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Cognitive deficits in alcoholism

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Résumé

Contexte : Les répercussions de l'alcool au niveau des fonctions cognitives sont bien documentées. Certaines hypothèses suggèrent que l'alcool affecte des fonctions cognitives spécifiques alors que d'autres avancent l'hypothèse de déficits diffus. Cependant, une ambigüité persiste concernant quelles fonctions cognitives sont le plus touchées par l'alcool, et à quel point la durée d'abstinence affecte la récupération cognitive. Nous avons procédé à une des premières méta-analyses qui s'intéresse aux différentes fonctions cognitives touchées par la consommation problématique d'alcool et à la durée d'abstinence requise pour une récupération au niveau des cognitions. **Méthodes :** Une recherche de la littérature a permis d'identifier 62 études évaluant les cognitions chez les personnes présentant des troubles liés à l'utilisation d'alcool. Les estimations de la taille d'effet ont été calculées avec la Comprehensive Meta Analysis –V2 pour les 12 domaines cognitifs suivants : quotient intellectuel, fluidité verbale/langage, vitesse de traitement de l'information, mémoire de travail, attention, résolution de problème/fonctions exécutives, inhibition/impulsivité, apprentissage verbal, mémoire verbale, apprentissage visuel, mémoire visuelle, habiletés visuo-spatiales. Parmi ces 12 domaines cognitifs, 3 estimations de la taille d'effet ont été calculées selon les durées d'abstinences suivantes : court- (<1 mois), moyen- (2 à 12 mois) et long- (>1 an) termes. **Résultats :** Les résultats ont révélé la présence de dysfonctions modérées dans 11 domaines cognitifs durant l'abstinence à court terme, et dans 10 domaines cognitifs pour le moyen-terme. Des dysfonctions

cognitives minimales furent notées durant l'abstinence à long-terme. **Conclusions :** Ces résultats révèlent des déficits cognitifs significatifs et diffus durant la première année d'abstinence. Déficits qui se normalisent après un an. Ces résultats soutiennent l'hypothèse de déficits cognitifs diffus reliés à l'alcoolisme et suggèrent que la cognition devrait faire partie intégrante du traitement d'alcoolisme.

Mots-clés : alcoolisme, déficits cognitifs, méta-analyse

Abstract

Background: The cognitive repercussions of alcoholism are well documented. However, the literature remains somewhat ambiguous with which distinct cognitive functions are more susceptible to impairment in alcoholism and to how duration of abstinence affects cognitive recovery. Some theories claim alcohol negatively affects specific cognitive functions while others assert that deficits are more diffuse in nature. We performed the first meta-analysis to examine cognition in alcoholism and how duration of abstinence affects cognitive recovery. **Methods:** A literature search yielded 62 studies assessing cognitive dysfunction among alcoholics. Effect size estimates were calculated using the Comprehensive Meta-Analysis V2, for the following 12 cognitive domains: intelligence quotient, verbal fluency/language, speed of processing, working memory, attention, problem solving/executive functions, inhibition/impulsivity, verbal learning, verbal memory, visual learning, visual memory, and visuo-spatial abilities. Within these 12 domains, 3 effect size estimates were calculated based on abstinence duration and partitioned into short- (<1 month), intermediate- (2 to 12 months) and long- (>1 year) term abstinence. **Results:** Findings revealed moderate impairment across 11 cognitive domains during short term abstinence with moderate impairment across 10 domains during intermediate term abstinence, and overall small effect size estimates during long term abstinence. **Conclusions:** Results suggest significant cognitive dysfunction during the first year following abstinence from

alcohol and that long term abstinence yields near normalisation of cognitive function. These findings support the diffuse brain deficits hypothesis. Clinical implications suggest that cognition may need to be considered an integral part of the treatment of alcoholism.

Key words: Alcoholism – cognitive deficits – meta-analysis

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CI: Confidence interval

CLAT: Conceptual levels analogies test

CMA-v2: Comprehensive meta-analysis version 2

COWAT: Controlled oral word association test

CVLT: California verbal learning test

DA: Dopamine

DSM (III, III-TR, IV, IV-TR): Diagnostic and statistical manual of mental disorders, third edition through fourth edition, text revision

E.S.: Effect size estimate

FCSRT: Free and cued selective reminding task

GABA: Gamma-aminobutyric acid

ICD-10: International statistical classification of diseases and health related problems, 10^{th} Revision

IGT: Iowa gambling task

IQ: Intelligence quotient

ITA: Intermediate term abstinence

LTA: Long term abstinence

MDMA: 3.4-methylenedioxymethamphetamine

N: Sum of alcoholics and healthy controls

NMDA: N-methyl-D-aspartate

ROCF: Rey-osterrieth complex figure

SSRT: Stop-signal reaction time

STA: Short term abstinence

TMT-A: Trail making test – A

TMT-B: Trail making test – B

WAIS: Wechsler adult intelligence scale

WCST: Wisconsin card sorting test

WMS: Wechsler memory scale

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1. Introduction

1.1 Costs and Consequences of Alcoholism

Globally, alcohol is one of the most commonly consumed psychoactive substances, closely trailing behind caffeine (Johnson-Kozlow et al 2002; Rehm & Patra 2010). While most individuals consume alcohol in moderation, approximately 10-15% of the general population develops a maladaptive or abusive pattern of consumption (Schuckit 2009). Highly developed countries have the highest rates of alcohol use disorders globally, with 12-month prevalence rates nearing 8.5% (Enoch 2008; Samokhvalov et al 2010). In the United States alone, 14 million individuals meet criteria for alcohol abuse or dependence (Pitel et al 2007a). Alcohol use disorders are an economic burden to society. In Canada the price tag of alcohol-related health care costs taxpayers approximately 2.3 billion dollars per year (Taylor et al 2007). Alcohol related problems are not only expensive for the health care system but are also accountable for productivity loss due to work-absenteeism, diminished quality of work and alcohol-related work accidents (Godfrey 1997; Gutjahr & Gmel 2001; Samokhvalov et al 2010). While costs to society are onerous, the costs to the alcoholic individual are more direct and often include a deterioration of physical and mental health, reduced life expectancy and an overall lower quality of life (Assanangkornchai & Srisurapanont 2007).

Alcohol has the potential to affect many organs in the body and to produce damaging and sometimes irreversible effects to the peripheral and central nervous systems. When consumed in large quantities over an extended period of time, alcohol may cause cirrhosis of the liver, pancreatitis, hypertension and may increase the chance of developing some forms of cancer such as liver cancer, or oesophageal cancer (Gutjahr & Gmel 2001). Alcohol consumption also increases the risk of developing other diseases such as alcoholic psychosis, alcoholic polyneuropathy, peripheral neuropathy and stroke (Gutjahr & Gmel 2001; Oscar-Berman et al 1997). While small to moderate consumption of alcohol has been shown to be protective against heart disease (Laonigro et al 2009) heavy users run the risk of developing heart failure or alcoholic cardiomyopathy (Gutjahr & Gmel 2001; Laonigro et al 2009). Persistent problems with excessive alcohol consumption significantly affect mortality rates and increase the risk of early death by nearly four times (Schuckit 2009). In the most severe and chronic of cases, alcoholics may develop central nervous system diseases such as Wernicke's Encephelopathy, Korsakoff's syndrome or alcohol-related dementia, which are characterized by profound cognitive dysfunction, ataxia, confusion, confabulation and severe memory impairment (Kopelman et al 2009). When diagnosed with one of these three neurological disorders, the individuals afflicted with an alcohol related disease often require long term care. Their quality of life is severely curtailed and costs to their families and to society become substantial.

In addition to the array of physical complications associated with alcohol use disorders, 37% of alcoholics suffer from a comorbid psychiatric disorder

(Regier et al 1990). Anxiety disorders, panic attacks and elevated rates of social phobia are closely linked with alcohol use disorders (Cosci et al 2007; Kushner et al 2000; Schuckit et al 1997a). Depression is also highly comorbid with alcoholism (Uekermann et al 2003) as recent investigations suggest a causal relationship between the two, with alcoholism acting as a risk factor for the development of major depression (Brown & Schuckit 1988; Fergusson et al 2009). Alcohol is a central nervous system depressant, and causes sedating effects such as somnolence, muscle relaxation and the feeling of being intoxicated (Schuckit 2009) Nearly 80% of alcoholics complain of depressive symptoms, while 30-40% actually meet criteria for major depressive disorder (Schuckit 1986; Schuckit et al 1997b). However, within two to three weeks post-detoxification most alcoholics experience significant reduction of their depressive symptoms, suggesting that many alcoholics presenting for treatment experience alcohol-induced depression (Schuckit 2009). Other severe forms of psychopathology including psychotic disorders and bipolar spectrum disorders are also highly comorbid with alcoholism, and consuming very high doses of alcohol has the potential of inducing a psychotic episode characterised by tactile and auditory hallucinations in otherwise healthy individuals (Cornelius et al 2003; Welch 2011). Alcoholics have high rates of suicidal ideation and a six-fold increase in suicide completion compared to the general population (Mann et al 2004; Schneider 2009). In general, psychiatric comorbities complicate treatment of alcohol use disorders and are often associated with higher rates of relapse to alcohol (Assanangkornchai & Srisurapanont 2007; Bradizza et al 2006).

Criteria for alcohol abuse differ from alcohol dependence. To be diagnosed with alcohol abuse according to the Diagnostic Statistical Manual (*DSM-IV-TR*) (American Psychiatric Association 2000), the pattern of consumption must cause clinically significant distress or impairment within the last 12 months as represented by *at least one* of the following symptoms: (i) the recurrent use of alcohol results in a failure to fulfill major role obligations at work, school or home; (ii) recurrent use of alcohol in hazardous situations (e.g. drinking and driving); (iii) recurrent alcohol-related legal problems; (iv) continued use despite persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of alcohol. Also, the individual must have never met criteria for alcohol dependence. According to the *DSM –IV-TR* (American Psychiatric Association 2000), to be diagnosed with alcohol dependence, the pattern of consumption must cause significant clinical distress or impairment and the individual must meet *three or more* of the following criteria within the last 12-months: (i) tolerance; (ii) withdrawal; (iii) alcohol used in larger quantities or for longer periods of time than was intended; (iv) unsuccessful efforts are made to cut down consumption; (v) a great deal of time is spent trying to obtain the substance; (vi) important social, occupational, or recreational activities are given up or reduced because of alcohol use; (vii) alcohol use is continued despite knowledge of having recurrent physical, or psychological problems.

Alcohol use disorders typically cause significant deterioration of interpersonal, recreational, social, occupational, and family functioning (Schuckit 2009). Alcohol abuse is considered less severe and associated with fewer

consequences than alcohol dependence. Approximately 10% of alcohol abusers actually go on to develop dependence (Schuckit 2009). However, both alcohol abuse and dependence have the potential to cause significant physiological and neurological harm, disturb cognitive function and mental health, and diminish overall quality of life (Assanangkornchai & Srisurapanont 2007; Cosci et al 2007; Gutjahr & Gmel 2001; Schuckit 2009).

1.2 The Neurobiology of Alcohol

Alcohol is a psychoactive substance that elicits both a euphoric and a relaxant response following mild to moderate consumption. Excessive alcohol intake, however, typically produces dysphoric effects including nausea, vomiting, memory lapses, and even loss of consciousness (Oscar-Berman & Marinković 2007). Alcohol, along with most drugs of abuse, has an effect on brain circuitry associated with motivation, reward and learned behaviours (McLellan et al 2000). Psychoactive substances influence neurotransmission within this circuitry, which consists mostly of the ventral tegmental area, anterior cingulate cortex, basal forebrain, amygdala and the nucleus accumbens (Cavacuiti 2011; Enoch 2008; McLellan et al 2000). Cortical and subcortical structures involved in the reward response also interact with emotional and memory centers of the limbic system which act to reinforce and often condition responses to a particular drug-taking behaviour (Cavacuiti 2011; McLellan et al 2000). For example, the reward circuit

interacts with the hippocampus, which in turn stores a memory of the associated drug-taking behaviour and rewarding response (Cavacuiti 2011).

Alcohol exerts its influence on the brain by stimulating or inhibiting the release of multiple neurotransmitters including gamma-aminobutyric acid (GABA), dopamine (DA), N-methyl-D-aspartate (NMDA), and glutamate (Enoch 2008; Harper & Matsumoto 2005; Hughes 2009; Nutt & Peters 1994). GABA is an inhibitory neurotransmitter consisting of two main classes of receptors, $GABA_A$ and $GABA_B$ (Nutt & Peters 1994). Ingesting ethanol potentiates the effects of the $GABA_A$-receptors through complex mechanisms that remain somewhat unclear and is associated with the calming and sedating response observed during acute alcohol intake (Enoch 2008; Schuckit 2009). Chronic consumption of alcohol leads to neural adaptations of $GABA_A$-receptor sensitivity, and is suggested to be a contributing factor to symptoms of anxiety and insomnia experienced during acute and protracted withdrawal (Schuckit 2009). In contrast to the sedating effects of alcohol observed during acute intoxication, the rewarding effect of alcohol such as feelings of euphoria are associated with an increase in synaptic dopamine in the brain's reward pathway (Enoch 2008; Schuckit 2009). Repeated activation of reward-related neuronal pathways is believed to be a contributing factor to cravings and drug-seeking behaviour seen among psychoactive substance abusers (Schuckit 2009). During acute alcohol intoxication, there is also tonic inhibition of glutamatergic NMDA receptor activity (Hughes 2009; Schuckit 2009). Chronic consumption of alcohol results in an adaptive up-regulation in the sensitivity of NMDA receptors in response to this tonic inhibition (Crews & Nixon 2009;

Harper & Matsumoto 2005; Nutt & Peters 1994). Once the consumption of alcohol is ceased and withdrawal commences, there is a hyper-stimulation of NMDA receptor response and a decrease in $GABA_A$ receptor response (Crews & Nixon 2009; Hughes 2009; Nutt & Peters 1994). Abrupt cessation of alcohol and subsequent withdrawal has the potential to induce seizures, delirium tremens and significant neural damage in part because of dysregulated receptor sensitivity, and therefore often requires medical and pharmacological intervention for safe recovery (Crews & Nixon 2009; Geibprasert et al 2010; Hughes 2009).

1.3 Cognitive Deficits Associated with Alcoholism

1.3.1 Three Main Hypotheses on Alcoholism and Cognition

The literature on alcoholism and cognition is governed by three main hypotheses; the frontal lobe hypothesis, the lateralization hypothesis and the diffuse brain deficits hypothesis. The frontal lobe hypothesis assumes that alcohol-induced cognitive insult resides in the anterior regions of the brain. Cognitive functions most affected would therefore include executive functions (such as: problem solving, working memory), attention, and response inhibition/impulsivity. Neuropsychological studies have shown that cognitive functions associated with frontal lobe functioning are heavily impaired in alcoholics, providing support for this hypothesis (Lawrence et al 2009b; Loeber et al 2009). Reviews and neuroimaging studies have provided further evidence for alcohol-related damage to the frontal lobes with findings of structural abnormalities in this region, in

addition to significant decreases in cerebral blood flow (Crews & Nixon 2009; Oscar-Berman et al 1997; Sullivan & Pfefferbaum 2005). On the contrary, other studies have demonstrated that cognitive impairment in alcoholism is just as significant for cognitive functions associated with regions other than the frontal lobe, negating the hypothesis of anterior lobe exclusivity (Beatty et al 1996; Davies et al 2005; Pitel et al 2007a; Ratti et al 1999; Shelton et al 1984).

A second hypothesis, dubbed the lateralization hypothesis, postulates that right hemisphere functions are more susceptible to the damaging effects of alcohol. Functions such as visual learning, visual memory, visuospatial and visuoconstructional abilities have been shown to be highly impaired in alcoholics (Beatty et al 1996; Beatty et al 2000; Dawson & Grant 2000; Fama et al 2004). It has been suggested that these cognitive functions are more resistant to recovery following extended periods of abstinence, providing support for claims of right hemisphere vulnerability (Di Sclafani et al 1995; Fein et al 1990; Fein et al 2006; Shelton et al 1984). A recent neuroimaging study demonstrated significant white matter abnormalities within the right hemisphere of alcoholics which may arguably render right hemisphere-dependent neuropsychological functions more susceptible to damage (Harris et al 2008). This claim is supported by studies that have shown that structural brain abnormalities often corroborate with the degree of cognitive functioning (Chanraud et al 2006; Duka et al 2003; Oscar-Berman et al 1997). However, studies have also shown that cognitive functions not pertaining to the right hemisphere are also resistant to recovery (Bolter & Hannon 1986; Pitel et

al 2007b; Ratti et al 1999; Uekermann et al 2003). It would seem that selective right hemisphere dysfunction is not universally observed in alcoholic individuals.

The final hypothesis debated in the literature is of diffuse brain dysfunction. Multiple cognitive functions including executive functions, attention, speed of processing, verbal/visual learning, verbal/visual memory, and visuospatial functions appear to be impaired in alcoholism, which lends support for the hypothesis of generalized dysfunction (Beatty et al 2000; Davies et al 2005; Harper & Matsumoto 2005; Noël et al 2007; Pitel et al 2009). Alcohol-related structural brain damage has also been detected in multiple brain regions including the cerebellum, limbic system, diencephalon, and the cerebral cortex (Harper & Matsumoto 2005; Oscar-Berman et al 1997). While structurally there appears to be support for generalized damage, from a cognitive perspective there is dispute on which cognitive functions are most affected by alcoholism. The degree of impairment in performance on neuropsychological tests differs across studies, with some showing selective susceptibility (Fein et al 2006; Shelton et al 1984; Uekermann et al 2003) and others showing widespread dysfunction (Beatty et al 1995; Davies et al 2005; Ratti et al 1999; Yohman et al 1985). Such findings suggest that some functions may be more vulnerable to the injurious effects of alcohol than others, insinuating that diffuse brain dysfunction may be too general of an assumption.

1.3.2 Scientific Contention on Cognitive Deficits in the Literature

Multiple cognitive functions that span many different regions of the brain have repeatedly been shown to be impaired in alcoholics. Executive functions, problem solving, attention, working memory, inhibition, impulsivity, speed of processing, learning, memory, and visuospatial functions are all negatively affected by alcohol consumption (Cordovil De Sousa Uva et al 2010; Davies et al 2005; Glenn & Parsons 1991; Lawrence et al 2009a; Moriyama et al 2002; Noel et al 2001; Pitel et al 2007b; Shelton et al 1984). While the extent of impairment across many different cognitive functions remains in contention, most can agree that excessive and chronic consumption of alcohol induces significant disturbance to cognitive integrity. Also, general consensus states that greatest cognitive dysfunction is presented during acute phases of abstinence (Eckardt & Martin 1986; Oscar-Berman & Marinković 2007; Parsons 1998). Reviews by Oscar-Berman & Marinković (2007) and Fein (1990), in addition to various cross-sectional studies describe that for the most part impairment is substantial during early abstinence, and that dysfunction typically abates over time and is reversible in most cases following extended abstinence (Dawson & Grant 2000; Fein et al 1990; Loeber et al 2009; Mann et al 1999; Reed et al 1992; Rourke & Grant 1999). While studies generally agree that alcohol is associated with dysfunction, the global portrait of how alcohol influences cognition over time remains unclear. It has been suggested that there is a differential rate of recovery for cognitive functions, with some functions improving immediately following abstinence and others requiring many

months or years of abstinence prior to normalization (Fabian & Parsons 1983; Pitel et al 2009). Reviews and neuroimaging studies compliment neuropsychological findings, as many studies have demonstrated that structural and functional abnormalities are partially reversible with extended abstinence (Bartels et al 2007; Oscar-Berman & Marinković 2007; Sullivan & Pfefferbaum 2005). With respect to tests of verbal fluency - employed to assess phonological and semantic fluency (Lezak et al 2004) - most studies report moderate to severe impairment in semantic and phonological fluency immediately following detoxification from alcohol (Beatty et al 1993; Hildebrandt et al 2004; Pitel et al 2007b). Similarly, significant impairment during short term abstinence on tasks measuring selective attention and attention/scanning has been reported in samples of alcoholics with less than 5 weeks abstinence (Beatty et al 1995; Cordovil De Sousa Uva et al 2010). One study by Easton et al (2008), however, detected only mild impairment on a sustained attention task during acute abstinence, defined as approximately 2 weeks of abstinence. As these studies assessed different facets of the attention domain, it is possible that alcohol differentially affects different aspects of the multidimensional construct of attention (Easton et al 2008). In similar vein, much of the literature on verbal and visual learning and memory function reports moderate to severe impaired performance on tasks measuring verbal learning, visual learning (Dawson & Grant 2000; Demir et al 2002; Pitel et al 2009; Uekermann et al 2003) verbal memory and visual memory (Beatty et al 1996; Dawson & Grant 2000; Ratti et al 1999; Rupp et al 2006) during early abstinence. There is a general consensus in the literature that alcohol significantly

compromises executive functions (Fama et al 2004; Moriyama et al 2002; Noël et al 2001; Pitel et al 2007a; Rourke & Grant 1999) and speed of processing (Beatty et al 2000; Easton et al 2008; Ratti et al 2002; Sparadseo et al 1983) during acute abstinence. Also, even though neuropsychological testing of impulsivity is less commonly studied in alcoholism, the few studies that have assessed inhibitory control have revealed that for the most part, alcoholics display moderate to high impairment immediately following detoxification (Cordovil De Sousa Uva et al 2010; Easton et al 2008; Lawrence et al 2009a).

Our understanding of alcohol's effects on cognition during long term abstinence is fairly coherent. Most researchers agree that by and large, impairment of most cognitive functions is reversible over time. However, there remains to be a dispute over the time necessary for recovery to take place, in adjunct to disagreement on which cognitive functions present resistance to recovery. In accord with reviews that illustrate recovery following long term abstinence (Fein et al 1990; Oscar-Berman & Marinković 2007) both minimal dysfunction on verbal fluency tasks (Davies et al 2005; Dawson & Grant 2000; Harris et al 2008; Munro et al 2000; Oscar-Berman et al 2004) and verbal memory tasks (Fein & McGillivray 2007; Fein et al 2006), in addition to normalization of performance on tasks of executive functions (Fein & McGillivray 2007; Fein et al 2006; Grant et al 1984; Oscar-Berman et al 2004) have been repeatedly shown in individuals with many years of abstinence from alcohol. Likewise, a study by Reed et al. (1992), assessing alcoholics with a mean of 7 years abstinence, found neuropsychological task performance to be comparable to healthy controls on

tasks of verbal and visual learning and memory. While for the most part, performance on a range of cognitive tasks following extended periods of abstinence appears comparable to healthy controls, some studies indicate lingering cognitive dysfunction among individuals with extended periods of abstinence. For example, a study by Saxton et al. (2000) reported that subjects with nearly 10 months abstinence yielded poor performance scores on verbal learning tasks. Another study by Yohman et al. (1985) revealed persistent impairments on tasks of abstraction and problem solving among alcoholics with 13 months abstinence, while Reed et al. (1992) revealed dysfunction in visual memory among individuals with up to 24 months abstinence. Lastly, speed of processing has been shown to be resistant to recovery, with persistent deficits found among individuals with up to 5 years abstinence (Davies et al 2005; Fabian & Parsons 1983; Harris et al 2008; Munro et al 2000).

1.3.3 The Connector: Coming to Terms with the Variable Findings

Four factors may help explain why the literature is peppered with variable findings: (i) the type of neuropsychological tests employed; (ii) cognitive domains assessed and classification of neuropsychological tests into cognitive domains; (iii) age of alcoholic participants, and; (iv) length of abstinence. To begin, choosing which neuropsychological tests to employ may influence study results. For instance, most cognitive processes are multidimensional, while any given neuropsychological test may assess only a portion of a particular cognitive

construct. Attention, for example, is a multidimensional cognitive domain that is comprised of selective, sustained and divided attentional constructs (Lezak et al 2004). Results from cross-sectional studies may vary depending on which neuropsychological tests are employed, as alcoholics may prove to have preserved *selective attention* capacities, with diminished *sustained attention*, or vice versa. Secondly, deciding which cognitive domains to assess and how to classify neuropsychological tests according to domains may likely influence findings. For example, at times studies opt for evaluating cognitive domains entitled learning or memory. However, these categories are quite broad and do not permit the scientific community to make more precise or detailed assumptions about cognitive impairment. The cognitive domains of learning and memory can be rendered more specific by partitioning them into verbal and visual domains. In doing so, localized assumptions on cognitive function may be easier to make; in general, the right hemisphere is associated with visual learning and memory, while the left hemispheres is believed to be responsible for verbal learning and memory (Lezak et al 2004). The more precise the cognitive domains, the more precise the classification of neuropsychological tests becomes within these domains. In turn, it may be postulated that fewer inconsistencies will be found across cross-sectional studies, should cognitive domains be defined similarly and consist of related classification patterns of neuropsychological tests. The third factor that is postulated to help explain the inconsistencies in the literature pertains to the age of alcoholic participants. Age is often a broad indicator of duration of abuse/dependence. Alcoholics undergoing neuropsychological testing in their

thirties may arguably perform differently than older alcoholics, for example in their sixties. Younger alcoholics may arguably fair better on cognitive assessments due to brain plasticity and the brain's ability to better recuperate from potential harmful effects of alcohol (Berlucchi 2011). Also, since alcoholics with longer duration of dependence typically fair worse on cognitive tests (Pitel et al 2009; Schottenbauer et al 2007) it can be argued that younger alcoholic samples with shorter duration of dependence who display better performance rates, may partly explain the discordance in the literature. Finally, the fourth factor that may help explain contradictory findings on how alcohol affects cognitive function is the duration of abstinence. Cross-sectional studies have assessed alcoholics with a large range of abstinence duration, varying from a few days of abstinence to many years of sobriety. There is no cogent outline describing expected recovery time for different cognitive functions in alcoholism. While some studies conclude that recovery of a particular cognitive domain requires several weeks or few months of abstinence, others report more persistent deficits that may linger for years following cessation of alcohol consumption. Currently, there is a lack of clarity on the extent to which alcohol-related cognitive impairment is reversible and how long must an individual remain abstinent from alcohol to reap full benefits of cognitive recovery. The melange of studies assessing patients with disparate abstinence durations poses a predicament. Thus, one of the major challenges appears to lie in grouping studies based on abstinence duration to identify an appropriate timeline of cognitive recovery for different cognitive functions. The best approach to elucidating findings in the literature is to perform a meta-analysis

on all studies on alcoholism and cognition. More specifically, a meta-analysis with a focus on cognitive recovery as a function of abstinence duration gives the opportunity to amalgamate findings and clarify the relationship between abstinence duration and cognitive recovery. A meta-analysis would also provide the opportunity to statistically measure how the other three above-mentioned factors - (i) neuropsychological tests, (ii) cognitive domains, and (iii) age of alcoholics - may influence performance on cognitive tasks.

1.4 What is a Meta-Analysis?

Meta-analyses synthesize, appraise and combine data from multiple independent studies to provide a statistical integration of a given body of related literature (Egger & Smith 1997; Stroup et al 2000). When performing a meta-analysis studies are selected based on their similarity of inclusion criteria and study variables, such as alcohol and cognition, and aim to produce a quantitative review of independent studies (Crombie & Davies 2009). Independent studies are conducted regularly to determine the relationship between two or more variables. It is not uncommon for single studies to fail to demonstrate statistical significance between two given variables or to produce contradictory results because of population variability (Crombie & Davies 2009; Gerbarg & Horwitz 1988). Meta-analyses employ a systematic review methodology to provide a summary of the current literature on a given topic, in our case how alcohol affects cognition (Crombie & Davies 2009). This methodology controls for between-study variation

across multiple independent studies, and provides a quantitative estimate of the aggregated effect that alcohol has on cognition across all included studies (Crombie & Davies 2009).

There are several steps to follow when performing a meta-analysis. A systematic search of the literature must be done using various electronic search engines (e.g. PubMed, Embase, Ovid) to ensure that the maximum number of studies is included in analysis. Strict inclusion/exclusion criteria must then be set to funnel studies, tighten study selection and ensure that all studies are assessing similar variables (Crombie & Davies 2009). This allows for a more cohesive analysis of findings. Once all studies have been acquired, a file for each study is typically created using the Comprehensive Meta-Analysis-version2 (CMA-v2). Within each study's file, all neuropsychological tests utilized within the study will be recorded with the mean and standard deviation, with the goal of calculating the effect size estimate for each neuropsychological test. In our case, we had accumulated 62 studies, and consequently produced 62 CMA-v2 files and listed all neuropsychological tests that had been employed to measure cognition in alcoholic samples within each of these studies. Following this step, the cognitive domains that will be included in analysis must be established and neuropsychological tests must be categorized according to their respective cognitive domains. In our meta-analysis we chose to assess 12 cognitive domains: intelligence quotient, verbal fluency/language, speed of processing, working memory, attention, problem solving/executive functions, inhibition/impulsivity, verbal learning, verbal memory, visual learning, visual memory, and visuo-spatial abilities. A second set

of CMA-v2 files was then created to represent each of these 12 cognitive domains. Within each of these new files, all independent studies that employed neuropsychological tests measuring that particular cognitive domain were included. For example, take the domain of problem solving/executive functions. Within this domain file, all studies that evaluated components of problem solving/executive functions will be included. To be more specific, let us take the Pitel et al. 2009 study that employed two different neuropsychological tests to measure problem solving/executive functions. A weighted mean effect size estimate of these two test measures was calculated and then considered to represent the mean effect size of the problem solving/executive function domain for the Pitel et al. 2009 study. This method of calculating weighted mean effect size estimates was repeated for all studies measuring problem solving/executive functions. Following suit, this method was repeated for each of the 12 cognitive domains. Once complete, within each of the 12 domains, moderator variables were introduced to measure which factors were influencing findings in the literature on alcohol and cognition. We chose to assess age of alcoholics, length of abstinence (which we divided into short-, intermediate- and long-term) and male to female ratio. To aggregate effect size estimates across studies, a random-effects model was employed because this model takes between-study variability into account and allows for population-level inferences (DerSimonian & Laird 1986). This model also allows for greater generalizability of results as compared to a fixed-effects model. Using this method of analysis, we were able to determine the short-, intermediate- and long-term mean effect size estimates for each of the 12 cognitive

domains. We also ensured that age of alcoholics did not act as a confounding factor; weighted mean age of alcoholics in each of the three time frames of abstinence (short-, intermediate- and long-term) was similar across cognitive domains. Results are presented in three tables near the end of Section 2 of the thesis (published article). Lastly, tests of heterogeneity can be performed using Cochrane's Q, to determine the heterogeneity of results (Crombie & Davies 2009). When the value of Cochrane's Q is small (level of significance $p<0.1$) the results from studies assessed are considered to be relatively homogeneous and results of the meta-analysis are considered to be a reliable reflection the aggregation of findings (Crombie & Davies 2009).

The major strengths of performing meta-analyses involve the ability to answer questions that single studies cannot answer alone. Problems faced by independent studies often involve sample size and variables of study; these problems can be targeted by meta-analytic studies (Egger & Smith 1997). The greater the number of studies utilized, and the greater the sample size, the more statistical power the meta-analysis holds. Aggregating data from independent studies with relatively smaller sample sizes increases the strength and reliability of results (Crombie & Davies 2009). In turn, results from meta-analyses are more generalizable than independent studies. Secondly, performing a meta-analysis allows for the investigation of multiple variables, also known as moderators variables that may help explain differences in findings across studies. The four main factors that we have postulated to influence the discordance in the literature on alcoholism and cognition (type of neuropsychological tests, choice of cognitive

domains, age of alcoholics, and length of abstinence) can each be investigated as moderator variables. Sub-analyses can be performed to assess to what extent each of these moderator variables is affecting cognitive performance in alcoholics.

This meta-analysis is the first of its kind within the field of alcoholism to investigate the global cognitive effects associated with alcohol abuse/dependence. However, many other meta-analyses studying cognition and other psychoactive substances such as cannabis, cocaine and benzodiazepines among others, have previously been performed. Prior to undertaking this project, a review of all other meta-analytic studies on cognition and substance abuse/dependence was performed to pinpoint the strengths and weakness of these analyses, with the goal of designing a meta-analysis for alcohol and cognition based on strong methodological grounds.

1.5 Review of Meta-Analyses on Cognition and Other Psychoactive Substances

Many meta-analyses have been performed to determine the effect of psychoactive substance abuse/dependence on cognition. These analyses have assessed cognition in abusers of cannabis, cocaine, 3,4-methylenedioxymethamphetamine (MDMA), benzodiazepines and methamphetamine. They have been performed in the attempt of providing the scientific community with a global depiction of how different substances of abuse affect cognitive function. The meta-analysis our team performed on alcohol abuse/dependence and cognition adds to the existing body of

literature on the effects of substances of abuse on cognition. While the overall technique of performing a meta-analysis is similar across studies on substances of abuse, each study differed with respect to moderator variables or cognitive domains assessed. Unfortunately many of the other meta-analyses on psychoactive substance dependence display methodological limitations, which will shortly be addressed in the paragraphs that follow. The meta-analysis performed on alcohol abuse/dependence benefited from taking these limitations into consideration, in order to design a methodologically stronger study.

The main goal of each of the meta-analyses on psychoactive substance abuse/dependence and cognition was to determine how cognition was affected by a distinct type of drug. In order to effectively answer this question, I would like to argue that consideration must be made for the duration of abstinence. An analysis that includes multiple studies that assess patients with a vast range of abstinence duration tells us little about the true effects that a particular substance has on cognition. For example, a meta-analysis on cocaine abuse and another analysis on methamphetamine abuse consisted of studies assessing patient samples with a wide variety of abstinence durations ranging from zero days to many years (Jovanovski et al 2005; Scott et al 2007). Subjects from all studies assessed in the meta-analysis on cocaine were placed into one large group and no concern was made for differences in abstinence duration. The results revealed moderate to high impairment among some cognitive functions such as visual memory and attention, with small to moderate dysfunction among other functions including verbal fluency and language (Jovanovski et al 2005). Findings from the systematic

quantitative review on methamphetamine revealed significant dysfunction of moderate magnitude in the following cognitive domains: episodic memory, executive function, information processing speed and psychomotor function. Small effect size estimates were found for attention, working memory, language and visuo-construction domains. It is difficult to interpret these results since there is no indication as to whether the findings are reflective of methamphetamine's effects on cognition for acute or protracted abstinence. Therefore, when performing a meta-analysis on how psychoactive substances affect cognitive function, it is important to consider the duration of abstinence as a moderator variable. The main question that should be asked is: how does the length of abstinence affect cognitive recovery? This is an important question to consider particularly in light of the fact that length of abstinence can cause the reader to reach problematic and possibly incorrect conclusions. Let us take for example the meta-analysis on methamphetamine that displayed moderate impairment on executive function and nearly no impairment on working memory. If the studies assessing executive function consisted of patients with 3 days of abstinence, and the studies measuring working memory consisted of patients with three years of abstinence, the reader will wrongfully interpret that methamphetamine affects executive functions but not working memory.

Another meta-analytic study also fell short of answering this question, with a systematic quantitative review of MDMA failing to report abstinence duration altogether (Kalechstein et al 2007). While the MDMA analysis concluded that this substance significantly affects multiple cognitive domains – with the most

impairment observed in the verbal learning/memory category, and moderate effect size estimates for attention/concentration, nonverbal learning/memory, executive functions and motor/psychomotor speed – the lack of reporting on abstinence duration leaves the reader questioning the implication of such findings. In sum, these methodological limitations make it difficult for the reader to properly interpret how a particular psychoactive substance affects different cognitive functions. Only one meta-analysis on psychoactive substance abuse/dependence and cognition appeared to have taken abstinence duration into consideration. Results from a meta-analysis on long term cannabis abuse, did evaluate a homogenous sample based on abstinence duration (Grant et al 2003). The cannabis users reported being abstinent for a certain number of hours. Very mild cognitive impairment was reported across eight cognitive domains, including attention, verbal/language, abstraction/executive function, perceptual motor, simple motor, learning, forgetting/retrieval and reaction time. These results can be interpreted as a lack of significant acute withdrawal effects among heavy cannabis users.

Apart from abstinence duration, it is also important to consider which cognitive domains to assess, and how to classify neuropsychological tests according to their respective cognitive domain depending on what functions they measure. There are hundreds of standardized neuropsychological tests available to researchers and neuropsychologists that can be administered to patients to assess cognitive impairment. Tests mostly differ in terms of time necessary to complete, and level of difficulty. Often, to assess a particular cognitive domain, multiple neuropsychological tests must be administered. When performing a meta-analysis

on cognition, it is therefore beneficial to quantitatively synthesize data based on cognitive domains, rather than on specific neuropsychological tests. Any given cognitive domain can be made up of a variety of neuropsychological tests designed to assess a common function. A meta-analysis on cocaine abuse/dependence evaluated test and test sub-score effect size estimates, rather than cognitive domain effect size estimates to determine the extent of cognitive dysfunction among chronic cocaine addicts (Jovanovski et al 2005). Findings revealed significantly elevated impairment among tests of attention, with moderate dysfunction on tests of visual memory and working memory. Minimal impairment was found on tests of verbal fluency/language and sensory-perceptual functions. However, tests of executive function revealed mixed findings, with some tests proving to be largely impaired and others revealing little-to-no impairment. This finding suggests that cocaine addicts may perform within the norm on certain measures of executive function, and fall short of success on others. The principle problem of this meta-analysis is that by regrouping studies that employed the same neuropsychological tests, the analysis produced numerous effect sizes based on a limited number of studies. However, the goal of a meta-analysis is to produce a systematic quantitative review of a large number of studies to increase the statistical significance of the aggregated data. It is therefore more effective to regroup neuropsychological tests into cognitive domains. Another advantage to assessing cognitive domains is that there is greater statistical power in performing a quantitative review of domains compared to individual cognitive tests.

Various methods are readily available to assist in the classification of neuropsychological tests within their respective cognitive domains. Factor analyses on alcoholism and cognition (Fein et al 2006; Yohman et al 1985), along with other meta-analytic studies measuring cognition and substance abuse/dependence are useful references (Grant et al 2003; Potvin et al 2008; Scott et al 2007). Detailed descriptions of neuropsychological tests provided by Lezak et al. (2004) in addition to their proposed test classification provide guidance when deciding how to categorize cognitive tests according to their appropriate cognitive domains. During test classification, it is also of interest to pay particular attention to sub-test scores. For example, the Continuous Performance Test is generally regarded as being an attention task. However, this task consists of sub-scores assessing omission and commission errors. The Continuous Performance Test omission sub-score is more reflective of attention, while the commission sub-score is more reflective of inhibition/impulsivity. Thus the different test sub-scores carrying the same neuropsychological test label may be best classified under different cognitive domains. The current meta-analyses on cognition and psychoactive substance abuse/dependence do not provide information on how test sub-scores were classified. For our meta-analysis on alcoholism and cognition, sub-scores were taken into consideration for effective categorization among cognitive domains.

Another important factor to consider when performing a meta-analysis is that the number of studies being assessed will affect the generalizability of results. Only 10 studies met final inclusion criteria for the benzodiazepine meta-analysis

(Barker et al 2004), 11 studies for cannabis (Grant et al 2003), 11 studies for MDMA (Kalechstein et al 2007), 15 studies for cocaine (Jovanovski et al 2005) and 18 studies for methamphetamine (Scott et al 2007). Lastly, to ensure that cognitive dysfunction is the result of the psychoactive substance of abuse, strict exclusion criteria must be enforced. The presence of other substances abused, as was the case for many of the other meta-analytic studies (Jovanovski et al 2005; Kalechstein et al 2007; Scott et al 2007), interferes with the interpretation of findings and may very well invalidate conclusions. For example, one of the limitations cited by Jovanovski et al. (2005) was that while subjects with alcohol dependence were excluded from analysis, subjects with concomitant alcohol abuse were included in analysis. Alcohol may have acted as a confounding factor in this particular systematic quantitative review. Most meta-analyses (Jovanovski et al 2005; Kalechstein et al 2007; Scott et al 2007) did not exclude for comorbid Axis I disorders either which may have acted as confounding factors and clouded the specificity of results.

1.6 Objectives

The main objective of this meta-analysis was to statistically quantify how alcohol abuse/dependence affects cognitive function by examining how cognitive recovery is achieved as a function of abstinence duration. To properly assess this question we aimed to accumulate all studies on alcoholism and cognition in order to perform a systematic quantitative review of the literature. Subjects were to be partitioned into groups based on duration of abstinence to clarify the relationship between abstinence duration and cognitive recovery-potential. The larger the number of studies utilized for statistical analysis, the greater the power of the results, which is why we chose to include all cross-sectional and longitudinal studies on alcoholism and cognition conducted since the introduction of the DSM-III. Secondly to better understand how cognitive deficits change over time we wanted to place particular importance on age of alcoholics, to prevent age from acting as a confounding factor. Thirdly, we aimed to assess multiple cognitive domains spanning many brain regions to more adequately assess how alcohol influences cognition as a whole. We wanted to avoid using broad cognitive domains, such as learning and memory, and instead employed specific domains such as verbal learning and visual learning to increase precision in the interpretation of results. Lastly, we wanted to both include a wide variety of neuropsychological tests in the analysis and meticulously classify each test and

test sub-score according to their respective cognitive domains to further increase the accuracy of results. With all these factors in mind that may potentially explain discordant findings in the literature, we performed a meta-analysis to uncover how alcoholism affects cognitive performance over time as a function of abstinence duration.

2. Article Publié en Addiction Biology

Le candidat à la maitrise a contribué à l'article publié en complétant l'intégralité de la recherche de littérature, la conceptualisation de l'étude, l'acquisition des données ainsi que l'interprétation des données, en écrivant la première ébauche de cet article et en participant à ses révisions subséquentes.

Stéphane Potvin a contribué à la conceptualisation de l'étude, à l'interprétation des données, et à la révision du manuscrit.

Julie Pelletier a contribué à l'interprétation des données et à la révision du manuscrit.

Tous les auteurs ont révisé et approuvé la version finale du manuscrit.

Widespread and Sustained Cognitive Deficits in Alcoholism: A Meta-Analysis

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Abstract

The cognitive repercussions of alcohol dependence are well documented. However, the literature remains somewhat ambiguous with respect to which distinct cognitive functions are more susceptible to impairment in alcoholism, and to how duration of abstinence affects cognitive recovery. Some theories claim alcohol negatively affects specific cognitive functions while others assert that deficits are more diffuse in nature. This is the first meta-analysis to examine cognition in alcohol abuse/dependence and the duration of abstinence necessary to achieve cognitive recovery. A literature search yielded 62 studies that assessed cognitive dysfunction among alcoholics. Effect size estimates were calculated using the Comprehensive Meta-Analysis V2, for the following 12 cognitive domains: intelligence quotient, verbal fluency/language, speed of processing, working memory, attention, problem solving/executive functions, inhibition/impulsivity, verbal learning, verbal memory, visual learning, visual memory, and visuo-spatial abilities. Within these 12 domains, 3 effect size estimates were calculated based on abstinence duration. The three groups were partitioned into short- (<1 month), intermediate- (2 to 12 months) and long- (>1 year) term abstinence. Findings revealed moderate impairment across 11 cognitive domains during short term abstinence, with moderate impairment across 10 domains during intermediate term abstinence. Small effect size estimates were found for long term abstinence. These results suggest significant impairment

across multiple cognitive functions remains stable during the first year of abstinence from alcohol. Generally, dysfunction abates following one year of sobriety. These findings support the diffuse brain deficits hypothesis and suggest that cognitive dysfunction lingers for up to an average of one year post-detoxification from alcohol.

Key words

Alcoholism – cognitive impairment – meta-analysis

Introduction

Excessive consumption of alcohol is associated with multiple cognitive deficits during both short- and long-term abstinence. Attention, working memory, speed of processing, visuo-spatial abilities, executive functions, impulsivity, learning, memory and verbal fluency have all been shown to be impaired in alcoholism (Beatty et al. 2000, Davies et al. 2005, Noel et al. 2007b, Pitel et al. 2009). In the most severe and chronic cases, alcoholics may develop Korsakoff's syndrome, Wernicke's encephalopathy, or alcohol-related dementia which are characterized by cognitive decline, mental confusion, confabulation, and profound memory impairment involving both retrograde and anterograde amnesia (Krabbendam et al. 2000, Saxton et al. 2000). The influence of alcohol on the development of dementia is substantiated by evidence suggesting that up to 29% of dementia cases are alcohol-related (Saxton et al. 2000). Even in the absence of Korsakoff's,

Wernicke's or alcohol-related dementia, chronic alcoholics have been repeatedly shown to display memory dysfunction and significant cognitive decline particularly during early abstinence (Reed, Grant & Rourke 1992, Pitel et al. 2007b). However, there is a lack of agreement on which cognitive functions are most severely affected by alcoholism (Ratti et al. 2002, Uekermann et al. 2003, Rourke & Grant 1999).

The literature is also replete with dissonant findings on the rate of cognitive recovery in alcoholism. General consensus describes greatest impairment during acute abstinence (Loeber et al. 2009, Reed et al. 1992, Eckhardt & Martin 1986). However, rates of recovery as a function of protracted abstinence remain controversial. Reviews by Oscar Berman & Marinkovic (2007) and Fein et al. (1990) concluded that while some cognitive functions improve following several weeks of abstinence, others present more persistent impairment over time. Other researchers have found similar results, with cognitive impairment subsiding within weeks or months following abstinence (Fein & McGillivray 2007, Mann et al. 1999). Additionally, many other studies have detected persistent impairment, suggesting that dysfunction among certain cognitive functions may linger for many months and even years following the cessation of consumption (Yohman, Parsons & Leber 1985b, Fabian & Parsons 1983, Rourke et al. 1999).

To explain these equivocal findings, many theories of cognitive insult to selective brain regions have been proposed. The frontal lobe hypothesis assumes greatest insult resides in anterior brain regions (Uekermann et al. 2003) while the lateralization hypothesis posits that right hemisphere functions are more

susceptible to the neurotoxic effects of alcoholism (Ratti et al. 2002). A third hypothesis of diffuse brain dysfunction helps explain additional findings in the literature that do not support the former hypotheses, asserting that cognitive deficits are disperse and nonspecific in alcoholism (Ratti et al. 1999). In support of the frontal lobe hypothesis, findings from multiple neuropsychological studies have revealed diminished functioning in problem solving, abstraction, working memory, attention and response inhibition/impulsivity (Ratti et al. 1999, Ratti et al. 2002, Oscar-Berman et al. 2004, Uekermann et al. 2003, Moriyama et al. 2002, Loeber et al. 2009). However, other studies have either found a lack of dysfunction in the frontal lobes or have revealed deficits in other regions, negating the hypothesis of frontal lobe exclusivity (Beatty et al. 1996, Harris et al. 2008, Fama, Pfefferbaum & Sullivan 2004). In support of the laterality hypothesis, researchers have compared verbal to non-verbal tasks and have repeatedly found visual learning, visual memory and visuo-spatial abilities to be more deficient and more often resistant to recovery (Fein et al. 2006, Harris et al. 2008, Shelton, Parsons & Leber 1984). A review by Fein et al. (1990) demonstrated that subjects with as much as 5 years of abstinence still displayed residual impairment on non-verbal tasks. Incompatible findings from other studies, however, have revealed a lack of support for this hypothesis (Uekermann et al. 2003, Beatty et al. 1996, Ratti et al. 1999, Bolter & Hannon 1986). Lastly, in regards to the diffuse brain deficits hypothesis, a review by Parsons (1998), described findings from cross-sectional and longitudinal studies. Findings revealed verbal, visuospatial and abstracting deficits, therefore supporting the diffuse brain deficits hypothesis.

Within this review, results from a longitudinal study reported persistent cognitive dysfunction in patients with up to 4 years sobriety.

While studies frequently make allusion to each of these three chief hypotheses, the literature remains coloured with inconsistent findings that do not always support the assumptions of either selective brain region susceptibility or diffuse dysfunction. The discrepancy in findings has prompted our team to conduct an analysis to elucidate which cognitive functions are likely targets for cognitive insult by examining functions that span multiple brain regions, with particular attention placed on recovery rate. Surprisingly, no meta-analysis has ever been performed on the global cognitive effects of alcohol dependence.

Upon review of other meta-analyses on psychoactive substance dependence and cognition, we discovered a number of methodological limitations most notably with respect to abstinence duration. A meta-analysis on cannabis reported length of abstinence in terms of hours (Grant et al. 2003), while a systematic quantitative review of MDMA (3,4-methylenedioxymethamphetamine) failed to report abstinence altogether (Kalechstein et al. 2007). In meta-analyses on cocaine and methamphetamine (Jovanovski, Erb & Zakzanis 2005, Scott et al. 2007), the duration of abstinence was reported in terms of a range spanning zero days to many years, which does not permit for differentiation to be made between cognitive recovery during acute and protracted abstinence. In addition to minimal consideration for how duration of abstinence influences cognitive recovery, most analyses did not exclude for comorbid Axis I disorders or other substances abused, such as alcohol, which may have acted as confounding factors and clouded the

specificity of results (Scott et al. 2007, Jovanovski et al. 2005, Kalechstein et al. 2007).

The objectives of this meta-analysis are to determine which cognitive functions are the most profoundly disturbed in alcoholics and to investigate how length of sobriety influences cognitive recovery-potential. We compared subjects based on acute and protracted abstinence to outline with greater precision than has been previously observed in other meta-analytic studies on psychoactive substance dependence, how abstinence duration affects cognitive recovery. We believe that taking account of the length of abstinence will clarify discordant findings in the literature and elucidate the effects that alcohol has on cognition.

Materials and Methods

Literature Search & Study Selection

An exhaustive search of Pubmed, Embase and Ovid was independently performed by two authors (KS, SZ) using the following key words: alcohol OR alcoholism AND cognition OR "cognitive dysfunction" OR "cognitive deficits" OR "problem solving" OR "executive functions" OR memory OR attention OR impulsivity. A consensus was reached between the authors on which studies to include and which to exclude from analysis. To ensure that the results obtained were reflective of alcohol's effects on cognition, strict exclusion criteria were enforced. Exclusion criteria consisted of: patients with co-morbid Axis I disorders, psychoactive substance abuse / dependence (not including alcohol), head trauma and other central nervous system diseases such as Korsakoff's syndrome, Wernicke's

encephalopathy, or alcohol-induced dementia, and history of significant medical illness such as cirrhosis. Studies that reported neuropsychological task performance while subjects were in a scanner and studies that described their subjects as "heavy drinkers" who were not diagnosed according to either DSM (III, III-TR, IV, IV-TR) or ICD-10 criteria were excluded. Studies that were written in foreign languages and studies that reported cognitive functioning according to clustered variables were also excluded from analysis.

Cognitive domains

The neuropsychological tests measured within each of these studies were grouped according to 12 cognitive domains: intelligence quotient (IQ), verbal fluency/language, speed of processing, working memory, attention, problem solving/executive functions, inhibition/impulsivity, verbal learning, verbal memory, visual learning, visual memory, and visuo-spatial abilities. To determine which neuropsychological tests would be assigned to which cognitive domain, the authors based their final decisions on test classification according to Lezak (2004), studies on alcohol and cognition that performed factor analyses (Yohman et al. 1985b, Fein et al. 2006), and other meta-analytic studies on psychoactive substance dependence and cognition (Scott et al. 2007, Grant et al. 2003, Potvin et al. 2008). Examples of neuropsychological tests included in each domain are as follows: *verbal fluency/language* [WAIS-Vocabulary, WAIS-Similarities, Controlled Oral Word Association Test (COWAT), Conceptual Levels Analogies Test (CLAT)]; *speed of processing* [WAIS-Digit Symbol, Trail Making Test A

and B (TMT-A, TMT-B), Reaction Time Tasks, Stroop reaction time, Grooved Pegboard]; *working memory* [Alpha Span Task, Digit Span forwards & backwards, Letter-Number Sequencing Task, N-Back]; *attention* [Continuous Performance Test, Attention Matrices Test, Alcohol-Shifting Task-omission errors]; *problem solving/executive functions* [Wisconsin Card Sorting Test (WCST), Stroop, Tower of London, Raven's Progressive Matrices, Object Alternation Task]; *inhibition/impulsivity* [Go/No-Go, Stop-Signal Reaction Time (SSRT), Continuous Performance task-commission errors, Iowa Gambling Task (IGT)]; *verbal learning* [WMS Logical Memory-immediate recall, WMS Verbal Paired Associates-immediate recall, California Verbal Learning Test (CVLT) trials, Free and Cued Selective Reminding Task (FCSRT)-immediate recall, Story Recall-immediate]; *verbal memory* [WMS Logical Memory-delayed recall, WMS Verbal Paired Associates-delayed recall, CVLT-delayed recall, FCSRT-delayed recall, Story Recall-delayed]; *visual learning* [WMS Visual Reproduction-immediate recall, WMS Visual Paired Associates-immediate recall, Benton Visual Retention Test, Rey-Osterrieth Complex Figure (ROCF)-immediate recall]; *visual memory* [WMS Visual Reproduction-delayed recall, WMS Visual Paired Associates-delayed recall, ROCF-delayed recall]; *visuo-spatial* [WAIS Block Design, WAIS Object Assembly, ROCF-copy, Embedded/Hidden Figures Test]. For tests less frequently used, such as the Sternberg, or the Little Man test, final classification was made based on their similarity to more commonly employed tasks and consensus was reached between authors (KS, JP & SP) on their respective domains.

Quantitative data synthesis

Comprehensive Meta-Analysis V2 (Borenstein & Rothstein 1999) was used to calculate effect size estimates of the differences in cognitive scores (mean and standard deviation) between alcoholics and healthy controls. The effect size estimates were derived using Cohen's d, which is defined as a standardized mean difference (Cohen 1988). Effect size estimates were calculated for each of the 12 cognitive domains analysed. The direction of the effect size was considered positive if cognitive performance of alcoholics was worse relative to healthy controls. Following the conventional standard of Cohen (1988) effect size estimates of 0.2, 0.5 and 0.8 were considered as small, medium and large, respectively.

Within each of the 12 cognitive domains, studies were regrouped based on length of abstinence. Studies were categorized into short term (STA), intermediate (ITA), and long term abstinence (LTA) based on the average abstinence provided by each study. STA was defined as less than one month (or 0 to 31 days) post-detoxification. The time frame for ITA ranged from the beginning of the second month to twelve months (or 32 to 365 days).The median length of abstinence of studies that assessed individuals with less than 1 year of abstinence was calculated to determine how STA and ITA categories should be divided. Calculations yielded a median split of one month, which is why the STA time frame was set to 0-31 days. LTA was defined as more than one year of sobriety.

Within each of the 62 studies, a mean effect size estimate for a particular cognitive domain (ex. problem solving) was calculated by aggregating effect size estimates of neuropsychological tests that measured this particular cognitive domain (ex. WCST, Object Alternation etc). This mean effect size estimate was then considered to represent the study's effect size estimate of that particular cognitive domain. Next, the composite effect size estimates for each of the 12 cognitive domains were then calculated by aggregating the effect size estimates from each study. For each of the 12 cognitive domains, 3 composite effect size estimates were calculated based on abstinence duration (STA, ITA and LTA) by aggregating effect size estimates of all the studies within the given time frame. A weighted average age of alcoholics was also calculated for each of the three time frames within each of the 12 cognitive domains to ensure that age did not act as a confounding factor.

Homogeneity of effect size estimates

It is more legitimate to aggregate effect size estimates when effect sizes are homogeneous. Thus, we have calculated the Q-statistic for the effect size estimates of the studies included in the meta-analysis. Level of significance was set at $p<0.1$. For both heterogeneous and homogeneous analyses, effect size estimates were aggregated using a random-effects model. Relative to fixed-effects models, random-effects models take between-study variability into account and allow population-level inferences (DerSimonian & Laird 1986). This model allows for greater generalizability of results. To reduce heterogeneity, a mean effect size of

all studies was calculated and a cut-off of two standard deviations away from this mean was enforced to exclude outlier studies, or specific outlier neuropsychological tests.

Results:

A total of 62 studies with a sample size of 5032 met final inclusion/exclusion criteria. Effect size estimates for all 12 neurocognitive domains are presented in **Tables 1, 2 & 3**.

Short Term Abstinence (STA)

During STA, effect size estimates were mostly moderate and ranged between 0.328 and 0.699. Unexpectedly, the lowest effect size was found for IQ, which was small-to-moderate. Verbal fluency, visual learning and visual memory also had small-to-moderate effect sizes. Attention sat at the opposite pole, with a moderate-to-high effect size of 0.699. However only three studies measured attention during STA, and we advise that this finding be interpreted with caution. The visual memory domain, consisting of 4 studies assessing 340 individuals, had a moderate effect size estimate of 0.567. After calculating the heterogeneity statistic Q, visual memory appeared to be the only heterogeneous domain ($Q= 8.174$, $p= 0.043$). Weighted mean age was controlled for and stable across all 12 domains, ranging from 41 to 45 years old.

Intermediate Term Abstinence (ITA)

Effect size estimates during ITA were comparable across most domains, and also comparable with STA values, with the exception of IQ (E.S. = 0.274), attention (E.S. = 0.291) and inhibition/impulsivity (E.S. = 0.766). Only two studies assessed attention during ITA, with a total of 145 individuals, while only one study measured inhibition/impulsivity with a sample size of 98. Putting aside these three cognitive domains, effect size estimates were all moderate and ranged from 0.434 (visual memory) to 0.607 (verbal memory). Calculation of Cochrane's Q indicated that all domains were homogeneous. Also, weighted mean age of the samples ranged from 42 to 48 years, indicating that age did not contribute significantly to differences in effect size estimates.

Long Term Abstinence (LTA)

The range of effect size estimates during LTA was small-to-moderate with values of 0.126 (attention) to 0.304 (speed of processing). No studies examined in this meta-analysis included measures of LTA inhibition/impulsivity. Long term functioning of attention was measured by only 2 studies, and we advise that the results be interpreted with caution. Weighted mean age did not vary considerably across cognitive domains, and for the most part remained between 50 and 55 years of age, with the exception of IQ (46 years old) and attention (61 years old). Weighted mean length of abstinence did not vary considerably either when excluding for attention (628.04 weeks, equivalent to 12.08 years). With the

exception of this domain, abstinence ranged between 366.11 weeks, equivalent to 7.04 years (IQ) and 496.49 weeks, equivalent to 9.55 years (working memory). Once again, across all cognitive domains assessed, calculation of Cochrane's Q indicated that all 12 domains were homogeneous.

Discussion

The objectives of this meta-analysis were to primarily identify which cognitive functions are most profoundly disturbed in alcoholics and secondly to determine how the length of abstinence influences cognitive-recovery potential. Effect sizes revealed significant impairment in STA across 11 cognitive domains. Performance on tasks of verbal fluency/language, speed of processing, working memory, attention, problem solving/executive functions, inhibition/impulsivity, verbal learning, verbal memory, visual learning, visual memory, and visuo-spatial abilities were all disrupted with effect sizes of mostly moderate magnitude by chronic alcohol consumption. IQ was the only domain that was not significantly affected by chronic alcoholism however it was nonetheless mildly influenced by consumption. Attention had a moderate-to-high effect size estimate but was only measured with three studies. We therefore advise that this finding be interpreted with caution in light of the relatively small number of individuals assessed. Effect size estimates calculated for ITA revealed significant impairment across 10 cognitive domains. However as previously mentioned, inhibition/impulsivity was assessed by only one study during ITA, and we advise that it not be over-interpreted. The values of each domain – with the exception of IQ, attention and

inhibition/impulsivity – resembled the effect sizes found during STA. Similar effect sizes in STA and ITA indicate that individuals with 1 month of abstinence have similar cognitive performance to individuals with up to 1 year of abstinence. Cognitive impairment therefore remains fairly stable and unwavering during the first year of sobriety. Subsequent analyses indicated less severe cognitive impairment among LTA patients. These results support findings from longitudinal studies that suggest cognitive recovery is possible with extended abstinence (Parsons 1998, Rourke et al. 1999). All cognitive domains assessed during LTA (with the exception of inhibition/impulsivity due to lack of studies) revealed mostly small effect size estimates. It can be inferred then that performance on multiple cognitive tasks does indeed improve with protracted abstinence in chronic alcoholism. However, the challenge appears to be maintaining abstinence during the first year post-consumption in order to benefit from cognitive recovery-potential.

Multiple non-selective cognitive functions have been shown in this meta-analysis to be comparable targets for cognitive insult. Findings therefore support the diffuse brain deficits hypothesis. Both the frontal lobe and the lateralization hypotheses are arguably incomplete. While frontal lobe functions including problem solving/executive functions, inhibition/impulsivity, attention, and working memory were shown to be dysfunctional we cannot state that alcohol's harmful effects are selective to this lobe. Additionally, since effect size estimates were comparable across both verbal and visual cognitive domains, the lateralization hypothesis cannot be deemed completely accurate. These findings

support studies and reviews that have reported diffuse cognitive impairment among alcoholics (Parsons 1998, Tarter 1975). Neuroimaging studies report that within the cerebral cortex, structural changes are more often pronounced in frontal brain regions (Ratti et al. 2002, Oscar-Berman et al. 2004), which does lend support for the frontal lobe hypothesis of alcoholism. However, many other studies report atrophy not only in the frontal lobes, but also in the medial temporal cortex, parietal cortex, subcortical structures (such as hippocampus and amygdala) and the cerebellum (Oscar-Berman et al. 2004, Noel et al. 2001a, Chanraud et al. 2007), which complements our finding of diffuse neuropsychological impairment.

A number of strengths accentuate the importance of findings from this meta-analysis. We have conducted the first meta-analysis on the global cognitive effects of alcohol abuse/dependence. Alcohol is a major health concern that causes hefty health care costs, lower quality of life and economic burden which is aggravated by productivity loss from disability and work absenteeism (Godfrey 1997). Alcoholism is associated with diminished psychosocial functioning (Pitel et al. 2007b) and executive dysfunction in particular is associated with poor social and occupational functioning (Moriyama et al. 2002). Knowing which cognitive functions are most affected by alcohol and the time necessary for recovery will influence our understanding of how alcoholism impacts the economy and health care system.

Findings from this meta-analysis also have important clinical implications for treatment strategies. Treatment is typically provided to patients during the first month of abstinence. However normalization of cognitive function appears to

generally require a minimum of one year sobriety. To effectively learn, retain and apply the strategies provided by therapeutic interventions for relapse prevention, verbal and visual learning and memory, as well as executive functions need to be functional (Dawson & Grant 2000, Pitel et al. 2007a). Proper decision making, controlling impulsive tendencies and making healthy lifestyle choices are also necessary for maintaining abstinence and have been shown to influence treatment outcome (Pitel et al. 2007b, Lawrence et al. 2009b). Short term remission rates among alcoholics who sought treatment range from 20-50% (Moos & Moos 2006), suggesting that current treatment strategies may need to re-evaluate their efficacy. While elevated rates of relapse may be due to multiple factors including stress or environmental triggers acting as conditioned cues (Heinz et al. 2009), the diminished reserve of cognitive abilities arguably adds to the difficulty of maintaining abstinence.

The main characteristic that distinguishes this analysis from other studies on alcoholism lies in the methodology. Conducting a meta-analysis has much greater statistical power than individual studies. As such, it is therefore a very powerful tool to weigh the different hypotheses that have been proposed to account for the residual effects of alcohol. The homogeneity of results further strengthens this meta-analysis, suggesting that our results are very reliable. The method utilized allowed us to replicate findings from some cross-sectional studies, longitudinal studies and reviews that report diffuse cognitive deficits (Fabian et al. 1983, Yohman et al. 1985b, Parsons 1998). Also noteworthy, having assessed 5032 individuals from 62 studies positively influences the generalizability of

results. Additionally, weighted mean age was calculated for each analysis performed and it did not appear to influence results. This indicates that the results were not partial to age of alcoholics or controls. Length of abstinence was considered a moderator variable, distinguishing this study from other meta-analyses performed on psychoactive substance abuse/dependence and neuropsychological function (see: Grant et al. 2003, Jovanovski et al. 2005, Scott et al. 2007, Kalechstein et al. 2007). The lack of systematic attention to abstinence duration makes it difficult to ascertain to what extent neuropsychological test performance is influenced by psychoactive substance abuse, and whether performance reflects acute or protracted dysfunction. Lastly, our meta-analysis is further strengthened by the fact that effect size estimates in all cognitive domains, with the exception of the visual memory domain during STA, were homogeneous across STA, ITA and LTA. Within-domain homogeneity indicates that all studies within each specific domain – and within their respective timeframe of STA, ITA, and LTA – had similar effect size estimates. This generalized homogeneity illustrates that the categorization of neuropsychological tests into cognitive domains has good validity. It also illustrates the validity of regrouping studies based on abstinence duration (STA, ITA, and LTA).

A number of study limitations need to be addressed. Regression analyses could not be performed with age of onset of alcoholism or duration of years of alcohol dependence due to unreliable data. Few studies questioned patients on when their problematic consumption patterns commenced. While it is often difficult to pinpoint the moment of dependence-onset, this is a question that many

researchers should aim to clarify in future studies. Individuals whose problematic consumption began at a very early age may have a different cognitive profile than individuals whose dependency began later in life due to brain plasticity (Casey & Jones 2010). On the one hand, the immature brain is arguably more vulnerable to alcohol-related insult (Casey et al. 2010). On the other hand because of plasticity, the young brain may be better at recovering from, or compensating for functional or structural damage (Berlucchi 2011). Secondly, the duration of dependence may equally influence neuropsychological task performance, with worse performance arguably observed in individuals who have been dependent for a longer period (Pitel et al. 2009, Schottenbauer, Hommer & Weingartner 2007).

A second concern involves a methodological limitation. Approximately 75% of studies utilized in our meta-analysis were easily classified into short, intermediate or long term abstinence. However, 25% of studies, while reporting mean abstinence within a specific time frame, had large standard deviations that threatened potential overlapping between time frames. The authors ensured that these studies had effect size estimates that were comparable to other effect size estimates from the other studies within the same time frame, and ensured that no outlier studies skewed results. Also, the 25% of studies produced results that were homogeneous across STA, ITA, and LTA, (with the exception of visual memory) suggesting that they were properly classified.

A concern that was observed during data analysis is the lack of females assessed in studies on alcoholism. Of the 63 studies examined in this analysis, 40% sampled only males, 19% assessed both males and females at a comparable

rate, and only 5% studied strictly female samples. Reasons for the discrepancy in gender ratio among samples may very well be attributed to the higher proportion of male alcoholics in treatment facilities available to participate in studies. Another possibility is the reluctance of women to seek treatment. A study by Dawson (1996) showed that women who seek treatment display severe symptoms of dependence, suggesting they are less likely to consult until the more advanced stages of their dependence. A downside to the scarcity of alcoholic women in samples is the limited generalizability of results. Women have been shown to be more vulnerable to the toxic effects of alcohol at lower doses than men (Hommer 2003). Within the last few decades it has become more socially acceptable for women to drink alcohol. Unsurprisingly, young women have been shown to abuse alcohol at nearly the same rates as men, a phenomenon that was not formerly observed (Stein & Cyr 1997). Therefore, assessment of cognitive decline in alcoholic women is timely and pivotal for a better understanding of the deleterious effects of alcohol on cognition.

A final limitation concerns the evaluation of long term abstinent alcoholics. Potential confounding factors particularly among elderly alcoholics may be due to selection bias and differential survivorship rates (Fein et al. 2007). Furthermore, studies assessing long term abstinence may have underestimated effect size estimates since patients who relapsed were not included in the analyses. Alcoholics who relapse following a prolonged period of abstinence experience a further decline in cognitive function (Pitel et al. 2009, Loeber et al. 2009). Greater cognitive impairment is associated with less treatment compliance and fewer days

of abstinence (Bates et al. 2006). Due to high relapse rates among alcoholics (Moos et al. 2006), those who are able to maintain abstinence may arguably have been more cognitively fit to begin with. In essence, our LTA samples may be filled with past alcoholics who were cognitively well-endowed and better able to respond to treatment. Also, our LTA sample excluded patients who developed Wernicke's encephalopathy, Korsakoff's syndrome and alcohol-related dementia, which further suggests that our LTA patients were less vulnerable to damaging effects of alcohol. Hence, the sample of LTA patients assessed in this meta-analysis arguably consisted of patients with the best outcome. As such, this may have underestimated the effect size estimate for long term abstinence in alcoholism.

In sum, alcohol is a substance capable of damaging multiple brain regions, and an array of non-selective cognitive functions particularly when chronically consumed over an extended period of time. Contrary to some findings in the literature that reveal rapid recovery post-withdrawal from alcohol, global cognitive dysfunction appears to persist even after many weeks or months of abstinence. Following one year of abstinence, cognitive performance appears within the normal range.

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Author Contributions

KS and SP were responsible for study concept and design. KS contributed to the acquisition of data via the literature search. KS was responsible for collecting data; KS, JP and SP contributed to data interpretation and analysis. KS drafted the manuscript; JP, and SP provided critical revision of the manuscript. All authors reviewed the content of manuscript and approved the final version.

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Table 1: Statistical analysis of cognitive domains during short term abstinence using a random effects model (0 to 31days)

Domain	# studies	N	Weighted mean age	Cohen's d	CI (95%)	p-value	Cochran's Q
IQ	8	731	43	0.328	{0.128, 0.527}	0.001	Q= 10.516 P= 0.161
Verbal Fluency / Language	14	1181	41	0.396	{0.247, 0.545}	0.000	Q=17.769 P= 0.166
Speed of Processing	17	1637	41	0.469	{0.356, 0.581}	0.000	Q= 18.645 P= 0.288
Working Memory	14	818	42	0.532	{0.363, 0.701}	0.000	Q= 16.146 P= 0.185
Attention	3	116	43	0.699	{0.319, 1.079}	0.000	Q= 0.817 P= 0.665
Problem solving / executive functions	20	1816	42	0.534	{0.438, 0.630}	0.000	Q= 19.009 P= 0.456
Inhibition / Impulsivity	6	268	45	0.460	{0.205, 0.715}	0.000	Q= 5.256 P= 0.385
Verbal Learning	13	980	45	0.453	{0.315, 0.591}	0.000	Q= 11.039 P= 0.526
Verbal	7	622	42	0.384	{0.146,	0.002	Q= 9.749

Memory					0.622}		P= 0.136
Visual Learning	8	519	45	0.368	{0.173, 0.563}	0.000	Q= 7.900 P=0.341
Visual Memory	4	340	43	0.567	{0.193, 0.942}	0.003	Q= 8.174 P= 0.043*
Visuo-spatial	10	1012	41	0.490	{0.357, 0.622}	0.000	Q= 8.693 P= 0.466

N= sum of alcoholics and healthy controls; CI= confidence interval; *=heterogeneous

Table 2: Statistical analysis of cognitive domains during intermediate term abstinence using a random effects model (32 to 365 days)

Domain	# studies	N	Weighted mean age	Weighted mean abstinence (weeks)	Cohen's d	CI (95%)	p-value	Cochran's Q
IQ	6	330	43	9.33	0.274	{0.056, 0.491}	0.014	Q= 2.107 P= 0.834
Verbal Fluency / Language	13	700	48	16.12	0.491	{0.338, 0.643}	0.000	Q=5.731 P=0.929
Speed of Processing	13	721	48	17.65	0.498	{0.347, 0.648}	0.000	Q= 6.247 P= 0.903
Working Memory	10	579	45	12.52	0.485	{0.305, 0.666}	0.000	Q= 10.143 P= 0.339
Attention	2	145	48	15.14	0.291	{-0.047, 0.630}	0.092	Q= 0.285 P= 0.593
Problem solving / executive functions	14	786	46	13.97	0.568	{0.422, 0.713}	0.000	Q= 11.213 P=0.593
Inhibition / Impulsivity	1	98	47	Range (12-52weeks)	0.766	{0.356, 1.176}	0.000	Q= 0.000 P= 1.000

Verbal Learning	10	659	44	11.33	0.459	{0.278, 0.640}	0.000	Q= 11.641 P= 0.234
Verbal Memory	6	319	46	12.59	0.607	{0.380, 0.835}	0.000	Q= 2.204 P= 0.820
Visual Learning	7	447	44	6.26	0.450	{0.211, 0.690}	0.000	Q= 9.293 P= 0.158
Visual Memory	4	275	42	9.73	0.434	{0.102, 0.767}	0.010	Q= 5.487 P= 0.139
Visuo-spatial	9	508	46	12.86	0.591	{0.410, 0.772}	0.000	Q= 4.597 P=0.800

N= sum of alcoholics and healthy controls; CI= confidence interval

Table 3: Statistical analysis of cognitive domains during long term abstinence using a random effects model (>365 days)

Domain	# studies	N	Weighted mean age	Weighted mean abstinence (weeks)	Cohen's d	CI (95%)	p-value	Cochran's Q
IQ	5	752	46	366.11	0.201	{0.046, 0.355}	0.011	Q= 3.956 P= 0.412
Verbal Fluency / Language	8	767	54	411.88	0.224	{0.081, 0.367}	0.002	Q= 3.364 P= 0.849
Speed of Processing	11	1297	50	389.43	0.304	{0.193, 0.414}	0.000	Q= 5.583 P= 0.900
Working Memory	4	442	56	496.49	0.209	{0.022, 0.397}	0.028	Q= 0.523 P=0.971
Attention	2	278	61	628.04	0.126	{-0.109, 0.361}	0.294	Q= 5.490 P= 0.441
Problem solving / executive functions	8	895	52	381.96	0.171	{0.038, 0.304}	0.012	Q= 1.674 P= 0.989
Inhibition / Impulsivity	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Verbal Learning	6	626	55	393.91	0.245	{0.073, 0.417}	0.005	Q= 6.803 P= 0.339

Verbal Memory	4	513	55	437.38	0.228	{0.053, 0.402}	0.010	Q= 1.571 P= 0.814
Visual Learning	6	649	54	439.78	0.239	{0.083, 0.395}	0.003	Q= 3.072 P= 0.800
Visual Memory	6	681	53	430.13	0.258	{0.105, 0.410}	0.001	Q= 4.253 P= 0.642
Visuo-spatial	10	1164	51	414.54	0.197	{0.081, 0.314}	0.001	Q=3.559 P=0.965

N= sum of alcoholics and healthy controls; CI= confidence interval

3. Conclusions

The aim of this study was to conduct the first meta-analysis on the cognitive deficits associated with alcoholism and to determine the rate of cognitive recovery as a function of abstinence duration. This has become the first meta-analysis in the literature to assess the relationship between alcoholism and cognition, ultimately providing the scientific community with a comprehensive depiction of how alcohol abuse/dependence affects multiple cognitive processes. From the results obtained, it has become evident that the effects of alcohol on cognitive function are most evident during acute abstinence. Eleven out of twelve cognitive domains assessed during the first month of abstinence (STA) revealed significant cognitive impairment. Knowing that cognition is significantly affected during acute abstinence, it can be argued that the level of dysfunction may be reflective of abstinence-effects on cognition, rather than alcohol-effects. However, during intermediate term abstinence (ITA), significant cognitive impairment was shown to persist across ten cognitive domains. Findings therefore suggest that multiple cognitive processes continue to be affected by alcohol abuse/dependence many months post detoxification. Therefore, if cognitive performance were only affected by acute abstinence-effects, we would arguable not observe persistent deficits with protracted abstinence. Also noteworthy of mention, is the finding that the aggregated effect size estimates for the majority of the twelve cognitive domains measured during STA are comparable to the aggregated effect size estimates in their respective cognitive domains during ITA. This finding suggests that

impairment during ITA not only persists but is also affected to nearly the same degree as is reported in STA. As expected, the aggregate effect size estimates calculated during long term abstinence (LTA) were small, indicating minimal cognitive dysfunction following one or more years of abstinence from alcohol. Our analysis does not permit us to state with conviction that this represents cognitive *recovery* per se because we only had access to the data on the cognitive performance of LTA patients while they were already abstinent for an extended period of time. We did not have access to the baseline data of these patients, which would have allowed us to compare baseline cognitive functioning to current functioning following an extended period of abstinence. From this information, we would have been better able to state that cognitive recovery actually took place. However, our findings of less severe cognitive impairment among long term abstinent alcoholics do corroborate with reviews and longitudinal studies that have demonstrated cognitive recovery-potential with extended abstinence (Fein et al 1990; Pitel et al 2009; Rourke & Grant 1999). Thus we can make the assumption that cognitive recovery does indeed take place with prolonged abstinence. To ensure that the above-mentioned effects were a corollary of alcohol consumption and not the result of potential confounding factors, the following strict exclusion criteria were enforced: patients with co-morbid Axis I disorders, psychoactive substance abuse/dependence (not including alcohol), head trauma and other central nervous system diseases such as Korsakoff's syndrome, Wernicke's encephalopathy, or alcohol-induced dementia, and history of significant medical illness such as cirrhosis. Furthermore, age of alcoholics did not act as a

confounding factor as weighted average age was calculated for each of the three groups measured (STA, ITA, LTA) across the 12 cognitive domains and was found to be comparable within STA, ITA and LTA. Lastly, the aggregate effect size estimates were homogeneous across nearly every single cognitive domain assessed, with the exception of visual memory during STA. Such strong and consistent homogenous effect size estimates are rarely found in meta-analyses assessing cognition, and prove that the methodological choices we made are extremely valid. By and large, the results obtained from this meta-analysis provide a rather accurate portrayal of how chronic alcoholism affects cognitive function and how cognitive recovery-potential is affected by abstinence duration.

Three hypotheses have been the main contenders in the debate on alcoholism and cognition for decades: the frontal lobe hypothesis, the right hemisphere hypothesis and the diffuse brain deficits hypothesis. Results from this meta-analysis strongly support the diffuse brain deficits hypothesis, which postulates that cognitive dysfunction is widespread and non-selective in alcoholism. With the exception of IQ, none of the cognitive domains assessed in this analysis were spared of impairment. Support for the diffuse brain deficits hypothesis is further espoused by neuroimaging studies. Structural and functional imaging studies reveal widespread cerebral atrophy among alcoholics, particularly during early abstinence (Crews & Nixon 2009; Geibprasert et al 2010; Harper 2007; Harper & Matsumoto 2005; Sullivan & Pfefferbaum 2005). In line with our findings of less severe cognitive impairment over time, neuroimaging studies have

also shown regeneration of brain structures following protracted abstinence (Crews & Nixon 2009; Pfefferbaum et al 2001; Sullivan & Pfefferbaum 2005).

Clinical implications of this study mainly ask the reader to reflect on what these findings signify for the treatment of alcoholism. Treatment strategies typically focus on the first four weeks following detoxification from alcohol. Alcoholics are taught ways to suppress their cravings, consider multiple alternatives to consuming alcohol, given guidance on proper decision making techniques and strategies on how to maintain abstinence. However, cognitive processing remains significantly impaired during at least the first year following detoxification. Learning, retaining and applying strategies on how to maintain abstinence arguably require intact cognitive processes, which recently sober alcoholics are evidently lacking. Cognitive processes such as learning, memory, abstract reasoning, decision making and problem solving are necessary for benefiting from treatment strategies (Dawson & Grant 2000; Lawrence et al 2009b; Pitel et al 2007a; Pitel et al 2007b). If the degree of cognitive function is indicative of an individual's ability to maintain abstinence, then it should come as no surprise that alcoholics present high relapse rates (>50%) during the first year post-withdrawal from alcohol (Moos & Moos 2006).

3.1 Limitations

A number of limitations must be addressed. We could not perform a regression analysis to assess how the duration of dependence affected cognitive performance

due to unreliable data. Ideally, future studies would systematically record age of onset of dependence to be able to estimate the duration of dependence. However, while ideal for statistical purposes, it is quite difficult from both a research and clinical perspective to pinpoint the exact moment of dependence onset. Differentiating between age at which the pattern of alcohol consumption becomes regular or chronic from the age at which an individual meets criteria for alcohol abuse/dependence is not always clear-cut. Regardless of these caveats, some studies have succeeded in calculating duration of dependence and measuring its effect on cognition. Few studies have indeed shown that the duration of dependence mediates cognitive function (Bolter & Hannon 1986; Fama et al 2004; Pitel et al 2009). However, many other studies have failed to find any correlations whatsoever between these two variables (Chanraud et al 2006; Grant et al 1984; Ihara et al 2000; Mann et al 1999). When calculating how duration of dependence affects cognitive performance, the trajectory of the alcohol use disorder becomes a second important variable to consider. Namely, how do we define duration of dependence? Chronic alcoholics often experience periods of heavy consumption followed by oscillating periods of brief or extended abstinence and relapse. Calculating dependence duration is thus complicated by the high incidence of relapse among alcohol use disorder populations. Ultimately, defining duration of dependence can be problematic, complex and potentially not the best predictor of how alcohol affects cognition.

On similar grounds, age of onset of alcoholism may be a mediating factor of later cognitive performance. Alcoholics who began consuming alcohol early

during adolescence are arguably affected differently than those who began drinking in their early twenties because of the trajectory of neural development, synaptic pruning and brain plasticity that manifest throughout adolescence (Witt 2010). Cortical and subcortical structures, particularly in frontal regions responsible for abstraction, problem solving, reasoning and inhibition continue to develop extensively up until adulthood (Crews et al 2007; Witt 2010). It has been suggested that the developing brain may be more vulnerable to the effects of alcohol given the extensive neural changes that occur during adolescent years (Casey & Jones 2010; Witt 2010). Studies have shown that adolescents with alcohol use disorders display marked decrease in cognitive function, with particularly poor performance on tasks of attention, memory and visuospatial function, compared to their non-alcohol abusing adolescent counterparts (Brown & Tapert 2004; Brown et al 2000). Early onset of alcoholism is also associated with poorer psychosocial functioning, lower education attainment and worse mental health status both during adolescence and later in life (Hicks et al 2010; Schuckit 2009). Early onset of dependence may very well be associated with more detrimental cognitive outcomes later in life. From a clinical perspective it is important to understand how cognition is affected by age of onset of dependence. Informing young alcoholics on the extent of damage alcohol can have on their lives may positively affect treatment outcome. For example, it is well documented that motivational interviewing for adolescents with alcohol and substance use disorders is an effective treatment strategy for reducing future consumption (Jensen et al 2011; Segatto et al 2011).

Above and beyond age of onset of alcoholism, it is considerably important to determine whether other pre-existing factors influence cognitive function among alcoholics. For instance children subjected to maltreatment, stressful environments, or family/non-family violence often display cognitive deficits, particularly among executive functions (DePrince et al 2009; Majer et al 2010; Strathearn et al 2001; Yang & Clum 2000). Furthermore, traumatic childhood experiences are associated with earlier onset of alcohol use, and present a risk factor developing alcohol use disorders later in life (De Bellis 2002; Enoch 2011; Keyes et al 2011; Young-Wolff et al 2012). In our meta-analysis, none of the subjects had been assessed for cognitive function prior to developing their alcohol use disorder. Therefore it would be incorrect to state that cognitive deficits observed in alcoholics are *exclusively* the result of alcohol. To control for this potential confounding factor, subjects would need to submit to cognitive testing during their youth, prior to developing an alcohol use disorder. However, from a design-methodology perspective, measuring alcoholics' cognitive performance prior to developing an alcohol use disorder is next to impossible. Sample sizes would need to be enormous, considering that only 10-15% of the general population will go on to develop an alcohol use disorder. Alternatively, alcoholic subjects should be questioned based on a longitudinal or timeline approach, which would permit for the identification of risk factors that may be contributing to the observed cognitive dysfunction.

Another limitation to our study was that we did not consider quantity of alcohol consumed as a moderator variable. A logical assumption would be that

larger quantities of alcohol consumed over time have a greater impact on cognitive performance. However, once again we were unable to perform a regression analysis due to unreliable data. On the one hand, there was a lack of studies recording quantity of alcohol consumed among their sample. On the other hand, of the studies that did report on the relationship between quantity consumed and cognition, the way in which they measured consumption quantity was not uniform. One study by Fama et al. (2004) reported that quantity of alcohol consumed was correlated with moderate visuospatial impairments. A second study by Sassoon et al. (2007) found a modest correlation between quantity consumed and performance on the digit symbol test, a neuropsychological test that assesses speed of processing. A review by Harper et al. (2007) suggested that the degree of brain atrophy is related to the quantity of alcohol consumed over a lifetime. However, many other studies have failed to find significant relationships between these two variables and have concluded that quantity consumed is not a good predictor of cognitive performance (Chanraud et al 2006; Grant et al 1984; Mann et al 1999). Surprisingly, of the studies that reported on quantity consumed very few actually performed regression analyses to determine whether any correlations existed between quantity and cognition. Most studies simply made note of quantity consumed while describing their sample (Dawson & Grant 2000; Fein & McGillivray 2007; Fein et al 2006; Loeber et al 2009; Pitel et al 2007a; Ratti et al 2002; Uekermann et al 2003). Another difficulty to consider pertains to *how* quantity of alcohol consumed can actually be measured? From a clinical perspective, alcoholism is often characterized as a loss of control over drinking

(Kahler et al 1995; Marlatt et al 1973). One of the main diagnostic criteria for alcohol dependence is the inability to control your consumption, namely *substance taken in a larger amount and for a longer period than intended* (American Psychiatric Association 2000). Alcoholics also often experience alcohol-induced black-outs or memory lapses, particularly while severely intoxicated (Rose & Grant 2010; White 2003). Lastly, people generally tend to underestimate the amount of alcohol they consume when asked to specify how many standard drinks they have had over the course of an evening (Devos-Comby & Lange 2008). Therefore, it can be assumed that alcoholics give a ballpark figure when questioned on their consumption pattern, and self-report cannot be objectively measured. On the other hand, the problem may not even lie in the quantity of alcohol consumed, but rather in the number of binge drinking occasions or the number of severely injurious events such as number of black-outs or detoxifications. It remains therefore questionable as to whether quantity of alcohol consumed should even be considered a good predictor of how alcohol mediates cognitive function over time.

A fourth study limitation that must be addressed concerns the lack of sex-difference analyses. We did not compare the cognitive profiles of male and female alcoholics. Gender differences in cognitive function among alcoholics is not well studied, however the few studies that do report on gender differences suggest that in general women display greater cognitive impairment particularly on tasks assessing visuospatial function, working memory and problem solving (Flannery et al 2007; Nolen-Hoeksema 2004; Sullivan et al 2002). While it would have been

beneficial for our team to determine whether gender differences were present across studies, the majority of our sample consisted of male alcoholics. In light of this, further insight on gender differences is discussed in the "Guidelines for Future Studies on Alcoholism" section.

A fifth caveat concerns a particular limit imposed by the methodology of a meta-analysis. In our meta-analysis we calculated aggregate effect size estimates for several cognitive domains including verbal and visual memory domains. These consisted mostly of studies assessing subject performance on tasks of immediate or delayed free recall, but not delayed cued recall. However, this does not allow us to differentiate between errors of encoding, consolidation or retrieval. Employing recognition memory tasks would clarify the type of memory impairment observed in alcoholics. Should subjects perform poorly on recognition tasks, it can be assumed that problems lie in the process of encoding or consolidation as the information has not been stored in memory. However, should subjects perform poorly on tasks of delayed free recall, but demonstrate improved performance on recognition tests, then it can be assumed that information was indeed consolidated, and that the problem lies in the strategies used for retrieval of that consolidated information. To address this issue, we returned to examine all studies that performed verbal and visual recognition tests to assess alcoholic subject's performance on such tasks.

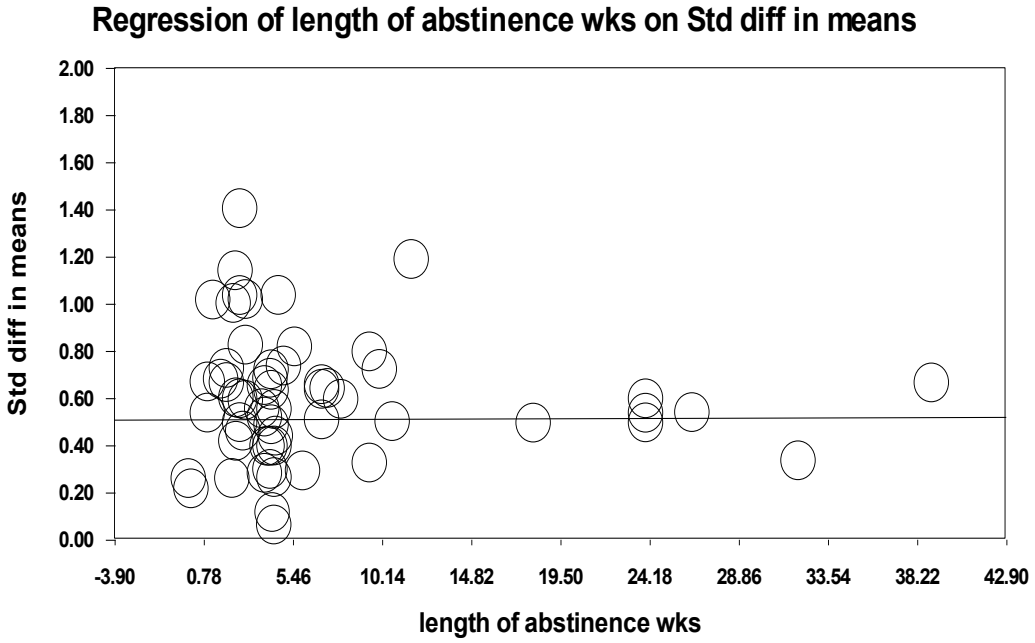
Verbal recognition was assessed by five studies, with a total sample size of 319 subjects. Studies were divided according to length of abstinence, with a total of two studies assessing STA, and three studies assessing ITA. The aggregate

effect size estimate for STA verbal recognition was calculated to be 0.370, suggesting moderate cognitive impairment. However, the heterogeneity statistic, Cochrane's Q, was found to be Q= 0.842, P=0.359 reflecting high heterogeneity. A random-effects model was used to calculate the aggregate effect size estimate in response to the heterogeneity. The three studies that assessed ITA verbal recognition memory, had a Cochrane's Q of Q=6.962, P=0.031 suggesting homogeneous results. A fixed-effects model was therefore used to calculate the aggregate effect size estimate, which was found to be 0.439, and reflective of moderate impairment. Visual recognition was assessed by six studies with a total sample size of 368 subjects. During the initial stages of data collection, a mean effect size estimate of all 62 studies was calculated and a cut-off of two standard deviations away from this mean was enforced to excluded outlier studies or outlier neuropsychological tests. Within the visual recognition data, two studies contained neuropsychological test performances with effect size estimates that exceeded our pre-determined cut-off point and were thus excluded as outliers. The two studies assessing STA (Q=1.245, P=0.265), three studies in ITA (Q=0.913, P=0.633) and three studies in LTA (Q=3.73, P=0.830) within the visual recognition domain were highly heterogeneous. A random-effects model was employed to calculate aggregate effect size estimates in response to high heterogeneity. Aggregate effect size estimates revealed moderate to high impairment across each the three respective time frames, STA (E.S. = 0.398), ITA (E.S. = 0.595), LTA (E.S. = 0.399).

Calculating visual and verbal recognition memory revealed overall moderate impairment suggesting the following: (1) alcohol has detrimental effects on encoding, since we know from our meta-analysis that immediate recall is impaired; (2) the effects of alcohol on visual and verbal long-term memory are not explained by retrieval impairments and; (3) consolidation processes *may* also be problematic. However, these conclusions must be interpreted cautiously particularly because of the limited number of studies assessing visual and verbal recognition, the relatively small sample sizes, and the high heterogeneity within time frames.

A final caveat that must be addressed was that we did not perform a regression analysis to determine how cognitive recovery was influenced by length of abstinence within the first year of sobriety. Therefore, we were not able to accurately state that cognitive function remains dysfunctional for an entire year following abstinence. What we were able to conclude was that during some point of the first year of abstinence, cognitive recovery takes place. We also concluded that past the one year mark of sobriety, we observe near normalization of cognitive function. To determine how STA and ITA categories should be divided, the median length of abstinence was calculated using studies that assessed individuals with $\leq$ 1 year of abstinence. Calculations yielded a median split of one month, which is why we chose to set the STA time frame from 0 to 31 days. Within the ITA group, the mean length of abstinence was 11.3 weeks, approximately 3 months. Therefore, across all studies measuring alcoholics with less than one year sobriety, the majority of our data reflected cognitive performance congregated

around the first few months of abstinence. However, to properly determine whether cognitive dysfunction persists up until the one year mark, a regression analysis should have been performed to make accurate conclusions on the trajectory of cognitive recovery from alcoholism. To address this concern, we decided to perform a meta-regression for all studies sampling alcoholics with ≤ 1 year sobriety. Although fewer studies assessed alcoholics nearing the one year mark of abstinence, the effect size estimates (referred to in the graph as standardized difference in means) remain essentially unchanged during the first year, meaning that cognitive impairment does indeed persist at least up to the 9 month mark (approximately 39 weeks).



3.2 Guidelines for Future Meta-Analytic Studies

A review of meta-analytic studies assessing psychoactive substance abuse/dependence and cognition was performed prior to commencing our meta-analysis on alcohol and cognition. This was done to assess the strengths and weaknesses of other meta-analyses with the goal of producing a methodologically powerful meta-analysis on alcoholism and cognition. From this assessment, the following future guidelines for meta-analytic studies can be proposed: (i) consideration for abstinence duration; (ii) selection of cognitive domains; and (iii) age of substance abusers.

Results from our meta-analysis on alcoholism and cognition provide evidence that consideration of abstinence duration is pivotal in understanding to what extent a particular substance affects cognitive processes and for how long do these deficits linger. The trajectory of recovery-potential as a function of abstinence duration permits researchers to postulate the harmful effects of psychoactive substances. It also elucidates how treatment strategies may or may not be beneficial during periods of significant cognitive dysfunction. In turn, cognitive recovery rate may partly explain relapse rates. Most of the current meta-analyses on cognition and psychoactive substance abuse/dependence do not take abstinence duration into consideration. This is true for the meta-analyses on MDMA, cocaine and methamphetamine; either no report at all was made concerning abstinence duration, or the choice was made not to group subjects based on abstinence duration (Jovanovski et al 2005; Kalechstein et al 2007; Scott et al 2007). Overall, the results from these meta-analyses reveal minimal effect sizes for certain cognitive domains including verbal fluency/language among

cocaine addicts and chronic abusers of cannabis, and attention among abusers of MDMA and methamphetamine. Moderate to significant impairment was found for other cognitive domains such as executive function among MDMA and methamphetamine users, and attention for cocaine abusers. However, findings from these studies are difficult to interpret particularly since the aggregate effect size estimates were calculated using the neuropsychological test performances of subjects with a wide range of abstinence duration; individuals with a few days of sobriety were grouped alongside subjects with protracted abstinence. It is difficult to know whether the results are being biased by long term abstinent subjects with normalized cognitive processes particularly in the case of results that reported minimal effect size estimates for certain cognitive processes. For example, the meta-analysis by Jovanovski et al. (2005) on cocaine that revealed minimal effect size estimates for measures of verbal fluency/language assessed subjects with abstinence durations that ranged from 0 days to 2.95 years. It is nearly impossible to know how the ratio of acute to protracted abstinent subjects may be biasing the results. This is turn could be masking the potentially harmful effects of a particular psychoactive substance during acute abstinence.

A second important guideline for future studies concerns the selection of cognitive domains. Evaluating multiple cognitive domains will provide a more comprehensive description of how psychoactive substances affect cognitive function as a whole. As outlined in our meta-analysis on alcoholism and cognition, cognitive domains were carefully selected to ensure that they were both specific and able to capture a global depiction of cognition. In the meta-analysis on

benzodiazepine abuse performed by Barker et al. (2004), cognitive domains assessed were similar to the ones we employed in our meta-analysis on alcohol. Most other meta-analyses on psychoactive substance abuse/dependence and cognition, however, were not as meticulous when choosing how to assess cognitive function. For example, Scott et al. (2007) regrouped neuropsychological tests into a general *memory* domain without differentiating between verbal and visual modalities, while Kalechstein et al. (2007) catalogued learning and memory as one cognitive domain. Here, we would like to argue the importance of being specific when deciding on how to categorize cognitive domains, as there may be significant difference in how a particular psychoactive substance affects for example verbal or visual memory. Additionally, the appropriate classification of neuropsychological tests into cognitive domains can greatly influence results obtained. In our meta-analysis, we meticulously categorized sub-scores of individual neuropsychological tests. For example, tests of sustained attention are comprised of omission and commission sub-scores, with errors of omission categorized in the attention domain and commission errors catalogued in the inhibition/impulsivity domain. We chose to aggregate the commission error sub-scores within the inhibition/impulsivity domain instead of the attention domain, because we felt that these sub-scores were more reflective of impulsivity. Supporting this decision, we found that nearly all of our sub-analyses produced homogeneous results, meaning that studies were measuring the same phenomenon. This lack of heterogeneity shows that our method was valid, and that our sub-scores were properly classified among cognitive domains. Future meta-analytic

reviews on cognition and psychoactive substance abuse/dependence could benefit from the success of this model.

Lastly, age of substance abusers at the time of neuropsychological testing is an important factor to consider as the aging brain may prove to be more susceptible to neurotoxicity. Both age-related neural and cognitive decline have been shown to be part of the normal aging process, as evidenced by structural and functional neuroimaging studies of healthy aging adults (Raz et al 2005; Samanez-Larkin & D'Esposito 2008; Yankner et al 2008). Cross-sectional studies and reviews on alcoholism have repeatedly shown that older alcoholics display more pronounced cortical atrophy compared to younger alcoholics (Di Sclafani et al 1995; Oscar-Berman & Marinković 2007; Pfefferbaum et al 1992; Pfefferbaum et al 1997). While enhanced dysfunction may be explained by a less resilient brain among older substance abusers, it may also be a reflection of the duration of psychoactive substance abuse/dependence. The duration of dependence may be accountable for deficits, more so than the diminished resilience of the brain. However, the reverse may also hold true. Future studies should attempt to discern between age-effects and duration of dependence effects when considering how psychoactive substances affect cognition by conducting regression analyses. Unfortunately, to perform such analyses we would need to have access to data on duration of dependence, which is not systematically reported in individual studies on psychoactive substance abuse/dependence.

3.3 Guidelines for Future Studies on Alcoholism

Findings from this meta-analysis on alcoholism and cognition have not only clarified questions that have been hotly debated in the literature over the last few decades but have also raised new questions that pave new avenues for future study. As mentioned in the article, one noticing trend among studies was the discrepancy of male to female alcoholic subjects. Nearly half (40%) of the studies on alcohol and cognition in the literature sample male-only subjects which is in stark contrast to a mere 5% of studies that test female-only subjects. Almost one fifth (19%) of studies do, however, test a comparable rate of male to female alcoholic subjects. We argued that this negatively influences the generalizability of results and hypothesized that the reasons for such inequity in the gender ratio may be attributable to either a greater number of males in treatment facilities or reluctance among women to seek treatment for their alcohol use disorder (Dawson 1996; Schneider et al 1995). In terms of the clinical significance of this gap between male and female subject assessment, essentially, our understanding of how chronic alcoholism affects the female brain remains cast to the shadows. The current research on gender differences in cognitive function of alcoholics remains somewhat limited. However, some studies have shown that alcoholic women have poorer performance on multiple cognitive measures in comparison to men (Flannery et al 2007; Nolen-Hoeksema 2004; Sullivan et al 2002). These studies have revealed greater dysfunction on tests assessing visuospatial function, working memory and problem solving (Flannery et al 2007; Sullivan et al 2002).

Neuroimaging studies have demonstrated that healthy non-alcoholic male and female young adults have different brain morphologies which correlate with cognitive performance (Gur et al 1999; Hommer et al 2001). Women and men therefore may be wired differently from both a morphological and functional standpoint. In concert with findings of greater cognitive impairment among female alcoholics, it has been suggested that women are more susceptible to the neurotoxic effects of alcohol than men (Harper & Kril 1990; Hommer 2003; Hommer et al 2001). Neuroimaging studies have revealed that at comparable rates of alcohol ingestion, women experience greater cortical atrophy and ventricular enlargement than their counterpart male alcoholic subjects (Harper & Kril 1990; Hommer et al 2001; Pfefferbaum et al 2001). In today's society, it has become increasingly more acceptable for women to consume alcohol. Epidemiological evidence reports that the number of women drinking alcohol is on the rise, as is the number of women entering treatment facilities for alcohol use disorders (Harper 2007; Schneider et al 1995; Stein & Cyr 1997). Future studies should focus on studying the cognitive effects of alcoholism in women. As studies assessing gender differences in cognitive function have shown that women experience greater impairment as a result of alcoholism (Flannery et al 2007; Nolen-Hoeksema 2004; Sullivan et al 2002), the results from this meta-analysis which sampled mostly male alcoholic subjects, may be downplaying the severity of cognitive impairment in female alcoholics. Future research may also focus more specifically on which cognitive functions are more affected by alcohol in women as compared to men, particularly because non-alcoholic women tend to perform

better on tasks of verbal learning and memory, while non-alcoholic men generally outperform women on visuospatial tasks (Herlitz & Loven 2009; Weiss et al 2003). To study gender difference in cognitive function, the cognitive performance of male and female alcoholics on an array of neuropsychological tasks would necessarily have to be compared to the cognitive performance of healthy male and female subjects. Such an approach would provide a better understanding of alcohol's impact on the male and female brain, which in turn could be corroborated with neuroimaging findings on gender-specific differential neurotoxicity rates of alcohol.

A second potential avenue of future investigation would be to study cognitive function of relapsing alcoholics. Our meta-analysis did not account for the number of relapses among our alcoholic samples because relapsing patients were excluded from individual studies. This in turn may have under-estimated the cognitive effects of alcohol reported by our meta-analysis. However, as relapse rates are particularly elevated during the first year of attempted sobriety (Moos & Moos 2006), it should be expected to see both first-time treatment seekers and relapsed alcoholics in detoxification programs. This mix of individuals would be found in samples of short term abstinent alcoholics. It becomes difficult to discern whether acute abstinence or number of relapses best explains cognitive dysfunction. This in turn may influence the results obtained on the cognitive performance of short term abstinent alcoholics, which in our meta-analysis revealed significant cognitive dysfunction. Neuroimaging and longitudinal studies have demonstrated that relapse is associated with a further decline in cognitive

function and an increase in cerebral atrophy (Duka et al 2003; Loeber et al 2009; Pitel et al 2009; Sullivan & Pfefferbaum 2005). Withdrawal from alcohol can be neurotoxic, and repeated episodes of withdrawal are associated with an increase in cognitive impairment (Duka et al 2003; Harper 2007). It would therefore be of interest to evaluate how the number of relapses may be influencing performance on cognitive tasks particularly during early abstinence. Logically emanating from this train of thought, long term abstinent alcoholics would arguably be a sub-group of alcoholics better apt at maintaining abstinence and possibly have a lower number of relapses. A test-retest study design by Fabian & Parsons (1983) assessed cognitive function of a group of alcoholics and compared their baseline performance to their follow-up performance nearly two years later. An emerging trend reported that alcoholics who had relapsed had actually performed worse during initial testing than alcoholics who were able to maintain abstinence at follow-up. The authors concluded that lower cognitive performance is a risk factor for relapse (Fabian & Parsons 1983). Further studies are required to confirm these initial findings to determine to what extent diminished cognitive reserve may render alcoholics vulnerable to relapse. Importantly, knowing how critical of a role cognitive function plays in maintaining abstinence has direct implications for the treatment of alcoholism.

To better understand the role that abstinence plays in cognitive recovery-potential, more longitudinal studies need to be conducted. Of the studies assessing long term abstinent alcoholics that were utilized in our meta-analysis, nearly none assessed baseline cognitive dysfunction. Therefore, the amount of cognitive

recovery remains somewhat ambiguous; these groups of long term abstinent alcoholics may have been less vulnerable to the harmful effects of alcohol, which may explain why they were better able to maintain abstinence. Thus we cannot state with certainty the extent of cognitive recovery that took place over time within our sample of alcoholics. While follow-up and longitudinal studies on alcoholism and cognition do exist in the literature (Parsons 1998; Rourke & Grant 1999; Sullivan et al 2000), the number of these studies remains limited.

The sample of long term abstinent alcoholics assessed in our meta-analysis excluded subjects with Korsakoff's syndrome, Wernicke's encephalopathy and alcohol-related dementia. Individuals diagnosed with these neurological conditions have been repeatedly shown to display severe cognitive impairment characterized by memory loss, confabulation, mental confusion and general cognitive decline (Kopelman et al 2009; Krabbendam et al 2000; Saxton et al 2000). We chose to exclude these subjects from our long term abstinent group because we believed that the inclusion of such patients would bias results, by suggesting greater cognitive impairment caused by alcoholism. Roughly 12-14% of alcoholics develop Wernicke's encephalopathy, which is caused by a deficiency in vitamin B1 (thiamine) (Kopelman et al 2009; Thomson et al 2009). While many alcoholics receive proper medical care for this relatively treatable condition, those who do not run the risk of developing Korsakoff's syndrome (Kopelman et al 2009). However, although we excluded these patients due to their potential to bias our results, it remains important to study such populations, particularly over time. Understanding why certain individuals develop an alcohol-related neurological

condition while others do not is crucial for developing appropriate treatment strategies. Future avenues of investigation in alcoholism may seek to determine the cognitive trajectory among Wernicke, Korsakoff, and alcohol-related dementia subjects by employing longitudinal studies. Designing studies to follow alcoholics from their first consultation for treatment until late in life may be done in the attempt to identify risk factors of the development of alcohol-related neurological conditions.

While most of the arguments put forth have focused on the detrimental effects of heavy alcohol consumption on cognitive function, alcohol is not always injurious to the human condition. In fact, studies have shown that light to moderate alcohol consumption does not impair cognition and may even enhance cognitive performance in adults over time (Arntzen et al 2010; Galanis et al 2000; Neafsey & Collins 2011). Some studies go so far as to suggest that alcohol in moderation actually decreases the risk of cognitive decline or dementia among older adults (Neafsey & Collins 2011; Peele & Brodsky 2000). However, documentation of the effects of moderate alcohol consumption has not unanimously revealed protective factors, and it is very likely that confounding factors (e.g. socioeconomic status, general health, intelligence quotient etc.) can help explain the observed positive effects of alcohol on cognition. While there is little indication in the literature that moderate consumption actually produces impairment, there is evidence that refutes the notion that moderate consumption plays a preventative role in cognitive decline among older adults (Cooper et al 2009; Lobo et al 2010). This pattern of consumption has also been shown to cause brain shrinkage which is correlated

with cognitive decline, thus further challenging the protective-factors hypothesis of alcohol (Verbaten 2009). In sum, alcohol appears to offer both protective cognitive factors when consumed in moderation and significant dysfunction when the pattern of consumption becomes abusive. The reasons for such discrepancy in the effects of alcohol remain largely unknown and merit future investigation.

3.4 In Sum

Alcohol is a widely consumed psychoactive substance that is enjoyed by many individuals across the globe. For approximately 10-15% of alcohol users (Rehm & Patra 2010), the pattern of alcohol consumption becomes excessive and maladaptive. Alcohol abuse/dependence is detrimental to the human condition in many ways; alcoholics often suffer from psychological and psychiatric problems, health complications, diminished quality of life, brain atrophy, cognitive impairment and may potentially develop neurologically debilitating disorders. Delineating how alcoholism influences cognitive function over time, in addition to the extent to which cognitive recovery is possible as a function of abstinence duration is important for our understanding of alcohol's impact on the brain from a cognitive standpoint. Our meta-analysis has provided the first glimpse into the trajectory of cognitive recovery in alcoholism as a function of abstinence duration. Results from this unique meta-analysis support the diffuse brain deficits hypothesis by stipulating that cognitive dysfunction is both widespread and non-selective in alcoholism and that near normalization of diverse cognitive functions

is possible with extended abstinence. Clinical implications of this analysis suggest that treatment strategies may need to be revised, and that cognition may need to be considered as an integral part of the treatment of alcoholism in the future. As previously mentioned, typical treatment programs focus on the first four weeks following admission for detoxification, while relapse rates during the first year of attempted sobriety remain at an alarmingly high rate as nearly half of abstaining alcoholics succumb to relapse. From this meta-analysis it has become evident that alcoholics remain cognitively impaired up to one year following abstinence. Application of treatment strategies during the first month of abstinence therefore appears somewhat incompatible with our findings of persistent cognitive impairment. Our meta-analysis provides a novel and methodologically sound way of analysing cognitive recovery-potential among alcoholics. Alcohol is significantly detrimental to cognitive function on a global scale during both acute and protracted abstinence; fortunately near normalization of cognitive recovery is possible with extended sobriety.

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Appendix I: Classification of Neuropsychological Tests into Cognitive Domains

IQ	- full scale = performance +verbal
Verbal Fluency / Language	- Specific items from the WAIS (Comprehension, Vocabulary, Similarities, Information) - Controlled Oral Word Association Test (COWAT) - Letter Fluency (word fluency) - Verbal Fluency Test (VFT) - Category Fluency - Verbal Judgement Test - Conceptual Levels Analogies Test (CLAT) - MicroCog Analogies - Boston Naming Test - Generate Category Exemplars Test
Speed of Processing	- Grooved Pegboard - Finger Tapping/Finger Oscillation Test - WAIS Digit Symbol Test - Digit Symbol Modality Test - Trail Making Test-A (TMT-A) - TMT-B - STROOP, time - Alcohol shifting task, reaction time - Reaction Time Task : simple vs choice reaction time task

	- MicroCog Timers 1& 2 - Continuous Performance Task (CPT), time
Working Memory	- Alpha Span Task - Digit Span (Forward & Backward) - MicroCog Numbers forward - MicroCog Numbers Backward - MicroCog Math Calculation - MicroCog Tic Tac - Letter-Number Sequencing/Letter-Digit Substitution - Arithmetic - Sternberg - Corsi Block Tapping Test - Corsi Spatial Span Test - N-Back - Paced Auditory Serial Attention Task (PASAT)
Attention	- CPT - Sustained Attention/Divided Attention - Digit Cancellation Test - Micro-Cog alphabet - Attention matrices test - Eriksen task - Alcohol shifting task, omission errors - Digit Vigilance
Problem Solving/ Executive Functions	- Wisconsin Card Sorting Task (WCST or MCST) - Bexsley-Maudsley Category Sorting

	- Concept Formation/concept shifting
	- Raven's Progressive Matrices
	- Tower of London
	- Hayling Task
	- STROOP, # of errors
	- Category Test
	- Progressive Planning Test (PPT)
	- Alternate Response Task
	- Object Alternation
	- Shift Learning/Concept Shifting Test from CANTAB
	- BADS subsets
	  o Rule Shift Card
	  o Action Program
	  o Key Search
	  o Temporal Judgement
	  o Zoo map
	  o Modified Six Elements
	- Brixton Task
	- Ruff Figural Fluency Task (RFFT), perseverations
	- SILS, Abstraction test

Inhibition / Impulsivity (orbito)	- Gambling Task - Go/No – Go - Stop-Signal Reaction Time Task (SSRT) - Delayed Discounting - Alcohol shifting task, commission errors - CPT, commission errors
Verbal Learning	- Wechsler Memory Scale (WMS) Story, immediate recall - California Verbal Learning Test

	(CVLT), trials 1 to 5 - Rey Auditory Verbal Learning Test (RAVLT), trials 1 to 5 - CERAD Word List Memory, trials - MicroCog Wordlist 1 - MicroCog Story 1 - Verbal learning task, immediate recall - Spondee test - Munich Verbal Memory Test, trials/immediate recall - Free and Cued Selective Reminding Test (FCSRT), trials/immediate recall - Auditory Verbal Learning Test (TME) - Selective Reminding Task - WMS Logical Memory, immediate recall - Verbal Paired Associate Learning Task, trials 1 to 5
Verbal Memory	- CVLT, delayed recall - Hopkins, delayed recall - WMS Paired Associate Learning Test, delayed recall - CERAD Word List Memory, delayed recall - Munich Verbal Memory Test, delay recall - Selective Reminding Task, delayed recall - WMS Logical Memory, delayed recall - Micro-Cog Story (or address), delayed recall

Visual Learning	- WMS Visual Reproduction, immediate recall - Recurring Digits (or figures) Test - Benton Visual Retention Test (BVRT) - Visuo-spatial Paired Associates - Figure Position - Rey-Osterrieth Complex Figure (ROCF), immediate recall - Memory for Designs, immediate recall - New Map Test, trials
Visual Memory	- WMS Visual Reproduction, delayed recall - ROCF, delayed recall - New Map Test, delayed recall - CERAD, figure delayed recall - Memory for Designs, delayed recall
Visuo-spatial	- Block Design - ROCF, copy - Mirror Star Tracing, copy - CERAD, figure copy - Object Assembly - Little Man Test - Mental Rotation Test - Hidden Figures Test/Embedded Figures Test - Pathfinding

Appendix II: Expansion of Methods Section

Short term abstinence (STA), included studies with 0 to 31 days of mean abstinence, while intermediate term abstinence (ITA) included studies with 32 to 365 mean days, and finally long term abstinent (LTA) included studies with >365 days. The median length of abstinence was calculated using studies that assessed individuals within 1 year of abstinence to determine how STA and ITA categories should be divided. Calculations yielded a median split of one month, which is why we chose to set the STA time frame from 0 to 31 days. Calculations were also performed to determine the mean split of these studies, and yielded a result of 7 weeks. To ensure the results did not differ greatly between mean and median division, two composite effect sizes were calculated for all studies with <1 year abstinence: the first was with a median split, and the second with a mean split. Comparing the two composite effect size estimates revealed minimal difference in value and thus we could be confident that results would not vary greatly depending on whether a mean or median split was imposed. A final decision to use a median split was made based on two major points: (1) most studies assess patients within the first month of sobriety and; (2) treatment is typically directed at the first 4 weeks of abstinence. Thus, we decided that a median split would be more representative of current research and clinical practice.

To ensure that studies did not greatly overlap in time frames, meaning that studies were not inappropriately classified, we used the mean abstinence duration provided by each study as a basic strategy of classification. When available, we

considered the standard deviation and/or the range provided to ensure that studies were well classified within STA, ITA or LTA. Upon reviewing the ranges of abstinence or the mean abstinence and standard deviation provided by each study, we concluded that 75% of studies had practically no overlap of subjects between time frames. Among these studies, the standard deviations ensured that the values were mostly within the given time frame, or ranges fell strictly within a given time frame (ex. 2 to 3 weeks abstinence). However, approximately 25% of our studies did have larger standard deviations, which may have caused problems in terms of overlap between time frames. Because of this issue, for each of these studies we verified if the effect size estimates of that particular study was comparable with effect size estimates from other studies within the same time frame. Studies that lay 2 standard deviations away from the composite effect size within a specific time frame (STA, ITA or LTA) would be excluded as outliers. Also, we calculated the heterogeneity statistic, Cochran's Q, which revealed that studies within each time frame across all cognitive domains were homogeneous (with the exception of visual memory during STA). Therefore, while we agree that the potential for overlap between time frames is a methodological limitation, the 25% of studies with larger standard deviations produced results that were homogeneous within STA, ITA and LTA time frame, suggesting that they were properly classified. We first applied a fixed-effects model to determine effect size estimates because of the overall homogeneity of our data. Next we re-calculated all our statistics by applying a random-effects model, to allow for between-study variability and to increase the generalizability of our results. We are confident that our results are

valid particularly because the effect sizes estimates were comparable when either a fixed- or a random-effects model was applied. This confirms the validity of our results and the strength of our methodology.