Alcohol-related cognitive impairment: neuropsychological findings and cognitive assessment in a clinical context

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July 2014

This thesis is submitted in partial fulfilment of the requirements of the degree of

Doctorate of Psychology (Clinical Neuropsychology)

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Thesis Abstract

Background: It is well established that chronic alcohol consumption can detrimentally impact brain structure and function. In the clinical setting, however, diagnosis of alcohol-related cognitive impairment (ARCI) is frequently complicated by the presence of comorbid psychiatric and health conditions. It is unclear which neuropsychological tasks best detect cognitive impairment in alcohol use disorder (AUD) samples in which these comorbid conditions are present.

Aims: The research included in the current thesis was designed to provide clinically useful findings regarding the neuropsychological features of ARCI, including the presentation of ARCI in individuals with comorbid conditions.

Method: A systematic review of the literature was conducted to examine the neuropsychological profile of two alcohol-related cognitive disorders: alcohol-related dementia and Korsakoff syndrome. In addition, two empirical studies were conducted. In the first, a neuropsychological battery was administered to 21 participants diagnosed with AUD and a control group matched on age, education and gender. Statistical comparisons between groups on cognitive tasks were performed. In the second, the diagnostic accuracy of the Mini Mental State Examination (MMSE), Addenbrooke's Cognitive Examination-Revised (ACE-R), and the Montreal Cognitive Assessment (MoCA) in detection of cognitive impairment was examined. This was evaluated in 30 individuals with substance use disorder diagnoses and 20 healthy controls using the receiver operating characteristic method.

Results: The results of the systematic review demonstrated the heterogeneity in methodological approaches, which preclude definitive conclusions being drawn regarding the neuropsychological profile of alcohol-related cognitive syndromes. The results of the first empirical study confirmed the high rates of comorbid psychiatric, neurological and health conditions that accompany individuals with AUD. Participants in the AUD group were most frequently impaired in the delayed memory domain, while semantic fluency and visuospatial memory tasks best distinguished the AUD group from controls. In the second empirical study, it was demonstrated that the ACE-R and the MoCA had superior discriminative qualities to the MMSE in the detection of cognitive impairment in the substance use sample. It was concluded that further validation of cognitive tasks appropriate for assessment of the SUD population is necessary in future research.

Candidate's Declaration

I hereby certify that the work presented in this thesis entitled, "Alcohol-related cognitive impairment: neuropsychological findings and cognitive assessment in a clinical context " has not previously been submitted for a higher degree to any other university or institution.

I also certify that this thesis is an original piece of research and that it has been written by me. Where appropriate, I have acknowledged any assistance in undertaking the research project and in preparing this thesis. I also certify that all sources of information and literature used in the preparation of this thesis have been indicated within the thesis and cited appropriately.

The research presented in this thesis was approved by the University of Wollongong HREC (Reference: HREC/11/007, 11th April 2011), and also by the Macquarie University HREC (Reference: 5201200044, 14th February 2012).

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July 2014

Acknowledgements

Firstly, I would like to thank my supervisors, Dr Jennifer Batchelor and Dr Adrienne Withall, for their generous advice and support through the research process. Their contribution to the preparation manuscripts was invaluable. I would further like to thank Dr Sue Meares for her constructive feedback on the journal articles, and Dr Eugene Chekaluk for his advice on statistical matters.

Furthermore, I am extremely grateful to the staff of the South East Sydney Local Health District Service, who embraced the project with enthusiasm and were pivotal in allowing this project to become a reality. I would also like to thank the team at INSPIRED, for all their assistance and support with their project, and their ongoing commitment to developing best models of care for individuals with early onset memory disorders.

I am extremely grateful to the patients at the SESLHS, and the group of carers, all who willingly gave their time and effort to partake in this research. It has been extremely humbling to meet a group of such diverse and resilient individuals, and I can only hope that the findings of this research serves to benefits treatment provision for the substance use population in the near future.

Lastly, I must thank my family and friends, who have encouraged and supported me every step of the way. I am forever grateful.

Explanation of Thesis Format

The current thesis comprises a collection of three research papers that have been prepared for submission for publication. Given the independent nature of these papers, some repetition of ideas or phrases throughout the thesis was unavoidable. The mechanical style and referencing is consistent with the American Psychological Association (6th Ed) style. For ease of comparison, however, references are periodically made to other chapters in the thesis. In addition, sections, tables and figures contained within each chapter have been re-numbered in consecutive order throughout the thesis. For ease of reading, reference lists have not been included at the end of each chapter but have rather been combined into one comprehensive reference list, which appears as Chapter 6 at the end of the thesis.

The thesis also includes a general introductory chapter in which the existing literature is reviewed, the justification for the current research is established, and the general aims and hypotheses of the research are detailed. A general discussion chapter has also been included following the third paper in order to bring together the findings from each study and to provide a conclusion to the research aims and hypotheses.

The candidate's role in this research project has comprised responsibility for conducting neuropsychological assessments, the analysis of data, and writing of the general introduction, general discussion, and the three journal articles. The candidate

took an active involvement in patient recruitment (including eligibility screening); however in accordance with ethical clearance, all initial patient contact was made by senior Clinical Nurse Consultants at the Langton Clinic and the St George/Sutherland Drug and Alcohol Services. Dr Jennifer Batchelor and Dr Adrienne Withall assisted with the design of studies and preparation of the thesis. Jody Kamminga assisted with a literature search review and quality rating assessment for the first paper.

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List of Commonly Used Abbreviations

ACE-R	Addenbrooke's Cognitive Examination Revised
ARD	Alcohol Related Dementia
ARBD	Alcohol Related Brain Damage
ARBI	Alcohol Related Brain Injury
ARCI	Alcohol Related Cognitive Impairment
AD	Alzheimer's Disease
AUD	Alcohol Use Disorder
CALD	Culturally and Linguistically Diverse Background
KS	Korsakoff Syndrome
MoCA	Montreal Cognitive Assessment
NPA	Neuropsychological Assessment
NSB	Neuropsychological Battery
SUD	Substance Use Disorder
TBI	Traumatic Brain Injury
WE	Wernicke's Encephalopathy
WKS	Wernicke Korsakoff Syndrome

CHAPTER ONE

General introduction

1. General Introduction

Alcohol is one of the most widely used – and misused – substances in the world (Hayes, Deeny, Shaner, & Nixon, 2013). The World Health Organisation estimates that harmful use of alcohol ranks among the five risk factors for disability and death throughout the world and is a causal factor in more than 200 disease and injury conditions (WHO, 2014). Alcohol use disorders can entail alcohol abuse (harmful use of alcohol), alcohol dependence (physiological dependence on alcohol) or symptoms of both (American Psychiatric Association, 2013). These disorders have been reported to be present in approximately 4% of the world's population (WHO, 2014) with a pronounced impact on disability and disease. While the adverse consequences of excessive alcohol consumption on physical health are well documented (Alfonso-Loeches & Guerri, 2011), research in recent decades has increasingly focused on the impact of alcohol on brain structure and function. Post-mortem evaluations suggest that one- to two-thirds of individuals with a history of an alcohol use disorder (AUD) demonstrate some degree of brain pathology on autopsy (Cook, Hallwood, & Thomson, 1998; Goldstein, 1980). This is consistent with behavioural observations of prevalent cognitive impairment in heavy users of alcohol (Stavro, Pelletier, & Potvin, 2012). In the clinical setting, however, diagnosis of alcohol-related cognitive impairment (ARCI) is frequently complicated by the presence of comorbid psychiatric and health conditions which have been shown to independently impact brain function (Fein, Di Sclafani, Finn, & Shumway, 2008; Petrakis, Gonzalez, Rosenheck, & Krystal, 2002). Systematic examination of the contributions of these factors to the cognitive dysfunction in AUD populations is lacking in the literature. In addition, there is limited consensus on the key

neuropsychological features of alcohol-related cognitive disorders. Further investigation of cognitive deficits that characterise this population has significant implications for detection and management of these cognitive disorders.

1.1. Aims

The research reported in the current thesis was designed to further knowledge regarding the profile of alcohol-related cognitive impairment. As this area encompasses an extensive amount of scientific knowledge, it was not within the scope of this study for all aspects of this topic to be examined. Instead, three specific lines of investigation were conducted, with the intent to provide findings relevant to those working with AUD samples on a clinical level. Firstly, a systematic review of literature in which the neuropsychological profile of alcohol-related cognitive disorders had been compared to other dementia syndromes was performed. Secondly, an empirical study was conducted to establish the neuropsychological profile of treatment-seeking individuals with AUD, including those with comorbid conditions. Lastly, a second empirical study was undertaken to examine the diagnostic accuracy of two screening measures in detecting cognitive impairment within a larger population of individuals with substance use disorders (SUD; this encompasses individuals with a diagnosis of an alcohol use disorder and/or any other substance use disorder). The following introduction provides an overview of the current literature regarding the mechanisms of alcohol related brain damage (ARBD), cognitive outcomes and clinical comorbidities in ARBD, and the implications of ARBD on treatment outcome. The specific research questions pertinent to this thesis are then detailed.

1.2. The neuropathology of alcohol-related brain damage

Early neuropathological studies revealed significant reductions in brain volume in individuals with a history of alcohol dependence compared with healthy controls (Harper & Blumbergs, 1982). Imaging studies have since confirmed enlarged ventricles and sulci secondary to volume loss in individuals with AUD, which occurs in both cortical and subcortical cerebral structures (Harding, Halliday, Caine, & Kril, 2000; Harper, 2009). Tissue loss is most prominent in the white matter of the frontal regions, corpus callosum and cerebellum (Buehler & Mann, 2012), however regional reductions in the grey matter in the superior frontal association cortex, hippocampus and cerebellum are also consistently observed (Harper, 2009). Volume loss in the parietal lobes, thalamus, hypothalamus and insula is also common (Pitel et al., 2012; Sullivan & Pfefferbaum, 2001). The frontal lobes and their extended circuitry (including limbic and cerebellar connections) appear particularly vulnerable to alcohol-induced damage, with substantial volume shrinkage, and abnormal glucose metabolism and perfusion observed on functional and structural imaging studies in the frontal lobes of alcohol dependent individuals (Brokate et al., 2003; Sullivan & Pfefferbaum, 2005). Importantly, abstinence can at least partially reverse many of these brain changes, with improvements in brain volume and function occurring with as little as a few days of sobriety (Kril & Halliday, 1999; Mason et al., 2005; van Eijk et al., 2013). While the reversibility of volume loss and functional loss is not completely understood, it seems to mimic general mechanisms involved in brain growth and plasticity such as neurogenesis (Crews and Nixon, 2009; Buehler & Mann, 2012). There appears to be regionally specific variations in rate of recovery, with studies indicating early recovery of global frontal white matter volume and fronto-cerebellar networks but more persistent regional neuronal loss in the superior

frontal association cortex, hypothalamus and cerebellum (Bartsch et al.,, 2007; O'Neill, Cardenas, & Meyerhoff, 2001). Harper (2009) suggests alcohol-related brain pathology may have two components – one reflecting permanent change, the other transient.

1.3. Mechanisms of alcohol-related brain damage

Alcohol-related brain damage (commonly used interchangeably in the literature with alcohol-related brain injury) – refers to structural injury sustained to the brain as a result of alcohol consumption (Harper, 2009). Theoretical models have historically distinguished two primary causes of ARBD - damage due to the direct neurotoxicity of alcohol and indirect damage due to nutritional deficiencies, specifically thiamine deficiency. Given findings that even individuals without apparent neurological complications have sub-clinical levels of nutritional deficiencies (Pitel et al., 2011), the validity of this distinction has been questioned. It is now clear that this simple approach is insufficient to explain the complex physiological interactions that can result in ARBD (Crews, 2008). Individuals with alcohol dependence are at increased risk for thiamine deficiency because alcohol directly compromises thiamine absorption and metabolism in the gastrointestinal tract (Hazell & Butterworth, 2009; Lough, 2012). In addition, alcohol-induced liver injury can compromise the liver's capacity to detoxify ethanol and can lead to production of inflammatory mediators that injure the brain (de la Monte & Kril, 2014). Given that individual variation in genes, diet and drinking patterns further complicate attempts to establish causality in human studies, there has been a large dependence on animal studies to inform models of alcohol-related brain damage (Crews, 2008; Pires, Pereira, Oliveria-Silva, Franco, & Riberio, 2005). The results from such studies have indicated that alcohol

can be directly neurotoxic through mechanisms such as pro-inflammatory gene expression, oxidative stress, glutamate excitotoxicity and disruption of neurogenesis (Alfonso-Loeches & Guerri, 2011; Crews, 2008). Time course studies which calibrate markers of neurodegeneration at various times during alcohol intoxication, withdrawal and periods of abstinence indicate that neuronal death occurs largely during intoxication at high blood alcohol concentration levels and progressively subsides with abstinence (Crews et al., 2004; Hayes et al., 2013). Whilst the ability to draw conclusions in human studies is restricted by reliance on cross-sectional research and in particular, limited knowledge of premorbid brain size and function, there is some support for neurodegeneration occurring during intoxication with recency and length of heavy drinking periods more consistently associated with brain volume reductions than overall lifetime consumption (Beatty, Tivis, Stott, Nixon, & Parsons, 2000; Konrad et al., 2012; Kril & Halliday, 1999).

Thiamine deficiency is the other main mechanism to which ARBD has been attributed. Specific neurological disorders can occur as a result of thiamine deficiency, the most-well known of which is Wernicke's encephalopathy (WE). This is an acute neurological disorder, traditionally defined by a clinical triad of oculomotor abnormalities, gait ataxia, and altered mental state (Lough, 2012; Sullivan & Fama, 2012). If left untreated, the encephalopathy may progress to a syndrome of profound memory impairment referred to as Korsakoff syndrome (KS; Kopelman, Thomson, Guerrini & Marshall, 2009; Oscar-Berman, 2012). It is now well accepted that a high degree of heterogeneity exists in symptom acuity, presentation and course of this disorder, and consequentially Wernicke-Korsakoff syndrome (WKS) is increasingly used as an umbrella term used to encompass these heterogeneous outcomes. Pathological correlates of the WKS include lesions to the

periventricular nuclei, mammillary bodies, colliculi and thalamus (Jung, Chanraud, & Sullican, 2012; Kril & Harper, 2012). Additional disruption to diencephalic-hippocampal circuitry (including thalamic nuclei and mammillary bodies) is thought to be responsible for the amnestic syndrome that may eventuate in up to 80% of alcohol-related cases (Sullivan & Marsh, 2003). Notably, while WE may occur in many clinical contexts (e.g., long term parenteral feeding), it rarely progresses to KS following a single episode of non-alcohol related WE as long as adequate thiamine is administered (Homewood & Bond, 1999). This may suggest an effect of prolonged subclinical levels of thiamine deficiency or a synergistic role of combined neurotoxicity and thiamine in brain damage (Moriyama, Mimura, Kato, & Kashima, 2006). Support for the synergistic view has emerged from human studies that have demonstrated alterations in brain regions in the WKS in areas not traditionally associated with thiamine depletion (Sullivan & Pfefferbaum, 2009; Zahr, Kaufman & Harper, 2011) and similarities in the regional distribution and severity of brain damage in alcoholics both with and without KS (Pitel et al., 2008; Pitel et al., 2012). The incidence of undetected WKS in alcohol-dependent individuals at autopsy also supports a greater role for thiamine deficiency in individuals without apparent nutritional deficiencies than appreciated clinically (Harper, Giles & Finlay-Jones, 1986; Sullivan & Pfefferbaum, 2009; Victor, Adams, & Collins, 1989).

1.4. Cognitive impairment and recovery in AUD

Cognitive impairment resulting from alcohol use is commonly described by the term 'alcohol-related cognitive impairment' (ARCI). Estimates of cognitive impairment in treatment-seeking individuals with AUD vary widely but typically range between one- to two-thirds of individuals (Bates, Bowden, & Barry, 2002; Fein, Bachman,

Fisher, & Davenport, 1990; Parsons & Nixon, 1993). Acute alcohol intoxication impairs multiple cognitive skills, including attention, psychomotor processing and the higher-order executive skills which regulate behavioural control (Oscar-Berman & Marinkovic, 2007). Cognitive impairments are commonly observed immediately after acute withdrawal (which may last several days). Fluid cognitive abilities involving controlled and effortful processing of novel information are most adversely impacted. These abilities include working memory, abstraction and problem-solving, response inhibition, selective and divided attention and psychomotor speed (Bates, Buckman, Voelbel, Eddie, & Freeman, 2013; Le Berre et al., 2014; Pitel et al., 2007). Visuospatial abilities are also commonly affected (Fein & McGillivray, 2007; Sullivan et al, 2002). Crystallised abilities such as general knowledge, vocabulary and language skills are thought to be typically resilient to alcohol-related insult (Bates et al., 2002; Fein et al., 1990).

There is general consensus in the literature that the most substantial cognitive recovery in individuals with AUD occurs in short term abstinence (the first few weeks following detoxification), with more modest gains mid to long term (Bates, Buckman, & Nguyen, 2013; Stavro et al., 2012). This is consistent with neuroimaging data that has been interpreted to suggest that the most substantial metabolic and volumetric recovery occurs very early in abstinence (Bartsch et al., 2007; van Eijk et al., 2013). However, there are dissonant findings on the rate of recovery of cognitive functioning in the literature. Chronic impairment in the processing of spatial information and associated grey matter reductions in the parietal lobe have been found in long-term abstinent individuals with a history of alcohol dependence (Fein et al. 2006; Fein, Shimotsu, Chu, & Barakos, 2009). This could be interpreted as consistent with the ‘right hemisphere (RH)’ vulnerability

hypothesis suggested by Jones and Parsons (1971); i.e., that functions typically subserved by right hemisphere, such as spatial processing, are more susceptible to damage from alcohol insult (for a review, see Oscar-Berman & Marinkovic, 2007). However, it is clear that the sensitivity of cognitive tasks to ARBD within specific cognitive domains also would influence results, and the outcomes of other studies have not supported this theory of lateralisation of impairment (Pitel et al., 2009; Stavro et al., 2012). Other authors suggest that executive functions may take longer to normalise than other cognitive abilities (Oostermann et al., 2011; Uekermann, Daum, Schlebusch, Wiebel, & Trenckmann, 2003; Zinn, Stein, & Swartzwelder, 2004). Again, however, findings have been discrepant with some authors reporting persistent impairment in abstinent individuals on tasks of decision-making (Fein & Di Sclafani, 2004; Kopera et al., 2012) and letter fluency (Munro, Saxton, & Butters, 2000) and others reporting normalisation of cognitive function following even short periods of abstinence (Dresler et al., 2012; Fein & McGillivray, 2007; Pitel et al., 2009). The dissonant findings are at least partially related to methodological discrepancies between studies, although differences in individual vulnerability to ARBD may also contribute. Most of these results were obtained from cross-sectional studies or from short-term longitudinal observations. Longitudinal studies that follow individual with AUD through the course of recovery over years are lacking. The complexity of defining cognitive impairment and recovery is compounded by the range of neuropsychological measures used within studies, timing of testing and the inconsistent exclusion of individuals with comorbid risk factors (Bates, Buckman, Voelbel, et al., 2013). The way in which cognitive abilities are defined also may influence outcome; that is, use of a single neuropsychological score to describe

cognitive ability may not reflect the divergent abilities within a domain of cognitive functioning.

The way in which a diagnosis of ARBD is made may also influence the cognitive profile that is observed on testing. Diagnosis of alcohol-related dementia (ARD) – a syndrome of profound, global and chronic cognitive impairment resulting from alcohol use - pin the literature has largely been dependent on clinical judgement (e.g., an inferred link between excessive drinking and the development of cognitive impairment) and has relied primarily on an exclusionary diagnosis (Gupta & Warner, 2008). The International Classification of Diseases – Tenth Revision (ICD-10) criteria for 'alcohol-induced amnesic syndrome' (World Health Organisation, 1992), also known as KS, specify impairment of recent memory in the absence of generalised cognitive impairment. However, there has been much variation in how these criteria have been operationalised in empirical research. Inclusion criteria for Korsakoff patients have frequently required a discrepancy between intellect and memory or a minimal number of WE symptoms for diagnosis (see Bowden, 1990). Anterograde memory dysfunction is suggested to be the prime deficit in both ARD and KS however it is clear that diagnostic and inclusion and exclusion criteria used in previous research have had a significant influence on sample characteristics. Thus, one aim of the research reported in the current thesis was to examine the methodology of literature in which the cognitive profile of ARD and KS has been compared to other dementia syndromes. The neuropsychological tasks used, and the comprehensiveness of reporting of drinking variables (e.g., abstinence) was also examined. As the tasks used in neuropsychological research may differ in their sensitivity to cognitive dysfunction in ARBD, identification of the tasks that are best able to detect cognitive impairment in this disorder will inform recommendations for

cognitive assessment in the clinical setting. In addition, a critique of the comprehensiveness of drinking variables reported is necessary, given the influence that length of abstinence and severity of recent drinking may have on cognitive performance.

1.5. Factors influencing outcomes

Vulnerability to ARCI is also mediated by individual and environmental factors. Age, education, gender, other substance use, comorbid psychiatric disorders and family history of alcoholism, for example, have all been implicated as factors that influence development of ARCI. The majority of evidence supports an 'increased vulnerability' model of premature aging (Oscar-Berman & Marinkovic, 2007), which suggests that the aging brain is more vulnerable to ARBD than the brain of a younger person. Older drinkers show greater structural and cognitive changes (Bates et al., 2002; Pfefferbaum, Adalsteinsson, & Sullivan, 2006) and are less likely to recover function once they stop drinking, even when controlling for duration of drinking history (Rourke & Grant, 1999). Lower levels of education are also associated with less cognitive recovery over time in studies of both individuals with AUD and KS patients (Bates et al., 2002; Fujiwara, Brand, Borsutzky, Steingass, & Markowitsch, 2008). It is unclear whether education is a protective factor or whether low premorbid intelligence is a risk factor for both cognitive impairment and poor educational attainment. Increased vulnerability to ARCI in females has been proposed, however, this remains a controversial finding, with some studies showing women to be more susceptible than men to brain damage and others showing no distinction (for a review, see Oscar-Berman & Marinkovic, 2007). It is possible that some of these inconsistencies may be accounted for by gender-related differences in

brain volume, body weight and fat proportion, which influence blood alcohol levels even when the same amount of alcohol is consumed (Kril & Halliday, 1999; Oscar-Berman & Marinkovic, 2007). Furthermore, hereditary factors, such as genetic variants for the enzymes of alcohol and thiamine metabolism (Thomson, Guerrini, & Marshall, 2012) and a family history of heavy drinking, which has been negatively associated with premorbid intracranial volume (Gilman, Bjork, & Hommer, 2007), may influence vulnerability to ARBD. While it is beyond the scope of the current thesis to undertake a comprehensive examination of these factors, it is clear that they should be considered in the interpretation of ARCI given their potential mediating influence.

Drinking patterns may also influence severity of structural changes (Bates, Buckman, & Nguyen, 2013). Attempts to establish a relationship between lifetime alcohol intake and severity of brain damage have been met with inconsistent findings (Kril & Halliday, 1999). Comparisons of study outcomes have been further complicated by variability in the measurement of standard drinks and 'at-risk' drinking levels between countries (Buehler & Mann, 2012). It has been suggested that recall of quantity of drinking over the lifetime by drinkers may also be more prone to inaccuracies than recall of periods of heavy alcohol use, rendering total lifetime drinks a measure of questionable validity (Bjork et al., 2003). However, level of alcohol intake and years of heavy drinking have been more consistently associated with volume reductions then overall lifetime intake, which suggests that brain volume is particularly affected by periods of heavy drinking (Bates, Buckman, & Nguyen, 2013; Crews, 2008; Sullivan & Pfefferbaum, 2005). Degree of excessive drinking in individuals with AUD has been found to be correlated with grey matter loss, particularly in the frontal lobes (Pfefferbaum et al., 1995). Bjork et al. (2003)

also reported that number of years of consumption of 90 or more drinks per month (90 American standard drinks; 1260 grams of alcohol) was negatively correlated with intracranial volume after controlling for the effects of age. Recency of drinking has also been reported to be significant; frontal cortical metabolites, which are increased in brain damage and observable on MRI, significantly correlate with alcohol consumption in the last 90 days (Ende, Walters, & Welzel, 2006.) There is also some evidence from animal studies that drinking patterns of repeated binges and withdrawals may lead to increased brain damage. Repeated withdrawals in rodent models have been linked to amygdala and hippocampal dysfunction, resulting in impaired associative learning and fear conditioning (Stephens & Duka, 2008). In a longitudinal follow-up of KS patients (Fujiwara, Brand, Borsutzky, Steingass & Markowitsch, 2008), lower incidence of past detoxifications was associated with better outcome. However, the relationship of withdrawals to cognitive outcome in humans is yet to be firmly established (Loeber et al., 2010).

1.6. Comorbidities of AUD

Individuals with AUD commonly have comorbid health conditions, substance use disorders, and mental health diagnoses, which can influence their clinical presentation. Medical conditions frequently associated with AUD include liver disease, cardiovascular disease and malnutrition, all which are independently associated with specific neurological and cognitive outcomes (for a review, see de la Monte & Kril, 2014). Comorbid mental health conditions are also common, particularly depression, anxiety and other substance use dependence. In the community-based American epidemiological survey by Grant et al. (2004), 41% of individuals with a current AUD who sought treatment had at least one current mood

disorder and one-third had at least one current anxiety disorder. The analysis by Stinson et al. (2005) of the same data indicated that prevalence of a drug-use disorder in respondents with AUD was 13%, with the most common being cannabis, cocaine and opioid disorders. In an Australian community-based study, Burns and Teeson (2002) found that individuals with AUD were ten times more likely to have a drug use disorder, four times more likely to have an affective disorder and three times more likely to have an anxiety disorder than those without AUD. High rates of externalising disorders (e.g. conduct disorder), personality disorders and schizophrenia have also been associated with AUD (Kessler, Chiu, Demler, Walters, & Merikangas, 2005; Margolese, Malchy, Negrete, Tempier, & Gill, 2004). A history of traumatic brain injury (TBI) is also commonly associated with AUD (Corrigan, Adams, & Larson, 2013), and this relationship appears to be bidirectional. Specifically, not only is alcohol use a substantive risk factor for TBI (Kelly, Johnson, Knoller, Drubach, & Winslow, 1997) but TBI may increase the risk of further substance misuse (Bjork & Grant, 2009; Corrigan, 1995).

Whilst the majority of studies have been conducted in community-based samples, high rates of comorbidities in individuals with AUD have also been observed in empirical research. In a UK sample of individuals with ARBD accepted for rehabilitation at a tertiary service, over 40% had a history of depression, 22% had a history of cerebral infarcts and 15% had a history of significant head trauma or anoxic brain damage (Wilson et al., 2012). Bates, Voelbel, Buckman, Labouvie, and Barry (2005) reported that one-fifth of the sample they recruited from multiple treatment facilities had other substance use dependence diagnoses in addition to AUD, despite exclusion of those on methadone maintenance. Rosenbloom, O'Reilly, Sassoon, Sullivan, and Pfefferbaum (2005) also reported that over one-half of the

patients recruited from treatment centres who took part in their study met lifetime criteria for at least one other Axis 1 diagnosis (mood 31%, anxiety, 19%, non-alcohol substance dependence, 30%). The presence of comorbidities in a treatment context is even more likely given findings that individuals with AUD make greater use of mental health services than those without (Wu, Kouzis, & Leaf, 1999), tend to have heavier drinking histories (Fein & Landman, 2005) and have greater rates of psychiatric comorbidities than non-treated samples (Di Sclafani, Finn, & Fein, 2008). While it is clear that reported rates of comorbidities vary depending on diagnostic approach and populations surveyed, it is surprising that very few studies (Copersino et al., 2009) have examined the characteristics of AUD samples as they present for treatment i.e. without exclusion criteria for specific psychiatric or neurological comorbidities.

While assessment of the cognitive deficits associated with alcohol use has been extensive, there has been comparably limited investigation of the combined influence of comorbid factors and AUD on cognition. Cognitive impairment has been reported in association with a number of psychiatric disorders. Schizophrenia has been reported to be associated with deficits in processing speed, attention and executive functioning (Dickerson et al., 2004; Keefe & Harvey, 2012). Users of amphetamines, cannabis and opiates have been found to demonstrate impairments in memory and executive functioning (Fernandez-Serrano, Perez-Garcia, Rio-Valle, & Verdejo-Garcia, 2010). TBI is associated with deficits in memory, psychomotor speed and executive functioning (Dikmen et al., 2009; Kelly et al., 1997). Depression and anxiety disorders are also associated with attention, learning, memory and executive function difficulties (Gallassi, Morreale, & Pagni, 2001; Robinson, Vytal, Cornwell, & Grillon, 2013). Given the frequency of these conditions in individuals

with AUD, understanding the impact that these comorbidities may have on cognitive outcome is essential for accurate differential diagnosis (Tracy, Josiassen, & Bellack, 1995). One hypothesis that has been proposed is that some alcohol users share a premorbid vulnerability to comorbidities due to genetically-based neurodevelopmental dysfunction (Herting, Fair, & Nagel, 2011; Tracy et al., 1995). If this is the case, cognitive dysfunction may predate development of these disorders. Other theories include an additive effect model in which cognitive deficits separately converge, resulting in more severe impairment, or a sensitivity model in which the individual is more sensitive to the effects of alcohol due to other comorbidities (Manning & van der Karre, 2011).

There has been insufficient empirical research to adequately test these theories. However, results of the few studies in which the combined influences of AUD and mood disorders have been examined have revealed limited evidence for an additive effect. Whilst Sinah, Parsons, and Glenn (1989) and Schafer et al. (1991) indicated a relationship between depressive symptoms and poorer neuropsychological performance, both studies had methodological limitations, including no comparison group of non-depressed patients with AUD. Later studies by Rosenbloom et al. (2005) and Uekermann et al. (2003), which included such comparison groups, did not find evidence for an additive effect. Studies of schizophrenia and AUD have more consistently indicated greater impairment in specific cognitive domains (attention, memory and executive functions) in dual diagnosis patients (Manning et al., 2009; Ralevski, Gianoli, Russo, Dwan, & Radhakrishnan, 2012; Tracy et al., 1995) although again this is not a universal finding (Thoma, Wiebel, & Daum, 2007). Furthermore, it is unclear whether poly-drug use further exacerbates any alcohol-related cognitive deficits, as a generalised profile of executive dysfunction

may present across substances (Fals-Stewart, Schafer, Lucente, Rustine, & Brown, 1994; Rogers & Robbins, 2001). Again, specific exclusion criteria (e.g., TBI psychotic disorders) were implemented in all of these studies. As far as is known, a study that has examined the cognitive profile of individuals inclusive of all presenting comorbidities has not been conducted in AUD research.

1.7. The implications of cognitive impairment for treatment of AUD

Treatment for AUD typically entails teaching new skills (e.g., coping strategies for stress) and implementation of behaviour modification techniques (e.g., examination of maladaptive drinking patterns; Teichner, Horner, Roitzsch, Herron, & Thevos, 2002). It has been argued that cognitive impairment can negatively impact treatment outcome, given the range of cognitive skills – including attention, memory, verbal skills and adaptive problem-solving – that are required for this process (Bates et al, 2002). However, studies that have examined the relationship between cognitive abilities and alcohol use treatment outcome have reported weak and inconsistent associations between cognitive impairment and treatment outcome (Bates et al., 2002; Bates et al., 2005; Fals-Stewart et al., 1994). It is possible that this is due to lack of consideration of cognitive impairment as a mediating rather than a direct cause of outcome. Bates, Pawlak, Tonigan & Buckman (2006) propose that cognitive impairment influences drinking outcome indirectly by altering 'therapeutic mechanisms of change' – this includes treatment compliance, the ability to resist urges to drink and readiness to change. There has been much empirical support for this proposal in AUD research. Cognitive impairment has been shown to negatively impact acquisition of drink refusal skills (Smith & McCrady, 1991), lead to lower self-efficacy and less treatment adherence (Bates et al., 2006) and lead to increased

denial of addiction (Rinn, Desai, Rosenblatt, & Gastfriend, 2002). Cognitive deficits may also lead to lack of motivation and treatment engagement, which may be interpreted as negative personality attributes by treatment providers (Fals-Stewart, Shanahan, & Brown, 1995). The association between cognitive impairment and poor treatment retention is of particular significance given that treatment retention is a strong predictor of treatment outcome (Bates et al., 2002; Bates et al., 2006). Therapists have been shown to rate therapeutic alliance higher and patients tend to stay in treatment longer when the therapist is informed of a patient's cognitive abilities (Grohman & Fals-Stewart, 2004). Use of interventions such as cognitive remediation (Fals-Stewart et al., 1994; Grohman & Fals-Stewart, 2003) and targeted treatment such as interactional therapy (Cooney, Kadden, Litt, & Getter, 1991) have also shown some success in use with cognitively impaired individuals with AUD, although this area of research is still in its infancy.

Identification of cognitive impairment at entry to treatment may inform clinical decision-making and allow treatment providers to modify treatment to suit the strengths and weaknesses of the client (Bates et al., 2002; Pitel et al., 2007). However, despite the potential advantages of neuropsychological assessment in this context, it is not routinely conducted in substance use treatment programs (Copersino et al., 2009). Limitations of comprehensive neuropsychological assessment include time constraints and the costly nature of specialist administration. In addition, patients may be deterred from engagement in cognitive assessment due to the lengthy nature of testing (Olson, Parkinson, & McKenzie, 2010). Cognitive screening provides a useful clinical alternative. Brief screening tools can provide focused evaluations of cognitive functioning and are practical and cost-effective (Lischka, Mendelsohn, Overend, & Forbes, 2012). Screening tools are not intended to replace

neuropsychological assessment but can serve a complementary role including the identification of patients who may require more comprehensive evaluation (Cullen, O'Neill, Evans, Coen, & Lawlor, 2007).

The choice of an appropriate screen should include consideration of test psychometrics (reliability and validity) within the population of interest. A key feature is the ability of the test to identify correctly both those who have cognitive problems (sensitivity) and those who do not have cognitive problems(specificity; Morris, Hacker, & Lincoln, 2012). These figures may change across different populations and consequentially it is important to validate each test within the population of interest. For instance, many tests that were originally designed for dementia assessment place disproportionate emphasis on memory function and neglect assessment of other cognitive domains (Cullen et al., 2007). The Mini-Mental State Examination (MMSE; Folstein, Folstein, & McHugh, 1975) is the most widely used cognitive screen (Manning & van der Karre, 2011). It is popular as it is quick and easy to administer, does not require any training or specialist equipment, and is familiar to clinicians across a number of care contexts (Ferguson & Lincoln, 2012). It has been criticised, however, for lacking sensitivity to mild levels of cognitive impairment and executive dysfunction (Paul et al., 2011; Strauss, Sherman, & Spreen, 2006). One investigation by Manning et al. (2009) of the utility of the MMSE in a dual diagnosis (schizophrenia and AUD) sample indicated that global MMSE scores were insensitive to the cognitive impairments commonly found in these clinical groups. It is clear that further exploration of the psychometric qualities of the MMSE and other screening tools within the alcohol use context is necessary to assist clinicians identify tests best suited for this population. Two tools that hold some promise in this context include the Addenbrooke's Cognitive Examination

Revised (ACE-R) and the Montreal Cognitive Assessment (MoCA). The MoCA has been shown to have acceptable levels of sensitivity and specificity for the identification of cognitive impairment in a sample attending treatment for substance dependence (Copersino et al., 2009). Performance on this task has also been shown to predict treatment attendance (Copersino et al., 2012). As far as is known, the ACE-R has not been validated in a substance use population but has shown sensitivity to cognitive impairment in individuals with subcortical dementias and traumatic brain injury, who typically demonstrate executive function deficits (Gaber, 2008; Komadina et al., 2011). Identification of the best screening measure for this population would not only assist clinicians to accurately identify cognitively impaired patients but could translate to improved treatment response if information regarding the clients' cognitive strengths and weaknesses is integrated into service delivery (Grohman & Fals-Stewart, 2004)

1.10. Research Questions

In a summary of the nature of substance-induced cognitive impairment, Bates et al. (2005) reflected:

> 'the equivocal results point to the complexity of defining cognitive impairment and recovery in relation to treatment for substance use disorders… the problem is compounded by the wide range of neuropsychological tests that are given to clients, as well as the timing of the initial and follow-up testing… the heterogeneity of the sample and the use of multiple drugs further add to the complexity of evaluating cognitive recovery in most populations' (2005, p 368).

It is clear that this is a complex and diverse population and that assessment of alcohol-related cognitive impairment requires evaluation of both the independent and combined effects of AUD and related comorbidities on cognitive function. This is an area that surprisingly has received relatively limited attention in AUD research. The overarching purpose of the research comprising the present thesis was to examine the profile of alcohol-related cognitive impairment both in terms of conventional diagnostic syndromes and in relation to the comorbid factors that commonly present in conjunction with AUD. The research was conducted to provide clinically applicable findings and direct further research. Three specific investigations were undertaken:

1) A systematic review of existing literature was conducted in which the neuropsychological profile of ARD and KS was examined. Given the breadth of the literature, this analysis was restricted to studies that compared these disorders to other dementia syndromes. The aim was to critically evaluate these studies in relation to methodological quality and tasks used to assess cognitive functioning.
2) An empirical study was designed to document the cognitive profile of a group of individuals presenting for treatment for AUD. This was inclusive of those who had comorbid psychiatric, neurological and health conditions. Cognitive performance was examined in relation to reported drinking history and in comparison to the profile of cognitive impairment that has typically been reported in AUD research.
3) The diagnostic accuracy of the ACE-R, the MoCA and the MMSE in the identification of cognitive impairment was examined in a broader substance use sample.

By evaluating the findings of all three studies, the authors sought to a) identify the methodological weaknesses present in previous ARBD research, b) isolate the areas of cognitive function that are most frequently disturbed in individuals with alcohol-related cognitive disorders, including those with comorbid neurological, psychiatric and physical health conditions, and c) provide recommendations for the use of specific screening tools within this clinical context.

CHAPTER TWO

Neuropsychological findings in alcohol-related cognitive disorders:

A systematic review of the literature

This chapter has been prepared for submission to *The Clinical Neuropsychologist*

Abstract word count: 185

Manuscript word count: 9745

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2.1. Abstract

Cognitive impairment due to chronic and excessive alcohol use has been documented in the literature; however specific neuropsychological features of the two syndromes of impairment traditionally defined, Korsakoff Syndrome (KS) and alcohol-related dementia (ARD), remain undetermined. In this paper we systematically review articles in which cognitive function in KS/ARD syndromes was compared with that of other dementia syndromes as well as control groups, in order to evaluate neuropsychological findings and methodological rigour. Studies were identified using Scopus and PsycInfo databases (January 1995 to April 2014), and ten studies met inclusion criteria; five for ARD and KS groups respectively. Major methodological issues were identified, including use of different diagnostic criteria, inconsistent inclusion and exclusion criteria, and inadequate matching of comparisons groups. Conclusions regarding cognitive profiles were limited by the large variability in tasks utilised and differences in population groups, although some trends in outcomes were identified. These included differentiation of Alzheimer's dementia and ARD groups on semantic tasks and verbal recognition memory indices, and executive dysfunction in KS relative to controls. Recommendations for future research, including the need for consistent and thorough methodological approaches, were specified.

2.2. Introduction

Chronic and excessive alcohol use may result in impairments in cognitive functioning, ranging from subtle transient deficits that may be reversible following abstinence (Stavro, Pelletier, & Potvin, 2012; Sullivan, Rosenbloom, Lim, & Pfefferbaum, 2000) to debilitating conditions involving permanent memory and executive deficits (Jacobson, Acker, & Lishman, 1990; Schmidt et al., 2005). Autopsy and in vivo evaluations suggest that up to 78% of individuals with a history of chronic and severe alcohol use, as typified by consumption levels in excess of 80 grams of alcohol per day over more than one decade, demonstrate some degree of brain pathology (Goldstein & Shelly, 1980; Harper, 1998). Neuroimaging and neuropathological evidence most consistently reveals neuronal loss in the prefrontal cortex, hypothalamus and cerebellum, white matter volume loss, and hippocampal abnormalities (for a review, see Harper, 2009). The clinical presentation of brain damage, however, is heterogeneous. This is likely a result of multiple influences, including the frequency, chronicity and severity of drinking, general health and nutritional status, traumatic brain injury (TBI), and comorbid substance and psychiatric disorders (Bates, Bowden & Barry, 2002; Sameti, Smith, Patenaude, & Fein, 2012; West, 2011).

2.2.1 Diagnostic criteria for alcohol related cognitive impairment

Past diagnostic criteria for alcohol-related cognitive impairment (ARCI) have focused on two main syndromes of impairment: alcohol-induced persisting amnestic disorder (Korsakoff Syndrome, KS) and alcohol-related dementia (ARD; American Psychiatric Association, 1994; World Health Organisation, 1992). The neurotoxic

effects of long-term excessive alcohol consumption are hypothesised to produce ARD (Smith & Atkinson, 1995) whilst thiamine deficiency in combination with heavy alcohol consumption may lead to Wernicke's encephalopathy (WE) and/or KS, together described as 'Wernicke-Korsakoff Syndrome' (WKS; Vetreno, Hall, & Savage, 2011; Zahr, Kaufman, & Harper, 2011). WE is an acute neurological reaction to thiamine deficiency and can occur in many clinical contexts (e.g., long-term parenteral feeding, gastric and bariatric surgery, hyperemesis gravidarum). Individuals with alcohol dependence are at increased risk for WE because alcohol directly compromises thiamine absorption and metabolism (Lough, 2012; Sechi & Serra, 2007). If left untreated, WE can lead to death in up to 20% of cases (Harper, Giles, & Finlay-Jones, 1986) or progress to KS, a syndrome of profound memory impairment (Kopelman, Thomson, & Guerrini, 2009). Accumulated evidence indicates that the WKS encompasses a spectrum of damage relating to thiamine deficiency, which may or may not be characterised by the traditional clinical 'triad' of symptoms of WE (oculomotor abnormalities, cerebellar dysfunction, altered mental state) and the anterograde memory deficit of Korsakoff syndrome (Harper & Matsumoto, 2005; Oscar-Berman, 2012). WE and KS are thought to share similar pathological substrates, including lesions to periventricular regions, mammillary bodies, colliculi and the thalamus, with additional disruption to diencephalic and hippocampal circuitry thought to be responsible for the amnestic impairment seen in KS (Harper et al., 2005; Sullivan & Pfefferbaum, 2009). Post mortem analyses suggest that only 20% of patients with pathologically diagnosed WE present with the full triad of clinical symptoms, with the severity of signs likely related to the extent of underlying pathology (Sullivan & Pfefferbaum, 2009). Given retrospective findings that many cases of pathologically diagnosed WE are not detected in vivo

(Harper et al., 1986), Caine, Halliday, Kirl, and Harper (1997) refined the operational criteria for the clinical diagnosis of WE to require only two of four features (dietary deficiency, ocular abnormality, cerebellar dysfunction and either altered mental state or mild memory impairment). These revised criteria have since been widely adopted in clinical and research settings (Galvin et al., 2010; Pitel et al., 2011).

Diagnostically, KS has been defined as involving an impaired ability to learn new information or recall previously learnt information (Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; American Psychiatric Association, 1994) in the absence of generalised cognitive impairment (International Statistical Classification of Diseases and Related Health Problems, Tenth Edition; World Health Organisation, 1992). Operationally, this has been conceptualised in the literature as a discrepancy between the Wechsler Intelligence (IQ) and Memory quotient (MQ; Wechsler, 1945), with IQ being 20 to 30 points higher than MQ (Butters & Cermak, 1980; Bowden, 2010). However, there is growing evidence for greater heterogeneity in cognitive abilities in KS than what the classical view of a circumscribed amnesic syndrome would suggest. It has been reported that some individuals with KS demonstrated a reduction in overall intellectual functioning as well as impairment of memory (Cutting, 1978; Jacobson, Acker & Lishman, 1990). Additionally, a substantial proportion of WKS cases identified pathologically have a clinical presentation of a dementia-like syndrome (Harper, Giles & Finlay-Jones, 1986). As Bowden (1990) argues, the use of KS criteria that require disproportionate impairment of memory, relative to other cognitive skills, creates a self-fulfilling selection bias, as cases not conforming to the desired stereotype are excluded. Squire and Shimamura (1986), for instance, screened WKS patients for inclusion in their research and found that only 40% of patients showed the selective reduction in

memory relative to IQ; only these patients were included in their investigation of memory function in KS. In addition, observations of impairment in other cognitive domains, including executive functions, working memory, and visuoperceptual difficulties, are prevalent in recent studies of KS (Maharasingam, Macniven, & Mason, 2013; van Geldorp, Bergmann, Robertson, Wester & Kessels, 2012; Van Oort & Kessels, 2009). Neuroimaging evidence of reductions in volume in the cerebellum, corpus callosum and frontal lobes in KS patients, in addition to disruption to hippocampal-thalamic (Jung, Chanraud, & Sullivan, 2012; Pitel et al., 2012) are consistent with reports of disparate cognitive impairment and lend weight to the view that a selective amnesia is only one of many clinical manifestations of WKS (Bowden, 2010).

Whilst the WKS has long been linked to thiamine deficiency, the pathogenesis of ARD has been a point of debate in the literature. Neuroimaging studies that demonstrate structural and functional brain abnormalities in 'uncomplicated' individuals with alcohol use disorders (those without nutritional deficiencies or physical health comorbidities) promote the view that alcohol is neurotoxic, i.e. can cause neurodegeneration without any nutritional deficit or additional cause (Pfefferbaum, Sullivan, Mathalon, & Lim, 1997). Experimental animal models indicate that alcoholic degeneration occurs largely during intoxication at high blood alcohol concentration levels and progressively subsides during abstinence, with neuroinflammation and oxidative stress being key neurotoxic mechanisms (Crews, 2008). Results from human studies are consistent with theories of neurodegeneration during intoxication, with length of abstinence and years of sustained, heavy drinking more consistently associated with severity of brain damage than overall lifetime alcohol consumption (Bjork, Grant, & Hommer, 2003; Ende et

al., 2006; Konrad et al., 2012; van Eijk et al., 2013). However, given that abstinence can restore many of these functional and structural deficits (for a review, see Buehler & Mann, 2011), the point of contention has been whether or not alcohol neurotoxicity in isolation can result in the lasting cognitive impairment seen in ARD. Investigation of this point has been complicated by methodological difficulties, including the variation in diet, genetics and brain and body composition between individuals. These factors can all modify blood alcohol and nutritional levels in the human body despite equivalent alcohol intake (Crews, 2008). Additionally, the effect of alcohol in disrupting the absorption and utilization of thiamine may result in inadequate end-organ intake of thiamine, despite sufficient nutritional intake. Thiamine deficiency has been reported in 30-80% of alcohol-dependent individuals, and Pitel et al. (2011) demonstrated that over a half of uncomplicated alcoholics meet at least one sign for WE. The close relationship between alcohol intake and thiamine deficiency, in conjunction with lack of distinct pathophysiological markers for a 'primary alcoholic dementia,' has led some authors to suggest that the underlying pathology behind clinical presentations of ARD is thiamine deficiency (Lishman, 1986; Torvick, Lindboe & Rodge, 1982; Victor, Adams & Collins, 1989. Moriyama et al. (2006) proposed that repeated episodes of subclinical WKS may lead to the chronic state of primary alcoholic dementia. This is supported by the retrospective autopsy evidence correlating chronic WKS lesions with clinical presentation of a global dementia (Torvick et al., 1982). Others have suggested that ARD and WKS are distinct disorders with overlapping clinical symptoms (Smith & Atkinson, 1995). The DSM-IV criteria (1994) for alcohol-induced persisting dementia reflect the ambiguous nature of this phenomenon, with broad criteria and

Table 1

Criteria for Alcohol-Induced Persisting Dementia in the Diagnostic and Statistical Manual of Mental Disorders- 4th Edition (American Psychiatric Association, 1994)

A. The development of multiple cognitive deficits manifested by both:
1. Memory impairment (impaired ability to learn new information or to recall previously learned information)
2. One (or more) of the following cognitive disturbances
a. Aphasia (language disturbance)
b. Apraxia (impaired ability to carry out motor activities despite intact motor function)
c. Agnosia (failure to recognise or identify objects despite intact sensory function
d. Disturbance in executive functioning (i.e., planning, organising, sequencing, abstracting)
B. The cognitive deficits in Criteria A1 and A2 each cause significant impairment in social or occupational functioning and represent a significant decline from a previous level of functioning.
C. The deficits do not occur exclusively during the course of a delirium and persist beyond the usual duration of substance intoxication or withdrawal
D. There is evidence from the history, physical examination or laboratory findings that the deficits are etiologically related to the persisting effects of substance use

reliance primarily on exclusionary criteria for diagnosis (see Table 1). In an effort to improve validity and reliability of a diagnosis of ARD, Oslin, Atkinson, Smith & Hendrie (1998) generated criteria which standardised alcohol consumption criteria (length and severity of alcohol use) and minimum abstinence time for a dementia diagnosis to be considered (Table 2). However, at present there have been limited attempts to validate these criteria (Oslin & Cary, 2003).

The recently released DSM-5 criteria (American Psychiatric Association, 2013) reflect a broader approach to alcohol-related cognitive disorders by including both WKS and ARD under the banner of "alcohol-induced neurocognitive disorders" rather than distinct diagnostic entities. While this may better reflect the heterogeneity of presentation in alcohol-related cognitive disorders - and offer better utility in a clinical setting - the key diagnostic features of these disorders have not yet been defined. It is noted in the DSM-5 manual (American Psychiatric Association, 2013)

that neurocognitive disorders due to alcohol manifest with a combination of impairments in executive function, memory and learning. Nevertheless, these features are not yet integrated into diagnostic criteria, and critical factors such as duration and stability of impairment and length of abstinence required for diagnosis are not defined. Whilst other dementia syndromes, such Alzheimer's disease (AD), have become increasingly well understood in terms of their neuropathology and corresponding neuropsychological presentation (Salmon & Bondi, 2009), diagnosis of alcohol-related disorders remains particularly difficult for clinicians given the lack of specific diagnostic guidelines and the influence of confounding factors such as length of abstinence, age-related cognitive changes and co-morbid substance abuse and medical conditions. There is also the potential to over-diagnose alcohol-related conditions in cases where there is a substantial history of alcohol consumption (Saxton, 1999).

2.2.2 Rationale and objectives

Whilst WKS has been well described in terms of its cognitive profile, this has been within the restrictions of diagnostic criteria that specify memory impairment. The influence this had had on comparisons of WKS to other dementia syndrome remains unclear. Alternatively, ARD appears to have been subject to limited neuropsychological evaluation. Given the recent inclusion of both of these syndromes under the one umbrella of alcohol-induced neurocognitive disorders in DSM-V (American Psychiatric Association, 2013) and debate as to the independence of these two alcohol-related cognitive syndromes, it is pertinent to investigate the particular neuropsychological profiles of these two disorders, both comparatively and

Table 2

Criteria for Probable Alcohol-Related Dementia

A*:* The criteria for the clinical diagnosis of Probable ARD include the following*:*
1. A clinical diagnosis of dementia at least 60 days after the last exposure to alcohol
2, Significant alcohol use as defined by a minimum average of 6 standard drinks a week (men), 28 (women) for greater than a period of 5 years. The period of significant alcohol use must occur within 3 years of the initial onset of Dementia.
B. The diagnosis of ARD is supported by the presence of any of the following:
1. Alcohol-related hepatic, pancreatic, gastrointestinal, cardiovascular, or renal disease i.e., other end-organ damage
2. Ataxia or peripheral sensory neuropathy (not attributable to other specific causes)
3. Beyond 60 days of abstinence, the cognitive impairment stabilises or improves
4. After 60 days of abstinence, any neuroimaging evidence of ventricular or sulcal dilatation improves.
5. Neuroimaging evidence of cerebellar atrophy, especially of the vermis.
C. The following clinical features case doubt on the diagnosis of ARD
1. The presence of language impairment, especially dysnomia or anomia.
2. The presence of focal neurologic signs or symptoms (except ataxia or peripheral sensory polyneuropathy)
3. Neuroimaging evidence for cortical /subcortical infarction, subdural hematoma, or other focal brain pathology
4. Elevated Hachinski Ischemia Scale score
D. Clinical features that are neither supportive nor cast doubt on the diagnosis of ARD included:
1. Neuroimaging evidence of cortical atrophy
2. The presence of periventricular or deep white matter lesions on neuroimaging in the absence of focal infarct(s)
3. The presence of the Apolipoprotein E4 allele

Note. Criteria adapted from Oslin et al., 1998. ARD = Alcohol-related dementia

relative to other neurocognitive disorders. Accordingly, the purpose of conducting the present review was to compare the profile of neuropsychological impairment in KS and ARD with that typifying dementia disorders and matched control groups, to assist with differential diagnosis at a clinical level. This was achieved through the analysis of studies that provided comparisons to both dementia and neurologically normal control groups, and entailed (1) a review of the neuropsychological findings and measures used to assess cognitive function in these subgroups and (2) analysis and comparison of the methodological criteria adopted in conducting the studies. The choice to conduct comparisons of ARD to dementia disorders was specifically

undertaken, firstly, as the breadth of the literature in which ARCI has been examined was too great to review all studies in depth, and secondly, as this would provide results that could be used to assist with differential diagnosis in a clinical setting. The inclusion of only studies in which control groups were used ensured that comparison data to neurologically normal samples would also be available.

2.3. Method

2.3.1. Literature search

The search terms (alcohol OR alcoholism) AND (dementia OR brain damage OR brain injury OR brain impairment OR cognitive impairment) were used as keywords in the databases SCOPUS and PsycInfo. Additional terms included (Wernicke's encephalopathy), (Korsakoff), (Alcohol Amnestic Disorder). When available, standard search categories or MESH terms were also used that matched the above terms, and were exploded. Limits included English language publications relating to adult human populations between January 1995 and April 2014. Two reviewers (N.R & J.K) with experience in research methods reviewed database results independently to initially identify, based on title and abstract, studies that reported data on cognitive performance by patients with a diagnosis of alcohol related brain damage (ARBD; e.g. alcohol-related dementia, Korsakoff Syndrome) as well as data from both comparative dementia and neurologically normal control groups. Full-text copies of these articles were retrieved and further inclusion criteria applied (see Figure 1).

2.3.2. Eligibility screening and selection of studies

Inclusion criteria for papers were that the study 1) reported cognitive performance of at minimum an ARBD group, a control group and comparative group with a diagnosis of dementia or major neurocognitive disorder syndrome; 2) examined a minimum of two cognitive domains, including memory; 3) was empirical; 4) was written in English and 5) examined an adult human population. Studies were excluded if they comprised only a case study or review, if the sole data reported was imaging/olfactory variables, if the sole cognitive task reported was a total score or measure of global cognition, or if the comparative group had only mild cognitive

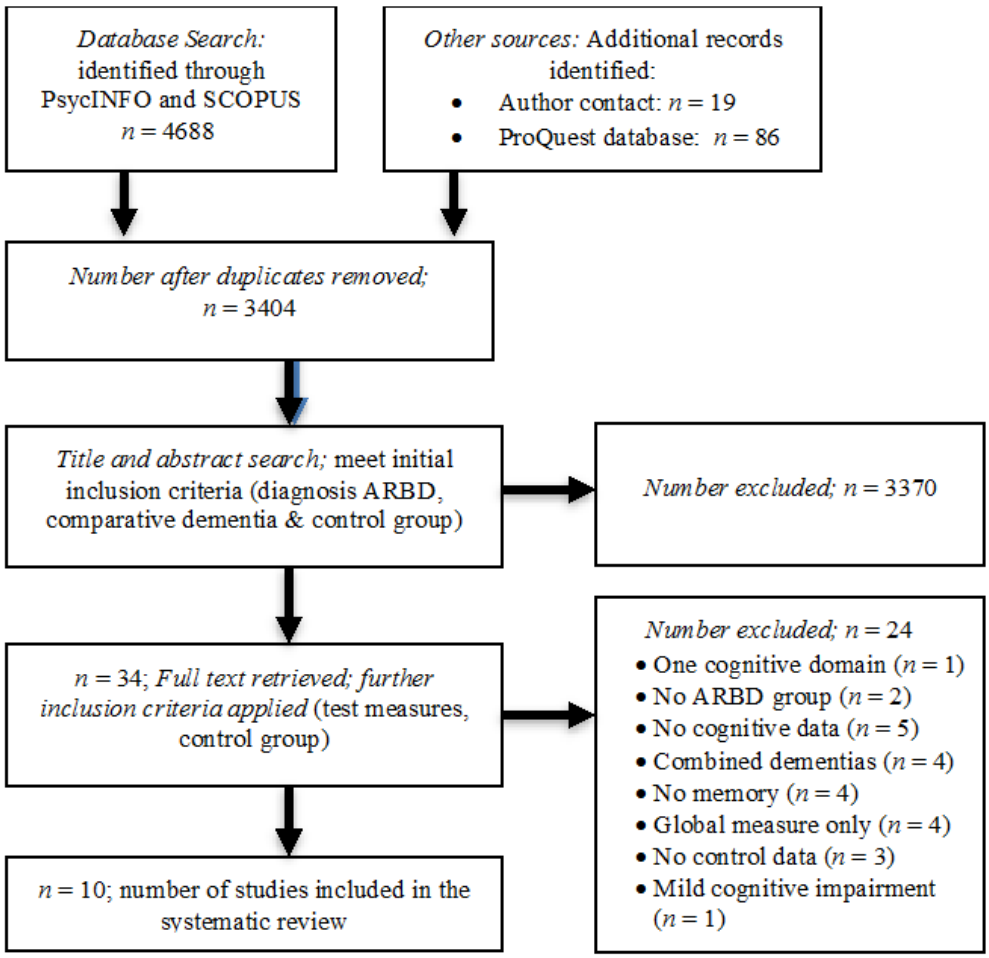

Figure 1. Process for inclusion of studies for search period January 1995 to April 2014

impairment. The reviewers screened studies separately with regard to these criteria, with any differences in opinion discussed and resolved. The reference lists of papers meeting inclusion criteria were scanned for further relevant papers. To identify other pertinent studies and unpublished data, authors of papers that met inclusion criteria as well as preeminent researchers in the field of alcohol-related cognitive impairment (as established from those authors most frequently cited in initial search results) were contacted (n = 100). The ProQuest Dissertations and Theses Database was also searched to screen for any unpublished data that met inclusion criteria.

2.3.3. Quality assessment of included studies

A 14-point quality assessment tool was developed in conjunction with a Senior Lecturer in Neuropsychology (J.B). The tool was designed with a specific focus on critically evaluating reporting variables relevant to alcohol-related cognitive disorders, as well as other aspects of study validity. One point was awarded for each of the following, resulting in a maximum total score of 14; 1) use of explicit diagnostic guidelines; 2) application or verification of these guidelines by individuals other than study authors; 3) defined source of participants; 4) reporting of whether participants with significant past or current psychiatric history were excluded/included; 5) reporting of whether participants with a poly-drug history were excluded/included; 6) reporting of whether participants with focal brain pathology not attributable to alcohol (i.e. neurological insult) were excluded/included; 7) matching of control group on age and education/IQ or statistical control of these variables; 8) reporting of a minimum of three demographic variables for all groups; 9) documentation of period of abstinence from alcohol; 10) inclusion of a quantitative measure of past alcohol use; 11) use of a standardised measure to assess

drinking history; 12) collaboration with another source regarding drinking history (informant or medical records); 13) use of published cognitive tests, and 14) appropriate statistical analyses. Two reviewers (N.R., J. K.) independently assessed each study with this tool. Initial ratings were compared and an inter-reliability analysis of these ratings using Cohen's Kappa was performed to determine consistency. Disagreements on ratings were discussed and resolved in one meeting.

2.3.4. Data extraction and analysis

Data was extracted and checked by two clinicians (N.R., J.K). Extracted data included participant characteristics (group, age, education), diagnostic criteria used, meeting inclusion/exclusion criteria, neuropsychological tasks utilised, and statistical results of between group comparisons. Key characteristics are presented in Table 3. Appendix B provides a summary of extracted data. Tasks were categorised as representative of a cognitive domain guided by their category assignment in the Compendium of Neuropsychological Tests (Strauss, Sherman, & Spreen, 2006) and via consensus with a Senior Lecturer in Neuropsychology (J.B). Meta-analysis was not considered an appropriate means of data analysis given the heterogeneity of tasks and analyses utilised, small number of included studies, and range in participant groups. Consequentially, a narrative synthesis of the data was undertaken.

2.4. Results

Ten studies that met inclusion criteria were identified. Eight articles were identified from database searches (Bigler, 1995; Brand, Kalbe, Fuijwara, Huber, & Markowitsch, 2003; Dirksen, Howard, Cronin-Golomb, & Oscar-Berman, 2006;

Fama, Marsh, & Sullivan, 2004; Munro, Saxton, & Butters, 2001; Saxton, Munro, Butters, Schramke, & McNeil, 2000; Schmidt et al., 2005; Weintraub et al., 2000), one from the ProQuest database (Konishi, 2009), and one from author contact (Saxton, 1999). In all ten studies, cross-sectional comparisons of the target groups were conducted. Of the ten final studies identified, seven represented independent population groups (Bigler, 1995; Brand et al., 2003; Dirksen et al., 2006; Fama, Marsh, & Sullivan, 2004; Konishi, 2009; Schmidt et al., 2005; Weintraub et al., 2000). Another three studies were published by duplicate authors and based on reported sources of participants likely had an overlap in patient samples (Munro et al., 2001; Saxton, 1999; Saxton et al., 2000). The decision was made to retain all three studies given some difference in the tasks utilised as well as differing participant numbers between studies. In total, five of the identified studies reported cognitive data on KS (Brand et al., 2003; Dirksen et al., 2006; Fama et al., 2004; Konishi, 2009; Weintraub et al., 2000) and five on ARD (Bigler, 1995; Munro et al., 2001; Saxton, 1999; Saxton et al., 2000; Schmidt et al., 2005). Comparative dementia groupings for ARD included Alzheimer's disease (AD; Bigler, 1995; Munro et al., 2001; Saxton, 1999; Saxton et al., 2000; Schmidt et al., 2005) and vascular/multi-infarct dementia (Bigler, 1995; Schmidt et al., 2005). Comparison groups for KS included AD (Brand et al., 2003; Fama et al., 2004; Konishi, 2009; Weintraub et al., 2000) and Parkinson's disease (Dirksen et al., 2006). Patients with alcohol dependence and other cognitively impaired groups were also assessed in four studies (see Table 3), however, these groups were not examined in this review as the focus was diagnosed alcohol-related cognitive disorders.

Table 3

Key Characteristics of ARBD Studies Meeting Inclusion Criteria

Author	Groups	ARBD criteria	Quality
Bigler, 1995	ARD, AD, VaD, CON	DSM-III 'dementia associated with alcoholism'	8
Munro et al., 2001	ARD, AD, ALC, CON	DSM-IV 'alcohol dementia'	11
Saxton, 1999	ARD, AD, ALC, CON	DSM-IV alcohol-induced persisting dementia'	10
Saxton et al., 2000	ARD, AD, ALC, CON	DSM-IV 'alcohol-related dementia'	12
Schmidt et al., 2005	ARD, AD, VaD, CON	Based on Oslin et al., 1998	9
Brand et al., 2003	AD, KS, CON	ICD-10 for alcohol-induced amnesic syndrome, DSM-IV for alcohol-induced persisting amnestic disorder	8
Dirksen et al., 2006	ALC, KS, ACoA, PD, CON	DSM-IV criteria for alcohol dependence, IQ 'normal', >10 points between WAIS VIQ and WMS General-Memory Score	13
Fama et al., 2004	KS, AD, CON	DSM-IV alcohol-induced persisting amnestic disorder	8
Konishi, 2009	KS, AD, CON	DSM-IV criteria for alcohol-induced persisting amnestic disorder	3
Weintraub et al., 2000	KS, AD, CON	Not stated	3

Note: ARD = alcohol-related dementia; AD = Alzheimer's disease; MID = multi-infarct dementia; CON = Control; KS = Korsakoff Syndrome; ACoA = patients with ruptured anterior communicating artery; PD = Parkinson's disease, , ALC = Patients with alcohol dependence; VaD = subcortical vascular dementia; DSM-III = Diagnostic and Statistical Manual-III; DSM-IV = Diagnostic and Statistical Manual-IV; NINCDS/ADRDA = National Institute of Neurological and Communicated Disorders and Stroke/Alzheimer's Disease and Related Disorders Association; ICD-10 = International Classification of Diseases – Tenth Revision

2.4.1. Characteristics of Included Studies

ARD groups were primarily sourced from community-based medical services, including outpatient neurological clinics (Bigler, 1995), medical and substance use treatment centres (Munro et al., 2001; Saxton et al., 2000; Schmidt et al., 2005) and memory clinics (Schmidt et al., 2005). Participants with KS were recruited from both outpatient and inpatient services including residential homes (Brand et al., 2003) and in-patient hospital units (Fama et al., 2004; Konishi, 2009) as well as outpatient neurology, psychology, and memory clinics (Dirksen et al., 2006). Subject groups for both ARD and KS samples were generally small (ARD: n = 6 to 14; KS: n = 5 to 10) with the exception of one large KS group (n = 50; Brand et al., 2003). KS groups had a wider variation in mean age (range 56 to 83 years) and mean education (range 9 to 16 years) than ARD groups (range of age means 64 to 80 years, range of education means 10 to 12 years). A large male majority in both clinical groups was observed in all but one ARD study (Saxton, 1999). The inter-rater reliability on quality ratings was Kappa = 0.76 ($p < .001$), indicating a high level of agreement. Studies ranged substantially in quality (range 3-13, median of 8.5).

In all but two studies (Konishi, 2009; Weintraub et al., 2000), established diagnostic guidelines for both ARBD and comparative dementia groups were used Clinicians other than study authors were used in four studies to make or verify diagnoses (Bigler, 1995; Dirksen et al., 2006; Konishi, 2009; Schmidt et al., 2005). The source of participants was generally well specified with the exception of two studies in which the source of the control group was not reported (Brand et al., 2003; Schmidt et al., 2005). In six studies (four ARD), control groups were matched for age and education (Bigler, 1995; Fama et al., 2004, Munro et al., 2001, Saxton et al., 2000), or statistical approaches were used to account for group differences in these

variables (Dirksen et al., 2006; Saxton, 1999). Demographic information for the groups was generally well documented with the exception of three studies (Konishi, 2009; Saxton, 1999; Saxton et al., 2000). The psychiatric history of participants was not reported in four ARD studies (Bigler, 1995; Konishi, 2009; Schmidt et al., 2005; Weintraub et al., 2000) and history of focal brain pathology was not documented in three (Bigler, 1995; Konishi, 2009; Weintraub et al., 2000). In four studies participants with past or present poly-drug use were identified (Dirksen et al., 2006; Munro et al., 2001; Saxton, 1999; Saxton et al., 2000) and in seven studies a quantitative measure of drinking history was provided (Bigler, 1995; Brand et al., 2003; Dirksen et al., 2006; Munro et al., 2001; Saxton, 1999; Saxton et al., 2000; Schmidt et al., 2005). Collaboration of drinking history, either with an informant (Brand et al., 2003; Fama et al., 2004; Saxton, 1999; Saxton et al., 2000) or via medical record review (Brand et al., 2003; Fama et al., 2004; Saxton et al., 2000) was undertaken in four studies, however, standardised measures to assess drinking history were only adopted in two studies (Dirksen et al., 2006; Saxton et al., 2000). In four KS studies, there was no information regarding length of abstinence (Brand et al., 2003; Fama et al., 2004; Konishi, 2009; Weintraub et al., 2000). Two studies used neuropsychological measures which had not previously been used in published literature (Fama et al., 2004; Konishi, 2009) and two studies provided insufficient information regarding statistical analyses (Bigler, 1995; Saxton, 1999).

Overall level of cognitive impairment of the ARD, KS and comparison groups, as measured by tests of global cognitive function such as the Mini Mental State Examination (MMSE; Folstein, Folstein & McHugh, 1975) varied between studies. The majority of KS participants fell in the mild range of impairment (MMSE = 21 to 26) and this was also the case for the ARD groups (MMSE = 22 to 25). AD

samples generally performed in the moderately impaired range (mean MMSE in KS studies = 17 to 20; mean MMSE in ARD studies = 18 to 22) with significant differences in MMSE performance between AD and ARBD groups in three studies; one ARD (Saxton, 1999), and two KS (Brand et al., 2003; Fama et al., 2004). This difference in overall dementia severity may have influenced comparability of cognitive profiles in these studies. The PD comparison group included in the study by Dirksen et al. (2006) fell in the non-impaired range of scores (MMSE = 29) whilst the VaD group was matched on severity to equivalent groups in the Schmidt et al. (2005) study (MMSE = 22). The Bigler (1995) study did not provide an MMSE score, however AD, VaD and ARD groups did not differ on full-scale WAIS-R IQ.

2.4.2. Diagnostic variables

Table 3 presents the diagnostic criteria adopted in the studies reviewed. In all studies, additional restrictions were applied in conjunction with diagnostic guidelines. In three studies (Munro et al., 2001; Saxton, 1999; Saxton et al., 2000), individuals were first required to meet criteria for alcohol dependence. A diagnosis of ARD was then made on the basis of an initial dementia cognitive screening battery and clinical interview. Bigler (1995) required participants with ARD to have Hachinski Ischaemic scores of <7 (Hachinski et al., 1975), possess CT and/or MRI studies compatible with ARD (diffuse atrophy including cerebellar regions), and also applied National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association (NINCDS/ADRDA) guidelines (McKann et al., 1984), although she did not specify how these were applied. Schmidt et al. (2005) based inclusion criteria on those proposed by Oslin et al. (1998) including a minimum drinking history of five years and minimum

abstinence of 60 days at time of diagnosis. However, they additionally specified no history of acute onset of symptoms associated with WE, which did not form part of the original criteria. Munro et al. (2001) also excluded participants with a history of WKS from their ARD group.

In KS studies, DSM-IV criteria for alcohol-induced persisting amnestic disorder (American Psychiatric Association, 1994) were applied in three studies (Brand et al., 2003; Fama et al., 2004; Konishi, 2009). Brand et al. (2003) additionally specified that ICD-10 (World Health Organisation, 1992) diagnostic criteria for alcohol-induced amnesic syndrome be met. Dirksen et al. (2006) required participants meet DSM-IV criteria for moderate to severe alcohol abuse and dependence, have an IQ 'within normal range', and a WAIS-III (Wechsler, 1997a) Verbal IQ score that was minimum of 10 points higher than the General Memory Score on the WMS-III (Wechsler, 1997b). In one study, diagnostic criteria for KS participants was not specified (Weintraub et al., 2000). Restriction of KS participants based on a minimum MMSE score (Folstein et al., 1975) was used by Dirksen et al. (2006), who required all participants to score within one standard deviation of normative data for their age and education, and Konishi (2009), who required all participants to score higher than 20 on the MMSE.

In all but one study that included an AD comparison group (Konishi, 2009), diagnoses of probable Alzheimer's Disease were based on NINCDS-ADRDA criteria (McKhann et al., 1984). Konishi (2009) recruited AD patients based on 'medical chart diagnosis' but did not specify how this was applied. For vascular dementia comparison groups, Bigler (1995) used DSM-III criteria (American Psychiatric Association, 1980) in conjunction with a Hachinski Index Score of 9 or greater (Hachinski et al., 1975), whilst Schmidt et al. (2005) applied criteria from the

State of California Alzheimer's Disease diagnostic and treatment centres (Chui et al., 1992). For the PD group (Dirksen et al., 2006), all participants had a diagnosis of idiopathic PD by a neurologist, were assessed to be in the mild to moderate stages of motor dysfunction using the Hoehn and Yahr (1967) scale and had a mean disease duration of 6.8 years. It could be debated whether this group could be classified as a 'dementia' syndrome, however, the authors note that a wide range of cognitive deficits have been found in individuals with this condition (Dirksen et al., 2006). The DSM-IV (1994) also lists Parkinson's disease as a specific medical condition to which dementia can be attributed.

The comparison groups, like the ARBD samples, tended to have small numbers of participants. The AD comparison groups were generally equal in sample size or a little larger than equivalent ARBD groups (n = 5 to 50); one VaD group had similar numbers to its respective ARD group (Schmidt et al., 2005, n = 13 compared to n = 14) and another had more participants than its ARD sample (Bigler, 1995, n = 15 compared to n = 6). The PD group (Dirksen et al., 2006, n = 18) had more participants than the KS group (n = 9). Small group numbers were a common feature across studies. Only three studies included 10 or more participants in each group; two ARD studies (group size ranging from n = 10 to 20; Munro et al., 2001; Schmidt et al., 2005) and one KS study (Brand et al., 2003). The latter had large numbers of participants in all KS, AD and control groups (n = 50 respectively).

2.4.3. Measures of use and history of drinking

Studies varied considerably with regards to minimum drinking amounts and how participant alcohol use was reported. Inclusion requirements for ARBD participants ranged from 'history of persistent chronic alcohol abuse - greater than 20 years'

(Bigler, 1995) to a current diagnosis of alcohol dependence according to DSM-IV criteria (American Psychiatric Association, 1994; Dirksen et al., 2006; Saxton, 1999; Saxton et al., 2000). In two studies minimum drinking history quantities were specified for ARBD groups; 21 alcoholic drinks per week for a minimum of 5 years (KS group; Dirksen et al., 2006), and 35 alcoholic drinks per week for men (28 for women) for greater than a 5 year period (ARD group; Schmidt et al., 2005). A quantitative estimate of the heaviest period of alcohol consumption was reported in two studies, documented in drinks per session/day (Saxton, 1999; Saxton et al., 2000). The period of time for which ARBD participants had been abstinent varied between 4 weeks (Dirksen et al., 2006; Munro et al., 2001; Saxton, 1999; Saxton et al., 2000) and two months/60 days (Bigler, 2005; Schmidt et al., 2005). Saxton et al. (2000) reported the length of abstinence for each individual participant, with a range of 4 to 504 weeks. Abstinence was not commented on in four KS studies (Brand et al., 2003; Fama et al., 2004; Konishi, 2009; Weintraub et al., 2000). DSM-IV criteria for alcohol-induced persisting amnestic disorder specify memory disturbance not persisting beyond the usual duration of substance delirium or withdrawal. The use of these criteria in two of these studies (Fama et al., 2004; Konishi, 2009) might imply that these participants were abstinent at time of study participation. However, this was not explicitly stated.

2.4.4. Neuropsychological findings in ARD studies

In ARD studies, 20 different neuropsychological measures were utilised, comprising14 different cognitive domains. Results on 35 individual tasks were reported (see Table 4). A number of these tasks were conducted as part of a screening measure or were extracted from a larger assessment battery (such as use of

Information and Similarities from the WAIS-R; Wechsler, 1981). A number of versions of the same measure were used, including modified and standard forms of the Boston Naming Test (Kaplan, Goodglass, & Weintraub, 1983), different administrations of 'Clock Drawing' and various categories for Category Fluency (clothing, animals, grocery items). Different versions of neuropsychological batteries (e.g., WAIS-R, WAIS-III) were also used. These tasks, along with Letter Fluency and the MMSE (Folstein et al., 1975) were the most frequently used neuropsychological measures. The majority of measures were published and information regarding reliability and validity was available in the literature (Strauss et al., 2006). Measures used in past studies with less well established psychometric properties included the Pursuit Rotor Learning Test (PRLT; Heindel, Butters, & Salmon, 1988), a test of procedural learning that had previously been used in alcohol-related populations (Dougherty, Bjork, & Bennett, 1998); and the Philadelphia (repeatable) Verbal Learning Test (PVLT; Libon et al., 2008), a relatively new nine word, 5 trial list-learning task modelled after the 9-word California Verbal Learning Test (CVLT; Delis, Kramer, Kaplan, & Ober, 1987). ARD groups were compared to AD populations in all five studies. Neuropsychological tasks that consistently differentiated groups included tests of verbal recognition memory e.g., the California Verbal Learning Test: Discrimination Index (Munro et al., 2001; Saxton et al., 2000), Recognition Memory: Words (Saxton et al, 2000) and Verbal Recognition (Schmidt et al., 2005); tests assessing semantic and language ability, i.e. category fluency (Munro et al., 2001; Saxton et al., 1999; Saxton, 2000) and the Boston Naming Test (Saxton et al., 2000); and tests assessing visuoconstructional ability, i.e. clock drawing (Schmidt et al., 2005). In the

Table 4

Neuropsychological Measures Used in Assessment of ARD and Dementia Groups

Domain	Tasks used
General Cognitive	WAIS-R (1); MMSE (6)(9)(8)
General Memory	WMS-R (1)
Language	CERAD: Modified BNT (6)(8); BNT (9)(8)(7); WAIS-R: Information (8); WAIS-R: Similarities (7)
Verbal Learning	CERAD: WLLT (6)(8); CVLT (6)(3); PrVLT (6)
Verbal Memory	CERAD: WLLT Delay (6)(8); CVLT Delay (6)(8); Recognition Memory Test: Words (8); PrVLT: Delay (6)
Visuospatial	CERAD: Construction (6)(8); Clock Drawing (6)(9)(8)(7); Rey-Osterrieth Complex Figure (9)(8); Benton Visual Form (8)
Visual Memory	CERAD: Figure Recall (6)(8); Rey-Osterrieth Complex Figure: Immediate/Delayed (9); Recognition Memory Test: Faces (6)
Processing Speed	TMT-A (6)(9)(8)
Procedural Learning	PRLT (6)
Premorbid Intelligence	NART (8)
Verbal Comprehension	Token Test (8)
Motor Control	Grooved Pegboard (8)
Attention	WAIS-R Mental Control (Boston version) (7)
Executive	Letter Fluency (1)(9)(8); Design Fluency (1), Category Fluency: Clothing (6); Animals (9)(8); TMT-B (6)(9)(8); WCST (9)(8); CVLT: Intrusions (6)(9)

Note. WAIS-R: Wechsler Adult Intelligence Scale Revised; MMSE: Mini Mental State Examination; WMS-R: Wechsler Memory Scale Revised; CERAD: Consortium to Establish a Registry for Alzheimer's Disease Battery; BNT: Boston Naming Test; WLLT: Word List Learning Test; CVLT: California Verbal Learning Test; PrVLT: Philadelphia Repeatable Verbal Learning Test; TMT: Trail Making Test; PRLT: Pursuit Rotor Learning Test; NART: National Adult Reading Test; WCST: Wisconsin Card Sorting Test. See relevant papers for test references. 1 = Bigler (1995), 6 = Munro et al. (2001), 7 = Saxton et al. (1999); 8 = Saxton et al. (2000); 9 = Schmidt et al. (2005).

three studies incorporating tasks of verbal recognition memory, the AD groups consistently performed significantly poorer than both control and ARD groups (Munro et al, 2001; Saxton et al, 2000, Schmidt et al., 2005). While ARD groups did not significantly differ from controls in Munro et al. (2001) and Saxton et al. (2000) on measures of verbal recognition memory, they scored lower than controls on verbal recognition in one study (Schmidt et al., 2005; *z*-score = -5). However, significance was not tested as control scores were used to generate the z-scores.

Semantic and language measures also differentiated patient groups. The ARD groups performed significantly better than the AD groups on measures of category fluency in two studies (Saxton, 1999; Saxton, 2000) and confrontation naming in another (Saxton et al., 2000), even when global cognitive functioning was equitable (Saxton et al., 2000). The ARD group did not significantly differ from controls on confrontation naming in three studies (Saxton, 1999; Saxton et al., 2000, Munro et al., 2001) although in another study (Schmidt et al., 2005) they scored lower than controls (*z*-score = -3.85). On category fluency tasks, the ARD group did not differ from controls in two studies (Saxton et al., 2000; Munro et al., 2001), but performed significantly poorer than controls in another (Saxton, 1999). The AD group performed significantly poorer than controls on category fluency and confrontation naming tasks in the three studies where this was assessed (Saxton, 1999; Saxton et al., 2000, Munro et al., 2001). In the one study which assessed verbal comprehension (Token Test; Saxton et al., 2000) no difference between patient or control groups were observed.

Visuoconstructional deficits were reported in ARD groups, with significant reductions in performance compared to controls (Munro et al., 2001; Saxton, 1999; Saxton, 2000) and AD groups (Schmidt et al., 2005) on clock drawing (Munro et al.,

2001; Saxton, 1999; Saxton, 2000, Schmidt et al., 2005) and copying tasks (Munro et al., 2001; Saxton, 1999; Saxton, 2000). Reduced performance on clock drawing was observed even when global cognitive function between dementia groups was equitable (Schmidt et al., 2005) and despite comparable performance from ARD and AD groups on a perceptual matching task (Saxton et al., 2000). Both groups performed significantly poorer than controls on this task.

In general, AD and ARD groups did not differ significantly in performance on verbal learning tasks (Munro et al., 2001, Saxton et al., 2000, Schmidt et al., 2005) or on verbal or visual delayed recall measures (Munro et al., 2001, Saxton et al., 2000, Schmidt et al., 2005). The AD group did perform significantly worse than a ARD group on one world list learning task (Saxton, 2000) and on delayed recall of a complex figure (Saxton, 1999). The two clinical groups were significantly poorer than control groups on these memory tasks (Munro et al., 2001; Saxton, 1999; Saxton et al., 2000).

On executive function tasks, equivalent performance in patient groups and significant reductions compared to controls were seen in generating novel designs (Bigler, 1995) and letter fluency (Bigler, 1995, Saxton, 1999). Inconsistent results between groups were found on a test of divided attention (Trail Making Test B). AD and ARD groups did not differ on time required to complete the task in two studies (Saxton et al., 2000; Munro et al., 2001) but the AD group required more time in another (Saxton, 1999). There were no differences between the ARD and control groups on this task in any study (Saxton, 1999; Saxton et al., 2000; Munro et al., 2001), however, the AD group did perform significantly worse than controls in two studies (Saxton, 1999; Saxton et al., 2000). No differences were found between patient or control groups on a test of conceptual problem-solving (Wisconsin Card

Sorting Test Categories; Saxton, 1999; Saxton, 2000). However, on a test of working memory (Mental Control; Schmidt et al., 2005), the ARD group performed significantly worse than the AD group (z = -3.64 vs -1.09).

Results were disparate on a processing speed task (Trails A). The AD group performed significantly worse than ARD groups and controls in one study (Saxton et al, 2000), but both AD and ARD groups performed equivalent to each other but significantly poorer than controls in two other studies (Saxton et al., 1999; Munro et al., 2001). The ARD group performed significantly worse than controls on a test of manual dexterity (Saxton et al., 2000), however, no significant differences in any groups on a procedural learning task were observed (PRLT; Munro et al, 2001) .

Two studies in which ARD and Vascular Dementia groups were compared revealed no between group differences on any measure (Bigler, 1995; Schmidt et al., 2005). In the Bigler (1995) study, both patient groups performed poorer than controls on measures of the ability to generate novel designs, letter fluency and on global IQ and MQ scores (Bigler, 1995). In the Schmidt et al. (2005) study, both ARD and VaD groups scored -1.5 standard deviations below the control mean on all measures other than clock drawing in the VaD group (z = - 1.42).

Importantly, all ARD studies received reasonably good quality rating scores (range 8 to12 out of 14). Strengths included the detailed reporting of drinking and abstinence variables and the use of established neuropsychological measures. However, one study did not match patient groups on overall dementia severity (Saxton, 1999; mean MMSE of 18 in the AD group and 25 in the ARD group), which may have limited the ability to interpret comparison scores. In that study the AD group performed equivalent to or worse than the ARD group on all tasks, and number of ARD participants was low (n = 7). One other study also had a low number

of ARD participants (n = 6) and also had the lowest quality rating from the five studies (8; Bigler, 1995).

The other three studies with high ratings (Munro et al., 2001; Saxton, 2000 and Schmidt, 2005) had larger number of participants and equated dementia severity. Three main findings emerged from those studies. Firstly, ARD groups consistently performed poorer than controls on visuoconstructional tasks (e.g., Clock Drawing, Copying), with worse performance than an AD group being reported in one study (Schmidt et al., 2005). Secondly, while performance on both visual and verbal learning and memory tasks in the ARD group was often equivalent to AD groups (e.g., learning of word list, delayed recall of word list and complex figures) and reduced relative to controls, performance on verbal recognition measures was consistently better for the ARD groups than the AD groups. Thirdly, the ARD group generally performed equivalently to controls on confrontation naming tasks, while the AD group consistently performed poorer than controls on semantic fluency and naming tasks.

2.4.5. Neuropsychological findings in KS studies

In KS studies, 40 different measures across 12 different cognitive domains were used, with results from 54 tasks reported (see Table 5). The MMSE was the most common measure, and measures of memory and executive functioning were frequently employed (15 and 12 tasks respectively). The Boston Naming Test (three different versions), Letter Fluency and the WCST were also frequently employed. Whilst many tasks were adopted from neuropsychological batteries with well-documented reliability and validity (e.g. the WAIS and WMS batteries), other tasks were less well established, with tasks in two studies not having previously been

reported on in the literature in the form they were used. The adaption of the Presidential Candidates Test by Fama et al. (2004), although appropriate to their specific investigation of different memory components, had not been used previously and consequently information regarding its psychometric properties is lacking. Konishi (2009) did not sufficiently document the origin of tasks used. Brand et al. (2003) applied tasks in a language other than English, however these were largely German equivalents of established neuropsychological measures (e.g., the Word-Colour test as a Stroop equivalent; see Brand et al., 2003).

KS populations were compared to Alzheimer's groups in four of the five studies (Brand et al., 2003; Fama, 2004; Konishi, 2009, Weintraub et al., 2000); in the fifth, a PD group was included, however that group was not compared directly with the KS group due to differing sample sizes (Dirkson et al., 2006). Conclusions regarding the neuropsychological profile of KS were limited, given the range of tasks utilised and minimal overlap between studies. Differences in global cognitive rating where AD groups had significantly lower means on the MMSE compared to KS groups (Brand et al., 2003; Fama et al., 2004) may have also influenced overall outcomes. The KS group only performed poorer than AD groups on one measure in these two studies (perseverative errors on the WCST; Fama et al., 2004). The AD group in the Fama et al. (2004) study also had a significantly lower premorbid IQ score than the control group, and this was not controlled for in their cognitive analyses. AD and KS groups did not significantly differ on the majority of measures of delayed recall for verbal and visual information (Brand et al., 2003; Fama et al., 2004; Konishi et al., 2009; Fama et al., 2004, Weintraub et al, 2000), however, the AD group performed significantly worse than KS groups on some tasks assessing

Table 5

Neuropsychological Tasks Used in Assessment of KS and Dementia Groups

Domain	Tasks used
General Cognitive	MMSE (2)(3)(3)(4)(9); WAIS-III (2)(3); WAIS-R (4)(10); MoCA (5); Blessed Dementia Scale (10)
General Memory	WMS-III (3) WMS-R (4)
Language	Modified BNT (4); BNT-15 item (5); BNT (10); WAIS-R: Vocabulary (4); Picture Naming (5)
Semantic Memory	HAWIE-R: Information (2); Presidential Candidates Test (4); Retrograde Memory Test (5); Word Meaning (5); Scenes (5); Semantic Decision (5), Faces (5)
Verbal Learning	Memo-Test: Immediate (2); Buschke Cued Selective Reminding (9)
Verbal Memory:	Memo-Test: Delay (2); Recognition Memory Test: Words (4); Buschke Cued Selective Reminding: Delay (5); 3W3S (10)
Visuospatial	CERAD: Construction (2); ROCF: Copy (2); Recognition Memory Test: Faces (4); MoCA: Clock Drawing (5); MOCA: Copy (5); 3W3S: Copy (10)
Visual Memory:	ROCF: Delay (2); 3W3S (10)
Processing Speed	Simple Reaction Time (5); Choice Reaction Time (5); Digit Symbol (5)
Premorbid IQ	NART (4)
Verbal Comprehension	AAT (2)
Attention/Working Memory	Digit Span (2)(5); Corsi's Block Span (2); Visual Search (5); Letter-Number Sequencing (5);
Executive	Letter Fluency (2)(3)(5); Category Fluency (5); Word-Colour-test (2); Stroop (5); WCST (2)(3)(4); LPS: Reasoning (2); TKS (2); OA Task (3); Trails B (3); WAIS-R: Picture Arrangement (4); Cognitive Estimation Test: 7 item (5); Mazes (5)

Note. MMSE = Mini Mental State Examination; WAIS-III = Wechsler Adult Intelligence Scale Third Edition; WAIS-R = Wechsler Adult Intelligence Scale Revised; MoCA: Montreal Cognitive Assessment; WMS-III = Wechsler Memory Scale Third Edition; WMS-R = Wechsler Memory Scale Revised; BNT = Boston Naming Test; HAWIE-R = German WAIS-R; 3W3S = Three Words Three Shapes; CERAD: Consortium to Establish a Registry for Alzheimer's Disease Battery; ROCF = Rey Osterreich Complex Figure. NART = National Adult Reading Test; AAT = Aachener Aphasie Test; WCST: Wisconsin Card Sorting Test; TKS: Cognitive Estimation Test; OA Task: Object Alternation task. See papers for test references. 2 = Brand et al., 2003; 3 = Dirksen et al., 2001; 4 = Fama et al., 2004; 5 = Konishi et al., 2009; 10 = Weintraub et al., 2000

immediate recall of verbal information (e.g., immediate recall on a verbal selective reminding test; Brand et al., 2003; Fama et al., 2004, Konishi, 2009). Both patient groups had significantly reduced scores on these immediate and delayed memory measures relative to control groups (Brand et al., 2003; Fama et al., 2004; Konishi, 2009; Weintraub et al., 2000). In two studies, higher numbers of perseverative errors on the WCST by KS patients compared to controls (Dirksen et al., 2006; Fama et al., 2004) and relative to an AD group (Fama et al., 2004) were reported. On other executive tasks, KS and AD groups both performed significantly worse than controls on tasks of verbal inhibition (Konishi, 2009; Brand et al., 2003), cognitive estimation (Brand et al., 2003, Konishi et al., 2009), picture arrangement (Fama et al., 2004), letter fluency and divided attention (Dirksen et al., 2006) and categories on the WCST (Fama et al, 2004).

There was some variability between studies in patient group comparisons. The AD group performed significantly worse on the verbal inhibition task than the KS group in one study (Brand et al., 2003) but not in another (Konishi, 2009), and no differences between groups were found on tasks of cognitive estimation (Brand et al., 2003; Konishi, 2009) or picture arrangement (Fama et al., 2004). On one measure of working memory (Digit Span Backwards), the KS group performed poorer than both AD and control groups (Konishi, 2009). However, a global index of verbal attention span (i.e., Digit Span Forwards and Backwards) was worse in the AD than the KS group in another (Brand et al, 2003). Both AD and KS groups scored significantly lower on these tasks than controls.

KS groups did differ from AD groups on performance on confrontation naming tasks, however AD groups performed significantly poorer than control groups (Konishi, 2009; Weintraub et al, 2000). Visuoconstructional ability, as

measured by copy and clock drawing tasks, did not differ between patient groups who performed significantly poorer than controls in one (Konishi, 2009) of the two studies that addressed this (Konishi, 2009; Weintraub et al., 2000). Performance on tasks assessing remote memory was significantly lower in patient groups compared to controls (Fama et al., 2004; Konishi, 2009), with the exception of one recognition task in which there was no difference between KS and control groups (Fama et al., 2004). The AD group also performed worse than the KS group on one measure of remote recognition memory (Candidate Recognition; Fama et al., 2004). The KS group was slower on a reaction time and colour-naming task than controls (Konishi, 2009); they were also slower than the AD comparison group on this latter task. Dirksen et al. (2001) categorised executive function measures according to related prefrontal surface areas e.g., orbitofrontal (Object-Alteration errors, WCST perseverative errors) and dorsolateral (WCST-categories, COWAT, Trails) function. KS performed significantly worse than a matched control group on all measures, whilst the PD group demonstrated a selective impairment on 'orbitofrontal' tasks compared to controls (Dirksen, 2001).

Two studies were rated poorly for quality (Konishi, 2009; Weintraub et al., 2000; rated 3 respectively). These studies provided limited information about the drinking history of KS participants, did not control for or exclude participants with psychiatric, neurological or other substance use histories, and did not report use of explicit diagnostic guidelines. The other three studies (Brand et al, 2003; Dirksen et al, 2001; Fama et al. 2004) received good quality ratings (ratings of 8-13), although again group numbers were very low (n = 5 to 9), with the exception of one study (Brand et al., 2003; n = 50). The ability to extrapolate from the results of the higher quality studies combined was extremely limited given the large variety of tasks used.

Only two common measures were used across all three studies (MMSE and Wisconsin Card Sorting Test) and performance was not compared to other groups in one study (Brand et al., 2003). Letter fluency was used in two of the three studies (Brand et al., 2003, Dirksen et al., 2006). Comparisons across groups were also limited by the fact that only some patient groups completed particular measures (e.g., WCST only by the KS group in Brand et al., 2003); and Dirksen et al. (2001) did not provide direct comparisons between patient groups.

Despite limitations in study design and reporting, trends in findings from the three methodologically stronger studies suggest that KS groups consistently performed poorer than controls on some executive measures (WCST categories and perseverative errors) and had comparable performance to AD groups on verbal and visual delayed memory measures, which were reduced relative to controls (Brand et al., 2003; Fama et al., 2004).

2.5. Discussion

The current systematic review was conducted to provide a comprehensive review of literature documenting cognitive deficits in KS and ARD, in comparison to other dementia syndromes as well as neurologically normal control groups. Such comparisons have been investigated in relatively few studies and heterogeneous research methodologies complicate the interpretation of results. Other complicating factors include the use of different diagnostic criteria, inconsistent inclusion and exclusion criteria with regard to psychiatric, neurological and other substance use comorbidities, and inadequate matching of comparison groups on education, age and general intellect. The clinical picture is further muddled by a lack of consistency

across studies in the tasks used to assess cognitive functioning, which restricts comparison of neuropsychological findings.

Both diagnostic criteria and inclusion and exclusion criteria varied considerably between studies. Additionally, interpretation of the terms used in inclusion/exclusion criteria differed across studies. For instance, exclusion due to neurological insult ranged from 'stroke, head injury involving loss of consciousness,' (Saxton, 1999) to a 'history of WKS' (Saxton et al., 2000) or 'lack of focal neurological signs, with the exception of ataxia or peripheral sensory polyneuropathy' (Schmidt et al., 2005). The same variability was evident in use of the term 'psychiatric history', with exclusion of schizophrenic disorders and current major depression in one instance (Dirksen et al., 2006) and 'current or history of psychiatric symptoms' in another (Saxton, 19999). In some studies, details regarding neurological (Bigler, 1995; Konishi, 2009; Weintraub et al., 2000) and/or psychiatric history of participants was not comprehensively reported (Bigler, 1995; Konishi, 2009; Schmidt et al., 2005; Weintraub et al., 2000). In only four studies was poly-substance use addressed (Dirksen et al., 2006; Munro et al., 2001; Saxton, 1999; Saxton et al., 2000).

There was also significant variability in how drinking history was assessed. In the majority of cases, clinical interview established prior and current drinking history. Some researchers attempted to corroborate self-reported drinking history via family members or review of medical records (Brand et al., 2003; Fama et al., 2004; Saxton, 1999; Saxton et al., 2000), however, standardised measures of alcohol use were only adopted in two studies (Dirksen et al., 2006; Saxton et al., 2000). Terminology used to describe drinking history was often vague without specific reference to drinking quantities, e.g., 'extensive alcohol consumption over 12 years'

(Munro et al., 2001) or ‘extensive history of heavy drinking’ (Konishi, 1999). In four studies that included KS patient groups, no information about length of abstinence was reported (Brand et al., 2003; Fama et al., 2004; Konishi, 2009, Weintraub et al., 2000). Abstinence has an important role in recovery of structural and functional ability and on performance on cognitive measures (Stavro et al., 2012), and has the potential to significantly impact study results.

The quality of studies varied, with those receiving higher methodological rankings using clear inclusion and exclusion criteria, employing established diagnostic criteria and providing comprehensive details regarding the alcohol history of participants. It should be noted, however, that a poor quality score might not reflect a poor study per se, but rather poor reporting of variables in that paper.
In the majority of studies, published neuropsychological measures were used and appropriate statistical analyses were adopted to deal with issues such as unbalanced group numbers. Matching of control and patient groups on age and education was common in ARD studies but less frequent in KS studies. One could argue that it is not appropriate to match KS samples with dementia groups on age or measures of global cognition; KS is typically of earlier onset than dementia syndromes (MacRae & Cox, 2003) and preserved performance on tests of cognitive functions other than memory may be expected on screening tasks if the traditional view of KS holds. The range in MMSE and ages seen in KS samples in this investigation, however, suggests there is variation in global cognitive scores and age within this cohort.

It is also unclear whether the MMSE (Folstein et al., 1975) is an appropriate measure to screen for global cognitive function in alcohol-related cognitive disorders. The MMSE, historically used as a marker of severity of dementia, has many items designed to assess language disturbance but a paucity of tasks that

address executive function, attention and visuospatial skills. This is an issue for assessment of this population, as the latter functions have been identified as impaired in those with ARBD. It has also been criticised for a lack of sensitivity to mild cognitive impairment (Dong et al., 2010; Pendlebury, Cuthbertson, Welch, Mehta, & Rothwell, 2010). If a more representative brief global measure of cognitive functioning across ARBD and other groups is to be obtained, it may be more appropriate to use a measure that is sensitive to a range of domains rather than one that relies heavily on a few, limited cognitive functions. The influence of screening tool choice on reported global functioning was demonstrated by Konishi (2009) in his comparison of AD and KS groups. In that study the AD group scored significantly lower on the MMSE while performance was equivalent on the Montreal Cognitive Assessment (Nasreddine et al., 2005). Future studies should attempt to further characterise the pattern of impairment shown by ARBD groups on neuropsychological testing, and determine how that corresponds to performance on different screening measures. This would allow clinicians to select tools that will optimise the detection of cognitive impairment in their respective populations.

Inconsistency in methodological approaches and reporting of important variables (abstinence and drinking history; psychiatric and neurological, and other substance use comorbidities) limits the ability to draw concrete conclusions regarding the neuropsychological profiles of ARD and KS. For the ARD group comparisons, three of five studies had overlap in authors and appear to have utilised a similar sample, which may mean that the results may be not be representative of the ARD population. For the same reason, however, the protocol was similar, allowing performance to be effectively compared across studies. Notably, the studies

did differ on some cognitive outcomes, which could be due to participant characteristics, variability in sample size, or the use of different versions of tasks.

A review of the neuropsychological results in the three studies that had larger participant numbers in addition to good methodological quality demonstrates some trends regarding ARD and AD group performances. The tasks that most frequently differentiated the two groups were semantic tasks and recognition memory indices. The AD groups were consistently poorer than controls on semantic fluency and confrontation naming tasks, while the ARD group typically demonstrated preserved naming ability. The AD groups also performed significantly poorer than ARD groups on verbal recognition memory indices despite equivalent verbal learning and overall delayed recall (verbal and visual) performance by both groups. The finding of semantic and salient episodic impairment is consistent with previous neuropsychological findings in AD (Salmon & Bondi, 2009). It was unclear whether performance on verbal recognition memory measures in ARD groups significantly differed from matched controls. In two of three studies the ARD samples did not differ from controls (Munro et al., 2001; Saxton et al., 2000). Although the ARD sample reported on by Schmidt et al. (2005) performed poorer than controls, significance was not assessed in that study. Improved recognition performance in the ARD group relative to free-recall performance may reflect a 'fronto-subcortical' pattern of performance, in which there is disruption to the processing and retrieval of new memories rather than an inability to store information (Buckner, Kelley, & Peterson, 1999). This is consistent with evidence of significant disruption to structure and function in frontal circuitry in ARBD (Harper, 2009) and neuroimaging evidence of reduced cortical (frontal) and subcortical (basal ganglia and thalami) cerebral blood flow in individuals with ARD (Chung et al., 2009). However, some level of

storage deficit cannot be ruled out, particularly given the poor performance of the ARD group on visual memory recognition measures. Replication and clarification of these findings is required.

The other notable trend in the ARD group was poorer performance relative to control groups on simple visuo-constructional tasks (e.g., Clock Drawing and Copying), with equivalent or poorer performance than AD groups on the same measures (Munro et al., 2001; Saxton et al., 2000, Schmidt et al., 2005). This is particularly salient given that deficits on visuo-constructional tasks are also common in the moderate stages of AD (Salmon & Bondi, 2009). The findings are consistent with reports that visuospatial deficits are common in individuals who have ARCI. Persistent deficits in spatial information processing and chronic grey matter volume loss in the parietal cortex have been observed in long-term abstinent individuals with a history of alcohol dependence (Fein & McGillivray, 2007; Fein, Shimotsu, Chu, & Barakos, 2009).

Both AD and ARD groups demonstrated poor performance on some tests of executive function (novel design generation, letter fluency) but preserved performance relative to controls on others (WCST). Again, these results are not definitive given the small number of studies on which they are based, low subject numbers and differences in tasks between studies. Only two studies compared a dementia group other than AD to the ARD groups; vascular dementia groups (Bigler, 1995; Schmidt et al., 2005). VaD groups did not differ from the ARD group on any cognitive task in these two studies, with performance below the control group on the majority of tasks utilised, including letter and design fluency, learning and memory, working memory, naming and verbal abstract reasoning.

Interpretation of the performance of KS groups on neuropsychological measures was again difficult given the variety of tasks used (n = 43) and differing participant characteristics. Only three studies demonstrated reasonable quality as evaluated by the quality scale. These studies targeted different cognitive domains and utilised disparate tasks. There was an indication of executive dysfunction in KS groups relative to control groups, and the AD group also demonstrated poor performance on the majority of these measures (verbal inhibition, cognitive estimation tasks). Perseverative errors on the WCST was a marked feature in the KS group in two studies, however, given the small number of studies this result cannot be further extrapolated. While memory deficits were similar to the AD populations in terms of free recall verbal and visual memory errors, the lack of recognition indices limit conclusions regarding the nature and extent of the memory deficit. It should be noted that memory impairment per se was an inevitable outcome given that the diagnostic criteria for KS specify memory impairment.

The present review does not represent the full literature regarding cognitive deficits in KS and/or ARD. The review was conducted in order to compare the profiles of cognitive deficits characterising KS and ARD with that typifying dementia disorders and matched control groups, to assist with differential diagnosis at a clinical level. Limitations were that comparative dementia syndromes were largely limited to AD and VaD populations, with few authors in the wider literature base comparing such groups. Further studies designed to explore the characteristics of other dementia populations relative to ARBD samples are required, as are longitudinal studies comparing changes in cognitive profiles of these disorders over time. One critical factor in consideration of alcohol-related cognitive impairment is that abstinence in individuals with a history of alcohol dependence has been shown

to lead to resolution of many cognitive deficits, although the rate and form of cognitive recovery remains controversial (Bates et al., 2002; Bates et al., 2005). Oscar-Berman and Marinkovic (2007) concluded that some functions improve following three to four weeks of abstinence, however, Fein, Bachman, Fisher, and Davenport (1990) reported residual deficits even following five years of abstinence. Stavro et al. (2012) concluded dysfunction abates with one year of sobriety. Given that diagnosis of a dementia syndrome was made in some studies included in this review with as little as four weeks of recorded abstinence, it is possible that many of the individuals that received an 'ARBD' diagnosis may have demonstrated improvement in both brain structure and function in subsequent months. Clarification of the time needed for stabilisation of cognitive function following abstinence would assist with setting minimum standards for diagnosis of chronic cognitive impairment. Additionally, it would allow for better investigation of factors that may influence outcome in cognitive recovery – nutritional deficiencies, previous TBI, age, gender and education (Bates, 2010). In this regard, longitudinal analyses are required, assessing individual variation in premorbid cognitive abilities and documenting alcohol consumption, nutritional status and risk factors over the lifespan.

The variety of tasks utilised and small number of comparison groups limited the detection of differences in the cognitive profiles of KS and ARD. Both groups have been reported to show deficits on measures of executive functioning and poor performance on measures of delayed memory. It is clear that the diagnostic criteria adopted played a significant role in restricting the type of participants admitted to studies, resulting in selection bias for individuals with memory impairment. The exclusion of individuals with neurological signs, including a history of WKS, from ARD studies, and the exclusion of individuals with global cognitive impairment from

the KS studies served to isolate these two populations from each other. This is in the context of an accumulation in clinical and pathological evidence suggesting overlap in clinical presentation, neurological signs and underlying pathology between KS and ARD (Ridley, Draper, & Withall, 2013). The adoption of the DSM-V criteria (American Psychiatric Association, 2013) for 'alcohol-induced neurocognitive disorder' may serve as a means to permit examination of the neuropsychological profile of alcohol-related cognitive disorders under one clinical banner. Future studies should investigate the overlap in neurological, pathological and neuropsychological symptoms of these historically divided cognitive disorders. This would allow the defining clinical features of each syndrome to be established, and determination of whether these disorders are best classified as separate entities or as part of a spectrum of alcohol-related cognitive disorders. There is a clear need for consistent and thorough methodological approaches – clear and defined diagnostic and exclusion criteria, detailed reporting of drinking variables, larger group numbers and use of similar neuropsychological tasks – if we are to adequately address the limitations of previous research.

CHAPTER THREE

Cognitive functioning in individuals presenting for alcohol use treatment: An exploration of comorbid risk factors and associations with drinking history

This chapter has been prepared for submission to *The Clinical Neuropsychologist*

Abstract word count: 149

Manuscript word count: 11034

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3.1. Abstract

Individuals attending treatment for alcohol use disorders (AUD) frequently present with concomitant conditions that pose a risk for cognitive impairment, including physical and mental health conditions, neurological injury and poly-substance use. However, studies of alcohol-related cognitive impairment have traditionally excluded individuals with comorbidities from investigations. The characteristics of a sample of 21 individuals attending treatment for AUD were examined in this current study. Results confirmed the high rates of comorbid psychiatric, neurological, and health conditions that accompany treatment-seeking individuals with AUD. The AUD group performed significantly worse than a matched control group on the majority of tasks, with performance on delayed memory measures most frequently impaired. Associations between drinking history, particularly the length of period of heaviest drinking, and cognitive performance were found. The need to consider the influence of comorbid conditions in future research of alcohol-related cognitive impairment, to allow generalisable application to the clinical setting, is discussed.

3.2. Introduction

Excessive alcohol consumption is associated with structural and functional brain changes, some of which may be permanent in nature (for a review, see Buehler & Mann, 2012; Harper, 2009). In vivo and post-mortem imaging studies have revealed significant volume loss in cortical and subcortical brain structures in individuals with alcohol use disorders (AUD), with disproportionate white matter loss and regional reductions most prominent in the frontal lobes, cerebellar vermis and hippocampus (Harper & Matsumoto, 2005; Pfefferbaum et al., 1995). Individuals with additional neurological insult from thiamine deficiency, such as in the Wernicke-Korsakoff syndrome (WKS), have additional disruption to diencephalic-hippocampal circuitry, although there is significant overlap between the regions damaged in alcohol dependent individuals both with and without WKS (Jung, Chanraud, & Sullican, 2012; Pitel et al., 2012).

3.2.1. Cognitive deficits in AUD

Given these neuropathological findings, it is not surprising that a sizeable proportion of individuals with AUD (one- to two-thirds) demonstrate some degree of neurocognitive deficit (Bates, Buckman, & Nguyen, 2013; Fein, Bachman, Fisher, & Davenport, 1990). Alcohol-related cognitive impairment (ARCI) may range from subtle or transient deficits to pervasive and severe cognitive disorders, such as those formalised by the Diagnostic and Statistical Manual of Mental Disorders – Fourth Edition (American Psychiatric Association, 1994) , i.e. ‘alcohol-induced persisting amnestic disorder’ (Korsakoff Syndrome; KS) and ‘alcohol-induced persisting dementia’ (ARD). Chronic, excessive alcohol consumption is thought to have a

selective effect on cognitive skills, with memory, visuospatial, psychomotor and fluid cognitive abilities most vulnerable to the effects of heavy alcohol use (Fein et al., 1990; Sullivan, Rosenbloom, & Pfefferbaum, 2000). These fluid abilities include impairment of executive functions; that is, higher-order skills requiring controlled processing of novel information, such as response inhibition, problem-solving and attentional control, along with deficits in learning and memory, visuospatial processing and psychomotor speed (Bates, Bowden & Barry, 2002; Fernandez-Sarrano, Perez-Garcia, Rio-Valle, & Verdejo-Garcia, 2010). Crystallised abilities, such as general knowledge, general intelligence and vocabulary are thought to be spared (Bates et al., 2002). Many of the structural and functional deficits resolve within a year of abstinence but residual impairments are common (Rosenbloom & Pfefferbaum, 2008; Stavro, Pelletier, & Potvin, 2012). It is generally accepted that the most substantial cognitive recovery occurs in the acute stage of abstinence and specifically, within the first month of cessation of drinking (Bates, Buckman, & Nguyen, 2013). There is, however, limited agreement on the rate of recovery by cognitive domain in the literature, with some authors suggesting chronic deficits in visuospatial processing (Fein & McGillivray, 2007; Fein, Shimotsu, Chu, & Barakos, 2009; Schandler, Clegg, Thomas, & Cohen, 1996) or executive functioning (Fein & Di Sclafani, 2004; Kopera et al., 2012; Munro, Saxton, & Butters, 2000). Other authors report normalisation of all of cognitive function following even brief periods of abstinence (Dresler et al., 2012; Pitel et al., 2009). Considerable methodological variation, including differences in how authors label cognitive tasks (e.g., task measuring ‘executive functioning’), definitions of ‘acute’ and ‘intermediate’ abstinence, comparisons of predominantly cross-sectional populations, lack of consideration of interim drinking and inconsistent exclusions of patients with

comorbid disorders may account for these discrepant findings. Cognitive deficits in more pervasive forms of alcohol-related cognitive impairment, i.e. formalised neurocognitive disorders such as ARD and KS, typically involve anterograde memory disturbance and additional disturbance to executive function and visuospatial functioning (Kopelman, Thomson, Guerrini, & Marshall, 2009; Saxton, Munro, Butters, Schramke, & McNeil, 2000). Again, use of differing inclusion criteria in research findings – such as memory impairment forming a key diagnostic feature of Korsakoff syndrome – may have biased these outcomes (for a review, see Ridley & Batchelor, 2014a).

3.2.2. Factors influencing outcome in ARBD

Multiple factors influence both the severity and permanency of ARBD and may partially explain the discrepant results regarding the rate of recovery of cognitive function. Length of abstinence from alcohol plays a critical role; cessation of drinking can at least partially reverse many brain changes, with improvements to brain volume and function observed with as little as a few days of sobriety (Kril & Halliday, 1999; Mason et al., 2005; van Eijk et al., 2013). Recovery of brain function may continue for many years (Fein, Price, & Di Sclafani, 2006; Gansler et al., 2000). Drinking patterns may also affect severity of damage; quantity of alcohol intake and years of heavy drinking have been more consistently associated with grey and white matter volume reductions than overall lifetime intake (Bjork, Gran, & Hommer, 2003; Buehler & Mann, 2012). Oslin, Atkinson, Smith, and Hendrie (1998) proprosed that a threshold of greater than 35 standard drinks a week for men (28 drinks for women) was sufficient to pose risk for alcohol-related dementia. However, as the authors note, this proposed threshold was largely arbitrary and requires further

validation. Repeated drinking patterns of binges and withdrawals may also be impair cognitive recovery; some authors have reported an association between higher number of detoxifications to poorer cognitive outcome following abstinence in individuals with AUD and KS (Fujiwara, Brand, Borsutzky, Steingass, & Markowitsch, 2008; Loeber et al., 2010). This relationship, however, is not firmly established. Psychosocial and individual factors may also influence the likelihood of development of alcohol-related cognitive impairment. Age, education, gender, and family history of alcohol dependence, for example, have all been implicated as factors which influence vulnerability to ARCI (Bates, Buckman, Voelbel et al., 2013; Fals-Stewart & Bates, 2003; Oscar-Berman & Marinkovic, 2007).

3.2.3. Comorbidities in AUD

Researchers that have studied alcohol-related cognitive deficits have typically examined impairment in isolation from other individual risk factors, that is, they have gone to lengths to exclude individuals with comorbid conditions which could influence cognitive functioning (Petrakis, Gonzalez, Rosenheck, & Krystal, 2002). It is therefore unclear how well the profile of ARCI that has been documented in 'pure' AUD samples generalises to AUD populations often seen clinically who have comorbid health, psychiatric and neurological conditions. This compromises the ecological validity of the results. Medical conditions that commonly present with alcoholism include liver disease, cardiovascular disease and malnutrition, which all can independently impact neurobehavioural functioning (e.g., hepatic encephalopathy, stroke, Wernicke's encephalopathy; de la Monte & Kril, 2014; Stranges et al., 2004). Substance use is well recognised as a significant risk factor for incurring traumatic brain injury (TBI). Acute and chronic alcohol use is associated

with high rates of TBI, and excessive alcohol use also has the potential to exacerbate the effects of TBI (Corrigan, Bogner, & Holloman, 2012; Kelly, Johnson, Knoller, Drubach, & Winslow, 1997(Bjork & Grant, 2009). Large scale community-based epidemiological studies have further confirmed the pervasiveness of psychiatric comorbidity in AUD (Burns & Teeson, 2002; Grant et al., 2006). Surveys in treatment samples have indicated strong associations between AUD and anxiety, depression and other drug use disorders (Fein, Di Sclafani, Finn, & Shumway, 2008; Rosenbloom, O'Reilly, Sassoon, Sullivan, & Pfefferbaum, 2005; Sameti, Smith, Patenaude, & Fein, 2011), while externalising (e.g., conduct disorder) and personality disorders also frequently co-present (Grant et al., 2004; Kessler, Chiu, Demler, Walters, & Merikangas, 2005).

Importantly, each of these disorders associated with AUD have distinct neuroanatomical and neuropsychological correlates, which have been well documented in the literature (Belanger, Curtis, Demery, Lebowitz, & Venderploeg, 2004; Gotlib & Joorman, 2010; Hoofan, Gilboa, Vakil, & Donovick, 2001; Keefe & Harvey, 2012; Schretlen & Shapiro, 2003). Deficits in attention, psychomotor activity, problem-solving and memory are common in depression, for instance, (Gallassi, Morreale, & Pagni, 2001; Gotlib & Joorman, 2010), whilst compromised verbal learning, manual speed, information processing, attention, memory and executive functioning are frequent concomitants of TBI (Dikmen et al., 2009; Hoofan et al., 2001). The dilemma that is faced by clinicians in the assessment of ARCI is the impact of comorbid conditions. Specifically, it is not clear whether cognitive deficits related to these disorders superimpose on alcohol-related cognitive deficits, exacerbate deficits or have minimal additional effects. Only a handful of

studies have attempted to address this question, largely in relation to additional substance use or the impact of psychiatric comorbidity.

3.2.4. Effects of comorbidities on cognition in AUD

Initial investigations suggest that level of alcohol consumption can have an independent effect on cognitive functioning even in the presence of other substance use, although the evidence is far from conclusive. Fernandez-Serrano et al. (2010) and Fernandez-Serrano, Perez-Garcia, and Verdejo-Garcia (2011) found that recently abstinent (two to three weeks) poly-substance users performed poorly across all executive domains compared to controls, including reductions in performance on tasks of working memory, mental flexibility and response inhibition. However, a regression model indicated subtle differences in patterns of impairment in individuals due to use of certain drugs, e.g. severity of alcohol consumption showed detrimental effects on verbal fluency and decision making abilities but not on other executive components (Fernandez-Serrano et al., 2010). Fals-Stewart and Bates (2003) reported a relationship between number of substances used and performance on speed and executive functioning measures in a large group of individuals admitted to substance use treatment programs. However, even despite the inclusion of participants with comorbid anxiety, depression and personality disorders within the sample, the length, recency and frequency of heavy drinking were related to performance on measures of memory, executive functioning and psychomotor speed. The finding that mood disorders do not necessarily exacerbate poor test performance associated with alcohol misuse has been replicated in a few studies (Rosenbloom et al., 2005; Uekermann, Daum, Schlebusch, Wiebel, & Trenckmann, 2003); however, other authors have reported dissonant findings. Sinha, Parsons, and Glenn (1989)

reported a strong correlation between depressive symptoms and overall cognitive impairment in a group of individuals with AUD, while Schafer et al. (1991) found depressive symptoms to be a significant predictor of neuropsychological performance in alcohol-dependent individuals both at treatment onset and at 3-month follow-up. These latter studies relied on correlational analyses, did not compare directly depressed individuals with AUD with non-depressed AUD, and lacked healthy control and depressed-only comparison groups. Along with these methodological issues, the small number of studies that have addressed the role of psychiatric comorbidities in ARCI limits the ability to draw conclusions from these findings.

3.2.5. Aims

While these previous investigations are pivotal in building the knowledge base of the cognitive effects of co-morbidities in AUD, most studies have addressed a specific relationship (e.g., poly-substance use or mood disorders) to the exclusion of other factors, such as neurological injury or psychiatric disturbance (Bates, Labouvie, & Voelbel, 2002; Fals-Stewart & Bates, 2003; Fernandez-Serrano et al., 2010). To our knowledge, no study has yet examined the presentation of ARCI in a context typical of daily clinical assessment; that is, with the inclusion of individuals with multiple comorbidities. The primary aim of the current study was to document the cognitive deficits present in a clinical sample attending for treatment for AUD, and to investigate whether in spite of additional comorbidities, a cognitive profile consistent with ARCI as described in the literature could be observed. Neurocognitive impairment can interfere with an individual's ability to engage in substance use treatment and may impact on outcome (Bates et al., 2002; Copersino et al., 2012).

Identification of a specific cognitive profile within this cohort, regardless of the aetiology of cognitive deficits, could inform and enhance treatment such as through implementation of cognitive remediation or compensatory strategies. However, at present it is unclear what cognitive deficits are expected in an AUD sample with multiple comorbidities.

A second aim was to investigate whether drinking history – including frequency, severity, and recency of alcohol use – was related to cognitive functioning in the group, over and above these comorbid risk factors. In 'pure' AUD samples, length of abstinence, and chronicity and severity of heavy drinking are the drinking variables consistently associated with cognitive outcome (Beatty, Tivis, Stott, Nixon, & Parsons, 2000; Oscar-Berman, Kirkley, Gansler, & Couture, 2004). It is unclear whether this relationship is observable in a sample of individuals with multi-factorial risk factors for cognitive impairment.

3.2.6. Hypotheses

This study was largely exploratory. However, it was hypothesised that:

1) A significant proportion of the sample would present with comorbid health, psychiatric and neurological conditions.

2) Cognitive deficits that have typified previous samples with a history of AUD, specifically impairments in memory, visuospatial ability, psychomotor speed and executive function, would be observed in the current sample. Given the presence of neuropsychological risk variables over and above heavy and regular alcohol use, it was further hypothesised that cognitive dysfunction would not be restricted to these domains.

3) The duration of the period of heaviest drinking and current period of abstinence would be the drinking variables most consistently associated with cognitive performance.

3.3 Method

3.3.1. Participants

Twenty-one adults (thirteen male, eight female) were recruited from two outpatient substance use clinics in the South East Sydney Local Health District (The Langton Clinic, Surry Hills, and the St George/Sutherland Drug and Alcohol Outpatient Clinic, Kogarah). Participants were identified as eligible to participate by the senior Clinical Nurse Consultant (CNC) if they: 1) had a DSM-IV (1994) diagnosis of alcohol dependence, as documented in their medical records; 2) were not acutely intoxicated or in alcohol withdrawal as determined by medical staff, and 3) were deemed by medical staff as competent to give consent. The inclusion criteria were designed to be as least restrictive as possible to maximise the ecological validity of study findings, without compromising the validity of neuropsychological results. Participants were not excluded on the basis of psychiatric history, neurological injury, health conditions or comorbid substance use. Following a brief clinical interview with the potential participant, the chief investigator applied further exclusion criteria. Specifically, individuals from culturally and linguistically diverse backgrounds (CALD) with limited English ability and individuals who had sensory deficits that could potentially interfere with their ability to respond to testing (e.g., significant hearing loss) were excluded. In total, 32 individuals were identified by the senior CNC as eligible to participate in the study. Of those, six were excluded due to

CALD with limited English ability. No individuals were excluded due to sensory deficits. In total, 26 individuals were invited to take part in the study, five of whom declined (Figure 2), leaving a total group number of 21. These participants are hence referred to as the AUD group.

Control subjects were recruited from a database of carers and supporters of individuals with early-onset memory disorders who had recently taken part in a mixed methods research project and had given their consent to be contacted

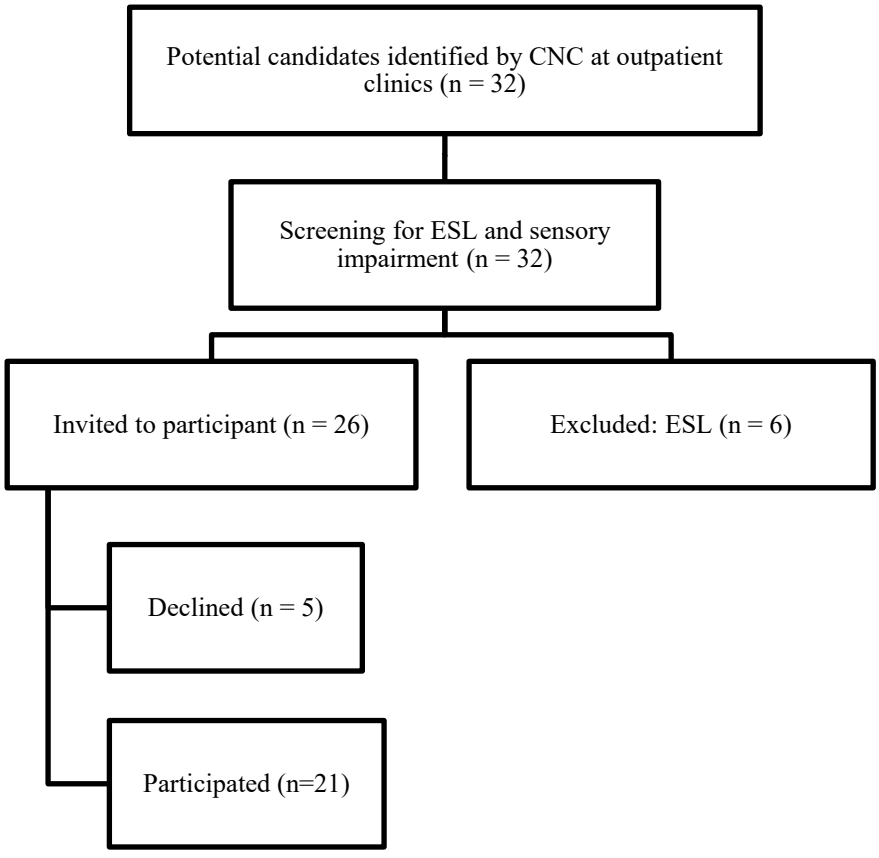

Figure 2. Flowchart of participation in the AUD group included in the current study

regarding associated research projects. No cognitive measures had been used with these subjects in the previous project. These participants were selected from the database to match the patients in the AUD group as closely as possible for age, education and gender. The chief investigator contacted potential participants by phone and brief screening for eligibility was conducted. Exclusion criteria for the control group included diagnosis of a current psychiatric or substance use disorder, a history of neurological damage or disease, current psychoactive medication, or alcohol consumption exceeding 14 standard drinks a week, in accordance with Australian guidelines for harm minimisation with alcohol use (National Health and Medical Research Council, 2009). Twenty-seven individuals from the control database were contacted. Of those, one was excluded due a current psychiatric condition, another for current alcohol consumption in excess of criteria, and four declined, leaving a final sample of 21.

All participants in the research completed the full protocol of tasks, with the exception that the control group did not complete the Depression, Anxiety Stress Scales, as this was used for descriptive purposes in the AUD group only. They did not complete the same interview (e.g., alcohol use, neurological history) completed by the patient group as control individuals already had been screened for exclusion criteria. On testing, the score of one control participant on one task (Trail-Making Test B) was not recorded due to equipment failure; this was coded as missing data. All participants provided written informed consent, as per the ethical approval obtained from the University of Wollongong/Illawarra Shoalhaven Local Health District and Medical HREC and Macquarie University (see Appendix A).

3.3.2. Measures

The Montreal Cognitive Assessment (MoCA)

The MoCA (Nasreddine et al., 2005) is a 30-point screening tool that has previously been found to be sensitive to cognitive impairment in individuals with substance use disorders (Copersino et al., 2009; Wester, Westhoff, Kessels, & Egger, 2013). It takes approximately ten minutes to administer and includes fourteen tasks that evaluate aspects of attention, orientation, language, visuospatial, executive and memory. The total possible score is 30 points, with an adjustment of +1 point made to the final score if the participant has less than 12 years of education. A score of 26 or greater is typically considered indicative of preserved cognition (Nasreddine et al., 2005). In the current study, the original English version (7.1) was used.

The Addenbrooke's Cognitive Examination Revision (ACE-R)

The ACE-R (Mioshi, Dawson, Mitchell, Arnold, & Hodges, 2006) is a brief cognitive test that consists of five-subscales assessing orientation, attention, verbal fluency, memory, language and visuospatial function. It takes between 12 and 20 minutes to administer in a clinical setting. The test incorporates the Mini-Mental State Examination (MMSE; Folstein, Folstein, & McHugh, 1975), with the maximum MMSE 30-point score included in the 100 point possible total score on the ACE-R, which is derived by adding sub-scales scores. In the current study, Form A of the Australian version was used. A score of 88 or over is suggested to reflect preserved cognitive function.

Repeatable Battery for Assessment of Neuropsychological Status (RBANS)

The RBANS (Randolph, Tierney, Mohr, & Chase, 1998) takes approximately 30 minutes to administer. It consists of 12 subtests, which yield 5 index scores and a

total score, all of which have a mean of 100 and a standard deviation of 15. The RBANS has acceptable psychometric properties in regards to test-retest stability, internal consistency, and convergent validity with traditional neuropsychological measures (Gontkovsky, Hillary, & Scott, 2002; Larson, Kirschner, Bode, Heinemann, & Goodman, 2005). It has demonstrated clinical utility in a number of neurological and psychiatric populations and in recent times has become a popular choice in assessment of substance-use related cognitive impairment (de Ville, Baker, Lewin, Bucci, & Loughland, 2011; Green et al., 2010; Schrimsher & Parker, 2008). The RBANS been show to be able to characterise differences in cognitive functioning between healthy controls and moderate to heavy drinkers (Green et al., 2010) and its ease-of-use and brevity is clinically advantageous. It does, however, require supplementation with additional measures of executive functioning as the RBANS does not provide targeted assessment of these abilities (Hobart, Goldberg, Bartko, & Gold, 1999). The RBANS normative data represented a stratified, nationally representative sample of 690 healthy Americans between 12 and 89 years of age. There are three alternate forms with co-normed index scores (Randolph, 2012).

A number of normative comparisons are available. The recently updated RBANS manual (2012) provides normative data for both index and sub-test scores for the standardisation sample, converted to standard scores or percentile bands and stratified by age and education levels. Duff et al. (2003) extended the original normative data through provision of age and education adjustments for both subtest and index scores, however, these adjustments are only provided for older adults (65+ years). Green et al. (2008) also provided preliminary Australian normative data for RBANS subtest scores stratified by age and education, generated from a group of

172 well-educated community dwelling adults.

The Immediate Memory Index consists of List Learning and Story Memory subtests. Both assess the individual's ability to remember information immediately after presentation. For the List Learning task, the examiner reads a 10-item word list over 4 trials. After each trial, the examinee recalls as many words as possible from the word list, with total raw score the total sum of words recalled over all four trials (range 0 to 40). For the Story Memory task, a short prose passage is read twice to the examinee; after each recitation the examinee attempts to recall the story verbatim. One point is given for each detail the examinee recalls correctly on each attempt, to a maximum of twelve for each trial.

The Attention index consists of the Digit span and Coding subtests. The Digit Span task is analogous to Digit Span from the Wechsler scales (Wechsler, 1981). For this task, the examiner reads sequences of numbers, which increase in length over trials. The examinee is required to repeat back the digits in the same order they are presented by the examiner. Each item includes two sequences of numbers of equal length; the second sequence is only administered if the examinee repeated the first one incorrectly. Two points are awarded if the examinee recounts the first string of an item correctly; one point is awarded if only the second string of an item is correctly recorded. The total raw score range is 0-16. The Coding test is similar to the Symbol Digit Modalities Test (Smith, 1982). Participants are required to fill in numbers corresponding to shapes, using a key above. They have 90 seconds to fill in as many numbers as possible, with the raw score the sum of the total number correct within that time.

The Visuospatial/Constructional Index consists of the Figure Copy and Line Orientation subtests. Figure Copy is similar to the Rey Complex Figure Test (Rey,

1941). The examinee is asked to copy a complex figure from the stimulus book within a 4-minute time limit. Drawing (correctness/ completeness) and placement points are awarded for individual elements of the drawing, Total raw score is obtained by summing all the item scores (range 0-20). The Line Orientation subtest is analogous to the Judgement of Line Orientation Test (Benton, Hamsher, & Spreen, 1983). For this subtest, examinees must match the orientation of two lines at the bottom of the page to two of thirteen lines that are placed at the top of the page. One point is awarded for each line identified correctly; ten items are presented for a maximum total subtest score of 20.

The Language Index consists of Picture Naming and Semantic Fluency. For Picture Naming, participants are asked to name ten line drawings of common objects. A semantic cue is provided only if the picture is obviously misperceived; no phonemic cues are given. One point is awarded for each item correctly named or following a semantic cue, to a maximum of 10 points. This is similar to, although shorter than, the Boston Naming Test (Kaplan, Goodglass, & Weintraub, 1983). In the Semantic Fluency subtest, the examinee is required to name as many fruits and vegetables (Stimulus Book A) or as many different zoo animals (Stimulus Book B) as possible within 60 seconds. One point is awarded for each correct response recorded within the time limit, to a maximum total score of 60.

The Delayed Memory Index assesses memory of items previously encountered in the test battery, and consists of List Recall, Story Recall, List Recognition, and Figure Recall subtests. The order in the booklet factors in a delay period from learning to recall for each task, typically 15 to 20 minutes. The List Recall subtest requires the examinee to recall as many words as possible from the words comprising the List Learning test. One point is awarded for each correctly

recalled word. In List Recognition, twenty words (10 targets from the List Learning task and 10 distractors) are presented in a yes/no format; the examinee is required to identify if the word was on the original list. One point is awarded for each correct answer, to a maximum total raw score of 20. The Story Recall subtest requires the examinee to recall details of the story read in the Story Memory subtest, with one point awarded for each correct detail recalled to a maximum of 12 points. The Figure Recall subtest requires the examinee to draw from memory the complex figure, again scored for correctness/ completeness and placement, to a maximum of 20 points. The total scores of the subtests that comprise each index are used to calculate each index score, which are converted to age-appropriate standardised scores (mean of 100, standard deviation of 15) through the use of an appendix in the stimulus book (Randolph et al., 1998). The Total Scale Index is computed from the sum of the Index Scale Scores, again converted through the use of the appendix.

For the analyses of this study, a number of scores were used. For group comparisons, both raw scores and standardised index and total scale scores were used. Raw scores were used to compare groups on measures other than the RBANS index and total scale scores, as differences in age, gender and education levels were accounted for by group matching of these variables. Age-standardised index scores are provided by the R-BANS authors to assess domain-specific performance and they were also used to investigate group comparisons at an index level.

Scores were also converted to age- and education-adjusted scores for the purpose of evaluation of performance at the individual level. This was deemed necessary as education levels and age can influence performance on cognitive tasks, including the RBANS (Duff et al., 2003; Green et al., 2008). To adjust for the potential effect of age and education at the sub-test level, the norms of Green et al.

(2008) were used. *Z*-scores were created for the purpose of these comparisons. These were calculated by taking the difference between the examinee's subtest raw score and the equivalent age/education cohort raw score, and dividing that number by the cohort standard deviation. As Green et al. (2008) only provided normative data for subtest scores, normative data from the R-BANS standardisation sample, which stratify index and total scores by age and education, was used to create age and education adjusted scores for the RBANS indices and total scores. Again, *z*-scores were calculated by taking the difference between the examinee's index standardised score and the equivalent age/education standardised score and dividing that number by the cohort standard deviation for that particular subtest. *Z*-scores have a mean of 0 and a standard deviation of 1.

The RBANS Effort Index (EI) was used to assess effort for each participant (Silverberg, Wertheimer, & Fichtenberg, 2007). This is an index which provides an embedded measure of effort, derived from two subtests of the RBANS thought to be relatively resilient to cognitive dysfunction (Digit Span and List Recognition). A revised Effort Index was recently proposed by Novitski, Steele, Karantzoulis, and Randolph (2012), however this is unsuitable for use with individuals with intact cognition (as expected in the control group due to ceiling effects and was therefore not appropriate to evaluate effort in the current study. Reliable Digit Span, a commonly used index of symptom validity in neuropsychological research (Schroeder, Twumasi-Anrah, Baade, & Marshall, 2012), was also computed to provide an additional measure of effort, as high rates of false positives have been reported when the EI has been used with patients with severe memory disturbance (for a review, see Novitski et al., 2012). Two AUD participants exceeded the published cut-score of the EI for suspected poor effort (Effort Index of >3, scores of

5 respectively). However, both exceeded the recommended cut-off for reliable digit span for groups with severe memory disorders (<7; Schroeder et al., 2012) and subsequently their data was retained for analysis.

Executive Tasks

Letter Fluency: This was used to assess verbal generativity, a function typically associated with frontal lobe function (Henry & Crawford, 2004). In this task, the examinee must produce orally as many words as possible beginning with a specified letter during a period of 60 seconds. The letters F, A, and S are most commonly used in cognitive research and were adopted for this task (Strauss, Sherman, & Spreen, 2006). As the letter 'F' is used to assess letter fluency in the MoCA, this study used the MoCA instructions for all letters in this task (Nasreddine et al., 2005). This includes rules regarding use of proper nouns, suffixes and numbers. The total correct on this task was the sum of all admissible words for the three letters (inadmissible words included rule violations and repetitions). Number of words on the 'F' trial of the MoCA was used as a component of the total FAS score (i.e., this trial was not repeated). The total raw score was used in analyses of group comparisons. For individual analyses, the total raw score was corrected for age, education and gender to yield T-scores using the normative data of Heaton, Miller, Taylor & Grant (2004). These T-scores (mean of 50, standard deviation of 10) were converted to *z*-scores (mean of 0, standard deviation of 1) to provide a similar metric to the other cognitive tests.

The Trail Making Test: The version adapted by Reitan (1955) was used to assess divided attention. The TMT, in particular part B, has been found to be shown to be sensitive to a range of neurological disorders, including poly-substance use

(McCaffrey, Krahula, Heimberg, & Keller, 1988). In Part A, the examinee is required to connect in ascending order 25 circled numbers randomly arranged on a page. In Part B, 25 circled numbers and letters are randomly placed on the page and the examinee is required to join these in alternating and ascending order. A time limit of 5 minutes was imposed on Part B, in accordance with the administration procedure of Heaton et al. (2004). Scores reflected time in seconds required to complete each of the two parts of the test. The total raw score for each part of the test was used in analyses of group comparisons. For individual analyses, the total raw score was converted to a T-score adjusted for age, education and gender through the use of normative data by Heaton et al. (2004) and these were further converted to *z*-scores, using the procedure described above. The directionality of *z*-scores was reversed on these tasks, so that a positive *z* score reflected better performance.

Digits Backwards: The Digits Backwards subtest of the Wechsler Adult Intelligence Scale-Fourth Edition (WAIS-IV; Wechsler, 2008) was used to assess working memory, a function association with dorsolateral prefrontal cortex function (Gerton et al., 2004). In this test, the examiner recites a number sequence and the examinee is required to repeat the number sequence in reverse order. The sequences increase in length over trials, until the examinee incorrectly recalls two sequences of the same length. One point is given for each number string correctly recited (the first four items are all two-item spans), with a raw total of 16 achievable. This raw score can be converted to an age-adjusted standard score (mean of 10, standard deviation of 3) through the conversion tables in the test manual (Wechsler, 2008). For study analyses, both raw and standard scores were utilised; the former for group comparisons and the latter for assessment of impairment at the individual level.

The National Adult Reading Test: Premorbid intellectual functioning was

estimated using the NART-2 (Nelson, 1982). This is a word pronunciation list of 50 irregularly spelled word. The total error score on this task can be used to predict Wechsler Adult-Intelligence Scale-III Full Scale, Verbal or Performance Intelligence Quotients (Wechsler, 1997). The predicted Full-scale IQ score was used in this study

The Hayling and Brixton Tests: These tests are designed to assess verbal inhibition and rule-attainment ability (Burgess & Shallice, 1997; Strauss et al., 2006). The Hayling Test (Burgess & Shallice, 1997) consists of two sets of 15 sentences, each of which have the last word missing. In the first section, the examiner reads each sentence aloud and the examinee has to complete the sentence with a logical word as quickly as possible. In the second section, the examinee has to complete the sentence with a word that is unconnected with the sentence. Both response speed scores (Section 1 and 2) and error scores (Section 2) are generated and these can be combined to generate an overall scaled score. The Brixton Spatial Anticipation Test (Burgess & Shallice, 1997) is a rule attainment task based on the Wisconsin Card Sorting Test (Heaton et al., 1993). The examinee is shown 56 pages in a stimulus book, which each have the same array of ten circles. On each page, one circle is filled in with a colour (blue); the position of this circle differs from page to page. The examinee is shown one page at a time, and is asked to guess where the next filled position will be based on a rule that can be identified from previous pages. Total number of errors form the raw score, which is converted to a standard score.

In both tests, the scaled score (SS) generated is based on percentile scores relative to the standardisation sample (e.g., a scaled score of 3 reflects performance at the fifth percentile in the standardisation sample, whilst a scaled score of 7 reflects performance at the 75% percentile). Age adjusted cut-scores are provided, based on the fifth percentile for each appropriate cohort. Raw data for the standardisation

sample is not provided. Scaled scores were used for group comparisons, and percentile scores for classification of impairment.

Mood Measure

The Depression, Anxiety, Stress Scales: Short Version (DASS-21): The DASS-21 (Lovibond & Lovibond, 1996) consists of a set of three self-report scales designed to measure the severity of symptoms of depression, anxiety and stress. It is used as a quantitative measure of distress, and has been validated in clinical and non-clinical populations (Henry & Crawford, 2005) . Each of the DASS scales contains 7 items, which are each scored on a four-point scale (0 = did not apply to me at all, to 3 = applied to me very much or most of the time). The individual indicates the presence of a symptom over the past week; responses to each of the sub-scales are summed to generate a raw score for each sub-scale. Scores for each subscale are doubled to allow comparison to normative data (Lovibond & Lovibond, 1996). This includes cut-scores for severity labels (i.e., normal, moderate, severe), which are used to describe the full range of scores in the population (i.e., not indicative of clinical levels).

3.3.3. Procedure

After providing written informed consent, participants completed all study measures at a single time point requiring approximately 1.5 to 2 hours. Participants were reimbursed with a $25 groceries gift card for compensation for their time. A structured clinical interview was conducted with the patient group at the commencement of the session in order to collect information regarding substance use, psychological and neurological history. Specific questions were asked relating to:

- Demographic information: current employment and marital status
- Level of education achieved, history of developmental delay
- Age at first use of alcohol
- Current days of abstinence from alcohol. Use of alcohol in the last 30, 90 and 365 days (average drinks/week, and periods of abstinence within this time)
- Age at heaviest period of drinking; duration of that period, time elapsed since that period and average drinks/week
- Average drinks/week throughout the lifespan (average drinks/week; changes in drinking patterns (increase/decrease), periods of abstinence
- Other substance use: past or present; frequency and severity
- Neurological history: history of concussions which resulted in loss of consciousness, seizures, stroke, or other significant neurological event
- Psychiatric history: past or present diagnosis of any psychiatric condition

In an attempt to verify information, the medical records of participants were reviewed to determine whether the self-report was consistent with the documented history, including use of substances. If there was inconsistency between accounts, the information in the medical records was treated as the accurate account.

The order of testing was determined by both consideration of the demands of the individual tests and the need for counter balancing when appropriate. Shorter memory tasks (e.g., memory items on the screening tests) were administered prior to longer tasks (e.g., memory items on the RBANS) to reduce the influence of proactive interference (past learning interfering with new learning. Tasks that included a delayed recall trial were administered earlier in the testing session. The screening tests were administered prior to any other cognitive measures, in a counter-balanced

order between participants. Identical tasks on different screening measures were not repeated (Cube-drawing, Serial Sevens) with the exception of clock drawing as the task details differed between tests. Other battery items (e.g., additional letters on verbal fluency) were used as interval measures as necessary to maintain the normal time delay of memory tasks. Following the screening measures, tasks other than the RBANS were administered in a counter-balanced order: NART, Trail Making Test, Hayling, Brixton. The RBANS was administered at the end of the cognitive battery to maximise the interval between memory tasks on the screening items and those undertaken on the RBANS. The DASS was administered following the RBANS. Individuals were monitored for fatigue throughout the assessment. Most completed testing without need for a break however a break was provided on request to two participants in the AUD group.

3.3.4. Scoring and classification of impairment

In addition to comparing raw and index scores by groups, classification of impairment at the individual level was made at both the domain and overall level, based on demographically adjusted scores. Index scores from the RBANS (Immediate Memory Index, Visuospatial/Constructional Index, Language Index, Attention Index, and Delayed Memory Index) were used to classify impairment across five domains. Impairment was based on index rather than sub-test scores because 1) the authors of the RBANS emphasise the primary focus of the RBANS is at the index not the subtest level (Randolph et al., 1998), and 2) we did not wish to classify impairment on the basis of one abnormal score, as even neurotypical participants often have large discrepancies between best and worst scores (Binder, Iversen, & Brooks, 2009). For each index, impairment was classified as a score of -

1.5 or greater standard deviations below the mean of the normative (age and education matched) sample, using the norms provided by Randolph (2012). For classification of impairment in the executive domain, the participant was required to demonstrate impairment on two tasks that fell 1.5 or more standard deviations below age and education equivalent norms (Letter Fluency, Trails B; Heaton et al., 2004) or at or below the fifth percentile for age on tasks which did not provide education adjustments (the Hayling and Brixton Tests; Burgess & Shallice, 1997).

3.3.5. Statistical analysis

A Shapiro-Wilk statistic was used to determine whether assumptions of normality were met for demographic and cognitive variables and the data checked for outliers via visual inspection. The Mann Whitney U test was performed for comparison of group results on ordinal data (Hayling SS and Brixton SS) and for non-parametric variables in which outliers (>3 box-lengths) were identified (MMSE, RBANS: Picture Naming). An outlier (>3 box length) was detected on Trails B however the subject was retained as this did not change whether statistical significance was reached. Given the resilience of the *t*-test to violations of the assumption of normality when sample sizes are equal, independent sample *t*-tests were applied for all other group comparisons. Bonferroni correction was applied for multiple comparisons, with significance level set at $p < .002$ for comparisons of cognitive variables. The Levene's Test for Equality of Variances was applied when data violated assumption of homogeneity of variance. One-tailed tests were used for group comparisons on cognitive measures as it was predicted that the substance use group would perform worse than controls across all cognitive measures. The effect size for group differences in neuropsychological test scores was calculated using

Cohen's *d,* with the exception of those tests for which the Mann-Whitney test was used (non-parametric comparisons. Cohen (1988) suggests $r = .3$ represents a small effect size, $r = .5$ a medium effect size, and $r = .7$ a strong effect size.

These criteria were adopted as they are commonly used in the ARBD literature. Associations between variables were assessed with the Pearson Product-Moment correlations for variables that met the assumptions of normality and Spearman Rank Order correlations for data that violated these assumptions. When associations were not monotonic, variables that violated assumptions of normality were transformed using appropriate transformations for direction and severity of skew. When monotonicity was not achieved after a transformation was applied to Picture-Naming: Z-score, one outlier was excluded. This resulted in acceptable monotony. For correlations $r = .1$ was used as the cut-score for a small correlation, $r = .3$ for a medium correlation, and $r = .5$ for a strong correlation (Cohen, 1988). Data was analysed using IBM SPSS Statistics version 22 (IBM Corporation, 2013).

3.4. Results

3.4.1. Descriptive data

The 21 AUD participants ranged in age from 32 to 76 years ($M = 51.24$, $SD = 10.85$). Years of education ranged from 7 to 14 ($M = 10.62$, $SD = 1.77$). Sociodemographic characteristics are summarised in Table 6. Of the participants who had lost consciousness due to a concussion, two had been hospitalised following these incidents, although a diagnosis of TBI or details regarding the severity of the injury was not documented in the medical records. No developmental delay was reported by any participant.

Sixteen participants (76%) had a current DSM-IV diagnosis. On the DASS-21, 8 individuals (38%) reported moderate or higher levels of depression, 11 (52%) reported moderate or higher levels of anxiety, and 7 (33%) reported moderate or higher levels of stress.

Seven participants (33%) currently used substances other than alcohol. Two participants had been long-term (>20 years) methadone maintenance patients, and met DSM-IV criteria for opioid dependence. Another four individuals (19%) used cannabis and another used methamphetamines monthly. Use of these substances was noted in the medical records but a substance use disorder other than alcohol was not specified with the exception of the methadone users. Other past lifetime substance use included cannabis (n = 8), methamphetamines (n = 6), cocaine (n = 6), ecstasy (n = 2), and heroin (n = 3). Twelve individuals (57%) were currently taking medications daily as part of their treatment for alcohol dependence. No individual in the group was free from a history of neurological injury, current psychiatric disorder or comorbid substance use when those factors were considered in combination.

3.4.2. Alcohol use history

The drinking history of AUD participants is collated in Table 7. Two individuals were on controlled drinking programs (reduced drinking) and reported current drinking habits of approximately 22 and 24 standard drinks a week respectively. Otherwise all individuals were on a program of abstinence. Age at first drink ranged from 12 to 20 years (M = 15.81, SD = 10.56) and average number of years drinking was 35.24 (SD = 8.87). Total standard drinks per week during the heaviest period of consumption ranged from 42 to 280 standard drinks a week (M = 140.48, SD= 81.69) and length of the heaviest period of drinking ranged from one to forty years

(M = 9.69, SD = 9.78). All participants exceeded the cut-off specified by Oslin et al. (1998) for 'heavy drinking' with the period of time above this cut off ranging from one to forty years (M = 15.85, SD = 10.56). Length of abstinence at time of testing ranged from two to 365 days (M = 53.05, SD = 88.92).

3.4.3. AUD and control group comparisons

There were no significant differences between groups in age, $t(40) = 2.41$, $p = .406$, education, $t(40)$, -1.58, $p = .061$, gender, $\chi^2(1, N = 42) = 2.40$, $p = .121$, or premorbid IQ (NART score), $t(40) = -1.63$, $p = .056$. The results of group comparisons on cognitive tests are reported in Table 8. The AUD group performed significantly poorer than the control group on all screening tests ($p < .001$, one-tailed). They also performed significantly poorer on all tasks in the executive battery with the exception of the Hayling Test ($p = .004$, one-tailed) and the Brixton Test ($p = .212$, one-tailed). On RBANS subtests, the AUD group performed significantly poorer on all subtests other than List Learning ($p = .003$, one-tailed), Line Orientation ($p = .017$, one-tailed), Digit Span, ($p = 0.245$, one-tailed), List Recognition ($p = .008$, one-tailed), Story Recall ($p = .004$, one-tailed) and Picture Naming ($p = .150$; one-tailed). Of the subtests that significantly differed between groups, the largest effect sizes were found for Semantic Fluency ($d = 1.85$), Coding ($d = 1.79$) and Figure Recall ($d = 1.42$). All RBANS indexes and the RBANS Total Score also significantly differed between groups ($p < .001$, $d > 1.16$). = .121.

Table 6

Characteristics of the AUD Group

	n	%		*n*	%
Relationship Status			*Neurological History*		
Married	1	5	Hydrocephalus	1	5
Separated	1	5	Stroke	2	10
Divorced	2	10	Wernicke-Korsakoff Syndrome	1	5
De facto	1	5	Seizures	3	14
Single	16	76	Concussion (lost consciousness)	6	29
Income			*Psychiatric History*		
Disability Pension	11	52	Current depressive disorder only	6	29
Unemployment benefits	6	29	Past depressive disorder, not current	2	10
Retired	3	14	Current anxiety disorder only	2	10
Employed full-time	1	5	Past anxiety disorder, not current	1	5
			Current comorbid depression and anxiety disorders	4	19
Health Conditions			Schizoaffective disorder & Social Phobia	1	5
Currently smoking	13	62	Depression, anxiety and Borderline Personality	2	10
Hypertension	5	24	Schizophrenia	1	5
High cholesterol	5	24			
Liver cirrhosis	2	10	*Medications*		
Hepatitis C	1	5	Antipsychotics	5	24
Fatty liver disease	2	10	Antidepressants	9	43
Peritonitis	1	5	Benzodiazapines	6	29
Diverticular disease	1	5	Disulfrim, Naltrexone, Baclofen, Acamprosate	12	57
Gastroesophageal reflux disease (GERD)	3	14	Blood pressure	4	19
Gastric ulcer	1	5	GERD	4	19
Bronchial secretions	1	5	COPD	2	10
Chronic obstructive airways disease (COPD)	1	5			
Asthma	1	5	*Other Substance Use*		
Arthritis	3	14	Methadone	2	10
Diabetes Mellitus Type 2	1	5	Cannabis - weekly	2	10
Kidney failure	2	10	Cannabis - monthly	2	10
Pancreatitis	1	5	Methamphetamines - monthly	1	5
Cancer	1	5			

Table 7

Alcohol Intake in the AUD Group

	Gender	Days Abstinent	Detoxes	Years Drinking	Lifetime Quantity[b]	Drinks week /Heaviest[b]	Time Heaviest	Time over Limit[c]	Drinks total /Heaviest[b]	Drinks 30 days[b]	Drinks 90 days[b]	Drink 365 days[b]
1	M	240	2	24	48360	50	15	15	39000	0	0	1000
2	M	2	2	34	101200	112	12	12.5	69888	360	1080	5208
3	M	70	2	34	376480	280	25	25	364000	0	840	14000
4	F	10	4	28	200964	252	2.5	20	32760	252	252	3024
5	F	83	5	33	287364	252	18	30	235872	0	252	9072
6	M	21	4	34	68640	280	1.5	14	21840	200	600	2080
7	F	365	1	19	40144	126	2	4	13104	0	0	0
8	M	5	2	34	80600	175	1	12	9100	625	2125	9000
9[a]	M	4	0	46	44408	42	1	1	2184	140	420	1456
10	M	12	1	31	84240	210	5	5	54600	630	2730	121800
11	M	70	3	57	110760	42	40	40	87360	0	0	1890
12	M	9	2	32	96460	140	7	32	50960	420	1820	7000
13	M	28	2	21	84240	100	15	15	78000	0	100	4800
14	F	8	1	45	129948	49	6	25	15288	154	616	2499
15	M	60	3	33	98280	105	10.5	23.5	57330	0	450	42000
16	M	14	1	36	263120	238	20	20	247520	476	2856	119000
17	F	4	1	30	17472	112	3	3	214032	5	965	4933
18	F	53	6	42	76700	147	5	5	38220	0	777	6552
19	F	28	1	44	46620	105	2.8	10	13860	0	900	4935
20	F	25	3	35	69264	91	5	15	23660	65	819	4459
21[a]	F	3	0	27	108160	42	6	6	91728	72	432	2080
Mean		53.05	2.19	34.24	376480	140.45	9.68	15.86	83824	161.86	858.76	17466
(SD)		(88.9)	(1.6)	(8.87)	(115877)	(81.69)	(9.78)	(10.56)	(97290)	(215.20)	(845.00)	(35323)

Note. [a]These participants were on a controlled drinking program; [b]Australian standard drinks (10g/12.7 ml alcohol)
[c]Minimum of 50 standard drinks/week for men, 40/week for women (Australian standard drinks; see Oslin et al., 1998)

Table 8

Cognitive Comparisons of AUD Group and Controls

	Controls (n = 21)		AUD (n = 21)				
	M	*SD*	M	*SD*	*t*(40)	*p*	*d*
ACE-R	95.05	3.07	85.43	7.77	-5.28	<.001	1.63
Mini Mental State Examination	Median: 30	Range: 29-30	Median: 28	Range: 21-30	349[b]	<.001	-
Montreal Cognitive Assessment	28.05	1.53	23.71	3.90	-4.71	<.001	1.46
Digit Span Backwards: Total	8.76	1.76	7.19	1.60	1.60	.002	0.93
Letter Fluency: Total	44.86	13.98	32.86	11.43	-3.05	.003	0.94
Trails A: Time	26.71	8.43	42.67	19.12	-3.49	<.001	1.08
Trails B: Time[a]	62.25	20.86	102.57	52.03	3.29	<.001	1.02
Hayling: Total SS	Median: 6	Range: 6-8	Median: 6	Range: 3-7	315[b]	.004	-
Brixton: Total SS	Median: 6	Range: 2-10	Median: 6	Range: 1-8	252[b]	.212	-
RBANS: List-Learning Total	29.33	2.42	24.62	6.62	-3.07	.002	0.94
RBANS: Story Memory Total	16.43	3.41	12.67	4.1	-3.29	.001	1.00
RBANS: Figure Copy	18.33	1.68	16.1	2.47	-3.43	<.001	1.05
RBANS: Line Orientation	16.81	3.00	14.67	3.34	-2.19	.017	0.67
RBANS: Picture Naming	Median: 10	Range: 9-10	Median: 10	Range: 9-10	242[b]	.150	-
RBANS: Semantic Fluency	26.62	4.19	19.24	3.77	-6.00	<.001	1.85
RBANS: Digit Span	11.86	2.44	10.86	3.07	-1.11	.245	0.36
RBANS: Coding Total	51.71	8.75	35.05	9.85	-5.80	<.001	1.79
RBANS: List Recall	7.05	1.32	4.57	2.93	-3.54	<.001	1.09
RBANS: List Recognition	19.29	0.85	17.67	2.75	-2.57	.008	0.80
RBANS: Story Recall	9.43	1.72	7.00	3.44	-2.90	.004	0.89
RBANS: Figure Recall	15.14	2.85	9.81	4.47	-4.61	<.001	1.42
RBANS: Immediate Memory Index	98.57	10.89	81.05	14.88	-4.40	<.001	1.34
RBANS: Visuospatial Index	100.29	14.36	83.05	15.38	-3.89	<.001	1.15
RBANS: Language Index	111.05	9.66	95.95	6.45	-5.96	<.001	1.84
RBANS: Attention Index	106.19	12.22	86.05	20.34	-3.99	<.001	1.20
RBANS: Delayed Memory Index	100.14	10.00	80.57	21.42	-3.79	<.001	1.17
RBANS: Total Score	103.81	8.27	81.14	12.62	-7.02	<.001	2.12

Note. One-sided t tests. ACE-R = Addenbrooke's Cognitive Examination Revised. [a] n = 20 for controls. [b] Mann-Whitney U statistic

3.4.4. Impairment classification on neuropsychological measures

No individual from the control group was classified as impaired based on domain index scores. In the AUD group, the highest proportion of impairment was in Delayed Memory (*n* = 9; 42%). One-third (33%) of participants were classified as impaired in the Attention and Immediate Memory Domains (*n* = 7 each), and six individuals (29%) were classified as impaired in the Visuospatial Domain and on the Total Score respectively. No individuals were classified as impaired on the Language Index. On executive function measures, a similar proportion of individuals were impaired on each of the tasks; three (14%) on Digit Span Backwards, Letter Fluency, Hayling and Brixton, and four (19%) on Trails B. This translated to five individuals in total (24%) who met criteria for impairment in the Executive Domain (≥2 tasks impaired). In total, 73% (*n* =15) of the AUD sample were classified as cognitively impaired according to criteria adopted in the current study. Almost half of this group (*n* = 6) demonstrated impairment in one domain only and the majority (*n* = 13) were impaired in three domains or less. While we did not have the statistical power to investigate the relationship of categorisation of impairment to presence of risk factors, the individuals that were not classified as impaired had a range of comorbid risk factors, including psychiatric conditions (*n* = 3*)*, concussion *(n* = 1*),* stroke (*n* = 1) and comorbid substance use (*n* = 1).

Table 9

Classification and Frequency of Impairment on Cognitive Measures in the AUD group

		Impaired		Total Domains Impaired		
Test	Cut-off	n	%		n	%
Executive Function Tasks						
Digit Span Backwards: Total	≤5th percentile age-adjusted score (SS <6)	3	14	0	6	29
Letter Fluency: Total	≤1.5 *SD* age, education andgender adjusted score[a]	3	14	1	6	29
Trails B: Time [a]	≤1.5 *SD* age, education and gender adjusted score[a]	4	19	2	2	29
Hayling: Total SS	≤5th percentile age-adjusted score	3	14	3	5	10
Brixton: Total SS	≤5th percentile age-adjusted score	3	14	4	1	24
				5	1	5
Domain Measures				Total > 0	15	73
Executive Battery: Total	Minimum two executive tasks impaired	5	24			
RBANS: Immediate Memory	≤1.5 *SD* age and education adjusted score	7	33			
RBANS: Visuospatial	≤1.5 *SD* age and education adjusted score	6	29			
RBANS: Language	≤1.5 *SD* age and education adjusted score	0	0			
RBANS: Attention	≤1.5 *SD* age and education adjusted score	7	33			
RBANS: Delayed Memory	≤1.5 *SD* age and education adjusted score	9	42			
RBANS: Total Score	≤1.5 *SD* age and education adjusted score	6	29			

Note. Percentages based on proportion of AUD group. [a] Heaton et al., 2004

3.4.5. Correlation between drinking variables and cognitive measures

A correlation analysis was undertaken to relate drinking variables to scaled scores on the Hayling and Brixton Tests, age-adjusted scores on Digit Span Backwards, and age- and education-adjusted scores on RBANS measures, Trails B and Letter Fluency. Only significant correlations are reported. Length of time of heaviest drinking period was the variable that had the most frequent significant associations with cognitive performance, with a strong negative correlation with performance on RBANS: List Recall, $r_s(19) = -.519$, $p = .016$, a strong negative correlation with performance on RBANS: Figure Recall, $r_s(19) = -.520$, $p = .016$, and a moderate negative correlation with performance on RBANS: Total, $r_s(19) = -.479$, $p = .028$. There was also a strong negative correlation between length of time in excess of heavy drinking threshold and performance on RBANS: Figure Recall, $r_{s(}19) = -.546$, $p = .010$, and also a moderate negative correlation between length of time in excess of heavy drinking threshold and performance on RBANS: Delayed Memory Index, $r(19) = -.462$, $p = .035$. An increase in total quantity of drinks consumed during the heaviest drinking period was moderately correlated with a decrease in performance in RBANS: List Learning, $r_{s(}19) = -.452$, $p = .010$. Interestingly, there was a strong positive relationship between drinks per week at period of heaviest consumption and performance on RBANS: Story Recall $r_{s(}19) = .595$, $p = .004$. An increase in total lifetime quantity of drinks was moderately correlated with reduced performance on RBANS: Figure Recall, $r_{s(}19) = -.452$, $p = .010$. There was a strong positive relationship between length of abstinence and performance on RBANS: Story Memory, $r_{s(}19) = .-.452$, $p = .010$., and also a strong negative relationship between

number of drinks in the last thirty days and performance on RBANS: Digit Span, $r_{s(}19) = .-.509$, $p = .018$.

3.5. Discussion

The primary aim of this present study was to document the profile of cognitive deficits in individuals attending for treatment for AUD, inclusive of those with comorbid risk factors for cognitive impairment, and to determine whether this was consistent with the profile of alcohol-related cognitive impairment. The secondary aim was to investigate whether drinking history related to current cognitive function despite these associated risk factors.

The first hypothesis, that a significant proportion of the sample would present with comorbid health, psychiatric and neurological conditions, was met. The results of this study confirm the high rates of concomitant psychiatric, neurological and health conditions that accompany alcohol use disorders in treatment seeking individuals. Over three-quarters of participants (76%) had a currently diagnosed psychiatric disorder; of these the vast proportion were being treated for one or multiple mood disorders. In line with this finding, a significant proportion of the sample reported that they were currently experiencing at least moderate levels of depression (38%), anxiety (52%) and/or stress (33%). The prominence of mood disorders within this clinical sample is consistent with previous findings regarding psychiatric conditions that accompany alcohol dependence (Burns & Teeson, 2002; Grant et al., 2006), with rates of depression (48%) and anxiety (29%) in this sample similar to those documented in other treatment seeking samples

(Kranzler, Del Boca, & Rounsaville, 1996; Rosenbloom et al., 2005). As expected, these rates are higher than that reported in population-based surveys of individuals with AUD (Burns & Teeson, 2002; Grant et al., 2006). Socio-demographic variables that characterise this sample mirror past demographic findings in samples of AUD, namely a high proportion of participants that are single (76%), reliant on unemployment or disability benefits for income (81%) and who suffer one or more of an array of physical health concerns (Blazer & Wu, 2011; Galea, Nandi, Vlahov, 2004). Concussion resulting in loss of consciousness and neurological events such as seizures, stroke and WKS were reported in one-third of cases. Notably, only two individuals had a comorbid substance use disorder (opioid dependence), although five individuals reported occasional use of substances in addition to alcohol. The low rates of comorbid substance disorders is likely a product of the selection bias related to recruitment, with individuals were only identified if they were attending the centre primarily for alcohol treatment. This meant that if other individuals were attending for other substance use treatment and had additional problematic alcohol use, they were not identified for the purpose of this study.

Even within this relatively modest AUD sample, a detectable cognitive profile was observed in the AUD sample. Compared to a control group matched for age, education and premorbid IQ, the AUD group performed significantly worse on the majority of tasks, with the exception of measures of verbal inhibition and rule attainment (i.e., the Hayling and Brixton tests), verbal learning (RBANS: List-Learning Total), visuoperceptual ability (RBANS: Line Orientation), confrontational naming (RBANS: Picture Naming), recognition memory for a verbal task (RBANS: List Recognition), and

delayed recall of narrative (RBANS: Story Recall). The effect sizes calculated for other, significant group differences ranged from large to very large (d = .93 to 1.84), which suggests that scores on measures would translate to observable differences in the clinical setting. Unsurprisingly, three of the tasks that best differentiated groups were more global measures that were sensitive to multiple aspects of cognitive functioning – the ACE-R, MoCA and R-BANS Total Score.

Other measures that best distinguished the AUD from the control group in this current study, with very large effect sizes, were Semantic Fluency, the Language Index (which includes Semantic Fluency), Figure Recall and Story Recall. The effect sizes were comparable to those reported in studies that have compared the cognitive profile of AUD and heavy drinking individuals to controls (range .17 to 1.60; Fitzpatrick & Crowe, 2013; Green et al., 2010). In addition, categorisation of impairment by cognitive domain at the individual level in the AUD group revealed that the Delayed Memory domain was most frequently impaired (42%), followed by Immediate Memory and Attention (33% respectively), Visuospatial (29%) and Executive (24%) domains. Trails B was the task most frequently impaired in the executive battery (19%). No individual on the AUD sample was impaired on the Language Index. This seemingly discrepant finding – that the Language Index discriminated well between groups but impairment was not found in AUD participants – suggests that although there may be a drop in performance relative to controls on this measure, this is not to a level that is classified as impaired based on demographic comparisons.

The second hypothesis that cognitive deficits associated with AUD would be present but that deficits would not be restricted to these domains was partially met. The

AUD group demonstrated cognitive deficits consistent with the profile of ARCI, however they did not perform poorly on all tasks thought to be sensitive to ARCI, or demonstrate diffuse cognitive impairment. Consistent with the profile of ARCI, participants in the AUD group were most consistently impaired in the delayed memory domain, and individual tasks of fluency and visuospatial recall best distinguished the AUD group from controls. The similar performance of controls and the AUD groups on tasks of verbal recognition memory and confrontational naming is consistent with reports of relatively preserved ability to store verbal information in AUD despite deficits in encoding and retrieval (Brokate et al., 2003; Pitel et al., 2007) and relatively preserved confrontational naming in alcohol-related cognitive impairment and ARD (Ridley & Batchelor, 2014; Saxton et al., 2000). Preserved verbal attention span has been a more consistent finding early in abstinence, and was also found in this group (Bartsch et al., 2007; Konrad et al., 2012). Furthermore, semantic fluency was significantly worse in the AUD group, which is consistent with previous reports of impairment in semantic fluency in individuals early in abstinence (Fitzpatrick & Crowe, 2013; Pitel et al., 2007). The contribution of this subset to the language index (semantic fluency and picture naming) could explain the overall significant reduction in performance on this index in the AUD group, compared to controls

However, while these deficits are consistent with those observed in AUD samples in previous research studies, the AUD group also performed equivalently to the control group on other measures on which alcohol-related deficits have been previously observed early in abstinence. This was namely for tasks assessing verbal inhibition, conceptual problem solving, visuoperceptual reasoning, and delayed recall of a

narrative. This finding was unexpected, particularly given the added neurological and psychological comorbidities in the AUD group, which were expected, if anything, to exacerbate cognitive difficulties. It is possible that the large variation in days of abstinence in our sample contributed to the finding of intact inhibition and conceptual problem-solving abilities. Studies that have examined executive functions in AUD groups have primarily assessed groups following short periods of abstinence (2-3 weeks), with conflicting findings on the presence of specific executive deficits following longer periods of abstinence (Fernandez-Serrano et al., 2010; Loeber et al., 2009; Stavro et al., 2012). One-third of our sample had been abstinent for longer than one month and it is possible that resolution of deficits following acute abstinence in some individuals influenced the ability to differentiate between groups on these tasks. It was also unexpected that performance on a visuoperceptual task (line orientation) did not differentiate the groups, given that reductions in visuospatial abilities have been consistently reported in short and long term abstinent AUD groups (Fein et al., 2009; Sullivan, Rosenbloom, & Pfefferbaum, 2000), However, the AUD group performed significantly poorer on the copy and delayed recall of a complex figure than the control group. One possible explanation for this discrepant finding is the contribution of other cognitive functions to performance on these tasks. Neuropsychological tasks require integration of multiple cognitive functions and a deficit in one function may translate to poor performance even if the task is designed to primarily assess cognitive function in another domain. Munro et al. (2000), for instance, compared the cognitive performance of older individuals with short (less than 6 months) and long (over 6 months) periods of abstinence. As the groups did not differ on simple measures of visuoperceptual ability, it

was proposed that poor performance on a complex figure task in the latter group reflected executive/planning deficits, rather than visuoperceptual impairment per se. It is possible that in our sample, poor planning and organisational abilities driven by executive dysfunction could account for poor performance on the Figure Copy despite generally preserved visual discrimination abilities. In the same vein, attentional or executive dysfunction can impact performance on memory measures. In KS and AUD studies, working memory and executive function impairments have been linked to performance on episodic memory measures, particularly to learning abilities (Pitel et al., 2008; Pitel et al., 2007). Given that some memory tasks did not differentiate groups in this current study, further exploration of the cognitive correlates critical to different memory tasks would help establish the main areas of impairment that underlie poor performance on such measures (Mann, Guenter, Stetter, & Ackerman, 1999).

The third hypothesis, that duration of the period of heaviest drinking and length of abstinence were the drinking variables most likely to be associated with cognitive outcome, was met. Length of time of the heaviest drinking period, time exceeding the heavy drinking threshold and drinks consumed during this period was associated with performance on delayed memory measures (Figure and List Recall, and Delayed Memory Index) and performance on a list-learning task. Length of abstinence was also related to performance on a story-learning task, and total drinks in the last thirty days was associated with performance on a verbal attention task (digit span). Lifetime quantity of drinking was only associated with one outcome – performance on recall of a complex figure. In the context of a participant sample who presented with multiple comorbid risk factors for cognitive impairment, the observed strong relationship of

drinking variables to cognitive performance in this study is somewhat unexpected. Even more surprising is the consistency of the findings with the accumulation of literature that has demonstrated a stronger association of duration and severity of heavy drinking to cognitive function than overall lifetime consumption of alcohol (Beatty, 2000; Fitzpatrick & Crowe, 2013; Sullivan, 2000). Furthermore, associations with drinking variables, apart from the association of drinks in the last thirty days and Digit Span, related solely to performance on memory and visuoconstructional tasks. These again are functions that are most typically reported to be vulnerable to damage by alcohol use (Fein et al., 1990). Duration of abstinence was related to only one cognitive outcome, however, the inclusion of two participants who were currently drinking (albeit at smaller levels) and the relatively short period of abstinence characterising the sample (range of 2 to 365 days) may account for this finding. Stavro et al. (2012) reported relatively stable cognitive function during the first year of abstinence (after an initial period of rapid recovery) but further improvement in cognitive functioning after one year. The relationship between participant's number of drinks consumed in the last thirty days and performance on a verbal attention task was also not surprising, given that white matter restoration is thought to account for brain volume regain early in sobriety and associations with measures of attention information and information processing have been documented (Bartch et al., 2007; Konrad et al., 2012). What was unanticipated was that the number of drinks per week during the period of heaviest consumption was associated with improved performance on delayed recall of a story. While the finding of better performance on a delayed memory measure and increased alcohol consumption was difficult to reconcile, it is possible that, given that length of abstinence was related

to performance on story learning, individuals with patterns of binges and withdrawals may perform better on memory tasks if they achieve abstinence compared to those who have prolonged periods of heavy drinking. Again, the differences in cognitive constructs between memory tasks and the relationship of drinking variables to performance on these measures is yet to be fully understood.

3.5.1. Limitations and strengths

There are a number of limitations in this current investigation. Firstly, the small sample size reduced the power to detect significant effects. Although significant results were observed, a larger sample size would likely improve power and effect sizes. Additionally, the large number of comparisons that were conducted necessitated the use of correction for multiple comparisons to control for Type II error rate and a conservative adjustment (Bonferroni correction) was used, resulting in a low significance threshold (p <.002). While the choice to utilise a conservative adjustment was a strength of the study in ensuring that significant effects represented true differences in group performance, it did restrict the number of comparisons undertaken, as this would have necessitated further adjustment of the significance level.

Furthermore, whilst the inclusion criteria for the study were designed to be as least restrictive as possible, participants were still subject to selection bias. Participants from CALD backgrounds who had limited English ability were excluded from participation and these represented almost one-fifth of possible or potential participants. Fourteen percent of eligible subjects also declined to participate. The participants in our group thus represent a discrete sample who were motivated to participate in research and

spoke English as a first language. In addition, it has been demonstrated that treatment seeking individuals tend to be more severely affected by alcohol use and have more comorbidities than people in the community who meet diagnostic criteria for alcohol dependence but have never sought treatment (Fein & Landman, 2005; Rosenbloom et al., 2005). It subsequently cannot be assumed that the results of this study will generalise to other clinical or community samples. It would have been optimal to examine the comorbid characteristics and cognitive profiles of individuals that did not take part or did not qualify in the study, however this was beyond the scope of this investigation. Furthermore, the group sampled presented with comorbid factors largely relating to mood disorders, with lower proportions reporting neurological events, comorbid psychiatric or personality disorders, or comorbid substance use. As evidence for additive effect of mood-associated cognitive deficits to the profile of cognitive impairment observed in AUD is limited at best (Rosenbloom et al., 2005; Uekermann, Daum, Schlebusch, Wiebel, & Trenckmann, 2003), it is possible that in a sample in which other comorbidities were more frequent, the observed cognitive profile and associations to drinking variables would not be apparent. Furthermore, the AUD group was relatively young (mean age of 51). Age is one risk factor that has been identified for ARCI, with support from neurobehavioural studies that aging increases vulnerability to alcohol-related injury (for a review, see Oscar-Berman & Marinkovic). While young age of onset of memory disorders is a common finding in epidemiological research (Ridley, Draper, & Withall, 2013), it is likely that the cognitive effects of alcohol consumption interacts with other risk factors at varying rates across the lifespan. Large-scale longitudinal studies, which utilise structural equation modelling to investigate the

relative contributions of risk factors to cognitive outcome, are required to fully assess the independent and additive effects of individual variables to performance on cognitive tasks.

One further limitation was that a comprehensive neuropsychological assessment was not conducted. The choice of the RBANS as tool of choice for overall assessment of cognitive function was made largely on practical grounds. Traditional neuropsychological batteries are lengthy and time-consuming, and individuals attending substance use treatment facilities are likely to have limited experience with cognitive testing (Copersino et al., 2009; Olson, Parkinson, & McKenzie, 2010). To increase patient acceptability the aim was to complete all aspects of assessment within a two-hour time frame, which was achieved. However to achieve this some aspects of clinical assessment were abbreviated, such as use of a short, specifically targeted clinical interview that did not include the use of established diagnostic questionnaires. Additionally, the use of multiple measures assessing the same construct in one short session (e.g., memory items) may have reduced typical performance on these measures if the individual was prone to the effects of proactive interference. Both participant groups were vulnerable to this disruption, and the order of administration was designed to minimise the potential for this to occur. However, it is possible that the impact of order effects differed depending on level of memory function, particularly given that individuals with AUD have demonstrated deficits in encoding the contextual and temporal context of information (Pitel et al., 2007).

The strengths of this study included the ecological validity and observational nature of the investigation, use of secondary methods (i.e., medical records) to confirm

participant reports, and the fact that the groups were well matched for age, education, gender and premorbid IQ. It should be reinforced that this study did not aim to determine causality of cognitive impairment, or assign a permanent status of cognitive impairment to individuals, given that they were recently abstinent or continuing to drink alcohol, had multiple physical and mental health comorbidities and were taking a range of psychoactive medications. It is also possible that some of these participants were in the latter stages of alcohol withdrawal, given that some individuals were assessed very early in abstinence. It is clear that in the clinical setting each individual needs to be assessed on a case-by-case basis, as the cognitive outcomes of a significant neurological event (e.g., stroke) would most likely override any deficits related to excessive drinking. In addition, syndromes with distinct aetiologies (e.g., depression) can present with similar cognitive features to alcohol-related cognitive impairment (e.g., executive dysfunction, memory difficulties), and consequentially the cognitive deficits observed in this sample cannot be easily attributed to alcohol-related impairment.

3.5.2. Conclusion

The main finding of this study that was even within a sample of individuals with AUD who had multiple comorbid risk factors for cognitive impairment, a distinguishable profile was observed. Whilst the presence of deficits was not entirely consistent for all tasks across cognitive domains (e.g., impairment on some memory tasks and not on others), features of preserved verbal recognition memory and confrontational naming, and poor performance on delayed memory and fluency measures were observed. Furthermore, cognitive performance was associated with drinking history despite the

presence of extraneous variables. It is notable that no participant in our sample presented without a psychiatric, neurological or substance use co-morbidity, thus raising the question of how generalisable previous findings of the profile of cognitive impairment in 'pure' AUD are to the clinical setting. Whilst the results of the current study should be interpreted conservatively given the limitations discussed above, these results should further encourage researchers to extend inclusion criteria to allow future research studies to best mirror the characteristics of the clinical setting. Further exploration of the deficits that typify this clinical population, and the contribution of factors such as age, education and gender to the severity and chronicity of such deficits, will serve to assist with intervention to ensure the best possible outcome for the individual in treatment for AUD is achieved.

CHAPTER FOUR

Cognitive screening in substance users: the clinical utility of the Mini Mental State Examination, the Addenbrooke's Cognitive Examination-Revised, and the Montreal Cognitive Assessment

This chapter has been prepared for submission to *The Clinical Neuropsychologist*

Abstract word count: 134 words

Manuscript word count: 7943 words

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4.1. Abstract

Despite the prevalence of cognitive impairment in substance using populations, there has been little investigation of the utility of cognitive screening measures within this context. In the present study the diagnostic accuracy of three screening measures in this population was examined – the Mini Mental State Examination (MMSE), the Montreal Cognitive Assessment (MoCA), and the Addenbrooke's Cognitive Examination-Revised (ACE-R). A sample of 30 substance users and 20 healthy controls was administered the screening measures and a neuropsychological battery (NSB). Agreement of classification of impairment by the screening measures and NSB was examined. Results indicated that the MoCa and the ACE-R had superior diagnostic accuracy to the MMSE in the classification of cognitive impairment. Sensitivity and specificity performance at various cut-scores are provided and recommendations for future investigations of cognitive screening specific to this population discussed.

4.2 Introduction

There is ample evidence in the literature that excessive alcohol and drug use can cause deleterious neuroanatomical changes and lead to detectable cognitive deficits (Buehler & Mann, 2011; Grohman & Fals-Stewart, 2004; Stavro, Pelletier, & Potvin, 2012). Estimates of cognitive impairment in individuals with substance use disorders (SUD) - used to describe those with symptoms of substance dependence and/or abuse (American Psychiatric Association, 2014) - vary widely but have been suggested to be in the vicinity of one- to two-thirds of individuals presenting for treatment (Grohman & Fals-Stewart, 2004; O'Malley, Adamse, Heaton, & Gawin, 1992; Parsons & Nixon, 1993; Teichner, Horner, Roitzsch, Herron, & Thevos, 2002). These deficits may range from the relatively subtle effects of cannabis use (Crane, Schuster, Fusar-Poli, & Gonzalez, 2013; Solowij & Pesa, 2012) to the persistent cognitive disorders associated with chronic alcohol use, including alcohol-related dementia and the Wernicke-Korsakoff Syndrome (Bowden, 2010; Moriyama, Mimura, Kato, & Kashima, 2006). The type of substance used may differentially impact clinical presentation and the potential for recovery with abstinence, although there is some overlap in the neurophysiological targets of most substances (Bates, Voelbel, Buckman & Labouvie, 2005; Rogers & Robbins, 2001). Chronic, heavy alcohol use, for instance, is associated with structural damage to the prefrontal, temporal and cerebellar parts of the brain, and deficits in learning and memory, executive functions, visuoperceptual abilities and psychomotor speed may persist for some time after drinking ceases (Fein, Shimotsu, Chu, & Barakos, 2009; Stavro et al., 2012). Acute cannabis consumption can also impede learning and

memory, attention and working memory, however evidence for enduring disruption of functions following abstinence is limited (Crane et al., 2013; Solowij & Pesa, 2012). However in the clinical setting, the ability to relate neuropsychological findings in substance users to a certain drug is complicated by the finding that most substance users simultaneously use and misuse more than one substance, even when there is a clear drug of choice (Fernandez-Serrano, Perez-Garcia, & Verdejo-Garcia, 2011). In addition, cognitive deficits may arise from additional factors which frequently accompany substance use disorders, such as head injury, psychiatric conditions, neurological disease and physical health conditions (RachBeisel, Scott, & Dixon, 1999). These factors may differentially impact the extent and rate of recovery and should be given careful consideration in the cognitive assessment of those with SUD.

4.2.1. Relationship of cognitive impairment to treatment outcome

Rogers and Robbins (2001) identify two ways in which cognitive impairment can contribute to drug misuse and addiction. Firstly, cognitive deficits may increase likelihood of drug-seeking behaviours through, for instance, failures of impulse control mechanisms and adherence to goal-directed behaviour. Secondly, they may interfere with the individual's capacity to engage in treatment programs, which often have cognitive emphasis. Theoretically, if treatment is viewed as form of learning, then disruption to functions that allow the individual to encode, integrate and retain information presented in therapy could hinder the learning of new behaviours (Grohman & Fals-Stewart, 2004). Executive dysfunction may restrict the individual's ability to develop and adhere to goal-driven behaviour, and disruption to inhibitory and problem-

solving abilities may be associated with relapse (Franken, 2003; Paulus, Tapert, & Schuckit, 2005). Yet, studies that have attempted to relate cognitive abilities at treatment onset to treatment outcome, such as maintenance of abstinence or amount of substance use following treatment, have reported weak and inconsistent outcomes (Bates, Buckman, & Nguyen, 2013; Knight & Longmore, 1994). This may be due to the emphasis that researchers have placed on cognitive status as a direct predictor of outcome, rather than the influence it may have on outcome via indirect pathways (Bates, Bowden, & Barry, 2002). For instance, there is more consistent evidence for an association of impaired cognition to treatment retention and adherence, which in turn is a strong predictor of outcome (Aharonovich et al., 2006; Bates, P., Tonigan, & Buckman, 2006; Teichner et al., 2002). Cognitive dysfunction has been associated with less treatment compliance in outpatient programs for cocaine (Aharonovich et al., 2006) and cannabis dependence (Aharonovich, Brooks, Nunes, & Hasin, 2008). In alcohol users, cognitive impairment has been associated with lower retention rates in residential programs (Fals-Stewart & Shafer, 1992), lower-self efficacy and poor acquisition of new coping behaviours (Bates et al., 2006), and denial of addiction (Rinn, Desai, Rosenblatt, & Gastfriend, 2002). Whilst the research emphasis has largely been alcohol use disorders, the evidence suggests that cognitive deficits can impact the treatment process across both different substances and treatment modalities.

Assessment of neuropsychological functioning at treatment entry may not only support diagnostic decision-making but assist with treatment planning. Specifically, early detection of deficits may allow matching of the cognitive demands of interventions to the cognitive strengths and weaknesses of the client, inform the expectations and

strategies of treatment providers, and determine the need for cognitive remediation (Bates et al., 2005). However, despite the recognised impact of cognitive deficits on adherence to treatment, cognitive assessment has not typically formed a standard part of patient evaluation in substance use settings (Copersino et al., 2009). This is of concern given that cognitively impaired SUD patients have not been found to be accurately identified by self-report (Horner, Harvey, & Denier, 1999) or clinical impression (Fals-Stewart, 1997). While extensive neuropsychological assessment (NPA) is the gold standard for cognitive evaluation, this is not always feasible in the clinical setting due to time constraints and the cost required for specialist administration. Clients may also be deterred from participation in cognitive assessment if that testing is lengthy (Olson, Parkinson, & McKenzie, 2010). Brief screening tools provide an alternate option for clinicians. Whilst not intended to be a substitute for a full NPA, a well-designed screening tool can provide an index of function in key cognitive domains and guide further assessment (Cullen, O'Neill, Evans, Coen, & Lawlor, 2007). The choice of an appropriate cognitive screening tool should be guided by both clinical utility (ease of use and administration time) as well as psychometrics, such as established high sensitivity (correct identification of individuals with impairment) and good specificity (correct identification of individuals with no impairment) in the population for which it is intended (Slater & Young, 2013).

4.2.2. Cognitive screening tools

The Mini Mental State Examination (MMSE; Folstein, Folstein, & McHugh, 1975) is one screening tool that has been extensively used with a range of clinical populations.

This instrument was originally designed to screen for early dementia in elderly people and had been shown to achieve acceptable sensitivity and specificity in detection of dementia in clinical samples (Mohs, Rosen, & Davis, 1983; Rosen, Mohs, & Davis, 1984). However, several limitations have been identified, including over-reliance on verbal functions, ceiling and floor effects, underrepresentation of memory tasks, absence of executive functioning measures, and low sensitivity to mild cognitive impairment (Boustani, Peterson, Hanson, Harris, & Lohr, 2003; Pendlebury, Cuthbertson, Welch, Mehta, & Rothwell, 2010). To address these shortcomings, Mathuranath, Nestor, Berrios, Rakowicz, and Hodges (2000) developed the Addenbrooke's Cognitive Examination (ACE), which was also intended as a dementia screening measure. The ACE incorporated the MMSE but added further memory, visuospatial, fluency and language components to provide a more balanced contribution of component tests to the total score. The subsequent revised version, the Addenbrooke's Cognitive Examination-Revised (ACE-R; Mioshi, Dawson, Mitchell, Arnold, & Hodges, 2006) included the provision of three alternate forms and allows derivation of five sub-scores, each of which represent a specific cognitive domain.

The ACE-R has validated clinical utility. It been shown to be sensitive to cognitive impairment in a variety of clinical adult populations including Parkinson's disease (Komadina et al., 2011; Rittman et al., 2013), traumatic brain injury (TBI; Gaber, 2008) and mild cognitive impairment (MCI; Alexopoulos et al., 2010). It also has good reported internal consistency and construct validity (Mioshi et al., 2006) and has been translated and validated in several languages (Alexopoulos et al., 2010; Carvalho, Barbosa, & Caramelli, 2010; Kwak, Yang, & Kim, 2010; Wong et al., 2013). In the

original validation study (Mioshi et al., 2006), an optimal cut-score of 88 points for identifying dementia was suggested, which was associated with high sensitivity (94%) and specificity (89%). A lower cut-score of 82 provided lower sensitivity (84%) but excellent specificity (100%). However, other optimal cut-scores have been suggested, which vary by clinical population (Crawford, Whitnall, Robertson, & Evans, 2012; Dudas, Berrios, & Hodges, 2005; Larner, 2013). The use of the domain sub-scores to differentiate dementia subtypes has not yet received consistent empirical support and requires further validation (Crawford et al., 2012). The conflicting findings on the utility of the domain sub-scores is potentially due to methodological variations across studies, including differences in severity of impairment and participant numbers

As far as is known, the ACE-R has not been used in SUD samples. Empirical support for its utility in this context comes from studies which have demonstrated the sensitivity of the test to mild cognitive impairment in individuals with subcortical-dementia (Komadina et al., 2011; Rittman et al., 2013) and traumatic brain injury (Gaber, 2008). These patients typically experience difficulties in attention, memory and executive function that are not dissimilar to the impairments demonstrated by individuals with chronic substance use. Given these conceptual similarities and the need for brief but valid screening measures in those with SUD, it is important to evaluate the diagnostic utility of the ACE-R within this population

One other screening measure that has shown promise in screening for cognitive impairment secondary to SUD is the Montreal Cognitive Assessment (MoCA; Nasreddine et al., 2005). The MoCA is a brief screening instrument that was specifically developed for assessment of mild cognitive impairment. It includes tasks designed to

assess memory, visuospatial abilities, executive function, attention and concentration, language, and orientation. Construct validity for categorisation of test items into these six cognitive domains has been demonstrated (Freitas, Simoes, Maroco, Alves, & Santana, 2012). It has also been reported to have high test-retest reliability and good internal consistency, at least as assessed in samples attending memory clinics (Bernstein, Lacritz, Barlow, Weiner, & DeFina, 2011; Nasreddine et al., 2005).

The MoCA has been shown to be sensitive to mild cognitive impairment in the context of neurodegenerative conditions such as Parkinson's disease (Nasreddine et al., 2005; Nazem et al., 2009), early cerebrovascular disease (Popovic, Seric, & Demarin, 2007) and stroke (Bocti et al., 2013). A cut-score of 26 was recommended by the authors, which had excellent sensitivity in identifying MCI (90%) and Alzheimer's disease (100%) and good specificity for detection of normal controls (89%). Other authors have since proposed that lower cut-scores are more appropriate for detection of MCI (Rossetti, Lacritz, Cullum, & Weiner, 2012). Copersino et al. (2009) reported acceptable sensitivity (83.3%) and specificity (72.9%) for the MoCA at an optimal cut-score of 26 in a sample of 60 substance users attending outpatient treatment. In addition, predictive validity was demonstrated, with classification of impairment on the MoCA associated with poorer treatment attendance (Copersino et al., 2012). Wester, Herten, Kessels, & Egger (2013) also reported good sensitivity (91%) and specificity (88%) of the MoCA at a cut score of 24 in distinguishing individuals with ARCI from healthy controls. Although these findings suggest that the MoCA holds promise as a screening tool for this population, further validation is needed.

4.2.2. Aims and hypotheses

The purpose of the present study was to examine the diagnostic accuracy of the MMSE, ACE-R and MoCA in the assessment of cognitive impairment in a sample of individuals with SUD. To do this, a number of steps were undertaken. Firstly, the diagnostic accuracy of the three screening measures in classification of cognitive impairment was examined in a sample of substance users and non-clinical control participants. This was achieved through use of a NSB as a criterion measure. It was hypothesised that the MoCA and ACE-R would have superior discriminative ability than the MMSE and that these two former measures would have comparable discriminatory ability. Secondly, the most appropriate cut-scores for classification of cognitive impairment on these three screening measures were examined through generation of sensitivity and specificity data. It was hypothesised that a score of 25 or 26 would best distinguish impairment on the MoCA, in line with previous findings. No hypothesis regarding the best cut-score for the ACE-R was made as its utility has not yet been investigated in a substance use context. Agreement of classification of impairment on the screening measures with classification of impairment on the NSB was also calculated at traditional and optimal cut-scores. Finally, the association of domain sub-scores of the MoCA and the ACE-R relative to the domains assessed on the NSB was examined. This was conducted in order to provide a measure of criterion validity, i.e. to determine the extent to which the screening measures were assessing the same cognitive domains as the NSB.

4.3. Methods

4.3.1. Participants

Thirty adults (eighteen male, twelve female) were recruited from two outpatient substance use clinics in the South East Sydney Local Health District (The Langton Clinic, Surry Hills, and the St George/Sutherland Drug and Alcohol Outpatient Clinic, Kogarah). Participants were identified as eligible to participate in the research by a Clinical Nurse Consultant (CNC) if they 1) had a DSM-IV (1994) diagnosis of substance use abuse or dependence, 2) were not acutely intoxicated, as determined by medical staff, and 3) were deemed by medical staff competent to give consent. Participants were not excluded on the basis of psychiatric history, neurological injury, health conditions or co-morbid substance use. Further exclusion criteria were applied by the chief investigator (NR) following a brief clinical interview. At that point, individuals from culturally and linguistically diverse backgrounds who had limited English ability (CALD) and individuals with significant sensory deficits that could potentially interfere with performance on testing were excluded. In total, 44 individuals were identified by the head CNC as eligible to participate in the study. Seven were excluded due to limited English ability, and no individuals were excluded due to sensory deficits. In total, 37 individuals were invited to take part in the study, seven of whom declined. This final group of thirty participants is referred to as the SUD group.

As per Ridley et al. (2014b), control subjects were recruited from a database of carers and supporters of individuals with early-onset memory disorders. As it was anticipated that the majority of the SUD group would perform poorly on cognitive

measures, recruitment of this group ensured that there would be a sufficient number of participants to examine cut-scores for the absence or presence of cognitive impairment. Recruitment of controls also allowed comparison of performance on screening measures between groups. These participants were specifically selected from the database to match the patients in the SUD group as closely as possible for age, education and gender. The chief investigator contacted potential participants by phone and during that phone conversation conducted a brief screening for eligibility. Exclusion criteria for the control group included diagnosis of a current psychiatric or substance use disorder, a history of neurological damage or disease, or alcohol consumption exceeding 14 standard drinks a week (National Health and Medical Research Council, 2009). Twenty-six individuals from the control database were contacted; of those, one was excluded due a current psychiatric condition, another for current alcohol consumption in excess of criteria and four declined, leaving a final sample of 20.

All participants in the research completed the full protocol of tasks, with the exception that the control group did not complete the Depression, Anxiety Stress Scales-Short Version (DASS-21), as this was used for descriptive purposes in the SUD group only. Additionally, the score of one control participant on one task (Trail-Making Test B) was not recorded due to equipment failure, and due to time restraints, one participant in the SUD group did not complete the Brixton Spatial Anticipation Test and one did not complete the DASS-21. These were coded as missing data. All participants provided written informed consent, as per ethical approval obtained from the University of Wollongong/Illawarra Shoalhaven Local Health District and Medical Human Research Ethics Committee (HREC) and the Macquarie University HREC (see Appendix A).

4.3.2. Measures

4.3.2.1. Screening Tools

The Montreal Cognitive Assessment (MoCA): The MoCA (Nasreddine et al., 2005) is a 30-point screening tool that contains fourteen tasks that evaluate aspects of attention, orientation, language, visuospatial, executive and memory. The total possible score is 30 points, with an education adjustment of +1 point to the final score if the participant has less than 12 years of education. Classification of impairment was examined at the traditional cut score of 26 and surrounding scores (Nasreddine et al., 2005). The original English language version (version 7.1) was used.

The Addenbrooke's Cognitive Examination Revision (ACE-R): The ACE-R (Mioshi et al., 2006) consists of five-subscales assessing orientation, attention, verbal fluency, memory, language and visuospatial function. The test incorporates the Mini-Mental State Examination (MMSE; Folstein et al., 1975), with MMSE questions and their maximum 30-point score contributing to the 100 point possible total score. In the current study Form A of the Australian version was used. Classification of impairment was investigated at the cut-scores provided by the authors (88 and 82) and surrounding scores (Mioshi et al., 2006).

For the MMSE, a cut-score of < 24 has traditionally been used to classify cognitive impairment, however, some authors have suggested that a cut-score of 27 has better diagnostic accuracy for well-educated samples (O'Bryant et al., 2008; van Gorp et al., 1999). Classification of impairment was examined at both scores.

4.3.2.2. Neuropsychological Battery (NSB) measures

Repeatable Battery for Assessment of Neuropsychological Status (RBANS): The RBANS (Randolph, Tierney, Mohr, & Chase, 1998) includes 12 subtests which yield 5 index scores and a total score, all of which have a mean of 100 and a standard deviation of 15. Normative data from the manual is based on 690 individuals between the ages of 12 and 89 years. The RBANS was used in this study to provide an index immediate and delayed memory, attentional, visuospatial and language abilities. The subtests that make up each index are described in detail in Ridley et al. (2014b). The Immediate Memory Index includes tasks requiring immediate recall of a story (Story Memory) and a list-learning task (List Learning). The Attention Index includes tasks that require immediate repetition of numbers presented verbally (Digit Span) and a code transcription task (Coding). The Visuospatial/Constructional Index includes tasks requiring the examinee to copy a complex figure (Figure Copy) and make judgments regarding the orientation of lines (Line Orientation). The Language Index consists of tasks requiring the examinee to name line drawings of common objects (Picture Naming) and quickly provide the names of items within a semantic category (Semantic Fluency). The Delayed Memory Index assesses retention of memory items previously encountered in the test battery (List Recall, Story Recall, List Recognition, and Figure Recall subtests).

Index scores were the main variables of interest in this analysis, as these were used to classify impairment in different domains. Age and education adjusted index scores were generated using normative data from the RBANS standardisation sample. Raw scores were converted to age-adjusted standard scores (mean of 100, standard deviation of 15) for each index (Randolph et al., 1998). To adjust for the effects of

education, Z-scores were calculated by taking the difference between the examinee's index standardised score and the equivalently educated cohort standardised score, and dividing that number by the cohort standard deviation for that particular subtest. Z-scores have a mean of 0 and a standard deviation of 1.

Executive Battery:

Letter Fluency: This was used to assess verbal generativity (Berg, 1948). The examinee must produce orally as many words as possible beginning with a specified letter during a period of 60 seconds. The letters F, A, and S were administered in this task, using instructions from the MoCA (Nasreddine et al., 2005). The total raw score was corrected for age, education and gender to yield T-scores using the normative data of Heaton (Heaton, Miller, Taylor, & Grant, 2004) These T-scores (mean of 50, standard deviation of 10) were converted to *z*-scores.

*The Trail Making Test***:** The version adapted by Reitan (1955) was used to assess divided attention. In Part A, the examinee is required to connect in ascending order 25 circled numbers randomly arranged on a page. In Part B, 25 circled numbers and letters are randomly placed on the page and the examinee is required to join these in alternating and ascending order. The normative data by Heaton et al. (2004) was used for conversion of Part B scores to an age, education and gender adjusted z scores.

Digits Backwards: The Digits Backwards subtest of the Wechsler Adult Intelligence Scale-Fourth Edition (WAIS-IV; Wechsler, 2008) was used to assess working memory.

The examiner recites a number sequence and the examinee is required to repeat the number sequence in reverse order. The sequences increase in length over trials, until the examinee incorrectly recalls two sequences of the same length. Raw scores were converted to age-adjusted standard scores (mean of 10, standard deviation of 3) through the conversion tables in the test manual (Wechsler, 2008).

The Hayling and Brixton Tests: These tests were used to assess verbal inhibition and rule attainment (Burgess & Shallice, 1997). The Hayling Test requires the examinee to complete sentences which each have the last word missing, firstly with a sensible completion, and secondly with a word unconnected to the sentence. Both response speed scores and error scores are used to generate an overall standard score. The Brixton Spatial Anticipation Test is a rule attainment task based on the Wisconsin Card Sorting Test (Heaton et al., 1993). The examinee is required to guess which position a coloured circle will move to next, based on previous patterns observed in a stimulus booklet. The total number of errors form the raw score, which is then converted to a standard score. The manual provides cut-scores for performance at the fifth percentile, stratified by age.

Other Measures

*The Depression, Anxiety, Stress Scales: Short Version (DASS-21)***:** The DASS-21 (Lovibond & Lovibond, 1996) is a self-report measure designed to assess severity of symptoms of depression, anxiety and stress. Each of the DASS scales contains 7 items, which are each scored on a four-point scale, and the individual is required to indicate the presence of a symptom over the past week. Scores for each subscale are doubled to

allow comparison to normative data (Lovibond & Lovibond, 1996). The manual includes cut-scores for severity labels (i.e., normal, moderate, severe).

*The National Adult Reading Test***:** Premorbid intellectual functioning was estimated using the NART-2 (Nelson, 1982), a word pronunciation list of 50 irregularly spelled words. Number of errors made on the NART is used to predict WAIS-III Full Scale Intelligence Quotient (Wechsler, 1997).

The RBANS Effort Index: The RBANS Effort Index (EI) was also used to assess effort for each participant (Silverberg, Wertheimer, & Fichtenberg, 2007). Reliable Digit Span (Schroeder, Twumasi-Anrah, Baade, & Marshall, 2012), was also calculated to provide an additional measure of effort. Three SUD participants exceeded the published cut-score of the EI for suspected poor effort (Effort Index of >3, scores of 4, 5 and 5). However, all exceeded the recommended cut-off for reliable digit span for groups with severe memory disorders (<7; Schroeder et al., 2012), and their data was retained for analysis.

4.3.3. Procedure

The procedure of testing was identical to that outlined in Ridley et al. (2014b). After providing written informed consent, participants completed all study measures at a single time point requiring approximately 1.5 to 2 hours. Participants were reimbursed with a $25 groceries gift card. A structured clinical interview was conducted at the beginning of the session to collect information regarding substance use and

psychological and neurological history. In an attempt to verify information, the medical records of patient participants were later reviewed to determine whether the self-report was consistent with the documented history. If there was inconsistency between accounts, the information in the medical records was treated as the accurate account.

Testing commenced following the clinical interview. The screening tests were administered prior to any other cognitive measures, in a counter-balanced order, to ensure novelty of screening items. Identical tasks on different screening measures were not repeated (Cube-drawing, Serial Sevens). Time delays on memory tasks were maintained through use of other tasks. After the screening measures, tasks other than the RBANS were administered in a counter-balanced order. The RBANS was always the last cognitive measure administered, to maximise the interval between memory tasks on the screening items and those undertaken on the RBANS. This was followed by the DASS. Individuals were monitored for fatigue throughout the assessment; most completed testing without need for a break however a break was provided on request to two participants.

4.3.4. Scoring and classification of impairment

All neuropsychological test results were scored and interpreted by the chief investigator. An individual was classified as impaired on the overall NSB if they were classified as impaired on any of the domain indexes. The domains included Immediate Memory, Visuospatial/Constructional, Language, Attention, Delayed Memory Index (all derived from the R-BANS indices) and the Executive domain. For the R-BANS scores, impairment was classified as a score of -1.5 or more standard deviations below the mean

domain score of the normative age and education matched sample (Randolph, 2012). For classification of impairment in the executive domain, the participant was required to demonstrate impairment on two tasks. This was classified as scores that fell 1.5 or more standard deviations below age and education equivalent norms (Heaton et al., 2004), or at or below the fifth percentile for age on tasks which did not provide education adjustments (the Hayling and Brixton Tests; Burgess & Shallice, 1997). The decision to require impairment on index scores and two tasks of executive function ensured that one abnormal score did not necessarily result in classification of impairment.

Criterion validity was assessed by looking at how well tasks on the screening measures related to performance on similar domains on the NSB. To facilitate comparison, tasks on the screening measures were categorised into domains of cognitive functioning. The ACE-R provides categories for five domains and these were retained. Items on the MoCA were classified based on the domains identified by the authors (Nasreddine et al., 2005), however some tasks were categorised alternately to maximise compatibility with ACE-R categories and NSB domains. Specifically, digits backwards and letter fluency were categorised as executive function tasks, and orientation was grouped with attention, as per the ACE-R. Table 10 presents classification of tasks.

4.3.5. Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics version 22 (IBM Corporation, 2013). A Shapiro-Wilk statistic was used to elucidate whether assumptions of normality were met for the demographic and cognitive variables which were used in group comparisons and correlational analyses. The assumption of normality was not met

for the following variables: MMSE, ACE-R (both total and domain subscores) and MoCA domain sub-scores. The diagnostic performance of the screening tests relative to the NSB was assessed using a Receiver Operator Characteristic (ROC) analysis. ROC curves were graphed and area under the curves compared. Plots of the sensitivity and specificity of the MMSE, ACE-R and MoCA at various cut-scores were calculated using MedCalc Version 8.0.2.0. The cut-scores for the best sensitivity and specificity was calculated according to the maximum Youden index (Youden index = sensitivity + specificity – 1). The kappa statistic (*k*) was used to measure chance corrected agreement of presence/absence of cognitive impairment on screening measures to the NSB; this was calculated for both established and experimental cut-scores for each screening measure.

Correlations between domain scores on the NSB and domain sub-scores on the screening measures were also calculated to assess criterion validity for individual cognitive domains. These correlations were conducted for the full sample (n = 50). Associations between screening measure scores and age and education were also undertaken. Associations between variables were assessed with the Pearson Product-Moment correlations for variables that met the assumptions of normality, and Spearman Rank Order correlations for data that violated these assumptions. Cohen (1988) suggests r = .3 represents a small correlation, r = .5 a medium correlation, and r = .7 a strong correlation. These criteria were adopted as they are commonly used in the SUD literature.

Group comparisons were conducted for the SUD group classified as impaired on the NSB (SUD-Imp) and matched controls (CON) to compare total screening measure

Table 10

Neuropsychological Battery Domains and ACE-R and MoCA Tasks Domain Classification

Domain	NSB tests	ACE-R Tasks	MoCA Tasks
Memory: Immediate, Delayed	List learning, Story learning, List recall, List recognition, Story recall	Delayed word recall, Name and address Registration, Recall and recognition, Retrograde Memory	Delayed word recall
Language	Picture naming, Semantic fluency	Sentence writing, word & sentence repetition, picture naming, picture comprehension, word reading	Picture naming, Sentence repetition
Visuospatial	Line orientation, Figure copy	Pentagon copy, Cube copy, Clock drawing, Dot counting, Letter identification	Cube copy, Clock drawing
Attention	Coding, Digit span	Backward spelling/Serial subtraction, Orientation, Word registration	Digits forwards, Serial subtraction, Tapping task, Orientation
Executive Function	Letter fluency, Digits backwards, Trails B, Hayling and Brixton tests	Letter fluency	Letter fluency, Digits backwards, Trails B

Note. NSB = Neuropsychological Battery; ACE-R = Addenbrooke's Cognitive Examination-Revised; MoCA = Montreal Cognitive Examination

performance and domain sub-scores.. The exclusion of SUD-Not Impaired Group from the analyses ensured that SUD users with potentially mild deficits not detectable on the NSB in this instance were not included in this validation analysis; i.e. the performance of the SUD-Impaired Group was compared to a 'pure' sample of cognitively intact controls. The Mann Whitney U test was performed for comparison of group results for non-parametric data and the χ 2 analysis was used for categorical data. The independent sample t-tests were applied for all other group comparisons. The Bonferroni correction was applied for multiple comparisons, with significance level set at p <.005. The Levene's Test for Equality of Variances was applied when data violated assumption of homogeneity of variance. One-tailed tests were used for group comparisons on cognitive measures as we predicted that the substance use group would perform worse than controls across all cognitive measures.

4.4. Results

4.4.1. Descriptive data

The 30 SUD participants ranged in age from 32 to 76 years (M = 52.30, SD = 10.43). Years of education ranged from 7 to 17 (M = 11.07, SD = 2.33). Substance use diagnoses (DSM-IV; 1994) included alcohol dependence (n = 21), opioid dependence (n = 8), and cannabis dependence (n = 1). Two individuals had comorbid diagnoses of alcohol and opioid dependence. Twelve individuals were currently using substances on at least a weekly basis (ten on methadone maintenance). Twenty-one participants had a current DSM-IV diagnosis of a psychiatric disorder; current diagnoses included major depressive disorder (n = 9), anxiety (n = 2) and comorbid depression and anxiety (n = 6).

One individual had a diagnosis of schizoaffective disorder and social phobia, two individuals had diagnoses of depression, anxiety and borderline personality disorder in combination, and another had a diagnosis of schizophrenia.

On the DASS-21, 13 individuals (45%) reported moderate or higher levels of depression; 17 (59%) reported moderate or higher levels of anxiety; and 10 (34%) reported moderate or higher levels of stress. Neurological events included a history of stroke (n = 1), brain hemorrhage (n = 1), Wernicke-Korsakoff Syndrome (n = 1), hydrocephalus (n = 1) and treatment with electroconvulsive therapy (n = 1). Three subjects had a history of seizures and seven had a history of concussion in which they had lost consciousness. Two of these individuals had been hospitalised following these incidents, although a diagnosis of TBI was not documented in the medical notes. Only two individuals in the group (one methadone and one cannabis user) were free from a history of neurological injury, current psychiatric disorder or current co-morbid substance use when those factors were considered in combination

4.4.2. Impairment classification on the NSB

Frequency of impairment on cognitive measures in the SUD group is presented in Table 11. In total, twenty of the individuals (66%) in the SUD group were classified as impaired on the NSB.

A control group was selected to match the individuals classified as impaired on age and education (n = 20). No individual from the control group was classified as impaired based on the domain scores. One individual was classified as impaired on the

Brixton Test, and another two on Letter fluency, however, they did not score below criteria for impairment on other executive function tasks and subsequently were not categorised as impaired in the executive function domain. No individual in the control group was classified as impaired on any scale at the highest cut-scores: on the MMSE at a cut- score of 27, on the MoCA at a cut-score score of 26 or on the ACE-R at the higher cut-off of 88.

The effect of education and age on screening performance was investigated in the total sample (n = 50). Level of education was associated with MMSE total score, r_s (48) =.33, p =.02 but not ACE-R total score, r_s (48) =.23, p =.10 or MoCA total score, r_s (48) =.19, p =.19. Age was not related to MMSE total score, r_s (48) =.-.07, p =.65, ACE-R total score, r_s (48) =.34, p = .82, or MoCA total score, r (48) = -.04, p =.78.

4.4.3. Performance on screening measures

The diagnostic accuracy of the MMSE, ACE-R and MoCA was examined in relation to the absence or presence of cognitive impairment on the NSB. A comparison of the ROC curves for the screening tests is shown in Figure 2. The ACE-R (AUC = .853) and the MoCA (AUC = .841) both had good discriminative ability. Both were superior to the MMSE (AUC = .788), which had fair discriminative ability. Table 12 displays how sensitivity and specificity change with varying cut-off scores. The optimal MoCA cut-score was ≤25, which offered a sensitivity of 75% and specificity of 77%. Higher sensitivity (90%) and a slight reduction in specificity (60%) was obtained at a cut-score of ≤26. The optimal ACE-R cut-score was ≤92 with a sensitivity of 90% and

Table 11

Classification and Frequency of Impairment on Cognitive Measures in the SUD group

Test	Cut-off	Impaired		Total Domains Impaired		
		n	%		n	%
Screening Test						
ACE-R	<88/100[a]	14	47	0	10	33
	<82/100[a]	6	20	1	9	30
Mini Mental State Examination	<27[b]	3	10	2	2	7
	<24[b]	1	3	3	6	20
Montreal Cognitive Assessment	<26[c]	19	63	4	2	7
				5	1	3
Executive Function Tasks				Total > 0	20	67
Digit Span Backwards: Total	≤5th percentile age-adjusted score (SS<6)	4	13			
Letter Fluency: Total	≤1.5 *SD* age, education and gender adjusted score[d]	5	17			
Trails B: Time [a]	≤1.5 *SD* age, education and gender adjusted score[d]	7	23			
Hayling: Total SS	≤5th percentile age-adjusted score	4	13			
Brixton: Total SS	≤5th percentile age-adjusted score	3	10			
Domain Measures						
Executive Battery: Total	Minimum two executive tasks impaired	7	23			
RBANS: Immediate Memory Index	≤1.5 *SD* age and education adjusted score	8	27			
RBANS: Visuospatial Index	≤1.5 *SD* age and education adjusted score	6	20			
RBANS: Language Index	≤1.5 *SD* age and education adjusted score	1	0.3			
RBANS: Attention Index	≤1.5 *SD* age and education adjusted score	8	27			
RBANS: Delayed Memory Index	≤1.5 *SD* age and education adjusted score	11	37			

Note. [a] Mioshi et al.(2006) [b]Folstein et al. (1975) [c]Nasreddine et al. (2005); [d] Heaton et al. (2004)

specificity of 73%. The traditional cut-score of ≤87 offered good specificity (90%) but poor sensitivity (55%).

4.4.4. Agreement between NSB and screening measures

Using a score of ≤ 26 (i.e., cut-score of 27) on the MMSE for cognitive impairment, overall agreement of classification of impairment by the MMSE and the NSB was 66%; chance-corrected agreement (kappa) was 18%. Using a conventional score of ≤23 (i.e., cut-score of 24) overall agreement of classification of impairment was 62%. At the optimal score of ≤28 (i.e., cut-score of 29), overall agreement of classification of impairment by the MMSE and by the NSB was 80%; chance-corrected agreement was 56%. On the ACE-R, overall agreement of classification of impairment by the ACE-R at a score of ≤87 (cut-score of 88) and by the NSB was 78%; chance-corrected agreement was 47%. The optimal score of ≤92 (cut-score of 93) on the ACE-R correctly classified 89% of participants classified as impaired by the NSB, chance-corrected agreement was 60%. On the MoCA, overall agreement of classification of impairment at the score of ≤25 (cut-score of 26) on the MoCA (also the optimal cut-score) to the NSB was 76%; chance-corrected agreement was 52%.

4.4.5. Associations between screening tasks and NSB domains

There was a moderate correlation between total score on the MMSE and ACE-R; r_s (48) =.61, p <.001 and the MMSE and the MoCA, r_s (48) = .51, p = .006, and a strong correlation between the MoCA and the ACE-R, r_s (48) = .81, p <.001. The RBANS: Total was strongly correlated with the MoCA, r(48) = .75, p <.001, and the ACE-R, r_s (48) = .81, p <.001, and moderately correlated with the MMSE, r_s (48) =.38, p = .04.

Table 12

Sensitivity and Specificity for MMSE, MoCA and ACE-R Cut-scores for Cognitive Impairment

Screening Test	≤21	≤22	≤23	≤24	≤25	≤26	≤27	≤28	≤29
MMSE									
Sensitivity, 95% CI	5, 1-25	5, 1-25	5, 1-25	10, 2-32	15, 3-38	15, 3-38	35, 15-59	60, 36-81	85, 62-97
Specificity, 95% CI	100, 88-100	100, 88-100	100, 88-100	100, 88-100	100, 88-100	100, 88-100	100, 88-100	93, 78-99	40, 7-59
Youden Index	5	5	5	10	15	15	35	53	25
% Correctly classified	62	62	62	64	66	66	74	80	73
AUC, 95% CI	.788, .648-.929*								
MoCA									
Sensitivity, 95% CI	35,15-59	55, 32-77	55, 32-77	60, 36-81	75,51-91	90, 68-98	95, 75-99	100, 83-100	100, 83-100
Specificity, 95% CI	97, 83-99	93, 78 – 99	87, 69-96	83, 65-77	77, 58-90	60, 41-77	37, 20-56	17, 6-35	10, 2-27
Youden Index	32	48	42	43	52	50	32	17	10
% Correctly classified	72	78	74	74	76	72	60	50	46
AUC, 95% CI	.841, .730-.951**								
	≤87	≤88	≤89	≤90	≤91	≤92	≤93	≤94	≤95
ACE-R									
Sensitivity, 95% CI	55, 32-77	55, 32-77	55, 32-77	70, 46-88	75, 51-91	90, 68-98	90, 68-98	90, 68-99	100, 83-100
Specificity, 95% CI	90, 73-98	90, 73-98	83, 65-94	77, 58-90	77, 58-90	73, 54-88	53, 34-72	47, 28-66	33, 17-53
Youden Index	45	45	38	47	52	63	43	37	33
% Correctly classified	78	78	72	74	76	89	68	64	60
AUC, 95% CI	.853, .748-.958**								

Note. MMSE: Mini Mental State Examination. MoCA: Montreal Cognitive Assessment. ACE-R: Addenbrooke's Cognitive Examination-Revised; AUC = Receiver Operating Characteristic Area Under Curve; CI = Confidence Interval
*p = .001 **p <.001

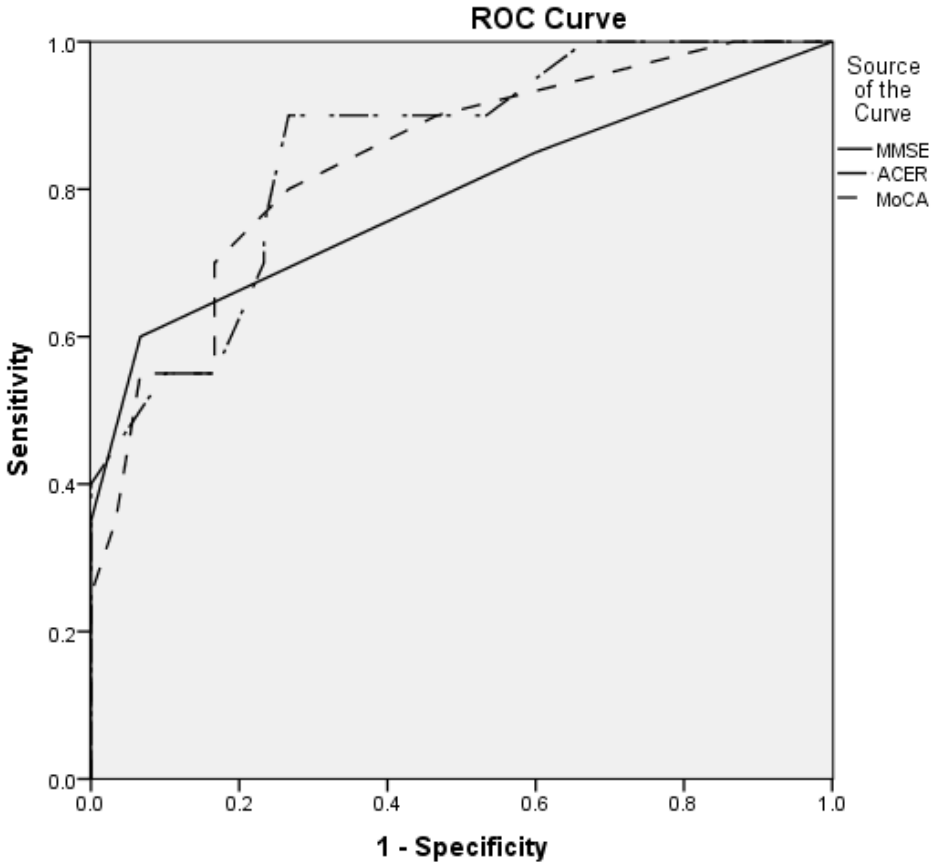

Figure 2. Comparison of the area under the ROC curves for MMSE, ACE-R and MoCA in the total sample

The correspondence between NSB domains and sub-scores on the screening measures in the SUD group is reported in Table 13. NSB indices were small to moderately correlated with corresponding sub-scores on the MoCA and the ACE-R in the Visuospatial, Immediate Memory, Delayed Memory and Executive Domains (r = .37 to .67). The Attention Domain had a small correlation with ACE-R: Attention & Orientation but not with MOCA: Attention & Orientation. The Language domain was not associated with either screening sub-scales, although a strong correlation with ACE-R Fluency was observed.

Table 13

Correlations Between Screening Test Subscores and Neuropsychological Battery Domains

	Neuropsychological Battery Domain					
Screening Test Subscore	Immediate Memory	Visuospatial	Language	Attention	Delayed Memory	Executive
ACE-R: Memory	.48**	.30	.31	.25	.67 **	.50**
ACE-R: Visuospatial	.42**	.59**	.25	.35*	.48*	.64**
ACE-R: Language	.56**	.37*	.23	.42	.40	.41*
ACE-R: Attention/Orientation	.24	.08	.29	.39*	.25	.37*
ACE-R: Fluency	.61**	.44**	.73**	.39*	.68**	.60**
MoCA: Memory	.37*	.22	.45**	.38*	.61**	.51**
MoCA: Visuospatial	.37*	.59**	.30	.40	.34	.46**
MoCA: Language	.36	.14	.16	.53**	.09	.55**
MocA: Attention/Orientation	.18	.16	.28	.16	.30	.24
MoCA: Executive	.42**	.35*	.17	.37**	.49**	.47**

Note. Correlations conducted with Spearman Correlation Coefficient.
* p <.05 level **p<.01

Table 14.

Group Comparisons on Screening Measures

	Controls (n = 20)		SUD- Impaired (n = 20)				
	M	SD	M	SD	t(38)	p	Comparison
Demographics							
Gender (male:female)	14: 6	-	7: 13	-	4.91[a]	.027	Chi-square
Age (years)	52.40	10.77	52.25	11.72	-0.04[b]	.327	T-test
Education (years)	11.90	2.08	11.15	2.66	0.97[b]	.967	T-test
National Adult Reading Test: Predicted Full-Scale IQ	107.00	6.24	103.75	10.76	0.25[b]	.252	T-test
Screening Tests (maximum scores)					*U*		
MMSE (30)	29.45	0.51	27.65	2.21	326	<.001	
Addenbrooke's Cognitive Examination - Revised (100)	95.45	2.24	84.85	7.87	380	<.001	
Attention & Orientation (18)	17.95	0.22	16.95	1.88	263	.045	
Memory (26)	23.90	1.48	20.10	4.30	309	.002	
Fluency (14)	12.70	1.26	10.10	2.38	331	<.001	
Language (26)	25.55	0.51	23.65	2.72	310	.001	
Visuospatial (16)	15.40	0.88	13.55	1.76	327	<.001	
Montreal Cognitive Examination (30)	28.20	1.36	23.15	3.90	-5.47[b]	<.001	T-test
Attention & Orientation (11)	10.80	0.41	9.95	1.88	230	.218	
Memory (5)	23.90	1.48	20.10	4.30	320	<.001	
Executive (5)	4.40	0.75	3.45	1.15	298	.004	
Language (5)	4.70	0.57	4.25	0.85	263	.045	
Visuospatial (4)	3.65	0.67	2.65	0.99	317	<.001	

Note. Mann Whitney Test used for group comparisons unless otherwise specified. One-tailed T-test for screening comparisons
[a] Chi-square test statistic. [b]Student T-test statistic.

4.4.6. Group comparisons of substance group (impaired) and controls

Table 14 presents group performance of the SUD individuals classified as impaired on the NSB (SUD-Imp) compared to the control group There was no significant difference in age, education or premorbid IQ between groups, but they did differ on gender. The control group performed significantly better than the SUD-Imp group on MMSE, ACE-R and the MoCA (p <.005, one-tailed). The SUD-Imp subgroup performed significantly poorer on all domain sub-scores on the MoCA and ACE-R with the exception on Attention & Orientation on both measures and the language subscale on the MoCA.

4.5. Discussion

The aim of the current study was to compare the diagnostic accuracy of three brief cognitive screening measures – the MMSE, ACE-R and the MoCA – in detecting cognitive impairment in a sample of SUD. In total, two-thirds of individuals in the SUD group were classified as impaired on the NSB. The proportion was consistent with the higher end of estimates of cognitive deficits in treatment-seeking individuals (Grohman & Fals-Stewart, 2004; O'Malley et al., 1992). However, this is not surprising considering that individuals with comorbid psychiatric, health and neurological conditions were included in the current study, and one-third of the sample were current users of substances (albeit the majority in a methadone treatment context). It could be expected that some deficits would resolve, at least in part, with abstinence in this sample.

The first hypothesis, that the ACE-R and the MoCA would both provide superior diagnostic accuracy than the MMSE, was supported. Whilst the MMSE demonstrated fair discriminative ability, the MoCA and the ACE-R had superior

ability to distinguish between individuals with and without cognitive impairment. The latter two tests were comparable to one another in discriminatory ability. The discriminative ability of the MoCA as calculated in this present study (AUC = .84) was highly similar to that reported in the two previous studies that have examined its utility in substance users (AUC of .85 to 86; Copersino et al., 2009; Wester, Westhoff, Kessels, & Egger, 2013). Examination of the diagnostic accuracy of screening measures at traditionally defined scores revealed that the use of the traditional cut-score of 26 for classification of impairment on the MMSE resulted in poor overall agreement with the NSB. A cut-score of less than 29 achieved optimal diagnostic accuracy, however this was largely due to excellent specificity at the expense of sensitivity. Only a cut-score of at least 29 achieved a reasonable level of sensitivity (85%). However, at this cut-score, specificity was poor. This confirms the large ceiling effect of the MMSE that has been reported previously (Pendlebury et al., 2010; Pendlebury, Mariz, Bull, Mehta, & Rothwell, 2012).

Comparatively, the ACE-R achieved best overall and change-corrected agreement at an optimal cut-score of 93, at which it correctly classified 89% of individuals. This cut-score, which is higher than the upper cut-score of 88 proposed by Mioshi et al. (2006) in a dementia sample, is consistent with the optimal scores of 93 reported by Pendlebury et al. (2012) and 94 by Komadina et al. (2011) for discrimination of cognitive impairment within their respective stroke and Parkinson's disease populations. It may be that in these specific populations – which differ from primary neurodegenerative illnesses in profile and course of cognitive impairment - a higher threshold is necessary to detect cognitive dysfunction.

Consistent with the second hypothesis, the optimal cut-score for the MoCA for this sample was 26 (a score of 25 or less). This is also the cut-score proposed by

the authors of the MoCA (Nasreddine et al., 2005) and that which is consistent with previous investigations with substance-related cognitive impairment (Wester et al., 2013). At 26, acceptable levels of sensitivity and specificity were achieved. However, a cut-score of 27 offered excellent sensitivity (90%) for lower specificity (60%). This may be a preferred cut-score of choice in the clinical setting, where it may be better to compromise specificity for sensitivity to ensure individuals with cognitive impairment are not missed by the test (Morris, Hacker, & Lincoln, 2012).

The association of domain sub-scores of the MoCA and the ACE-R relative to the domains assessed on the NSB was also examined to provide a measure of criterion validity. Total score on the RBANS was strongly related to total score on the MoCA and the ACE-R, providing initial support for criterion validity. Investigation of individual domains also revealed a reasonable level of association between the NSB indices and performance on memory, visuospatial and executive tasks on both screening measures. However, the attention and language sub-tests correlated less well with the corresponding NSB indices. This could suggest poor criterion validity for these two domains or that classification of subtest items was not optimal. It is possible that differences in performance on items may reflect how items were classified, rather than differences in underlying cognitive ability. For instance, semantic fluency is commonly categorised as a task of frontal lobe functioning, however, involvement of temporal lobe structures is also prominent (Henry & Crawford, 2004). The language index on the R-BANS includes semantic fluency as part of the language index, whilst the ACE-R includes both letter and semantic fluency within an overall fluency sub-score. This was used in this study as a measure of executive function. Thus, whilst attempts were made in this study to maximise comparability of screening and NSB domains, this was not fully achieved. Other

studies have also inconsistently categorised tasks of MoCA into cognitive domains (Ahmed, de Jager, & Wilcock, 2012; Lam et al., 2013). The validation study by Freitas et al. (2012) reported that letter fluency could be aptly placed in either executive or language domains, based on evaluation of regression weights. There is a clear need to establish the cognitive correlates of screening tasks and provide standardised domain classification for these measures if the findings of studies are to be reliably compared.

It is also likely that cognitive load influenced discrepant performance on some measures. Tasks on the screening measures tended to be simpler and shorter than index measures. Crane et al. (2013) suggests that less complex tasks may be less sensitive to subtle brain abnormalities among substance users but as difficulty increases, impairments in performance may emerge. Cognitive load may therefore be an important factor to consider in future comparisons of screening and neuropsychological measures. Furthermore, identification of items on the screening measures that best differentiate impaired and non-impaired substance users may also allow further development and refinement of screening measures specific to this population. Whilst extended investigation of this was beyond the scope of the current study, comparisons of the group of impaired SUD with controls revealed that the language sub-score on the MoCA, and attention and orientation sub-scales on both screening tasks did not differ between groups. Further studies of larger samples that employ regression analyses to identify items that most frequently detect cognitive impairment could provide further insight as to the cognitive deficits that characterise this group and the relevant functions to be assessed when using screening instruments.

4.5.1. Limitations and strengths

It is clear that the present study has a number of limitations. The small number of substance users assessed, in particular the number categorised as cognitively intact, necessitated the need to include control participants in the analyses to ensure that discriminatory ability of the screening measures could be adequately examined. Given that the control group differed significantly from the impaired SUD group on screening performances, application of the results of this study (e.g., cut-scores) to a substance use group population should be made with caution. Furthermore, the substance and control groups significantly differed on gender characteristics, with a higher proportion of males in the SUD group. The impact of gender on performance on the ACE-R and the MoCA has not been examined in great detail, however some studies have indicated a relationship of gender to ACE-R total score, although directionality is not clear (Amaral-Carvalho & Caramelli, 2012; Dos Santos Kawata et al., 2012). Whilst our ability to control for the effect of gender was impeded by limited access to male control participants and the use of non-parametric analyses, it is possible that this may have influenced group results.

Another limitation was that the influence of age and education on screening measure scores was not thoroughly examined. Previous studies have shown significant effects on age and education (Dos Santos Kawata et al., 2012; Komadina et al., 2011; Konstantinopoulou et al., 2011; Kwak et al., 2010), although the majority of these findings have been reported by studies in which the validity of translations of the ACE-R in other languages has been examined. This current study did not find a relationship between age or education to ACE-R score, however it is possible that the inclusion of controls, who largely performed at ceiling on screening measures, impacted this outcome. Alternatively, the MoCA provides an education

adjustment, which was adopted in this present study, due to recognition by the authors that people with lower levels of education tend score lower on this measure (Nasreddine et al., 2005). However, it has been reported that this can cause a detrimental effect on sensitivity with only a slight increase in specificity (Gagnon et al., 2013). Clinical judgment of premorbid functioning is also a factor that should be considered in interpretation of total score even in the presence of education correction, as in previous generations, level of education may more reflect limited opportunity rather than low premorbid intelligence (Gagnon et al., 2013). Whilst it was beyond the scope of this study to examine the influence of these factors, it is clear their effects need to be systematically examined in larger samples, and that development of norms appropriate for different age and education levels are needed to ensure diagnostic accuracy. Furthermore, the current sample represented a relatively homogenous group of individuals, as those with limited English ability were excluded. It is clear that choice of screening measures needs to be made in relation to the cultural context of the individual, and that formation of screening tools and items specific to the population of interest is necessary for a valid evaluation of cognitive status (Dingwall, Pinkerton, & Lindeman, 2013; Storey, 2004).

One last limitation of the present study related to the use of an abbreviated neuropsychological battery – the RBANS – as the criterion measure for cognitive impairment. The RBANS has established convergent validity with longer neuropsychological measures (Gontkovsky, Hillary, & Scott, 2002; Randolph et al., 1998) and has demonstrated good clinical utility within substance use populations (deVille, Baker, Lewin, Bucci, & Loughland, 2011; Green et al., 2010). It was chosen to provide a time efficacious yet comprehensive measure of a range of cognitive domains. However, a comprehensive neuropsychological battery remains

the gold standard for cognitive assessment and further studies should investigate the validity of screening measures relative to this standard.

The strength of this study was the inclusive approach that was taken to participation, which maximises external validity. It should be reiterated that this study was not designed to diagnose cognitive impairment; the aim was to examine the proficiency of screening tools in detecting cognitive impairment at the point of assessment. The main finding of this study was that the MoCA and ACE-R provided better diagnostic accuracy than the MMSE within a substance-use cohort. Choice of which measure is preferential is dependent on the clinical context – such as preference for sensitivity or specificity, or time constraints. The MoCA is a briefer measure which may better suit the needs of staff in a SUD setting, however the ACE-R may be preferential in a memory-clinic setting, as it includes a larger number of language components sensitive to naming and language deficits that are often found in neurodegenerative disorders. A revision of the ACE-R, the ACE-III (Hsieh, Schubert, Hoon, Mioshi, & Hodges, 2013), has recently been released and the comparability of the two measures remains to be determined.

It is clear that the findings of this study are only preliminary. Gifford and Cummings (1999) outline methodological standards that should be reported for dementia screening tools. These include measures of reliability and validity, including calculation of ratios based on base ratios to assist with clinical decision-making (e.g., positive predictive values). As the base rate of cognitive impairment within this study population is not known, these calculations were not conducted. Furthermore, the reliability of these screening measures within this specific population – a critical feature if repeat testing is required – is not established. Further studies should seek to determine the prevalence of cognitive impairment within

substance using populations and further examine the psychometrics of screening tools if the most appropriate test for cognitive screening within the substance use population is to be established.

CHAPTER FIVE

General conclusions and directions for future research

5. General conclusions and directions for future research

The research detailed in the current thesis was conducted in order to further knowledge regarding the nature of ARCI. Three specific lines of investigation were undertaken. A systematic review was conducted in order to compare the profile of cognitive deficits characterising KS and ARD with that typifying dementia disorders and matched controls groups, to assist with differential diagnosis at a clinical level. An empirical study was then undertaken to establish the cognitive profile of treatment seeking individuals with AUD, including those with comorbid conditions. Lastly, the diagnostic accuracy of two screening measures in detection of cognitive impairment within a larger population of substance users was examined.

5.1. Methodological weaknesses in ARBD research

The systematic review presented in Chapter 2 revealed significant heterogeneity in methodological approaches to investigate the cognitive syndromes of ARD and KS relative to other dementia syndromes. Researchers varied significantly in their use of diagnostic criteria, inclusion or exclusion of groups with psychiatric, neurological and substance use comorbidities, and tasks selected to assess cognitive functioning. In addition, the manner in which drinking history was reported differed considerably between studies. Terminology used to describe drinking history was often vague without specific reference to the quantities of alcohol consumed and no information about length of abstinence was reported in a number of studies. These limitations significantly restrict comparability of study results and may have impacted on the

validity of cognitive findings, particularly if the role of abstinence was not considered. While the difficulty of obtaining an accurate self-report of drinking quantities is well-recognised in ARBD research, establishment of minimum periods of abstinence required for a diagnosis and quantitative limits for definitions of heavy drinking would help clarify the relationship between drinking and cognitive outcomes. This standardisation has previously been proposed by Oslin, Atkinson, Smith, and Hendrie (1998), however, has not yet been fully adopted in ARBD research.

The results of the review also demonstrated the influence of choice of diagnostic criteria and exclusion criteria on study outcomes. The exclusion of individuals with a history of neurological signs from ARD studies and exclusion of individuals with global cognitive impairment from KS studies served to create two distinct syndrome groups with specific cognitive profiles. This is in spite of clinical and pathological evidence that suggests an overlap in clinical presentations and underlying pathology between KS and ARD. The new DSM-V criteria (American Psychiatric Association, 2013) for 'alcohol-induced neurocognitive disorders' encourages a more inclusive approach and the term 'alcohol-related brain damage' is already preferentially used over ARD/KS in many countries (Jauhar & Smith, 2009). These terminologies appear to have good clinical utility in describing the heterogeneity in clinical presentations and cognitive impairment related to alcohol use. Given the recent introduction of such terms, it is clear that their value in a research setting needs further investigation.

5.2. The profile of alcohol-related cognitive disorders

Two distinct investigations were undertaken to evaluate the characteristics of alcohol-related cognitive impairment; a systematic review with the aim of evaluating the cognitive profile of ARD and KS relative to other dementia syndrome and control groups (Chapter 2) and an investigation of the cognitive profile of a group of individuals with AUD (Chapter 3). ARD groups were best characterised by poor performance on visuoconstructional and delayed memory measures, with improved performance on verbal memory recognition tasks compared to their free delayed recall. Executive dysfunction and delayed memory disturbance was observed in the KS group relative to the control group. In the second study, the AUD sample was most consistently impaired on tasks assessing delayed memory. Delayed recall of a narrative and of a complex figure, in addition to semantic fluency, were among the tasks that best distinguished the AUD group from healthy controls. Recognition memory for a verbal task and confrontational naming ability were preserved. The significant relationships that were found between duration of heaviest drinking period and performance on memory and visuoconstructional tasks provide further support for the impact of alcohol on these cognitive abilities. While the results of the study in Chapter 3 were not entirely consistent with the profile of cognitive function that has been reported to typify alcohol-related cognitive disorders (e.g., intact conceptual problem-solving), this may be due to variability in length of abstinence and the multiple comorbidities which accompanied individuals in the sample.

In summary, the results of these two investigations indicate the importance of evaluation of memory, visuoconstructional and executive abilities in assessment of

alcohol-related cognitive disorders. These abilities were most frequently impaired, whilst confrontational naming and verbal recognition memory tasks were relatively preserved. This information can be used to assist with differential diagnosis in the clinical setting. Whilst these findings need further replication, this research builds upon previous investigations of ARCI, which have largely reported similar findings. In addition, the results from Chapter 3, which indicated a relationship between length of time of heaviest drinking period and performance on delayed memory measures despite the inclusion of individuals with multiple comorbidities, can be used to encourage researchers to extend inclusion criteria in future research studies. Specifically, longitudinal studies which evaluate the impact of drinking, neurological, psychiatric and health variables on cognitive performance and treatment outcome are necessary in future research. As individual factors such as age, gender, premorbid intelligence and nutritional intake can significantly influence the outcome of heavy alcohol consumption, cross-sectional analyses are insufficient to draw clear conclusions about the key causes of ARBD. These longitudinal studies are well suited to a treatment setting, where the impact of risk factors can be evaluated at the start, during and following a course of treatment.

5.3. The utility of the MMSE, the MoCA and the ACE-R in a substance use context

In Chapter 4, the diagnostic accuracy of three cognitive screening measures in detecting cognitive impairment in a sample of substance users was examined. The results support the proposal that that screening instruments need to be validated in the population in which they are intended to be used. The ACE-R and the MoCA tests had superior

discriminative qualities than the MMSE in classification of cognitive impairment. Cut-scores of 26 on the MoCA and 93 on the ACE-R provided the best diagnostic accuracy and acceptable levels of sensitivity and specificity (75% and 77% on the MoCA, 90% and 73% on the ACE-R, respectively). Whilst further investigation of the reliability and validity of these measures in samples of substance use is necessary, the current research provides initial support for the use of these measures in preference to the MMSE in screening for cognitive impairment in substance use populations. These results both extend the work of Copersino et al. (2009), who first assessed the validity of the MoCA in substance use context and provide novel findings, given that as far as is known the utility of the ACE-R in a substance use context has not been investigated

5.4. Strengths and limitations of the current research

The main strength of the empirical studies reported in the present thesis was the ecological validity of study results; the sample in both studies included individuals with a range of neurological, psychiatric and health conditions, which reflects the characteristics of AUD samples in clinical practice. In addition, the cognitive tests used have good evidence for validity and reliability and control groups were well matched on age, education and premorbid IQ.

The limitations of the research are discussed in detail in the included studies. Limitations common to both empirical studies included the small sample size and the relatively homogenous cultural background of participants. Given these restrictions, it cannot be assumed that the results of these two studies generalise to other clinical or community samples. Furthermore, the comorbidities that individuals in these studies

presented with were primarily affective disorders. Given that the evidence is weak for a compound effect of ARCI and mood disorders, it is possible that increased rates of psychiatric and neurological conditions would have modified study outcomes. Future studies that investigate the individual and compound effects of these influences on ARCI are necessary before any definitive conclusion regarding such relationships can be reached.

A further limitation was the use of an abbreviated neuropsychological battery – the RBANS - as the main measure for categorisation of cognitive impairment. The RBANS has established convergent validity with traditional neuropsychological measures and has been demonstrated to have good sensitivity to cognitive impairment in substance using populations. However, a comprehensive neuropsychological assessment remains the gold standard for cognitive assessment and future studies should examine the equivalence of screening measures relative to this standard. In addition, the research comprising this thesis did not investigate the influence of age, gender or education on performance on cognitive measures. As these are factors that have been shown to mediate the outcome of ARBD, further research that examines the impact of these variables on performance on screening measures and any interaction with comorbid characteristics on cognitive outcome, would extend the knowledge base on mediating variables in alcohol-related cognitive impairment.

One criticism that could be levelled at the empirical studies is the inclusion of individuals who were currently using substances or early in abstinence. It should be emphasised that the purpose of the two studies was not to determine causality of cognitive impairment or assign a permanent status of cognitive impairment to

individuals. Rather, the intent was to document cognitive status and evaluate the accuracy of screening instruments in detection of cognitive impairment. Whether or not to conduct a cognitive assessment when patients continue to drink also reflects a dilemma faced by clinicians. There are no established guidelines for the timing of cognitive assessment in substance use disorders, which is reflected in the variability in timing of assessments reported by researchers. Cognitive assessment is typically not conducted within the acute stages of intoxication and withdrawal, as these conditions can exacerbate cognitive deficits. Moreover, assessment is often not practical due to side-effects such as physical symptoms and behavioural disturbances (Mayo-Smith et al., 2004). Whilst further clarification of the course of cognitive recovery in alcohol-related cognitive disorders is necessary, assessment of cognition on an ongoing basis from early in the treatment process will allow any improvement, stabilisation or deterioration to be detected (Ridley, Draper, & Withall, 2013). Clear documentation regarding intermediate alcohol use, medications, and health events over this period will clearly enhance clinical judgement of influences on these performances.

5.5. Recommendations from research

In summary, the research within this thesis has demonstrated a significant need for use of consistent and thorough methodological approaches in alcohol-related cognitive research. This includes consistent and thorough evaluations of past neurological, psychiatric, nutritional and substance use history at point of assessment and on follow-up; consistent adoption of the same terminology and criteria for diagnosis. The use of 'alcohol-induced neurocognitive impairment' from the DSM-5 (American Psychiatric

Association, 2013) as a diagnostic title is recommended in order to move towards consistent labelling of cognitive disorders relating to alcohol use, without the stigma of a dementia title. In addition, neuropsychological evaluation of, in particular, memory, visuospatial abilities, and executive functions in alcohol-related disorders should be assessed both by screening measures and in more extensive neuropsychological batteries, given the increased likelihood of these abilities being affected by alcohol intake. The results of Chapter 4 indicate that the MMSE performs poorly as a screening tool for cognitive impairment within the substance use context, and that the ACE-R and MoCA provide viable alternatives for clinical use. The research also has promoted the need to consider the impact of other psychiatric, neurological and health comorbidities in alcohol-related research. Until this is achieved, the applicability of findings regarding the profile and nature of alcohol-related cognitive impairment to the clinical context is only limited.

CHAPTER SIX

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APPENDIX A

University of Wollongong Human Ethics Committee and Macquarie University Human Research Ethics Committee approval letters

UNIVERSITY OF WOLLONGONG

AMENDMENT APPROVAL - ISLHD

In reply please quote: HE11/007

Further Enquiries Phone: 4221 3386

30 January 2013

Professor Brian Draper
C/- Ms Nicole Denham
Research Associate
Dementia Collaborative Research Centre
Room 304, Level 1 AGSM Building
University of New South Wales
SYDNEY NSW 2052

Dear Professor Draper,

I am pleased to advise that amendments dated 18 January and 22 January 2013 to the following Human Research Ethics application have been **approved.**

Ethics Number:	HE11/007
AuRED Number:	HREC/11/WGONG/4
Project Title:	Improving Service Delivery for Early Onset Memory and Related Disorder: The INSPIRED Study
Name of Researcher/s:	Professor Brian Draper, Dr Adrienne Withall, Professor Robert Cumming, A/Professor Julian Trollor, Dr Clement Loy, A/Professor Susan Quine, Professor Bruce Brew, Professor Henry Brodaty, Professor John Hodges, A/Professor Nicholas Lintzeris, A/Professor Chris Poulos, Professor Perminder Sachdev, A/Professor Peter Gonski, Ms Nikki Ridley, Dorinda Chew, Ms Lauren Keppler, Ms Colleen McKinnon, Christine Metusela, Ms Fiona White; Ms Nicole Denham;Dr James Oldham; DrAbdullah Demirkol
Date for Renewal:	10 April 2013
Amendment Approval Date:	29 January 2013
Amendments Approved:	1. Amendment letter dated 18 January 2013 2. Amendment application 3. Description of Proposed Measures for INSPIRED Sub-

Study

4. Participant Information Sheet for People Living With Younger Onset Memory and Related Disorders v. 18 January 2013

5. Participant Consent Form for People Living With Younger Onset Memory and Related Disorders v. 18 January 2013

6. Revocation of Consent for People Living With Younger Onset Memory and Related Disorders v. 18 January 2013

7. Participant Information Sheet for Supporters, Family and Carers of People Living With Younger Onset Memory and Related Disorders v. 18 January 2013

8. Participant Consent Form for Supporters, Family and Carers of People Living With Younger Onset Memory and Related Disorders v. 18 January 2013

9. Revocation of Consent for Supporters, Family and Carers of People Living With Younger Onset Memory and Related Disorders v. 18 January 2013

10. Subject referenced study amendment text inclusion in Southern Courier's free volunteer listing: email dated 22 January 2013; amendment application and text Form 13-01-22 volunteer listing

Please remember that in addition to reporting proposed changes to your research protocol, the HREC requires that researchers immediately report:

- serious or unexpected adverse effects on participants
- unforseen events that might affect continued ethical acceptability of the project.

The University of Wollongong/Illawarra Shoalhaven Local Health District Health and Medical HREC is constituted and functions in accordance with the NHMRC *National Statement on Ethical Conduct in Human Research.*

A condition of approval by the HREC is the submission of a progress report annually and a final report on completion of your project. The progress report template is available at http://www.uow.edu.au/research/rso/ethics/UOW009385.html. This report must be completed, signed by the appropriate Head of School and returned to the Research Services Office prior to the expiry date.

If you have any queries regarding the HREC review process, please contact the Ethics Unit on phone 4221 3386 or email rso-ethics@uow.edu.au.

A copy of this advice has been forwarded to the ISLHD for their records.

UNIVERSITY OF WOLLONGONG

Yours sincerely,

Associate Professor Sarah Ferber
Chair, UOW & ISLHD Health and Medical
Human Research Ethics Committee

cc: Governance Officer, Research Directorate, ISLHD

Ethics Unit, Research Services Office
University of Wollongong NSW 2522 Australia
Telephone (02) 4221 3386 Facsimile (02) 4221 4338

External Approval Noted- Batchelor (Ethics Ref: 5201200044)

Ethics Secretariat (ethics.secretariat@mq.edu.au) Add to contacts 14/02/2012
To: Dr Jennifer Batchelor
Cc: Miss Nicole Joy Ridley

Dear Dr Batchelor

Re: "The neuropsychological profile of alcohol-related dementia"

The above application was considered by the Executive of the Human Research Ethics Committee. In accordance with section 5.5 of the National Statement on Ethical Conduct in Human Research (2007) the Executive noted the final approval from UNSW and your right to proceed under their authority.

Please do not hesitate to contact the Ethics Secretariat if you have any questions or concerns.

Please do not hesitate to contact the Ethics Secretariat at the address below, if you require a hard copy letter of the above notification.

Please retain a copy of this email as this is your official notification of external approval being noted.

Yours sincerely

Dr Karolyn White
Director of Research Ethics
Chair, Human Research Ethics Committee

Re: Ethics Ref: 5201200044: Amendment Notification

Next

Ethics Secretariat (ethics.secretariat@mq.edu.au) Add to contacts 19/02/2013
To: Nikki Ridley
Cc: Jennifer Batchelor

Dear Nikki

Thank you for your email and amendments approved by the University of Wollongong and the Illawarra Shoalhaven Local Health District Health and Medical HREC. These amendments have been accepted.

Please do not hesitate to contact me if you have any questions.

Kind regards
Fran

APPENDIX B

Summary of extracted data from studies included in the Systematic Review

Part A: Comparisons of ARD and dementia groups on neuropsychological measures

Authors	Participants	Age (A) % Male (G) Education (E)	Tests used	Results
Bigler (1995) QR: 8	ARD: 6 AD: 17 VaD: 15 CON: 16	ARD: A = 68 G = 83 E = 10 AD: A = 71 G = 29 E = 13 MID: A =71 G = 40 E = 12 CON: A = 70 G = 25 E = 13	WAIS-R WMS Design Fluency Letter Fluency	Patient groups performed worse than control: *WAIS-R*: VIQ, PIQ, FSIQ; *WMS*: MQ Patient groups performed same as each other and controls: *Designs*: Total, Perseverations Patient groups performed same as each other, but worse than controls on: *Designs:* Novel designs; *Letter Fluency*
Munro (2001) QR: 11	ARD: 10 AD: 11 ALC: 29 CON: 20	ARD: A = 70 G = 90 E = 12 AD: A = 74 G = 36 E = 12 ALC: A = 65 G = 90 E = 12 CON: A = 70 G = 45 E = 14	MMSE CERAD: 15-item BNT Category Fluency (clothing) Word list: Total, Delay Figure: Copy, Delay Trails A & B Clock Drawing CVLT PRLT	ARD group only performed worse than controls on: *Figure:* Copy*; Clock Drawing* ARD and AD performed same as each other, worse than controls on: *MMSE; Word list:* total, delay; *Figure:* delay; *Trails A*: Time; *CVLT:* Total trials 1-5, cued recall, intrusions AD only performed worse than controls: *15-item BNT; Category Fluency* AD group performed worse than ARD, controls on: *CVLT:* discrimination index No differences between groups on: *Trails A:* errors; *Trails B:* time, errors; *PRLT*
Saxton (1999) QR:10	ARD: 7 AD: 5 ALC: 26 CON: 21	ARD & ALC: A = 64 G = 88 AD: A = 75 G = 40 CON: A = 69 G = 52	MMSE Trails A & B Clock Drawing BNT Fluency: Animals Letter Fluency ROCF: Copy, Immediate, Delay WCST: Categories	ARD group only performed worse than controls on: *Clock Drawing* ARD and AD performed same as each other, worse than controls on: *Trails A, Letter Fluency, ROCF:* Immediate AD performed worse than ARD, who were both worse than controls: *MMSE, Category Fluency, ROCF:* Delay AD only performed worse than controls on: *BNT; ROCF:* Copy AD group performed worse than ARD, controls on: *Trails B: Time* No differences between groups on: *WCST*

Saxton (2000) QR: 12	ARD: 10 AD: 9 ALC: 29 CON: 15	ARD: A = 70 G = 90 E = 12 AD: A = 73 G = 50 E = 12 ALC: A = 65 G = 90 E = 12 CON: A = 71 G = 53 E = 13	MMSE NART-R CERAD: Word list: Total, Delay Figure: Copy, Delay Category Fluency (clothing) 15-item BNT Trails A & B Clock WAIS-R: Information CVLT BNT Fluency: Animals, FAS Token Test ROCF BVF Recognition Memory Test: Words, Faces WCST: Categories Grooved Pegboard	ARD group performed worse than controls only on: *Figure:* copy*, Clock, Fluency:* FAS *Grooved Pegboard:* Dominant, Non-dominant ARD, AD performed same as each other, worse than controls: *MMSE, Word list:* Delay*, Figure:* Delay*, CVLT:* Total trails 1-5, Delayed recall, *ROCF:* Immediate, Delayed*, BVF, Recognition Memory:* Faces AD worse than ARD, who were worse than controls on: *Word list:* Total AD performed worse than controls only on: *15-item BNT: Category Fluency:* Clothing*, Trails B:* Time*, WAIS- Information, ROCF:* Copy AD group performed worse than ARD, controls on: *Trails A; BNT; Animal Fluency; CVLT:* Discrimination index; *Recognition Memory:* Words No differences between groups on *NART, Token test, WCST;* Categories
Schmidt (2005) QR: 9	ARD: 14 AD: 15 VAD: 13 CON: 20	ARD: A = 80 G = 50 E = 12 AD: A = 78 G = 27 E = 12 VAD: A = 80 G = 23 E = 12 CON A = 76 G = 30 E = 14	MMSE Mental Control Clock Drawing Boston Naming Task Similarities Verbal Learning Verbal Recall Verbal Recognition	No difference between groups: *MMSE; Similarities, Boston Naming Task; Verbal Learning; Verbal Recall* ARD no different than VaD on any measure ARD performed worse than AD on: *Mental Control; Clock Drawing* AD performed worse than ARD on: *Verbal Recognition* No direct comparisons with controls (control scores used to form z-scores); ARD -1.5 *SD* below controls on all measures

Note. Age = mean age. E = mean years education. Only tests administered to and differences relating to the question of interest (between dementia groups and/or controls are reported. Test results only reported if statistical comparisons between groups reported. QR = Quality Rating Score; ARD = Alcohol Related Dementia; AD = Alzheimer's Disease; VaD = Vascular Dementia; ALC = Individuals with alcohol dependence; CON = Control group; WAIS-R = Wechsler Adult Intelligence Scale Revised; WMS = Wechsler Memory Scale; MMSE = Mini Mental State Examination; CERAD = Consortium to Establish a Registry for Alzheimer's Disease Battery; BNT; Boston Naming Test; CVLT = California Verbal Learning Test; PRLT = Philadelphia Repeatable Verbal Learning Test; ROCF = Rey Osterrieth Complex Figure; WCST = Wisconsin Card Sorting Test; NART-R = National Adult Reading Test Revised; BVT = Benton Visual Form Discrimination Test

Part B: Comparisons of KS and dementia groups on neuropsychological measures

Authors	Participants	Age (A) % Male (G) Education (E)	Tests used	Results
Brand (2003) QR: 8	KS: 50 AD: 50 CON: 50	KS A = 56 G = 64 E = 9 AD: A = 68 G = 50 E = 10 CON: A = 65 G = 38 E = 10	MMSE CDR Memo: Imm, Delay Digit Span Corsi's Block Span CERAD: Copy (AD) RCF: copy, delay (KS) Letter Fluency AAT (AD only) FWT: Words, Colours, Interference, HAWIE-R TKS	Patient groups performed same as each other, worse than controls on: *Memo*: Delay AD performed worse than KS on: *MMSE, CDR* AD performed worse than KS, who performed worse than controls on: *Memo*: Immediate; *Letter Fluency; HAWIE-R:* Information, Digit Span; Corsi's Block Span; FWT: Word, Colours, Interference; TKS
Dirksen (2001) QR: 13	KS: 9 ALC: 28 PD: 18 ACoA: 4 CON: 70	KS: A = 72 G = 89 E = 13 ALC: A = 57 G = 75 E = 15 PD: A = 63 G = 36 E = 18 ACoA A = 64 G = 0 E = 12 CON: A = 56 G = 31 E = 16	MMSE WAIS-III WMS- III OA Task WCST Letter Fluency TMT- Part B	Different control subgroups were generated for each subset of groups (ALC & KS, ACoA, PD); no direct comparisons between dementia groups KS performed worse than controls on: *OA; WCST:* Peseverative errors, Categories; *Letter Fluency*; *Trails B* PD performed worse than controls on: *OA; WCST:* Peseverative errors, Categories AcoA performed worse than controls on: *OA*; *WCST:* Peseverative errors

Fama (2004) QR: 8	KS: 5 AD: 8 CON: 24	KS: A = 64 E = 16 AD: A = 70 E = 16 CON: A = 65 E = 17	NART MMSE WRMT WMS-R WAIS-R: Vocab, Picture Arrangement BNT- Modified WCST PCT: Candidate Recall Candidate Recog. Election Year Recog. Candidate Pair Recog. Photo Naming Candidate Sequencing	Patient groups performed same as each other, worse than controls: *WRMT:* Faces; *WMS-R:* Verbal, Visual, General, Delayed Memory I Indexes; *WAIS-R:* Picture Arrangement; Ca*ndidate Recall, Candidate Pair Recognition; Photo Naming, Candidate Sequencing* KS performed worse than AD, NC: *WCST:* Perseverative errors AD performed worse than KS, who were worse than CON: *MMSE; WRMT:* Words; *WMS-R:* Logical Memory; *WAIS-R:* Vocab *WCST:* Categories; *Candidate Recognition* AD performed worse than controls only: *NART, WMS-R*: Attention Index, BNT, *Election Year Recog.*
Konishi (2009) QR: 3	KS: 10 AD: 7 CON: 10	KS: A = 83 G = 90 AD: A = 85 G = 100 CON: A = 86 G = 100	MMSE MoCA: Total, Copy, Clock Drawing; Simple Reaction Time Choice Reaction Time WAIS: Digit Span, Digit Symbol WMS: LNS BCSR RMT Picture Naming Word Meaning Scenes Semantic Decision Faces BNT- 15 item Stroop Letter Fluency Animals CET Mazes	KS performed worse than AD, CON: *WAIS:* Digit Span Backward KS group only performed worse than controls on: *Simple RT; WAIS:* Digit Span Forward; *Semantic Decision; Mazes* KS and AD performed same as each other, worse than controls; *MMSE; MoCA:* Total, Clock*; BCSR:* Free recall, Delayed recall; *RMT:* Early, Recent; *Picture Naming; Word Meaning; Scenes, Faces, BNT, Stroop:* Words, *Stroop:* Colors, Words; *CET; WAIS:* Digit Symbol; *WMS:* LNS, KS performed worse than AD, who were worse than CON: *Stroop:* Dots AD performed worse than KS, who was worse than CON: *BCSR:* Cued, Free No differences between groups on: *Copy*

Weintraub (2000) QR: 3	KS: 7 AD: 21 CON: 14	KS: AD: CON:	A = 62 E = 10 A = 66 E = 13 A = 71 E = 14	BNT Three Words – Three Shapes: Copy, Learning, Incidental Recall, Acquisition, Delayed Recall, Recognition	KS, AD performed same, worse than CON: *Incidental Recall; Learning; Delayed Recall* (words, shapes); *Recognition* AD performed worse than CON only: *BNT; Acquisition:* Shapes No differences between groups: *Copy, Acquisition:* Words

Note. No report of age demographics in the Konishi (2009) study. No report of gender demographics in the Weintraub (2000) study. Age = mean age. E = mean years education. Only tests administered to and differences relating to the question of interest (between dementia groups and/or controls are reported. Test results only reported if statistical comparisons between groups reported. QR = Quality Rating Score; KS = Korsakoff Syndrome; AD = Alzheimer's Disease; CON = Control group; ALC = Individuals with alcohol dependence; PD = Parkinson's Disease; ACoA = Individuals with rupture of the anterior communicating artery; MMSE = Mini Mental State Examination; CDR = Clinical Dementia Rating Scale; CERAD = Consortium to Establish a Registry for Alzheimer's Disease Battery; AAT = Aachener Aphasie Test; FWT = Colour Word Test (German); HAWIE-R = German Version of the WAIS-R; TKS = Cognitive Estimation Test (German); WAIS-III = Wechsler Adult Intelligence Scale Third Edition; WMS-III = Wechsler Memory Scale Third Edition; OA Task = Object Alternation Task; WCST = Wisconsin Card Sorting Test; TMT = Trail Making Test; NART = National Adult Reading Test; WRMT = Warrington Recognition Memory Test; WMS-R= Wechsler Memory Scale Revised; WAIS-R = Wechsler Adult Intelligence Scale Revised; BNT = Boston Naming Test; PCT = Presidential Candidates Test; MoCA = Montreal Cognitive Assessment; WAIS Wechsler Adult Intelligence Scale; WMS = Wechsler Memory Scale; BCRS = Buschke Cute Selective Reminding; RMT = Retrograde Memory Test; CET = Cognitive Estimation Test