least 10% of this screening will be independently conducted for accuracy.

Data synthesis

Due to the heterogenous nature of methodologies, a narrative synthesis will be produced, and meta-bias shall not be assessed. Popay, Roberts [46] and the University of York's Centre for Reviews and Dissemination [44] suggest four key elements of a narrative synthesis; 1) developing a theory of how the intervention works, 2) developing a preliminary synthesis of results, 3) exploring relationships in the data, 4) assessing robustness of the synthesis. Our review will not be evaluating an intervention, therefore as in Heirene, Roderique-Davies [47] we will not use the first feature.

The synthesis will group, describe and discuss data according to functions assessed, and neuropsychological measures used, using Lezak, Howieson [48] for guidance. Some studies may be represented multiple times. Key study aspects will be summarised within groups, and then differences/similarities will be compared to draw conclusions, with regards to review outcomes.

Tables and figures will be used to support the synthesis, including a table of study characteristics, and a table summarising the measures used in each study, domains assessed, and outcomes. Both tables shall be grouped by risk of bias, as suggested by Cochrane Handbook Chapter 12.4.1. We also aim to provide a review matrix mapping recovery of neuropsychological function, in a similar fashion to the matrix created by Pask, Dell'Olio [49] of opiate impacts on cognition. Finally, robustness of findings will be discussed using JBI Quality Appraisal Checklist results and limitations of the synthesis process itself.

Amendments

If amendments are made to the methodology outlined here, they will be recorded along with rationale and date. AP shall be responsible for documenting this, but any changes will be approved by all authors. Changes will not be incorporated into the protocol, but will be added to the PROSPERO registration, and will be summarised in the final manuscript.

Supporting information

S1 Checklist. PRISMA-P 2015 checklist.
(PDF)

S1 File. Systematic search strategies for APA PsycInfo, EBSCO MEDLINE, CINAHL, and Web of Science.
(PDF)

S2 File. Data extraction form.
(PDF)

Author Contributions

Conceptualization: Anna Powell, Harry Sumnall, Catharine Montgomery.

Methodology: Anna Powell, Harry Sumnall, Catharine Montgomery.

Project administration: Anna Powell.

Supervision: Harry Sumnall, Catharine Montgomery.

Writing – original draft: Anna Powell.

Writing – review & editing: Harry Sumnall, Jessica Smith, Rebecca Kuiper, Catharine Montgomery.

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Subjective executive function deficits in hazardous alcohol drinkers

Anna Powell[1], Harry Sumnall[2,3], Cecil Kullu[4], Lynn Owens[3,5] and Catharine Montgomery[1,3]

Abstract

Background: Dependent alcohol drinkers exhibit differences in the structure and function of the brain, and impairments in cognitive function, including executive functions (EFs). Less is known about the impact of non-dependent but hazardous use (that which raises the risk of harm), and it is also unclear to what extent executive impairments in this cohort affect real-world function. The current study examines the relationship between alcohol use, EF and alcohol-related problems, in the general population.

Methods: A between-groups cross-sectional design assessed EF across two levels of drinking; hazardous (Alcohol Use Disorders Identification Test (AUDIT) score of ⩾8) and non-hazardous. Alcohol drinkers (n=666; 136 male; 524 female; six not disclosed; aged 28.02 ± 10.40 years) completed validated questionnaires online assessing subjective EF, alcohol use and alcohol-related problems.

Results: Organisation, Strategic Planning, Impulse Control and overall function were significantly impaired in hazardous drinkers. Furthermore, the effect of alcohol on EF, partially mediated the relationship between alcohol use and alcohol-related problems.

Conclusion: Hazardous drinking was associated with lower subjective EF, and this mediated the effect of alcohol on alcohol-related problems. This may be due to changes in prefrontal brain regions, which could indicate greater risk for the development of alcohol dependence (AD). Future research should use additional means to assess EF in hazardous drinkers, including recovery of function, development of AD and the relationship between cognition and alcohol-related daily problems.

Keywords

Cognitive function, executive function, alcohol, binge drinking

Introduction

Globally, harmful alcohol use is estimated as the seventh leading risk factor for premature death/disability (Griswold et al., 2018). Alcohol-related harm is estimated to cost the NHS £3.5 billion a year (Public Health England, 2014). In the UK in 2018, 7551 deaths were related to alcohol-specific causes (Office for National Statistics, 2019), and in England, there were approximately 358,000 directly alcohol-attributable hospital admissions (NHS Digital, 2020).

Acutely, alcohol acts on GABAergic receptors to potentiate gamma aminobutyric acid (GABA) release, inducing inhibitory sedative effects, and also inhibits glutamatergic receptors, suppressing excitatory glutamate release (Abrahao et al., 2017; Lovinger and Roberto, 2013; Zorumski et al., 2014). Both neurotransmitters contribute to prefrontal cortex (PFC) working memory (WM) processes (Bañuelos and Wołoszynowska-Fraser, 2017). Processes impaired by acute alcohol intoxication include executive functions (EFs; Day et al., 2015), higher-order cognitive functions that govern goal-directed action (Hughes, 2013). Well-supported EF models propose clearly separable, yet related processes (Miyake et al., 2000) with response inhibition (inhibiting dominant behavioural response), task shifting (transferring cognitive resources between tasks) and updating WM (replacing outdated information) emerging as key domains (Diamond, 2013; Miyake and Friedman, 2012). Together, these domains enable critical abilities, such as reasoning, formulating goals, sustained attention, motivation and the flexibility to adapt plans if circumstances change (Aron, 2008). However, although there is generally agreement on these core functions, there is no single accepted definition of EF (Goldstein and Naglieri, 2014), other than that EF is multidimensional (Otero and Barker, 2014), with various processes covered by the 'umbrella term' (Chan et al., 2008).

Response inhibition is impaired in acute alcohol use (Day et al., 2015; Field et al., 2010) and associated with decreased brain activity in EF-implicated regions, including the lateral PFC (Anderson et al., 2011). Furthermore, alcohol dependence (AD) is associated with multiple EF impairments linked to prefrontal brain changes (Abernathy et al., 2010; Chanraud et al., 2006; Noel, 2002), which can predict treatment outcomes (Domínguez-Salas et al., 2016). Meta-analysis suggests inhibition in particular is impaired in AD (Smith et al., 2014), and it

[1]School of Psychology, Liverpool John Moores University, Liverpool, UK
[2]Public Health Institute, Liverpool John Moores University, Liverpool, UK
[3]Liverpool Centre for Alcohol Research, University of Liverpool, Liverpool, UK
[4]Mersey Care NHS Foundation Trust, Liverpool, UK
[5]University of Liverpool, Liverpool, UK

Corresponding author:
Catharine Montgomery, School of Psychology, Liverpool John Moores University, Byrom Street, Liverpool, L3 3AF, UK.
Email: c.a.montgomery@ljmu.ac.uk

may be an important factor in developing AD (Holcomb et al., 2019). While EF deficits in AD are well-documented, less is known about the relationship between non-dependent hazardous drinking and EF, how this affects daily life, or how deficits compare to those in AD and could influence drinking behaviour and the development of AD.

The definition of hazardous drinking can vary, but the National Institute for Health Clinical Excellence (2010) defines it as alcohol use that increases risk of harm, which is how it is interpreted in the current study. It is often defined similarly to heavy drinking; both relate to consumption that may increase risk and exceed a specific threshold (Reid et al., 1999). Current UK guidelines recommend ⩽14 units per week, spread evenly over three or more days (Department of Health, 2016). Consequently, drinking patterns that could identify a person as increased risk (Hatton et al., 2009) include drinking over 14 units continuously across the week, or consuming large amounts during drinking sessions (heavy episodic drinking (HED); Wechsler and Nelson, 2006, or 'binge drinking'; Adan et al., 2017). Such behaviours are included in many alcohol screening tools, including the Alcohol Use Disorders Identification Test (AUDIT; Saunders et al., 1993) used in the current study, with higher scores indicating increased risk.

A systematic review of seven studies investigating EF in heavy drinking reported inconsistent findings, and the meta-analysis found no overall EF impairment (Montgomery et al., 2012). However, their subsequent cross-sectional experimental study of 41 young adults found heavy drinkers (identified using AUDIT data median split) performed worse on all EF tasks: inhibition, shifting, updating and access to semantic memory. Similarly, a more recent systematic review concluded that HED in young adults is associated with poor inhibitory control, and that there is tentative support for deficits in shifting and updating (Carbia et al., 2018b).

In contrast, Carbia et al. (2018a) followed 63 young adults (from age 18) for 11 years and found continuous HED (continuous scores of ⩾4 on AUDIT-Consumption, AUDIT-C) associated with poor inhibition (Stroop Test) and updating (self-ordered pointing test, SOPT), but not shifting (trail making task, TMT). This was not supported in a later cross-sectional study of EF, drinking motives, alcohol use, heavy drinking and related problems (e.g. regretted sexual activity) in 801 21–35-year olds (Martins et al., 2018). They found no association between heavy drinking and inhibition or updating, and no EF components predicted alcohol-related problems. Interestingly, better shifting-specific abilities associated with heavy drinking. While this appears counterintuitive, strong shifting-specific abilities differ from other EF by undermining self-control (Friedman and Miyake, 2017; Herd et al., 2014). Known as the 'stability-flexibility trade-off', high shifting enables moving attention to appealing alternatives, but impairs maintenance/shielding of long-term goals (Hofmann et al., 2012).

Others have found impaired response inhibition in HED young adults on Go/NoGo task (Ames et al., 2014; Czapla et al., 2015; Lannoy et al., 2020). Furthermore, Lannoy et al. (2019b) and Kim and Kim (2019) also found that in young HED adults, inhibition performance on the Flanker task was impaired compared to controls, though shifting (Number Letter task) and updating (Letter Memory task) abilities were not. The authors suggested that this highlighted the importance of inhibitory control in alcohol use, and that a distinction between binge and dependent drinking may be lack of a 'general' executive deficit.

However, many researchers have also found hazardous drinkers do not differ significantly to controls on EF task performance. This includes on Go/NoGo tasks assessing inhibition (Blanco-Ramos et al., 2019; Lannoy et al., 2017; López-Caneda et al., 2012, 2014), and *n*-back tasks, which assess updating (Park and Kim, 2018; Schroder et al., 2019). A possible explanation for these discrepancies is a 'neurocompensatory mechanism' in young drinkers, in which increased cognitive effort enables performance preservation, which loses efficiency over time and continued hazardous drinking (Almeida-Antunes et al., 2021; Gil-Hernandez et al., 2017; Tapert et al., 2004). Indeed, the Go/NoGo studies above all found electrophysiological differences in hazardous drinkers, including delayed latencies and/or higher amplitudes of event-related potentials (ERPs) indexing executive control. Furthermore, Smith and Mattick (2013) found hazardous drinkers had poorer Stop Signal Task inhibition, but higher P3 amplitudes on successful versus failed trials. A critical review by Lannoy et al. (2019a) noted studies showing reduced electrophysiological activities indexing attentional/executive processes (e.g. Maurage et al., 2009, 2012) are typically those using less executive experimental paradigms. Additionally, functional neuroimaging reveals that while decreased activity in frontoparietal areas during EF tasks may be a precursor for hazardous drinking, these areas often display hyperactivation during EF tasks *after* the onset of this (Lees et al., 2019; Spear, 2018).

Structural neuroimaging indicates that HED (determined by questions on consumption speed and frequency of 6+ drinks in one occasion, or Alcohol Use Questionnaire (Mehrabian and Russell, 1978) questions on HED frequency) is associated with whole-brain white matter degradations, and anomalies in prefrontal grey matter (Doallo et al., 2014; Smith et al., 2017). This was linked to poor updating on the Cambridge Neuropsychological Test Automated Battery (CANTAB) Spatial Working Memory test and the non-computerised version, the SOPT. However Smith et al. (2017) found no relationship between white matter degradation and the inhibition assessed by the CANTAB Stop Signal Task.

While EF has been investigated in hazardous drinkers using behavioural paradigms and neuroimaging, few studies have addressed the effects of alcohol on EF by using subjective assessments. This becomes interesting especially when one considers that increased cognitive effort to achieve satisfactory performance (as in the neurocompensation hypothesis) may be better reflected in self-report assessment of difficulties. Research using subjective measures is conflicting, with Heffernan et al. (2004) finding that excessive drinkers experienced more problems related to the executive component of memory. Similarly, Houston et al. (2014) found greater alcohol use associated with poorer EF measured by subjective EF (Dysexecutive Functioning Questionnaire), and task performance (TMT, Go/NoGo and Wisconsin Card Sorting Test). However, Czapla et al. (2015) found that HED and controls did not differ in overall response inhibition on a Go/NoGo task, or self-reported impulsiveness, though there was an impairment on the task for alcohol-related stimuli.

Finally, hazardous drinking has a considerable effect on overall function and quality of life, including on interpersonal relationships, finances and employment (World Health Organization,

2004). The relationship between alcohol use and EF may contribute to this, as EF affects much of everyday life (Snyder et al., 2015), and EF dysfunction in AD decreases quality of life (Brion et al., 2017). However, there is little evidence of how this relates to non-dependent hazardous drinking. One study of 62 college students found EF mediated the relationship between alcohol use and overall life functioning (assessed by the Barkley Functional Impairment Scale); however, this was in an ADHD population predisposed to EF deficits (Langberg et al., 2015). Another study found a small dose effect with the heaviest drinkers (10+ drinks a week) demonstrating lower general cognitive function and poor reported daily life functioning (Hendrie et al., 1996). While this supports a relationship between daily functioning and the effect of hazardous drinking on cognitive function, it did not specifically examine EF. In contrast, Martins et al. (2018) found no relationship between EF and alcohol-related problems.

Clearly, EF is affected by hazardous drinking to some extent, but the aetiology is not always consistent. This could be due to neurocompensation in individuals, which may be better reflected in subjective judgement of EF. Furthermore, while EFs are predictive of clinical outcomes in AD, less is known about the relationship between EF and daily-life outcomes in the general population. The current study investigated subjective EF deficits in adult non-dependent hazardous drinkers using an online survey and explored the relationship between deficits and self-reported alcohol-related problems. Based on the literature above, we hypothesised that (1) hazardous drinkers would have significantly poorer subjective EF than non-hazardous drinkers, and (2) the relationship between alcohol use and alcohol-related problems would be mediated by the effect of alcohol on subjective EF.

Methods

Design

A factorial design assessed EF between male and female hazardous and non-hazardous drinkers. The independent variables were alcohol use with two levels; non-hazardous and hazardous drinking (determined by AUDIT cut-off score; ⩾8 deemed hazardous drinking; World Health Organization, 2001), and gender with two levels – male and female. The main dependent variable was EF.

Participants

Eight hundred and three individuals took part. Upon initial screening, 128 incomplete datasets were removed (15.9%), and nine more were removed as outliers.[1] Thus, the study comprised of 666 participants (136 male; 524 female; six gender not disclosed; aged 28.02 ± 10.40 years). Participants were recruited globally (73.6% UK, 9.6% Ireland, 6.2% USA, 2.6% Australia and 7.7% rest of world). Participants were categorised into non-hazardous (n=323 (48.50%); 56 male, 264 female; three gender not disclosed, aged 29.73 ± 10.68 years; mean AUDIT total score=4.72, SD=1.77) and hazardous (n=343 (51.50%); 80 male, 260 female; three gender not disclosed, aged 26.40 ± 9.85 years; mean AUDIT total score=13.04, SD=4.80) drinkers, using AUDIT score (⩾8 deemed hazardous).

Recruitment channels included an advert on the Liverpool John Moores University (LJMU) website and personal/professional social media, referrals from previous participants, research team acquaintances and an email to LJMU students. Each advert contained a link to the Qualtrics survey. Potential participants self-identified as eligible if they were alcohol drinkers aged 18+. There were no exclusion criteria. The original recruitment target was 282 participants, based on a multivariate analysis of variance (MANOVA) sample size calculation with a 95% confidence level ($f^2 \geqslant 0.02$, a small effect size; Cohen, 2013) using GPower version 3.1.94 (Heinrich Heine – Universitat Dusseldorf, Germany) (Faul et al., 2009), adjusted for MANCOVA (Dattalo, 2008).

Materials

Demographics. Participants answered questions on age, gender, country of residence, employment status, education level, housing status, mental health diagnoses and medication.

Executive function. This study used the Executive Function Index (EFI; Spinella, 2005) which is a 27-item, five-point Likert-scale questionnaire assessing five EF components derived from factor analysis; Motivational Drive, Strategic Planning, Organisation, Impulse Control and Empathy. Motivational Drive items assess interest in novelty, activity level and behavioural drive. Strategic Planning items measure ability to use strategies, plan and think ahead. Organisation assesses sequencing, multitasking and holding information in the WM to inform decisions. Impulse Control measures self-inhibition, social conduct and risk taking. Empathy items assess prosocial behaviours, a cooperative attitude and concern for others' wellbeing.

Higher total (global measure) and subscale scores indicate better EF. Subscale scores are calculated by summing relevant items (taking account of reverse scoring). The EFI corresponds well with neuroanatomical findings (Spinella, 2005), and also into a three-factor model, in which Impulse Control and Empathy form one factor, Strategic Planning and Organisation another and Motivational Drive a third. These correspond to the model of functional organisation of orbitofrontal, dorsolateral and medial prefrontal circuits (Cummings, 1993; Miller and Cummings, 2017). In initial development, EFI had a Cronbach's α ranging between 0.69 and 0.76 for the five subscales, with a total α of 0.82, an acceptable internal consistency (Spinella, 2005). In our study, Cronbach's α ranged from 0.76 to 0.80 across the items, and a total α of 0.76. It was lower for the subscales, ranging from 0.55 to 0.63, and a total of 0.63.

Mood state. The Hospital Anxiety and Depression Scale (HADS) was used to assess state Anxiety and Depression (Zigmond and Snaith, 1983). HADS is a four-point, 14-item Likert-scale, scored 0–3 by separately summing subscales (some items require reverse scoring). Condition boundary points for both subscales are; 8–10=mild, 11–14=moderate and 15–21=severe. A general population review of 747 studies found HADS demonstrates good validity and reliability (Bjelland et al., 2002).

Alcohol use. The AUDIT is a 10-item five-point Likert-scale assessing harmful/hazardous drinking developed by the World Health Organization (Saunders et al., 1993). A cut-off score of 8+ is recommended as an indicator of hazardous/harmful alcohol use, and possible alcohol dependence (World Health Organization, 2001), and so in this study, participants were grouped as scoring <8 (non-hazardous) or ⩾8 (hazardous). In addition, a

composite score of the first three questions can be used to assess level of alcohol consumption, classed as the AUDIT-C scale (Bradley et al., 2007). The AUDIT is reliable (Donovan et al., 2006; Fiellin et al., 2000) and validated within primary health care in six countries (World Health Organization, 2001) and the general population (Aalto et al., 2009). Indeed, a systematic review by Fiellin et al. (2000) concluded that the well-used cut-off of 8 for the AUDIT is more sensitive for identifying hazardous and harmful drinkers than two other measures – CAGE (Ewing, 1984) and Short Michigan Alcoholism Screening Test (Selzer et al., 1975).

Alcohol-related problems. The Alcohol Problems Questionnaire (APQ) by Drummond (1990) is a 44-item tool rated yes(1)/no(0), contributing to a common score, and eight separately summed subscales. Five subscales apply to all participants: the perceived drinking impact on Financial, Legal, Physical, Social and Psychological issues. The Alcohol Problems Questionnaire Common (APQC) score is comprised of total scores of these five subscales and demonstrates high reliability coefficients, internal consistency and stability over time (Drummond, 1991; Williams and Drummond, 1994). Where relevant, subscales of impact on Work, relationships with Children and Spouse are also assessed. Lower scores within each subscale indicate fewer alcohol-related problems. APQ demonstrates high test–retest reliability (Williams and Drummond, 1994) that has been validated within a clinical population (Drummond, 1990; Williams and Drummond, 1994) and a sample of college students (Drummond, 1991) and is the UK measure of choice for alcohol-related problems (Raistrick et al., 2019).

Procedure

Potential participants read the online study information and confirmed eligibility. They were reminded of confidentiality, right to withdraw, or omit questions, and provided consent through a tick-box. When finished, participants were provided with a full debrief, with no reward for completion, but could enter a prize draw for one of three shopping vouchers. This study was approved by LJMU Research Ethics Committee.

Statistical analyses

All analyses were completed using SPSS v26 (IBM Corp., Armonk, NY, USA). Factorial MANOVA assessed mood state (HADS Anxiety and Depression scores) across gender and drinking level. A 2×2 Factorial MANCOVA was then performed on EFI subscales (dependent variables assessing EF), with drinking category (non-hazardous and hazardous) and gender (male and female) as the between-groups independent variables. Mood state and age were included in the model as continuous covariates, chosen due to their associations with EF (Best and Miller, 2010; Grissom and Reyes, 2019; Gulpers et al., 2016; Snyder, 2013; Zaninotto et al., 2018) and alcohol use (Jane-Llopis and Matytsina, 2006; Mooney et al., 1987; Wilsnack et al., 2009).

Finally, a hierarchical multiple regression was conducted with alcohol use (AUDIT-C) and EF (EFI subscales) as predictors of alcohol-related problems, with a subsequent mediation analysis, using the PROCESS plugin version 3.5, as in Hayes (2017), examining the mediation of EF (EFI total score) on the relationship between alcohol use (AUDIT-C) and related problems (APQC). Mood state, age and gender were included in the mediation as covariates, which was further supported by their significant contributions in the Factorial MANCOVA.

Results

Table 1 shows descriptives for mood state and alcohol problems.

Factorial MANOVA assessed differences in state anxiety and depression (HADS) across gender and drinking level (see Table 1).[2] The Levene's and Box's tests were acceptable ($p < 0.05$). There was a significant main effect of gender [$F(2, 651) = 11.50$, $p < 0.0001$, Wilks' $\Lambda = 0.966$, $\eta_p^2 = 0.03$], but not drinking level [$F(2, 651) = 2.14$, $p = 0.12$, Wilks' $\Lambda = 0.993$, $\eta_p^2 = 0.01$], and no significant interaction between the two factors [$F(2, 651) = 0.07$, $p = 0.94$, Wilks' $\Lambda = 1.00$, $\eta_p^2 = 0.00$]. Pairwise comparisons revealed that females had significantly higher state anxiety than males [$F(1, 652) = 19.47$, $p < 0.0001$, $\eta_p^2 = 0.03$], but that there was no gender difference for state depression ($p = 0.39$).

Executive function

For the factorial MANCOVA, scatterplots indicated approximately linear relationships between each pair of dependent variables, and between the covariates and each dependent variable. Homogeneity of regression was achieved at $p > 0.05$ for covariate by drinking level interaction, covariate by gender interaction and covariate by drinking level by gender interaction, in all cases. The Levene's test indicated the homogeneity of variance assumption was met for all EFI subscales between groups ($p > 0.05$). The Shapiro–Wilk tests with a Bonferroni correction indicated residual normality was met for 18 out of 20 conditions ($p > 0.003$), which was deemed acceptable. The Box's test of equality of covariance matrices was met ($p = 0.12$).

The 2×2 factorial MANCOVA (see Table 2) found a significant effect of each covariate on EFI scores: age ($F(5, 615) = 11.34$, $p < 0.0001$, Wilks' $\Lambda = 0.916$, $\eta_p^2 = 0.08$), depression ($F(5, 615) = 38.97$, $p < 0.0001$, Wilks' $\Lambda = 0.759$, $\eta_p^2 = 0.24$) and anxiety ($F(5, 615) = 11.70$, $p < 0.0001$, Wilks' $\Lambda = 0.913$, $\eta_p^2 = 009$). After controlling for these, there was a significant difference between drinking level groups on EFI scores ($F(5, 615) = 12.90$, $p < 0.0001$, Wilks' $\Lambda = 0.905$, $\eta_p^2 = 010$). Gender was also included in the model as a fixed factor, displaying a significant effect on EFI scores ($F(5, 615) = 4.50$, $p = 0.0002$, Wilks' $\Lambda = 0.961$, $\eta_p^2 = 0.04$); however, there was no significant interaction between gender and drinking level ($F(5, 615) = 0.34$, Wilks' $\Lambda = 0.997$, $p = 0.89$, $\eta_p^2 = 0.00$).

Hazardous drinkers had lower scores on all EFI subscales (with the exception of Empathy); differences were significant for EFI subscales Organisation ($F(1, 619) = 5.44$, $p = 0.02$, $\eta_p^2 = 0.01$), Strategic Planning ($F(1, 619) = 27.53$, $p < 0.0001$, $\eta_p^2 = 0.04$) and Impulse Control ($F(1, 619) = 41.91$, $p < 0.0001$, $\eta_p^2 = 0.06$]) There was no significant difference between drinking level groups on the Motivational Drive and Empathy subscales ($p = 0.93$ and 0.70, respectively). Therefore, hazardous drinking was associated with worse subjective EF compared to non-hazardous drinking.

Table 1. Adjusted means for anxiety and depression, and unadjusted APQ means, by gender and drinking level.

Hospital anxiety and depression scale (MANOVA)	Anxiety		Depression	
	M	SE	M	SE
Drinking level				
Non-hazardous	7.94	0.31	3.87	0.24
Hazardous	8.80	0.27	4.24	0.21
Gender				
Male	7.46*	0.37	3.92	0.28
Female	9.28	0.19	4.19	0.14

Alcohol problems questionnaire (unadjusted)	Friendships		Partner		Children		Work		Money		Legal		Physical		Psychological	
	M	SD	M	SD	M	SD	M	SD	M	SD	M	SD	M	SD	M	SD
Drinking level																
Non-hazardous	0.09	0.29	0.11	0.41	0.02	0.13	0.16	0.37	0.20	0.40	0	0	0.84	1.07	0.29	0.78
Hazardous	0.71	0.80	1.12	1.63	0.24	0.78	0.44	0.86	0.36	0.79	0.03	0.17	1.74	1.38	0.41	0.78
Gender																
Male	0.50	0.66	0.67	1.01	0.04	0.20	0.38	0.88	0.25	0.53	0.04	0.20	1.17	1.31	0.42	0.83
Female	0.26	0.59	0.42	1.20	0.12	0.57	0.32	0.65	0.26	0.56	0	0	1.18	1.26	0.30	0.76

MANOVA: multivariate analysis of variance.
Mood state = hospital anxiety and depression scale anxiety and depression scores; alcohol problems = alcohol problems questionnaire scores; hazardous drinking = alcohol use disorders identification score of ⩾8.
*$p < 0.0001$.

Table 2. Adjusted means for executive function index (EFI) subscales, by drinking level and gender, controlling for mood state and age.

	Motivational drive		Organisation		Strategic planning		Impulse control		Empathy	
	M	SE	M	SE	M	SE	M	SE	M	SE
Drinking level										
Non-hazardous	14.05	0.17	16.87*	0.23	25.54***	0.24	16.43***	0.21	26.01	0.18
Hazardous	14.03	0.15	16.15	0.20	23.90	0.21	14.62	0.19	26.11	0.16
Gender										
Male	13.86	0.21	16.48	0.28	24.44	0.28	14.94***	0.25	25.68**	0.22
Female	14.22	0.10	16.54	0.14	24.99	0.14	16.11	0.13	26.43	0.11

Subjective executive function = executive function index subscales (motivational drive, organisation, strategic planning, impulse control, empathy); hazardous drinking = alcohol use disorders identification score of ⩾8; mood state = hospital anxiety and depression scale anxiety and depression scores.
From smallest, *$p < 0.05$. **$p < 0.01$. ***$p < 0.001$.

Males had lower scores on all EFI subscales, but this difference was significant for EFI subscales Impulse Control ($F(1, 619) = 16.77$, $p < 0.0001$, $\eta_p^2 = 0.03$], and Empathy ($F(1, 619) = 9.57$, $p = 0.002$, $\eta_p^2 = 0.02$). There were no differences between males and females on the Motivational Drive, Organisation and Strategic Planning subscales ($p = 0.12$, 0.86 and 0.09, respectively). Therefore, males had worse subjective EF compared to females.

Relationship between subjective executive function and real-life alcohol-related problems

A hierarchical regression modelled the relationship between EF and alcohol-related problems, with continuous APQC score as the dependent variable. Variables were entered simultaneously in successive model blocks: demographic variables (age and gender) in model one, alcohol use (AUDIT-C scores and expected to account for the most variance) in model two, mood state (HADS Depression and Anxiety scores) in model three and EFI subscales (Motivational Drive, Impulse Control, Organisation, Strategic Planning and Empathy) in model four, thereby ensuring that cognitive factors were added successively. Model parameters are shown in Table 3.

Model one significantly predicted alcohol-related problems $F(2, 608) = 16.38$, $p < 0.0001$, as did model two $F(3, 607) = 56.85$, $p < 0.0001$ and model three $F(5, 605) = 78.13$, $p < 0.0001$. For these three models, gender was not a significant predictor. Finally, model four also significantly predicted alcohol-related problems $F(10, 600) = 47.92$, $p < 0.0001$ (though gender, Motivational Drive, Strategic Planning, and Empathy were not significant predictors). The addition of EFI subscales explained an additional 44% of the variance, taking overall explained

Table 3. Hierarchical multiple regression parameters with alcohol problems questionnaire common score as the dependent variable.

	Unstandardized and standardized coefficients			Squared semi-partial correlation coefficients	Obtained I and I values		Obtained I values			
	B	SE B	β	sr^2	t^a	P	R	R^2	ΔR^2	p
Model 1							0.226	0.051	0.051	<0.0001
Constant	6.231	0.714			8.725	<0.0001				
Age	−0.069	0.012	−0.231	0.051	−5.722	<0.0001				
Gender	−0.345	0.307	−0.045	0.002	−1.122	0.262				
Model 2							0.468	0.219	0.168	<0.0001
Constant	1.871	0.752			2.488	0.013				
Age	−0.054	0.011	−0.183	0.031	−4.948	<0.0001				
Gender	0.172	0.283	0.023	0.000484	0.609	0.543				
AUDIT-C	0.599	0.052	0.417	0.168	11.437	<0.0001				
Model 3							0.626	0.392	0.173	<0.0001
Constant	−0.048	0.688			−0.070	0.944				
Age	−0.046	0.010	−0.156	0.022	−4.716	<0.0001				
Gender	−0.029	0.252	−0.004	0.000016	−0.115	0.908				
AUDIT-C	0.568	0.046	0.395	0.151	12.246	<0.0001				
Anxiety	0.111	0.028	0.155	0.016	3.964	<0.0001				
Depression	0.298	0.036	0.313	0.068	8.207	<0.0001				
Model 4							0.666	0.444	0.052	<0.0001
Constant	3.985	1.427			2.792	0.005				
Age	−0.025	0.010	−0.084	0.006	−2.520	0.012				
Gender	0.138	0.246	0.018	0.000289	0.562	0.574				
AUDIT-C	0.470	0.048	0.327	0.088	9.743	<0.0001				
Anxiety	0.072	0.028	0.100	0.006	2.558	0.011				
Depression	0.217	0.040	0.223	0.026	5.307	<0.0001				
Motivational drive	−0.061	0.043	−0.052	0.002	−1.415	0.158				
Organisation	−0.108	0.033	−0.122	0.010	−3.277	0.001				
Strategic planning	−0.011	0.033	−0.012	0.0001	−0.329	0.742				
Impulse control	−0.190	0.036	−0.196	0.025	−5.223	<0.0001				
Empathy	0.083	0.041	0.067	0.004	2.003	0.046				

Depression and anxiety = hospital anxiety and depression scale subscales; motivational drive, organisation, strategic planning, impulse control and empathy = Executive Function Index subscales.
AUDIT-C: Alcohol Use Disorders Identification Test-Consumption.
[a]Model 1: $df = 608$; model 2: $df = 607$; model 3: $df = 605$ and model 4: $df = 600$.

variance in alcohol-related problems to 44.4%. Beta coefficients and partial correlations indicated that in model four, predictor order of importance was as follows: alcohol use, state depression, Impulse Control, Organisation, state anxiety and age (β = 0.327, 0.223, −0.196, −0.122, 0.100 and −0.084, respectively, p-values <0.05). The final model effect size was calculated as $f^2 = 0.80$, a large effect (Cohen, 1988), and the local effect size of the EFI subscales was calculated at $f^2 = 0.094$ (using local effect size calculation proposed by Selya et al., 2012), a small effect.

Mediation analysis was then used to assess the relationship between alcohol use, EF and alcohol problems. This indicated that alcohol use (AUDIT-C) was indirectly related to alcohol-related problems (APQC) through its relationship with EF (EFI total score), after controlling for covariates. As shown in Figure 1, EF mediated the relationship between alcohol use and alcohol-related problems. Higher consumption was associated with poorer EF ($a = 0.930$, $p < 0.001$; standardized $a = -0.205$), which was subsequently related to more alcohol-related problems ($b = -0.064$, $p = 0.001$; standardized $b = 0.203$). A 95% bias-corrected confidence interval based on 10,000 bootstrap samples indicated the indirect effect, $ab = 0.060$, BCa CI [0.033, 0.091] was statistically significant. However, the direct effect of alcohol use on alcohol-related problems was also significant $c' = 0.509$, $p < 0.001$, indicating partial mediation of EF. The completely standardized indirect effect was $ab_{cs} = 0.042$, BCa CI [0.024, 0.063].

Discussion

The current study examined drinking behaviour and EF. Hypothesis one was partially supported as some EFI subscales (Strategic Planning, Impulse Control, and Organisation) were significantly lower in hazardous drinkers, indicating poorer performance. Hypothesis two was also supported, as EF partially mediated the relationship between alcohol use and alcohol-related problems.

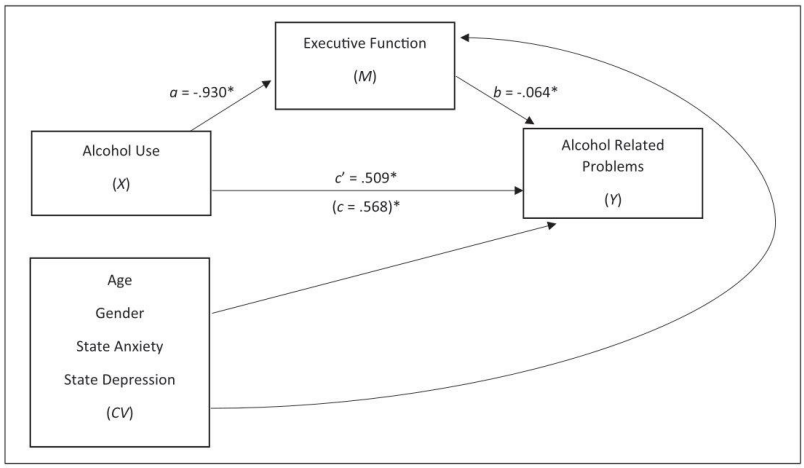

Figure 1. The mediating effect of executive function (EF) on the relationship between alcohol use and alcohol related problems, while controlling for age, gender, and state anxiety and depression.
Note: All presented effects are unstandardized; *a* is effect of alcohol use (alcohol use disorders identification test-consumption) on EF; *b* is effect of EF (executive function index total score) on alcohol-related problems (alcohol problems questionnaire common); *c'* is direct effect of alcohol use on alcohol-related problems; *c* is total effect of alcohol use on alcohol-related problems. State anxiety and depression = hospital anxiety and depression scale subscales. $^*p < 0.001$.

After controlling for covariates, hazardous drinking was associated with worse EFI Strategic Planning, Impulse Control, and Organisation, but not Empathy and Motivational Drive. This suggests hazardous drinkers in this study struggle with planning/using strategies, self-inhibition, risk taking and holding information in mind or multitasking, but not prosocial behaviours or motivation. This supports research showing EF deficits in hazardous drinkers (Doallo et al., 2014; Martins et al., 2018; Smith et al., 2017), particularly in inhibition (Ames et al., 2014; Carbia et al., 2018a, 2018b; Czapla et al., 2015; Kim and Kim, 2019; Lannoy et al., 2019b, 2020; Montgomery et al., 2012), as Impulse Control was the largest subscale deficit found.

This highlights potential similarities between EF in hazardous drinking, and AD such as in Smith et al. (2014). Furthermore, these results may contrast with those showing no inhibitory deficit in hazardous drinking (Blanco-Ramos et al., 2019; Czapla et al., 2015; Lannoy et al., 2017; López-Caneda et al., 2012, 2014; Martins et al., 2018; Smith et al., 2017) due to the varied age range; 48.4% of participants were above 24 years old, which has been proposed as a more appropriate 'end of adolescence' in relation to various biological and social factors, including neurodevelopment (Sawyer et al., 2018). It is therefore possible to infer that the current sample was diverse with regard to neurological development (and years of continuous hazardous drinking), which may have reduced the ability of neurocompensation to preserve inhibition, contrasting with studies focusing on young adults. These results also support a possible distinction from AD as reported in Kim and Kim (2019), as not every EFI subscale was significantly poorer in hazardous drinkers. Importantly, poor EF (particularly inhibition) appears to be involved in the development and maintenance of addictions, including AD (Hester et al., 2010). Results such as the current study therefore indicate a potentially vulnerable cohort. However, it is likely the relationship between EF and alcohol use is cyclical, with elements of EF being heritable and increasing risk of problematic drinking (Benzerouk et al., 2013).

The current findings may result from anomalies in prefrontal structures; indeed, the EFI subscales differentially associate with three prefrontal EF systems (Cummings, 1993; Miller and Cummings, 2017); Impulse Control and Empathy with orbitofrontal, Strategic Planning and Organisation with dorsolateral, and Motivational Drive with medial (Miley and Spinella, 2006). These areas are disrupted in AD, associated with decreased EF (Abernathy et al., 2010). This is partially reversible with long-term abstinence, but to what extent is unclear (Moselhy et al., 2001). Less is known about hazardous drinking and neural function, though as discussed, there is evidence HED leads to prefrontal anomalies associated with impaired EF (Doallo et al., 2014; Smith et al., 2017).

Specific subscale impairments indicate more potential damage to orbitofrontal and dorsolateral regions, which may differentiate hazardous and dependent drinkers. There is evidence to suggest hazardous drinking cessation leads to partial cognitive and neural recovery, though not to the same level as control participants (Lees et al., 2019). However, such interpretation of the results with regard to brain structure/function is speculative, due to the nature of the assessments used. Future EF research should use additional paradigms (neuroimaging, ERP and objective EF assessments) to investigate changes in the brain structure/function of hazardous drinkers, the cause/effect, reversibility or chronic nature of any changes and predictability of assessments to indicate risk of progression from hazardous drinking to AD.

Our second prediction was supported as hazardous drinking predicted alcohol-related problems, and this was partially mediated by

EF. Although the APQC score does not indicate specific issues, its high internal consistency indicates problems assessed within it may co-occur, indicating general problematic tendencies (Drummond, 1991). It is understandable how problems planning/using strategies, self-inhibiting, managing risk taking and holding information in mind or multitasking could contribute to items included in APQC. Indeed, hazardous drinkers (⩾8 AUDIT score) experience more mental health problems, hospital admissions and social issues (Conigrave et al., 1995), and alcohol use contributes to financial, legal and workplace problems (Rehm, 2011). EF is associated with all of these domains (Allan et al., 2016; Gulpers et al., 2016; Spinella et al., 2004; Snyder, 2013; Wolf, 2010; Yeh, 2013), so it is possible alcohol-related EF impairments may partially underlie the disruptive impact of problematic drinking for some people, even before considering whether hazardous drinking/poor EF increases risk of AD. Further research could examine which alcohol-related problems are mediated by EF (and by which EF specifically) and consider whether this knowledge could be used to reduce alcohol-related problems (e.g. through EF training or other interventions).

This study had a number of limitations. Conducted during the first 2020 COVID-19 lockdown, this may have induced drinking pattern changes due to stress/boredom (Institute of Alcohol Studies, 2020). Indeed, a general population survey suggested 21% of UK adults reported drinking more than normal, whereas 35% reduced/abstained (Alcohol Change UK, 2020). Another large self-selecting online survey ($n=40{,}000$) found 44% of respondents reported an increase in drinking (Global Drugs Survey, 2020), and 23.8% reported an increase in HED (though 30.5% of these said this increase was slight). However, the Alcohol Change survey found people whose drinking increased were those who already drank heavily prior to the lockdown. Furthermore, during lockdown, drinking may be somewhat different, the AUDIT asks questions in relation to the previous 12 months, so classification of drinking group should have remained stable.

We also aimed to keep the survey short to increase engagement; thus, no data were collected on abstinence period from alcohol. It is possible participants experienced alcohol acute/subacute effects (such as residual intoxication), which may have impacted their responses. However, as hazardous drinkers had higher overall alcohol consumption and were the group demonstrating poorer EF, the effects found are unlikely related to subacute intoxication, even if this occurred for some people. Statistical limitations include the lower Cronbach's α coefficients for subscales of the EFI, indicating potential internal inconsistencies and future research should seek to use additional methods of EF assessment. Additionally, as this was a cross-sectional survey, it was not possible to discern whether lower EF was a cause or effect of hazardous drinking in this cohort.

Finally, the lockdown and survey-length restrictions also influenced the type of data that could be collected; hence, the study only included self-report measures and not objective assessments as a measure of comparison. While all measures used are well-validated, it is possible that self-report assessment of EF may be more vulnerable to inaccuracies as a result of alcohol effects on metacognition (Le Berre et al., 2017), or due to other uncontrolled extraneous factors, such as education (Spinella and Miley, 2003) or personality (Buchanan, 2016). We also had no control over time of testing. As EF displays diurnal variations and individual differences resulting from circadian typology (Adan, 1993), future studies should control for time of testing and include the use of objective EF measures, such as validated experimental tasks.

Despite these limitations, this study highlights the nature of EF deficits in hazardous drinking, and the mediating effect of EF and drinking on real-world functioning, suggesting hazardous drinkers may be more vulnerable. Research has shown EFs can be improved via intervention (Diamond and Ling, 2016). Furthermore, EF training has successfully reduced alcohol consumption in hazardous drinkers (Houben et al., 2011a, 2011b, 2012), so a targeted intervention improving EF in a hazardous drinking cohort could reduce the risk of developing AD and other alcohol-related problems.

Conclusion

In conclusion, the current study examined hazardous drinking and EF. Hazardous drinkers reported significantly lower subjective EF, and the relationship between alcohol use and alcohol-related problems was partially mediated by the effect of alcohol use on subjective EF, indicating the importance of understanding and addressing poorer EF in hazardous drinkers. Further research should use additional methods to assess EF in hazardous drinking, including recovery of function, study whether this contributes to AD development (and if this is predictive), examine which alcohol-related problems are mediated by EF, and to consider options for interventions.

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ORCID iDs

Anna Powell https://orcid.org/0000-0002-4879-4124
Lynn Owens https://orcid.org/0000-0001-7549-9350
Catharine Montgomery https://orcid.org/0000-0003-2805-5807

Notes

1. Inspection of Mahalanobis Distance and Standardized Residuals during the main analysis identified nine outliers (three male; six female; three non-hazardous; six hazardous). These participants were removed from all final analyses and descriptives.
2. The Shapiro–Wilk tests using a Bonferroni correction indicated normality of mood state across gender and drinking level was violated for six out of eight tests ($p<0.006$). While this suggests the results should be interpreted with caution, due to there being no non-parametric MANOVA equivalent, and due to MANOVA being fairly robust with regard to normality violations, it was decided to continue with this analysis.

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Appendix 5: Published Paper – Younger, drunk, and fast: Paradoxical rapid reaction time in hazardous drinkers

Original Paper

Younger, drunk, and fast: Paradoxical rapid reaction time in hazardous drinkers

Anna Powell[1,2], Harry Sumnall[2,3] and Catharine Montgomery[1,2]

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Abstract

Background: Research consistently links hazardous alcohol use with reduced cognitive function but is less consistent with regard to processing speed, which underpins many cognitive functions. Using vibrotactile perception to assess cognitive function may have benefits over other sensory stimuli, as this method gives lower variability in reaction time (RT) and shorter latency.

Aims: This study aimed to assess performance on vibrotactile simple and choice RT tasks between hazardous and non-hazardous drinkers.

Methods: Participants (n=86) completed vibrotactile tasks and alcohol, mood and subjective function (Executive Function Index (EFI)) questionnaires. Multivariate analyses of covariance were performed on average RT scores, and on EFI scores, to investigate function, and a bivariate correlation assessed the relationships between subjective and objective measures.

Results: Hazardous drinkers exhibited significantly faster choice RT. With regard to subjective executive function, Strategic Planning and Impulse Control were significantly better in non-hazardous drinkers. Finally, Organisation and Impulse Control both significantly positively correlated with choice and simple RT, indicating that as subjective function improved, RT increased (a decline in performance).

Conclusions: These results are considered in the context of the premature ageing hypothesis, impulsivity and the impact of alcohol use on various neurotransmitter systems. Furthermore, the poorer subjective function in young hazardous drinkers indicates a possible metacognitive deficit, increased effort or issues with vibrotactile perception as a cognitive function assessment in this group.

Keywords
Cognitive function, vibrotactile perception, executive function; alcohol, hazardous alcohol use

Introduction

Around one-third of the population drink alcohol globally (Griswold et al., 2018), with alcohol named as a leading risk factor for disease burden (Rehm et al., 2003). Evidence suggests that Heavy Episodic Drinking (HED or binge drinking), even at non-clinical levels, is associated with Executive Cognitive Function (ECF) deficits that can affect daily function (Houston et al., 2014; Montgomery et al., 2012). A recent meta-analysis found that young people with HED were significantly impaired relative to controls in ECF (inhibitory control, decision-making) (Lees et al., 2019). Similar results have been observed across broader age ranges of HED adults with impairments in tasks assessing the ECFs response inhibition and cognitive flexibility after controlling for age and gender effects (Houston et al., 2014); increased Stroop RT and decreased accuracy associated with HED with corresponding decreases in brain activity in regions mediating these functions have also been observed (Affan et al., 2018). Carbia et al. (2018)also highlight the effects of HED on response inhibition and to a lesser extent attentional switching and memory updating in their review. While objective assessments of ECF are important in identifying component processes of ECF that may be affected by HED, self-reported problems with ECF function provide an interesting insight into subjective cognitive state which may be more indicative of the effects of HED on cognitive effort required in performing these ECFs in real-world settings. In line with this, heavy drinking has also been shown to affect subjective ratings of ECF, with hazardous drinkers reporting subjectively worse Organisation, Strategic Planning and Impulse Control than non-hazardous drinkers (Powell et al., 2021a) and greater dysexecutive function (Houston et al., 2014).

Processing speed is a task-independent construct that underpins more complex abilities including the ECF outlined above (Fry and Hale, 2000), and determines the efficiency at which cues are interpreted and a task-appropriate response is selected (Fisk and Warr, 1996; Gordon et al., 2018). Processing speed can be thought of as a general construct, but can be divided further into simple psychomotor speed such as the time taken to complete a rapid motor movement, for example, in box completion, horizontal line marking and digit copying, and higher order 'perceptual' tasks requiring executive control alongside motor control, for example, colour naming and addition/subtraction tasks (Cepeda et al., 2013). A variety of tasks are often used for 'reaction time' (RT), which can be 'simple' (one stimulus and one response type) or 'choice' (requiring more executive control,

[1]School of Psychology, Liverpool John Moores University, Liverpool, UK
[2]Liverpool Centre for Alcohol Research, Liverpool, UK
[3]Public Health Institute, Liverpool John Moores University, Liverpool, UK

Corresponding author:
Anna Powell, School of Psychology, Liverpool John Moores University, James Parsons Building, Byrom Street, Liverpool, Merseyside L3 3AF, UK.
Email: A.Powell@2019.ljmu.ac.uk

usually multiple possible stimuli each requiring a different response) RT (Cepeda et al., 2013). Processing speed is impaired by acute administration of alcohol (Maylor and Rabbitt, 1993; Tzambazis and Stough, 2000), as well as alcohol hangover (Grange et al., 2016). People diagnosed with alcohol use disorders (AUD) also show RT impairments (Crowe, 2019; Stavro et al., 2012).

Hazardous alcohol use has been defined as a pattern of alcohol use that increases risk of harm (World Health Organization, 2019). The relationship between hazardous use and processing speed is unclear. Some studies have shown no difference between hazardous and non-hazardous drinkers. For example, studies using Digit Symbol Substitution and pattern comparison tasks (requiring identification and copying of symbols into a matrix over a set time period) have found no difference in the number of correct substitutions made between HED and controls (Affan et al., 2018; Winward et al. 2014a, 2014b) in addition to absence of effects of age and age × drinking level interactions (Woods et al., 2016). Similarly, tasks requiring letter or number sequencing like the Trail Making Test A (TMT-A) and Delis–Kaplan Executive Function System letter/number sequencing have demonstrated no HED-related differences in the overall time to complete (Winward et al., 2014a, 2014b; Nguyen-Louie et al., 2015), with one study demonstrating that heavier drinkers aged 70 years showed no effects of binge drinking (ranging from 0 to 3+ drinks daily) on TMT-A, and that performance did not decline over the 7 years from time 1 (age 70 years) to time 2 (age 77 years) (Hogenkamp et al., 2014). Congruent Stroop RT has been shown to be comparable between moderate drinkers and HED on a spatial Stroop task (Kashfi et al., 2017). Rodgers et al. (2005) have also reported that light drinkers were superior to abstainers and occasional drinkers in a simple and choice RT task composite score (requiring pressing a response box when a specified light appeared), though hazardous and harmful drinkers did not differ significantly from any of the other groups.

However, using a similar paradigm with vibrotactile presentation of stimuli, drinking level-related differences were observed (Nguyen et al., 2013). There is also evidence that heavier non-dependent drinkers have faster processing speed than their lighter drinking counterparts. For example, Townshend and Duka (2005) demonstrated that binge drinkers were faster in eight-pattern matching to sample choice RT, with no increase in errors indicating that this was not due to a speed-accuracy trade-off. In a longitudinal study, Zanjani et al. (2013) utilised a task requiring finding and matching of figures, finding that overall males showed consistent decline across drinking status (abstainer, moderate drinker, at-risk drinker) while female abstainers showed the greatest decline relative to moderate and at-risk drinkers. This suggests that gender might be an important factor in alcohol-related changes in processing speed. These effects of heavier drinking on processing speed were supported in a recent systematic review including 18 studies assessing processing speed in HED, where HED was found to be associated with significantly faster processing speed in the meta-analysis (Lees et al., 2019). In addition, Piumatti et al. (2018) conducted a longitudinal analysis and found that RT was faster (improved) with every 1 g/day of alcohol but slowed as this increased beyond 10 g/day, with increasing age also identified as a factor in cognitive decline.

While the evidence above suggests little negative effect of heavy alcohol consumption on processing speed, some studies have identified processing speed deficits in heavy drinkers. For example, using the Paced Auditory Serial Addition Task requiring addition of pairs of two-digit numbers at different presentation speeds, people with HED were found to make fewer correct responses at faster presentation rates of 1.2 and 1.6 s (Hartley et al., 2004). Moreover, in a study that controlled for effects of age, sex, physical activity, age of onset of HED and other demographic variables, performance in TMT-A was found to be impaired in HED; there was also a significant effect in females only when stratifying the, sample indicating female HED, but not male HED, performed worse on TMT-A (Salas-Gomez et al., 2016). This was supported by Houston et al. (2014) who found that heavier alcohol consumption was associated with slower TMT-A completion. It is clear from the preceding two paragraphs that there are mixed findings regarding the effects of heavy drinking on processing speed and RT, and that gender, age and classification of drinking status could be potential confounds. For example, methods used to classify drinking behaviours (e.g. interview vs questionnaire, using frequency/quantity of consumption vs broader elements such as grouping into hazardous/non-hazardous vs assessing alcohol use as a continuum, and in studying hazardous drinkers generally vs specific consumption patterns, e.g. HED) varied between individual studies and could result in differential classification of a participant as at risk/hazardous or not.

In addition, the method of processing speed assessment, and the response modality could also affect the results. There were a range of tasks used in previous research that include pencil and paper, manual responding to visual or auditory presentation and manual responding to vibrotactile presentation. Cognitive functions are often objectively assessed using tasks that involve stimulus perception, for example, a RT assessment may rely on the pressing of a button upon seeing or hearing certain stimuli. Moreover, previous research also suggests that impairments may be domain specific, with Woods et al. (2016) finding no difference for perceptual speed, but an impairment in psychomotor speed. Consequently, modality of presentation and response may impact results. Previous research using inhibitory control tasks has identified that inhibition assessed using an auditory Go/No-go task is more consistent in finding impairment when alcohol is administered than when visual stimuli are used (Christiansen et al., 2013; Guillot et al., 2010). Vibrotactile perception, the perception of vibration through touch, can be assessed via tasks that stimulate the fingertips and record responses (Holden et al., 2012), and may be a useful method of assessing cognitive functions for a number of reasons. Firstly, the organisation of the somatosensory system is somatotopic (adjacent regions of the body represented adjacently), and is therefore ideal for inducing cortico–cortical interactions in adjacent or near-adjacent cortical regions (Nelson and Chen, 2008). Secondly, compared to auditory or visual input, it is also easier to limit competing somesense distractions (Holden et al., 2020; Tommerdahl et al., 2016). With regard to RT assessment specifically, noise can be added by computer systems, core processors, screen refresh rates and other hardware/software processing latencies (Holden et al., 2020). Holden et al. (2019) suggest that tactile stimulation using dedicated hardware is the most accurate method for RT assessment compared to visual stimuli with various response methods, and the one with the least RT variability. To date, most studies have used visual presentation and manual responding (Hogenkamp et al., 2014; Houston et al., 2014; Nguyen-Louie et al., 2015; Winward et al., 2014a, 2004b; Woods et al., 2016; Zanjani et al.,

2013). Two studies used dedicated hardware, with Rodgers et al. (2005) using a 'box' that displayed lights and had response buttons, and Nguyen et al. (2013) using the dedicated vibrotactile device mentioned previously. These methodological variations could account for some of the variability in findings.

In an earlier study, we used vibrotactile presentation with response via computer mouse to identify alcohol-related changes in processing speed during early residential detox in individuals with an AUD (Powell et al., 2021b). This approach also identified differences in the ability to discriminate between different amplitudes in heavy and light drinkers (Nguyen et al., 2013) and in young (aged 18–26 years) drinkers, and therefore appears sensitive to alcohol-related cognitive changes. The current study aimed to assess simple and choice vibrotactile perceptual RT and subjective ECF between hazardous and non-hazardous drinkers. We hypothesised that (1) hazardous drinkers would have slower RTs than non-hazardous drinkers, (2) hazardous drinkers would report poorer subjective ECF than non-hazardous drinkers and (3) there would be a negative correlation between objective and subjective measures, with slower RT scores (worse performance) correlating with poorer subjective function.

Methods

Design

A between-groups cross-sectional design assessed cognitive function via vibrotactile perception tasks and subjectively rated questionnaires between hazardous and non-hazardous drinkers. The independent variable was alcohol use, with two levels: non-hazardous and hazardous (Alcohol Use Disorders Identification Test (AUDIT; Saunders et al., 1993); ⩾8 categorised as hazardous drinking; World Health Organization, 2001). The dependent variables were simple RT, RT variability, choice RT and RT Fatigue and subscales of the Executive Function Index (EFI; Spinella, 2005). Gender, age and mood state were covariates in all main analyses.

Participants

Potential participants self-identified as eligible if they were aged 18+ and were fluent in English. Exclusion criteria which could affect RT were history of alcohol or substance use disorder, learning disabilities, neurological impairment, pregnancy, use of cocaine within the last month or a condition impacting sensation in dominant hand. A total of 90 individuals took part. Four participants were removed from the main analyses.[1] Therefore, the study comprised of 86 participants. All individuals lived in the United Kingdom and were recruited from the Northwest of England. Participants were categorised into hazardous ($n=36$) and non-hazardous drinkers ($n=50$) using AUDIT score (⩾8 classed as hazardous drinking). Age was significantly higher in the non-hazardous group $t(83.65)=2.621$, $p=0.010$ (see Table 1 for participant characteristics).

Materials

Demographics. Participants answered questions on age, gender, employment status, housing status, education level, mental health diagnoses, medication and country of residence.

Subjective executive function. The EFI (Spinella, 2005) is a 27-item five-point (1–5) Likert-type scale assessing five ECF elements derived via factor analysis; Strategic Planning, Motivational Drive, Impulse Control, Organisation and Empathy. Scoring involves summing relevant items (some reversely), and higher total and subscale scores indicate better function.

Scores on the EFI reflect the integrity of prefrontal cognitive abilities, and link well to the factor structure (Spinella, 2005); items group into a three-factor model; with Organisation and Strategic Planning as the first factor, Impulse Control and Empathy and the second factor and Motivational Drive as the third factor. These relate to the model of functional organisation of dorsolateral, orbitofrontal and prefrontal medial circuits (Cummings, 1993; Miller and Cummings, 2017). EFI had a Cronbach's α total of 0.82 in initial development, an acceptable internal consistency, ranging between 0.69 and 0.76 for the five subscales (Spinella, 2005). In our study, Cronbach's α totalled 0.80, and ranged from 0.78 to 0.80 across the items. It was lower for the subscales, which were as follows: Motivational Drive=0.42, Impulse Control=0.49, Strategic Planning=0.67, Organisation=0.74, Empathy=0.78.

Mood state. The Hospital Anxiety and Depression scale (HADS; Zigmond and Snaith, 1983) is a 14-item Likert-type scaled questionnaire used to assess the state of anxiety and depression. In this study, Cronbach's α totalled 0.80, and ranged from 0.77 to 0.80 across the items. For the subscales it was 0.77 (anxiety) and 0.66 (depression).

Alcohol use was assessed using the AUDIT (Saunders et al., 1993), a 10-item, five-point (0–4) Likert-type scaled questionnaire used to indicate hazardous/harmful drinking, via a cut-off score of 8+ (World Health Organization, 2001); in the present study, we did not utilise an upper limit for dependent drinking. AUDIT is validated within the general population (Aalto et al., 2009), and primary health care in six countries (World Health Organization, 2001), and is reliable (Donovan et al., 2006; Fiellin et al., 2000). Currently, Cronbach's α totalled 0.80 and ranged from 0.74 to 0.81 across the items (though item 6, 'How often during the last year have you needed a drink first thing in the morning to get yourself going after a heavy drinking session?' was removed from this internal consistency assessment due to there being no variance as every participant scored 0, 'Never').

Reaction time. This was assessed using dedicated hardware with an inbuilt microprocessor (the Brain Gauge Pro), which is the same size/shape as a computer mouse. A customised test battery was used to target prefrontal function, with two cylinders (5 mm diameter) delivering vibrotactile stimulation to the middle and index finger of the dominant hand. The device software provides participants with instructions on the computer screen and consists of a series of practice trials, and 10 successive trials, which are separated by a randomised intertrial interval of 2–7 s (Kim et al., 2020; Zhang et al., 2011). All participants in the present study were able to proceed past the practice trials to the main tasks. Participants completed both simple and choice RT as detailed in the procedure section. In addition to the simple and choice RT scores a *RT variability* score (the standard deviation of the 10 trials) and a *Fatigue* score (comparing the first and last tasks) are also generated. Averaged scores of simple RT, RT variability and choice RT were used in all analyses (milliseconds), as was the composite score of Fatigue.

Table 1. Characteristics of participants.

Measure	Non-hazardous (n =50)				Hazardous (n =36)			
	Min	Max	*M*	SD	Min	Max	*M*	SD
Age	18	80	37.40	18.83	18	70	28.00	14.41
AUDIT total	0	6	3.44	1.96	8	22	12.06	3.76
HADS anxiety	0	17	6.78	4.07	3	15	8.61	3.50
HADS depression	0	13	3.02	2.63	0	10	3.08	2.27
Gender	Count		Percentage		Count		Percentage	
Female	36		72.0		21		58.3	
Male	14		28.0		15		41.7	
Educational level								
Levels 1 – 5 (secondary school – Cert/HNC/HND or equivalent)	19		38.0		21		58.3	
Level 6 (BSc, BA or equivalent)	10		20.0		4		11.1	
Levels 7 and 8 (MSc, MA, doctoral or equivalent)	16		32.0		6		16.7	
Trade, technical or vocational training (level unknown)	4		8.0		5		13.9	
Employment status								
Full-time work	10		20.0		8		22.2	
Part-time work	13		26.0		14		38.9	
Student	8		16.0		5		13.9	
Retired	7		14.0		2		5.6	
Unemployed	12		24.0		7		19.4	
Mental health disorders								
None	43		86.0		30		83.3	
Reported mental health condition (e.g. anxiety, personality, eating, neurodevelopmental)	7		14.0		6		16.7	
*Cognition impacting medication**								
No medication	34		68.0		27		75.0	
Medication which could impact cognition (including contraceptive pill, antidepressants, PPI or H1/H2 antagonist)	14		28		8		22.2	
Other medication not affecting cognition	2		4.0		1		2.8	

HNC: Higher National Certificate; HND: Higher National Diploma; NSAID: non-steroidal anti-inflammatory drugs; PPI: proton pump inhibitors.
*No participants took antiparkinsonian, antibiotic, antipsychotic, pain relief (opioid or NSAID), anticonvulsant, anxiolytic, alcohol-related or high-dose vitamin medications.

Procedure

Potential participants were recruited using opportunity sampling via various methods. Student participants were recruited via an internal recruitment database, posters in university buildings, Listserv emails and the Liverpool John Moores University (LJMU) research participation website. Members of the public were recruited via social media adverts (Twitter) and the LJMU Psychology Research Participation Panel. Recruited participants were invited to LJMU for an individual testing session in a psychology laboratory. After giving informed consent, participants completed the vibrotactile tasks (simple, choice and then a repetition of simple to create the Fatigue score). For simple RT, participants were instructed to press the opposing tip (index finger) as soon as they felt a tap (25 Hz, 300 µm, 40 ms) on their middle finger. For choice RT participants were instructed to press the opposing tip as soon as they feel a vibration to the other finger. In this condition, either index or middle finger may be tapped each time, so responding involves choice. Participants first completed a series of practice trials for which they must correctly respond three consecutive times to proceed, and 10 successive trials, which are separated by a randomised intertrial interval of 2–7 s. After completion of the RT tasks, the questionnaires were completed in a counterbalanced fashion. Overall, the testing session lasted between 45 and 60 min per participant and participants were given a debrief sheet explaining the purpose of the study with information about where they can seek help for their/others' drinking problems if they are concerned, and given a £10 shopping voucher as a thank you for their participation. The study was approved by LJMU Research Ethics Committee (19LJMUSPONSOR0037).

Statistical analyses

Analyses were conducted using SPSS v28 (IBM Corp., Armonk, New York, USA). To assess differences in mood state between the groups, we used multivariate analysis of variance (MANOVA) with drinking level (hazardous vs non-hazardous) as the between-groups independent variable and HADS anxiety and depression as the dependent variables. Shapiro–Wilk tests using a Bonferroni correction indicated normality of mood state across drinking level was violated for two out of four tests. Due to there being no non-parametric MANOVA equivalent, and due to MANOVA being robust regarding normality violations, this analysis was considered the most appropriate. Two multivariate analysis of covariance (MANCOVA) analyses were performed on average RT scores, and on EFI scores, using drinking level (non-hazardous and hazardous) as the between-groups independent variable. In both analyses, mood state, age and gender were included as covariates, due to their associations with both alcohol use/consequences (Novier et al., 2015; Tovmasyan et al., 2022; White, 2020) and ECF (Best and Miller, 2010; Ferguson et al., 2021; Grissom and Reyes, 2019; Mitchell and Phillips, 2007; Zaninotto et al., 2018). MANCOVA assumptions were assessed, linearity and residual normality were acceptable. For the RT MANCOVA, Box's test was violated ($p=0.01$) so Pillai's Trace statistics are reported. Homogeneity of regression slopes were achieved in all cases except drinking level × gender ($p=0.05$). Therefore, this violation indicates that a moderator approach would be more appropriate, so the drinking level × gender interaction term is subsequently included in the model. We also created age-related drinking groups and repeated the RT MANCOVA with age-related drinking level (four levels: 'older' (30+ years) hazardous; older non-hazardous; 'younger' (18–29 years) hazardous; younger non-hazardous) as the between-groups independent variable, average RT scores as the dependent variables and gender and mood state as covariates to assess the effects of age-related drinking level on RT measures. Finally, to investigate relationships between subjective and objective function, a bivariate correlation was conducted.

Results

Descriptive statistics for mood state, subjective ECF and RT in hazardous and non-hazardous drinkers, and RT in age-grouped drinking levels are displayed in Table 2.

Inspection of Table 2 shows that while self-reported depression state scores were comparable between the groups, the hazardous drinking group had higher mean scores for anxiety state indicating higher subjective levels of anxiety. Using MANOVA, the multivariate main effect of drinking level on mood approached significance, $F(2,83)=2.86$, $p=0.06$, with univariate analyses demonstrating that anxiety, $F(1,84)=4.75$, $p=0.03$, but not depression, $F(1,84)=0.01$, $p=0.91$, differed significantly between the groups.

Reaction time

Table 2 shows that there was little difference between the groups in covariate adjusted means for simple RT, RT variability and Fatigue. There were no significant differences in percentage correct on choice RT between hazardous (93.33%) and non-hazardous (93.80%) drinkers, $F(1,83)=0.06$, $p=0.81$]. However, the hazardous drinkers had lower scores for choice RT indicating that they were faster (better) than the non-hazardous drinkers. We used MANCOVA to assess between-group differences in RT measures; for brevity, only multivariate effects are reported in full below (see Table 3 for full MANCOVA statistics). There was a significant multivariate main effect of drinking level on overall RT performance, $F(4,76)=2.80$ $p=0.03$, $\eta_p^2=0.13$. Age, $F(4,76)=14.56$, $p<0.001$, $\eta_p^2=0.434$, and gender, $F(4,76)=3.09$, $p=0.02$, $\eta_p^2=0.14$, were also significant as covariates, as was the gender × drinking level interaction, $F(4,76)=2.70$, $p=0.04$, $\eta_p^2=0.12$. State depression, $F(4,76)=0.19$, $p=0.12$, and state anxiety, $F(4,76)=0.19$, $p=0.12$, were not significant as covariates. Table 3 reveals that age (RT, RT variability, choice RT) and gender (RT variability, choice RT) were both significant covariates for differing RT scores in the MANOVA, while the effects of drinking level on choice RT was the only significant difference after controlling for the effects of age, gender and state mood.

Due to the significant covariate effect of age in all analyses, we categorised participants as 'older' (30+ years) hazardous ($n=8$) and non-hazardous ($n=25$) drinkers and 'younger' (18–29 years) hazardous ($n=28$) and non-hazardous ($n=24$) drinkers, and repeated MANCOVA. The mean scores for these groups in Table 2 demonstrate that the two younger groups have lower (faster) RT scores than the older groups, and that the younger hazardous drinkers are faster than the other groups. There was a significant multivariate main effect of age-related drinking group, $F(12,234)=2.77$, $p<0.001$, $\eta_p^2=0.12$, and significant

Table 2. Descriptive statistics for mood, RT and EFI for hazardous and non-hazardous drinkers.

	Non-hazardous		Hazardous	
	M	SE	*M*	SE
HADS anxiety	6.78*	0.54	8.61	0.64
HADS depression	3.02	0.35	3.08	0.41
MANCOVA adjusted RT scores				
Simple RT	310.97	9.46	301.01	11.27
RT variability	28.78	2.89	28.78	3.44
Choice RT	462.07*	11.84	442.64	14.10
Fatigue	–9.04	9.39	–12.83	11.19
MANCOVA adjusted EFI mean scores				
Motivational Drive	15.36	0.33	14.49	0.39
Organisation	16.97	0.43	15.88	0.51
Strategic Planning	26.75***	0.54	23.48	0.63
Impulse Control	17.40***	0.32	14.93	0.38
Empathy	25.70	0.44	26.11	0.52

	Younger non-hazardous		Younger hazardous		Older non-hazardous		Older hazardous	
MANCOVA adjusted RT scores for age-grouped drinking levels								
Simple RT	295.06	14.96	267.19****	14.27	345.73**	14.88	357.18*	25.96
RT variability	22.19	4.26	26.00	4.06	38.84	4.26	26.59	7.39
Choice RT	421.47**	18.99	401.28****	18.11	520.61****	18.88	489.95	32.94
Fatigue	–1.97	13.15	1.64	12.55	–22.27	13.08	–43.85	22.82

Differences significant at: *$p<0.05$. **$p<0.01$. ***$p<0.001$. ****$p<0.0001$.
RT: reaction time; EFI: Executive Function Index; AUDIT: Alcohol Use Disorders Identification test; HADS: Hospital Anxiety and Depression scale; SE: standard error; MANCOVA: multivariate analysis of covariance.

covariate effects of gender, $F(4,76)=2.79$, $p=0.03$, $\eta_p^2=0.13$ and depression state, $F(4,76)=2.68$, $p=0.04$, $\eta_p^2=0.12$, but not anxiety, $F(4,76)=1.87$, $p=0.12$. Pairwise comparisons (Table 4) indicated that young hazardous drinkers performed better than both older groups on simple RT; non-hazardous older drinkers had significantly worse RT variability than non-hazardous younger drinkers; and non-hazardous older drinkers performed worse than both young groups on choice RT.

Subjective executive function

Table 2 displays the MANCOVA adjusted means for the EFI subscales, indicating that for all subscales except Empathy, non-hazardous drinkers score higher (better subjective ECF). MANCOVA found significant covariate effects of age, $F(5,75)=5.94$, $p<0.001$, $\eta_p^2=0.28$, depression state, $F(5,75)=6.45$, $p<0.001$, $\eta_p^2=0.30$ and anxiety, $F(5,75)=6.34$, $p<0.001$, $\eta_p^2=0.30$, but not of gender, $F(5,75)=0.75$, $p=0.60$. After covariates were controlled for, there was a significant multivariate main effect of drinking group on subjective ECF, $F(5,75)=7.56$, $p<0.001$, $\eta_p^2=0.34$. Follow-up univariate ANCOVAs found that while non-hazardous drinkers reported better subjective ECF on all measures (except for Empathy), this difference was only significant for Strategic Planning, $F(1,79)=14.38$, $p<0.001$, $\eta_p^2=0.154$ and Impulse Control, $F(1,79)=22.81$, $p<0.001$, $\eta_p^2=0.224$. There were no significant differences between hazardous and non-hazardous drinkers for Motivational Drive, Organisation or Empathy, $p=0.11$, 0.12 and 0.57, respectively).

Subjective and objective Function

To assess the relationships between subjective and objective function, bivariate correlations (Kendall's τ) were run on average RT scores and EFI subscale scores (see Table 5). There were significant positive associations between Organisation and simple, $\tau_b=0.20$, $p=0.01$, and between Impulse Control and simple, $\tau_b=0.25$, $p=0.001$, and choice RT, $\tau_b=0.25$, $p=0.001$. This suggests that as subjective function improved, RT performance worsened (response latency increased).

Discussion

This study assessed hazardous drinking-related differences in vibrotactile simple and choice RT. In contrast to hypothesis 1, hazardous drinkers were faster than non-hazardous drinkers at choice RT, though they reported poorer subjective EF. There was a positive correlation between objective and subjective measures, slower simple or choice RT scores (worse performance) correlated with better self-reported ECF on certain EFI subscales (Organisation and simple RT, and Impulse Control and simple and choice RT). After controlling for covariates, hazardous drinking was associated with faster choice RT, but not with simple RT, RT variability or Fatigue. This suggests that hazardous drinkers, in this study, were better at responding quickly on the more executive-oriented task, but that this advantage did not extend to simple RT, the variability between simple RT trials (an indicator of attention) or the Fatigue score.

Table 3. MANCOVA between subject effects for (i) drinking level on RT controlling for mood state, age and gender with a gender × drinking level interaction term and (ii) age-related drinking level on RT controlling for gender and mood state.

Effects		(i) Drinking level (hazardous vs non-hazardous)			(ii) Age-related drinking group		
		F	p	η_p^2	F	p	η_p^2
Drinking level × gender, $F(1,79)$	RT	0.08	0.78	0.00	–	–	–
	RT variability	0.09	0.76	0.00	–	–	–
	Choice RT	4.69	0.03	0.06	–	–	–
	Fatigue	0.04	0.84	0.00	–	–	–
HADS anxiety, $F(1,79)$	RT	0.09	0.77	0.00	0.05	0.83	0.01
	RT variability	0.37	0.54	0.00	0.34	0.56	0.01
	Choice RT	1.15	0.29	0.01	0.68	0.41	0.01
	Fatigue	1.66	0.20	0.02	2.02	0.16	0.03
HADS depression, $F(1,79)$	RT	0.61	0.44	0.01	1.72	0.19	0.02
	RT variability	3.81	0.05	0.05	3.21	0.08	0.04
	Choice RT	1.17	0.28	0.01	1.93	0.17	0.02
	Fatigue	0.27	0.61	0.00	0.02	0.89	0.01
Age, $F(1,79)$	RT	39.68	0.01	0.33	–	–	–
	RT variability	16.53	0.01	0.17	–	–	–
	Choice RT	43.88	0.01	0.36	–	–	–
	Fatigue	3.62	0.06	0.04	–	–	–
Gender, $F(1,79)$	RT	3.68	0.06	0.04	2.94	0.09	0.04
	RT variability	4.25	0.04	0.05	4.52	0.04	0.05
	Choice RT	7.48	0.01	0.09	5.86	0.02	0.07
	Fatigue	3.06	0.08	0.04	3.11	0.08	0.04
Drinking level, $F(1,79)$, or age-related drinking level, $F(3,79)$	RT	0.01	0.94	0.00	6.04	0.001	0.19
	RT variability	0.08	0.77	0.00	2.77	0.05	0.10
	Choice RT	5.61	0.02	0.07	7.91	0.001	0.23
	Fatigue	0.07	0.79	0.00	1.41	0.25	0.05

MANCOVA: multivariate analysis of covariance; RT: reaction time; HADS: Hospital Anxiety and Depression scale.

Research with clinical populations of people with AUD consistently shows impaired processing speed (Crowe, 2019; Stavro et al., 2012). It has been assumed that hazardous drinking can be considered a precursor stage to developing an AUD, and therefore that many of the impairments observed at the dependent stage would be seen in hazardous drinkers, albeit to a lesser extent (Lees et al., 2019). However, the current results challenge this assumption, and are more consistent with other studies showing faster RT in hazardous drinkers (Bø et al., 2016; Hartley et al., 2004; Kashfi et al., 2017; Lees et al., 2019; Mazumder et al., 2021; Townshend and Duka, 2005; Zanjani et al., 2013), and those that show no relationship (Affan et al., 2018; Cohen-Gilbert et al., 2017; Hogenkamp et al., 2014; Nguyen et al., 2013; Rodgers et al., 2005; Winward et al., 2014a, 2014b; Woods et al., 2016). This finding is of interest and suggests that perhaps hazardous drinkers require less time to make a choice in a choice RT task than non-hazardous drinkers (as proposed by Townshend and Duka, 2005). There are a number of possible tentative explanations for this. Firstly, in animal models, acute alcohol administration reduces longer RTs on the five Choice Serial Reaction Time task, with longer RT emerging during abstinence, and peaking 30 days after last acute administration (Wright et al., 2013). Consequently, it is possible that in the present study, the hazardous drinkers were faster due to recent heavier alcohol use, and that slower RT might have become apparent under longer periods of abstinence. Higher levels of gamma-aminobutyric acid (GABA) due to recent heavy alcohol consumption could lend support to this explanation. GABA increases cortical inhibition and thus higher GABA may be beneficial for tasks involving response selection, as it limits neuronal noise, enabling selective neural activity (de la Vega et al., 2014; Munakata et al., 2011; Snyder et al., 2010).

Secondly, while in the present study it is unlikely that the increased RT reflects a speed-accuracy trade-off as there were no significant between-group differences in percentage correct in choice RT, it is possible that the choice RT task was too simple to elicit errors, with only two possible choices. Other studies that have found a speed-accuracy trade-off have used more complex choice RT tasks, or those that require adaptive learning after responding, for example, Bø et al.'s (2016) adaptive Go/No-go where people with HED were faster but failed to adapt to incorrect responses in line with controls. Such speed-accuracy trade-offs are often seen in ECF tasks measuring response inhibition, though tasks assessing this ECF do not solely measure response inhibition, and include elements of processing speed; such as average RT in the Go/No-go task, mean RT in Go trials of the Stop-Signal Task and prosaccade latency in the Antisaccade task (Weiss and Luciana, 2022). As described in the introduction, in one previous study that found faster processing, there was a speed-accuracy trade-off (quicker responses but fewer correct choices), interpreted as indicating an inhibitory control deficit (Kashfi et al., 2017), which may in part explain the initiation of

Table 4. Mean differences in pairwise comparisons in MANCOVA of age-related drinking groups.

		Hazardous older	Non-hazardous younger	Non-hazardous older
RT	Hazardous younger	−89.99*	−27.88	−78.54*
	Hazardous older		62.11	11.45
	Non-hazardous younger			−50.67
RT variability	Hazardous younger	−0.58	3.91	−12.84
	Hazardous older		4.40	−12.26
	Non-hazardous younger			−16.65*
Choice RT	Hazardous younger	−88.67	−20.18	119.32*
	Hazardous older		68.49	−30.65
	Non-hazardous younger			−99.14*
Fatigue	Hazardous younger	45.48	3.61	23.90
	Hazardous older		−41.88	−21.58
	Non-hazardous younger			20.30

MANCOVA: multivariate analysis of covariance; RT: reaction time.
*Mean difference significant at $p < 0.01$ after Bonferroni correction.

Table 5. Kendall's τ correlation matrix for RT and subjective executive function.

	Simple RT	RT variability	Choice RT	Fatigue	EFI-MD	EFI-ORG	EFI-SP	EFI-IC
RT variability	0.393*	–						
Choice RT	0.451*	0.280*	–					
Fatigue	−0.173	−0.082	0.120	–				
Motivational Drive	0.091	0.069	0.077	0.043	–			
Organisation	0.198*	0.093	0.161	−0.002	0.214*	–		
Strategic Planning	0.084	0.041	0.116	0.125	0.255*	0.249*	–	
Impulse Control	0.252*	0.103	0.251*	0.032	0.218*	0.452*	0.200	–
Empathy	−0.030	−0.115	−0.019	−0.028	0.113	0.042	0.161	0.398

RT: reaction time; EFI: Executive Function Index; MD: Motivational Drive; ORG: Organisation; SP: Strategic Planning; IC: Impulse Control.
*$p \leq 0.01$ (two-tailed).

hazardous alcohol use (Blakemore and Robbins, 2012; Gullo and Dawe, 2008). However, in Cohen-Gilbert et al. (2017); Townshend and Duka (2005), several of the studies assessed in Lees et al. (2019), and in the current study, there was no evidence of such a trade-off, even though individuals who responded faster were those who scored lower on the subjective Impulse Control subscale of the EFI. While impulsivity is often viewed negatively, perhaps in some circumstances (particularly those with low capacity for risk) it can lead to favourable outcomes (Gullo and Dawe, 2008). Alternatively, as suggested by Scaife and Duka (2009), the choice RT task may not be complex enough to produce errors in performance at this level of alcohol use, regardless of impulsivity. Another consideration is that young adult drinkers may be faster due to better response monitoring (slowing down following errors, allowing success/failure to guide performance) (Bø et al., 2016), which was not assessed in the current study.

In the age-related drinking group analysis, the participants demonstrating fastest processing speed on simple RT were younger hazardous drinkers, while those with the poorest speed on choice RT were non-hazardous older drinkers. Considered against the 'premature aging hypothesis', where AUD in clinical populations may either accelerate ageing of the brain in individuals of any age, or brains of older drinkers with AUD may be more vulnerable to the effects of alcohol (Ellis and Oscar-Berman, 1989; Oscar-Berman and Marinkovic, 2003; Oscar-Berman et al., 2000), this finding in non-clinical hazardous drinkers suggests that the phenomena may not be so clear cut. One study comparing whole-brain contrasts of patients with AUD and controls, provided support for the premature ageing hypothesis, suggesting that increased age increases vulnerability to the cognitive effects of alcohol, and that youth provides protection (Guggenmos et al., 2017). Therefore, considering the current finding that young hazardous drinkers performed better than all older drinkers at simple RT, perhaps the performance difference is preexisting, but alcohol use eventually negates this, just not to the extent of clinical cases of AUD, as hazardous older drinkers were no worse than the other groups. As processing speed is a task-independent construct (Fry and Hale, 2000), it is unlike other functions examined in the literature. Indeed, the findings regarding higher order ECF in hazardous drinkers are more inconsistent in younger drinkers, while older drinkers generally display impairment compared to controls, likely due to a neurocompensatory mechanism of increased cognitive effort/neuronal labour in younger subjects (Gil-Hernandez et al., 2017). Furthermore, some of the processing speed studies previously mentioned found higher brain activation in areas supporting cognitive processes during tasks, which was interpreted as possible neurocompensation (Affan et al., 2018; Kashfi et al., 2017; Pérez-García et al.,

2022). The systematic review by Lees et al. (2019) also found greater brain activity during tasks involving attention, inhibition and working memory in HED. It is worth considering whether perhaps an initial processing speed advantage in younger hazardous drinkers could contribute to their ability to perform executive tasks at a comparable level to non-hazardous drinkers, and future research should seek to clarify this.

The finding of poorer subjective function in hazardous drinkers initially appears to contrast with the result of better processing speed. Additionally, the finding of a positive correlation between objective and subjective function is intriguing, as those who were fastest, reported worse day-to-day subjective function. However, given that the strongest relationship was found between Impulse Control and the RT scores, this suggests that slower individuals may have been more prone to thinking before acting. That there was no speed-accuracy trade-off limits this theory, but again, may be due beneficial elements of impulsivity (Gullo and Dawe, 2008), or the relatively easy choice RT task (Scaife and Duka, 2009). Alternatively, this finding may be due to other alcohol effects, such as on metacognition (Le Berre et al., 2017), increased cognitive effort required for tasks (neurocompensation, as described) or methodological issues with vibrotactile perception as an assessment in this cohort. To assess the possibility of metacognition, future studies should compare subjective assessment with validated ECF tasks, alongside processing speed, considering how each of these interrelates. Processing speed in this context should also be assessed using a range of modalities and difficulties, to ensure the previously reported high-RT accuracy of the Brain Gauge compared to other modalities (Holden et al., 2019) is replicable relating to alcohol use, and to further examine accuracy and inhibitory control. Assessment of neural activity during these varied processing speed tasks would also be beneficial.

It is important to note that while the current study found faster processing in hazardous drinkers, particularly in younger hazardous drinkers, the literature is obviously still inconsistent, and the study is not without its limitations. Firstly, while the article used two versions of the RT task, neither were particularly complex, which as mentioned, may have disguised any speed-accuracy disadvantages of quick responding (Scaife and Duka, 2009), indicating that future researchers should use a range of tasks to assess processing speed. Secondly, while it is interesting to speculate about causes for the current findings, this study did not use direct brain measurements relevant to processing speed. Future research could assess hazardous and non-hazardous drinkers using structural methods linked to neural transmission speed, such as those assessing myelination (via recent myelin magnetic resonance imaging techniques (van der Weijden et al., 2021) or indirectly through diffusion tensor imaging (Aung et al., 2013; Song et al., 2002)), or functional methods that assess temporal information about neural processes, such as event-related potentials (ERP). A further limitation of the current study is that it did not assess across patterns of hazardous drinking (e.g. daily drinking vs HED). Maurage et al. (2012) found ERP deficits associated with specific drinking patterns, indicating that researchers should consider how these different patterns affect function. While roughly equal numbers of hazardous (26%) versus non-hazardous (28%) drinkers were tested in the morning versus afternoon testing session, we cannot rule out that some of the effects may have been due to the effects of individual circadian rhythms on cognitive function (Adan, 1993; Valdez, 2019). Future research should seek to assess participants' circadian preferences (via e.g. the morningness-eveningness questionnaire) and allocate to a testing session as appropriate, and consider how circadian rhythmicity may also confound via influence on alcohol use behaviours (Adan, 2013). Cronbach's α also revealed varied internal consistency for the subscales of the EFI. These were acceptable in total, across the items, and for the subscales Organisation and Empathy, but were poor for the subscales Motivational Drive, Impulse Control and Strategic Planning. This indicates that any interpretations of the analyses using the EFI must be considered potentially unreliable, particularly those about the subscale Impulse Control. Future research assessing subjective function should consider whether other tools such as the Behaviour Rating Inventory of Executive Function-Adult (Roth et al., 2013) or the Comprehensive Executive Functions Inventory (Naglieri and Goldstein, 2013) would be more appropriate. Finally, the relatively small sample size (particularly in the groups in the age-related drinking group analysis), and lack of a priori power calculation reduces dependability of the findings.

In conclusion, we found that hazardous drinkers were significantly faster at choice RT, and when examined in age-groups, younger hazardous drinkers were fastest at simple RT, while older non-hazardous drinkers were poorest at choice RT. This was discussed in the context of the premature aging hypothesis, impulsivity and neurotransmitters. Furthermore, subjective function was poorer in hazardous drinkers, specifically in young hazardous drinkers, indicating either a possible metacognitive deficit, increased effort or issues with vibrotactile perception assessment in this cohort. Further research should use additional methods to assess RT in hazardous drinking, including assessing neurotransmitter or functional temporal activity during vibrotactile RT, comparing vibrotactile RT with other objective assessments and examining whether these assessments differ across different hazardous drinking patterns.

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ORCID iDs

Anna Powell https://orcid.org/0000-0002-4879-4124
Catharine Montgomery https://orcid.org/0000-0003-2805-5807

Data availability statement

The authors will share the anonymised dataset on the Liverpool John Moores University Research Data Repository. It will be available at https://opendata.ljmu.ac.uk/

Note

1. One participant was removed from all analyses due to nerve damage in their dominant hand that was not disclosed until testing was complete. Three participants were removed due to initial boxplot outlier inspection revealing that they had invalid scores due to not meeting the choice reaction time response threshold required.

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