Variables associated with cognitive impairment in adults who misuse alcohol as assessed by the Addenbrooke's Cognitive Examination (revised)

MAJOR RESEARCH PROJECT and CLINICAL RESEARCH PORTFOLIO

Volume 1

(Volume 2 bound separately)

Volume 1 and 2 total word count: 29117

Sarah Macdonald (MA Hons)

Academic Unit of Mental Health and Wellbeing

University of Glasgow

Submitted in part fulfilment of the requirements for the degree of

Doctorate in Clinical Psychology (D Clin.Psy)

September 2012

Acknowledgements

I would like to thank Professor Tom McMillan for his guidance and seemingly endless patience whilst supervising my research portfolio. I am also very grateful to Dr Sharon Mulhern for her support with this project, especially when it seemed there was no project to be had! Thank you too to Janie Hunter for her help collating the data and the Alcohol Liaison Team for enabling me to complete this study within their service.

I feel very fortunate to have undertaken my training with a group of such brilliant women. In particular, I am grateful to my three study group pals for the kindness and light relief they have provided throughout the course. It has made this experience massively easier and even enjoyable.

I am also hugely indebted to my wonderful friends and family. I have every intention of investing in you the same time I have given to my laptop over the past three years. Thank you for being there to remind me that clinical training is far from the most important thing in my world.

Most of all, I would like to thank Neil, who has lived this course blow by blow with me and always believed I could make it. It would have been impossible without you.

TABLE OF CONTENTS

Volume 1

Chapter 1

Systematic Literature Review

Recovery of executive cognitive functions during abstinence from alcohol

(7836 words inc. lay summary, abstract and references)

Written according to guidelines for submission to the journal *Alcoholism: Clinical and Experimental Research*

(Author's Instructions – see Appendix 1.1)

Address for Correspondence:

Academic Unit of Mental Health and Wellbeing

Centre for Population and Health Sciences

Gartnavel Royal Hospital

1055 Great Western Road

Glasgow, G12 0XH

Lay Summary

The ability to plan, use new information and switch between tasks is very important if a person is to live independently. These abilities have been broadly grouped together using the term 'executive cognitive functions'. Misusing alcohol for a long time damages the parts of the brain that control these abilities. There is some evidence that when people stop drinking heavily, the brain and these abilities recover. This review combines recent evidence about how long it takes executive cognitive functions to recover once a person stops drinking alcohol. The review also looks at whether there is evidence that aspects of ECF, such as the ability to think flexibility, recover more quickly or to a greater extent than other aspects.

Papers from 2000 onwards which look at ECFs in people who misuse alcohol were found using searches of electronic databases and examination of relevant journals. Twenty-six papers were found. All of these papers used methods that were of medium or high quality.

The papers included in this review showed that in the first month after a person stops drinking, ECFs are impaired in people who misuse alcohol. Once people have been abstinent for six months, ECFs appear to return to normal. There was not enough evidence to be sure if different aspects of ECF all recover to the same extent. Limitations of the review, such as lack of any standard way in which the results of different studies were combined, make it unclear how accurate the findings this review are. Future research should follow up large samples of people who are abstinent from alcohol to understand how recovery happens in the long term.

Abstract

Objectives

Alcohol misuse can progressively damage the frontal lobes and impair associated executive cognitive functions (ECFs). With abstinence, some recovery can occur. This review synthesises evidence regarding recovery of ECF during abstinence and examines whether all aspects of ECF recover to the same extent.

Literature search

Systematic electronic searches were undertaken in: Ovid MEDLINE (1996 - January 2012), Embase (1996 – 2012 Week 01); EBSCO-host CINAHL, Health Source nursing/academic edition, PsychARTICLES, Psychology and Behavioural Science Collection, PSYCHINFO; Web of Knowledge. Hand searches of study references lists and journal contents pages were also made. Studies published since 2000 which examined ECF in alcohol dependant individuals during abstinence were included in the review.

Quality analysis

Two reviewers rated the methodological quality of studies independently using quality criteria developed by the author. Criteria were based on the case-control checklist developed by the Scottish Intercollegiate Guideline Network (SIGN nd.) and CONSORT guidelines (2010).

Findings

Twenty six studies were included in the review. All were rated as high or medium quality. ECF is impaired during very early abstinence (up to thirty

days). After 6 months or more of abstinence ECF appears to be broadly similar to healthy participants. There was insufficient evidence to conclude whether all aspects of ECF recover to the same extent. Given the methodological weakness of the studies reviewed, conclusions are tentative. Future research should employ longitudinal designs to examine ECF recovery during long-term abstinence, with large samples.

Introduction

Alcohol Related Brain Damage (ARBD) refers to changes in brain structure and function due to chronic consumption of alcohol at hazardous levels (Cox, Anderson and McCabe 2004). Damage may be caused directly by the toxic effects of alcohol or indirectly through vitamin B1 (Thiamine) deficiency (McCabe 2005).There is no agreed definition of ARBD. Zhar, Kaufman and Harper (2011) describe ARBD as one of a spectrum of disorders associated with alcohol misuse. Along this spectrum, sits Wernicke's Encepalopathy, Korsfakoff's Syndrome (KS) and other clinically defined disorders. In contrast to this, policy and literature published in Scotland uses ARBD as an umbrella term to encompass a range of neurological and cognitive difficulties caused by alcohol misuse. Although there are differences in the way the term ARBD is applied, what these definitions both highlight is that alcohol misuse does have a deleterious effect on the brain and associated functioning.

People with cognitive impairment due to alcohol misuse are likely to have memory problems and may experience confusion and disorientation (Kopelman, Thomson, Guerrini, and Marshall 2009). They may have difficulties processing emotional information and show little spontaneous behaviour (Oscar-Berman, Hancock, Mildworf, Hutner, and Weber 1990; Montagne, Kessels, Wester, De Haa 2006). Some of the difficulties observed may be associated with damage to the frontal lobes (Moselhy, Georgiou and Kahn, 2001)

The frontal lobes make up 30% of the cortical surface (Miller in Miller and Cummings 2007). They are the anatomical basis for a range of cognitive functions. Post mortem and in vivo MRI studies reveal that the frontal lobes are highly vulnerable to the direct effects of alcohol consumption (Ratti, Bo, Giardini, and Soragna 2002, Chanraud, Martelli, Delian et al 2007). Schweinsburg, Taylor, Alhassoon et al (2001) noted decreased levels of N-Acetylaspartic acid in frontal lobes of recently detoxified alcoholics as compared to healthy control participants and relative to other brain regions. They stated that this chemical acts as a 'marker of neuronal integrity' (p.g. 925) whereby reduced levels indicate neuronal loss. At a molecular level, the frontal lobes are vulnerable because of the high volume of NMDA receptors in this region. Cell death occurs in part because of over-activation of these receptors caused by of excessive secretion of glutamate, stimulated by ingestion of alcohol (De Witte, Pinto, Ansseau and Verbanck 2003).

While general intellectual functioning may appear intact, Moselhy et al (2001) state that 'detailed testing [of people who misuse alcohol]....has shown deficits in cognitive flexibility, problem solving, verbal and non verbal abstraction, visuomotor coordination, learning conditioning and memory' (pg. 363). These functions many be broadly thought of as executive cognitive functions (ECF), the anatomical basis of which is widely accepted as the frontal lobes (Miller in Miller and Cummings 2007). ECFs 'draw on the individual's primary cognitive skills (i.e. attention, language, memory and perception) to generate higher levels of creative

and abstract thought' (Swanson 2005, pg.117). ECFs are necessary for a person to be able to organise, plan and problem solve effectively. If frontal lobes are intact and ECFs preserved there may be little evidence of any impairment in a person's overall presentation even if they are experiencing impairment in another aspect of cognitive function. A deficit in even one of the aspect of ECF however is likely to cause pervasive difficulties in daily functioning (Lezak 2004).

Stuss (in Miller and Cummings 2007), suggests that the term ECF has been misused to inaccurately describe all cognitive functions associated with the frontal lobes. Stuss (2007) explains that the functions of the frontal lobe can be divided into four main domains, based on anatomical divisions. He suggests that executive cognitive functions are best understood as 'high level cognitive functions...that are involved in the control and direction (e.g. initiation, monitoring, switching, inhibiting) of lower more automatic functions' the anatomical basis of which is the lateral prefrontal cortex. This definition includes attention and working memory. The three other domains of functioning proposed by Stuss are: behavioural and emotional self regulatory functions, involved in 'behavioural rewards' recognition and so decision making; self regulation of drive, deficits in which appear as apathy and finally meta-cognitive processes involved in theory of mind and self awareness.

Although chronic alcohol misuse affects cognitive function, at least partial recovery can occur if abstinence is maintained (Smith and Hillman 1999, Kopelman et al 2009). Johnson-Greene et al (1997) found that 'cognitive and metabolic deficits' improved partially in alcohol dependent people abstinent for 30 days as compared to alcoholic individuals who had relapsed. Rapid recovery has been observed in the early weeks of abstinence on various neuropsychological assessments including assessments of ECF (Mann, Gunther, Stetter and Ackernann 1999). Moselhy et al (2001) highlight that however that some abnormalities can be seen in brain structure several years after the onset of abstinence. It is also unclear if all aspects of ECF recover to the same extent.

Objective:

This review synthesises evidence regarding recovery of ECF during abstinence. It is hoped that this review will add to a broader discussion of the extent of ECF impairment in people who misuse alcohol.

Review questions:

1. To what extent do executive cognitive functions recover during abstinence in people with a history of alcohol dependence?

2. Do all aspects of ECF recover to the same extent?

Method

Search Parameters

Searches were undertaken week beginning 2nd January 2012. Searches were conducted in: Ovid MEDLINE (1996 - January 2012), Embase (1996

– 2012 Week 01); EBSCO-host CINAHL, Health Source nursing/academic edition, PsychARTICLES, Psychology and Behavioural Science Collection, PSYCHINFO; Web of Knowledge, Web of Science (lemmatization on). Search terms were initially mapped to subject headings where appropriate for the database. Mapped terms included: alcohol, abstinence, cognition, executive function and frontal lobe. Terms were then searched unmapped. Searches included the following terms: {[alcohol*] OR [korsakoff*] OR [wernicke*] OR [ARBD]} and {[abstinence] OR [abstain*] OR [detox*] OR [withdraw*]} and {[execut*] OR [front*] OR [dysexecutive]}. Searches were combined with the Boolean term 'and'. Searches were limited to studies published since 2000 due to the review of literature pertaining to frontal lobe function and alcoholism published by Moselhy et al (2001).

To check the comprehensiveness of the electronic search, reference lists of all articles included in the review were scrutinised. Contents pages from the journal 'Alcoholism: Clinical and Experimental Research' and 'Alcohol and Alcoholism' from 2000 to week 1 2012 were also hand searched given the high proportion of selected papers included in the review published in these journals.

Inclusion criteria.

1. Studies published in English
2. Studies which include people with alcohol use disorders or receiving treatment for alcohol misuse

3. Studies which include assessment of ECF as defined by Stuss (2007)

4. Studies that examined abstinent alcoholic participants

Studies were excluded for the following reasons:

1. Studies examining abstinence from substances other than alcohol (including tobacco) which did not include an examination of alcohol misuse

2. Studies examining polysubstance users

3. Studies examining frontal lobe functioning not included in Stuss's definition of 'executive cognitive function'.

4. Case studies or unpublished dissertations

5. Previous literature reviews and systematic reviews.

Methodological Quality

The selected studies were assessed using a checklist measure developed by the trainee (appendix 1.2) based on the case-control checklist developed by the Scottish Intercollegiate Guideline Network (SIGN nd.) and CONSORT guidelines (2010) Studies were rated high moderate or low quality, based on arbitrary cut-offs (high:>79%, medium:40–79%, low:<39%). A second trainee rated all studies independently.

Data extraction

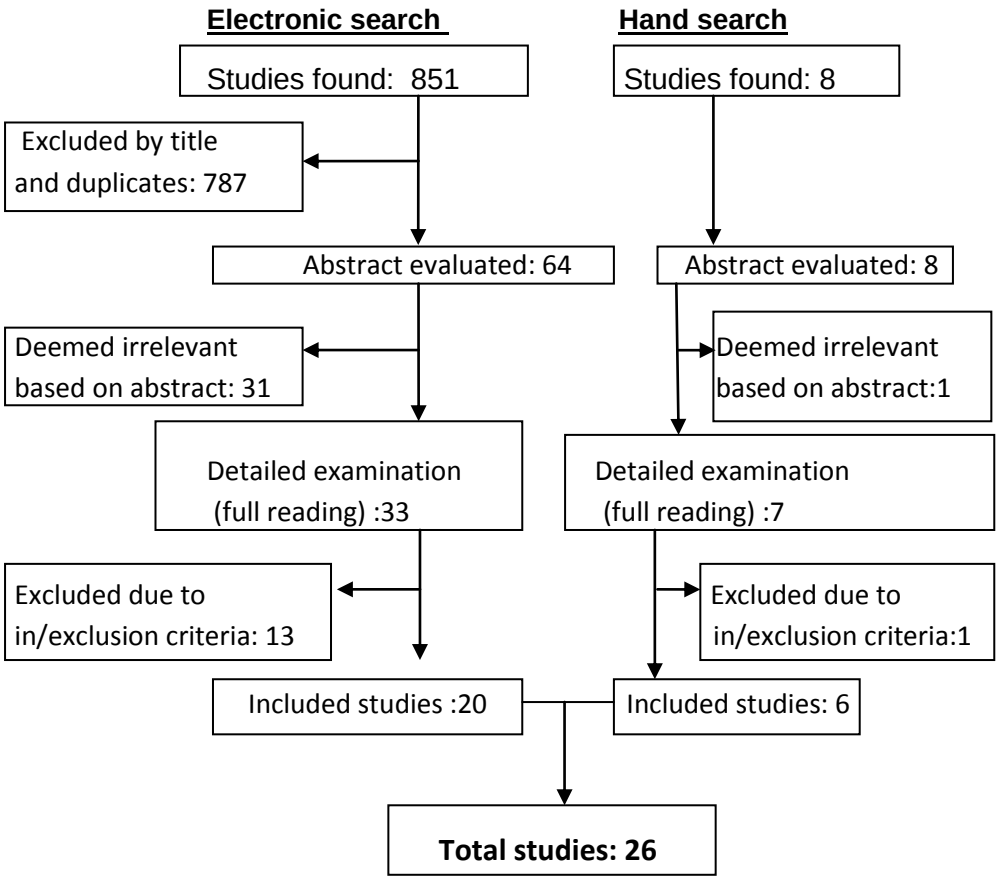
Information about participant characteristics, study design, ECF assessment tools used and main findings related to ECF was extracted from included studies. Where effect sizes were not reported, these were calculated if possible. In reporting results, reference is made only to one executive cognitive function examined by each assessment (e.g. cognitive flexibility) based on Suchy (2009) where appropriate.

Results

Study characteristics

An initial electronic search identified 851 studies. Examination of titles and abstracts excluded 818 studies through removal of duplicates and irrelevant studies. Thirty-three studies were examined in full. Thirteen were excluded after application of the inclusion and exclusion criteria. Hand searches identified a further 8 studies: one was removed after examination of the abstract and one after full review and application of the inclusion criteria. In total 26 studies were included in the review (figure 1).

Figure 1: Search Results



Studies included in review

A summary of each study is provided here. Only study findings related to ECF are reported. Agreement between the quality scores of each independent rater was reached for 91% of items. Discrepancies were discussed and final scores assigned. All studies reviewed were rated as medium quality (scoring between 15 and 19 points out of 24, 63 -79%) or high quality (scoring between 20 and 21 points, 83-88%). Seven longitudinal studies were found. Studies have been divided by design (longitudinal or cross sectional) and then into four sub-categories based on length of abstinence. In the case of longitudinal studies, the shortest follow up time was used to categorise studies as this enabled examination

of the shortest period in which recovery may have occurred. Longitudinal studies are presented here separately from cross-sectional studies. This is because longitudinal studies provide a better account of change in participant groups over time whilst avoiding potential between group confounding variables. Across studies, set clinical criteria such as those provided in the Diagnostic Statistical Manual (version three and four) or the International Classification of Diseases (version ten) were generally used to diagnose alcohol dependence. A summary table of study findings is provided in appendix 1.3).

Longitudinal Studies

- Up to 30 days abstinence

Cordovil De Sousa Uva, Luminet, Cortesi, Constant, Derely, and de Timary (2010) Quality Rating: 88%

This study compared ECF in 35 alcohol dependant participants (DSM-IV) at the start of abstinence and at 14 to 18 day follow-up with 22 healthy control participants matched for age, gender and education using the D2 cancellation test, Trail Making Test part B (TMTB) and the Stroop task. Performance of the alcohol dependant participants improved on the cancellation task and TMTB between baseline and follow up, suggesting an improvement in attention and cognitive flexibility (medium effect size (ES) difference time 1 vs. time 2).

Manning, Wanigaratne, Best, Hill, Reed, Ball, Marshall, Gossop, and Strang (2008) QR 83%

The authors examined ECF changes in 30 alcohol dependant participants (ICD-10) during inpatient detoxification. ECF was examined 4 days after admission and 26 days later using task of letter-number sequencing, letter and categorical fluency, the Hayling task, a set shifting task and the Stockings of Cambridge Test (based on the ToL test). The authors found that performance on measures of verbal aspects of ECF had improved significantly at follow up (small effect size difference from time 1 as compared to time 2) although potential retest effects were not controlled for. Non-verbal ECF was not found to improve significantly.

Dingwall, Maruff and Cairney (2011) QR:83%

This study examined cognitive impairment in 40 chronic and 24 episodic alcohol users in an Aboriginal sample. Chronic users drank more than 6 standards drinks a day per occasion, more than four days a week; episodic users consumed more than 6 standards drink per occasion fewer than four days a week. They were compared with 41 control participants who drank less than 6 standards drinks on fewer than 4 day a week. Participants were initially assessed 10 days into a rehabilitation programme and again four and eight weeks later. ECF was assed using tests from the CogState computerised battery (cited in Dingwall et al 2011) (the Groton Maze Learning Test, a visual working memory task and an attention task). After 4 weeks of abstinence, there were no differences

between chronic and episodic alcohol users compared to participants on these measures of ECF.

- 30 days to 6 months abstinence

Sullivan, Rosenbloom, Pferfferbaum and Lim (2000b)QR: 79%

The study examined ECF in 42 alcohol dependent men (DSM-IV) at 32 days abstinence and then at follow up 2 to 12 months later using WCST, the Brown Peterson Distracter task, digit span (reversed) and the Wechsler Memory Scale figure copy subtest. At follow-up 20 alcohol dependant participants had abstained and 22 had relapsed. The authors noted that improvement in both groups between baseline and follow up on the WCST (categories completed: cognitive flexibility; preservative errors: inhibition) although improvement in abstainers was larger (small to medium effect size difference between time1 and time2 in abstainer group vs. small ES differences between t1 and t2 in relapsers). Worsening in performance was observed the digit span reversed and WMS copy task in the relapsing group.

- **More than 6 months abstinence**

Pitel, Rivier, Beaunieux, Vabret, Desgranges and Eustache (2009)QR: 83%

Forty-four alcoholic participants (DSM-IV) were assessed at 11.5 days abstinence and 34 were followed up at 6 months. Fourteen had remained abstinent, 20 had relapsed. Performance was compared with 50 control participants matched for age, gender and education. ECF was examined

using letter and category fluency, Stroop, alternate response task, 2n-back task, an integration task and a verbal, spatial and multimodal span task. Sustained and divided attention were also examined using 2 subtests of the Attentional Assessment Test (Zimmerman and Fimm 1993 cited in Pitel et al 2009) Participants who had remained abstinent for 6 months performed comparably to control participants suggesting all aspects of ECF had recovered with 6 months abstinence. ECF deficits evident at baseline, worsened in people who relapsed (small to medium ES between t1 and t2 in relapsed group).

- More than 12 months abstinence

Fujiwara, Brand, Borsutzky, Steingass, and Markowitsch, (2007)QR: 83%

ECF was examined in detoxified alcoholics with KS (ICD-10 and DSM-IV) over a 2 year period by which time the average length of abstinence was 10 years. Forty-one KS participants were included at baseline, 20 were present at follow up, 20 participants were included at baseline. Measures of ECF were: Stroop test, digit span (reversed), ROCFT (copy) and a letter fluency test. At both test sessions, performance of the KS group was inferior to controls on but did not decrease between baseline and follow up assessment. Remaining difficulties reflected deficits in working memory and generativity.

Cross-Sectional Studies

- Up to 30 days abstinence

Noël, Van der Linden, Schmidt, Sferrazza, Hanak, Le Bon, De Mol, Kornreich, Pelc, and Verbanck (2001) QR: 83%

This study compared 30 alcohol dependant individuals (DSM-III) who were 3 to 4 weeks abstinent with 30 control participants matched for age, gender, education and vocabulary skills. ECF was assessed by: a modified Tower of London tasks, Hayling and Brixton tasks, fluency tasks (letter, category and alternate category), TMTB, flexibility task (alternate uses for tools), the alpha span task and the Stroop task. The authors found that the performance of alcoholic participants was significantly poorer across various aspects of ECF (initiation, inhibition, cognitive flexibility and working memory) (medium ES differences between groups).

Noël , Bechara, Dan, Hanak and Verbanck (2007) QR: 83%

This study examined ECF using the Hayling and Brixton tasks and the alpha span task. Thirty alcohol dependent participants (DSM-IV) between 18 and 21 days abstinent were compared to 30 control participants matched for age, gender and education. The authors found that performance was poorer on all tasks of ECF in the alcohol group (large ES difference between groups). Working memory, inhibition, cognitive flexibility and initiation appeared impaired.

Daig, Mahlberg, Schroeder, Gudlowski, Wrase, Wertenauer, Bschor, Esser, Heinz, and Kienast (2010) QR: 83%

This study compared the performance of 25 alcoholics (DSM-IV) who had been abstinent for 7 to 10 days with 15 healthy controls matched for age, gender and education on the Rey-Osterreich Complex Figure task (ROCF) (copy subtest) using the Rey handbook to score copy accuracy and strategy. No significant differences were found between groups. It was not possible to calculate effect sizes. This suggests alcoholic participants were able to employ well-ordered organisational strategies to the same extent as control participants.

Zinn, Stein and Swartwelder (2004) QR: 79%

This study examined ECF deficits in early abstinence (average 21.7 days) in 27 alcohol dependent participants (DSM-IV) as compared to 18 age-matched control participants. ECF was examined using: TMTB, ROCF(copy) task, Ruff Figural Fluency Task (RFFT) and letter fluency. They found deficits in ECF in alcoholic participants relative to control participants on TMTB and RFFT (medium to large ES differences between groups). This may suggest deficits with generativity and cognitive flexibility.

Ratti, Bo, Giardini and Sorogna (2002) QR:75%

This study compared ECF in 22 male alcohol dependant individuals abstinent for approximately 3 weeks (DSM-IV) with 22 healthy control participants. Alcohol dependant participants ECF performance was

impaired on all tasks (symbol digit modalities task, TMTB, Stroop, digit cancellation task and the Wisconsin Cards Sorting Test (WCST)). This suggests difficulties with attention, inhibition and cognitive flexibility (medium to large ES differences between groups).

Brokate, Hildebrandt, Eling, Fichtner, Runge and Timm (2003) QR: 75%

Differences in ECF between 23 alcohol dependent participants (ICD-10) who were between 14 and 21 days abstinent, 17 alcoholics with Korsakoff Syndrome (KS) (ICD-10) and 21 control participants were examined using letter and categorical fluency tasks, WCST, the n-back task and an alternative response task. Participants with KS performed significantly more poorly than both other groups on all measures of ECF (medium to large ES). Alcoholic participants performed more poorly than the control group only on the alternate response task (medium ES difference between groups) suggesting difficulties with inhibition.

Goldstein, Leskovjan, Hoff, Hitzemann, Bashan, Khalsa, Wang, Fowler and Volko (2004) QR: 75%

Forty alcohol dependant participants abstinent for an average of 17 days (DSM-III) were compared with 42 control participants and 72 crack cocaine addicts on assessments of ECF (a cancellation test, TMTB, WCST(error), Symbol Digit Modalities Test). ECF was impaired in the alcohol group as compared to the control group (small to medium ES differences between groups). Deficits were evident in attention, cognitive flexibility and inhibition.

Pitel, Beaunieux, Witkowski, Vabret, Guillery-Girard, Quinette, Desgranges and Eustache (2007) QR: 75%

This study compared ECF performance in 40 alcohol dependent participants (DSM-IV) in early abstinence (average 11.5 days) with 55 control participants matched for age and years of education on letter and category fluency tasks, the Stroop, alternate response task, 2n-back task, and an integration task. Alcohol dependant participants were impaired on all assessments as compared to the control group (medium to large ES differences between groups). Tasks of working memory and inhibition were especially impaired (large ES differences between groups).

Ihara, Berrios and London (2000) QR: 71%

Seventeen 'non-amnesic alcoholics' (DSM-IV) abstinent for 3 weeks were compared to 17 control participants matched for premorbid IQ and age using a Cognitive Estimation Test, verbal fluency, TMTB, WCST, Stroop, and the Behavioural Assessment of Dysexecutive Syndrome (BADS). The authors found that alcoholic participants were significantly impaired on across assessments of ECF even when premorbid in intelligence was within the normal range (medium to large ES differences between groups). Cognitive flexibility, initiation and inhibition appeared to be impaired.

Tedstone and Coyle (2004) QR: 71%

This study compared ECF performance on different aspects of attention in 98 abstinent alcoholics (57% of whom were abstinent for fewer than 30 days) to 30 control group participants matched for age and education. It was not clear how diagnosis was made. ECF was examined using:

Erikson Task, Stroop and a task of divided attention. The authors found a similar pattern of response across tasks in both groups, however detoxified alcoholics performed significantly worse than controls on measures of inhibition and divided attention (medium to large ES differences between groups).

Hildebrandt, Brokate, Eling, and Lanz (2004)QR: 63%

This study compared the ECF of 24 alcoholic participants and 12 participants with KS (ICD-10) who had been abstinent between 14 and 21 days with 40 control participants. On all assessments of ECF (letter and category fluency, alternate response task and 2Nback task) participants with KS performed more poorly than alcoholic and control participants (medium to large ES between KS group and other groups). On a task of cognitive inhibition and generativity, alcoholic participants performed more poorly than control participants (medium to large ES difference between AL and CG).

- 30 days to 6 months abstinence

Moriyama, Mimura, Kato, Yoshino, Hara, Kashima, Kato, and Watanabe (2002) QR: 83%

ECFs in 22 alcohol dependent participants (DSM-III) abstinent for an average of 7 weeks were compared to 15 control participants matched for education and age using a range of tools: Symbol Digit Modalities Task, a figure position test, TMTB and subtests of the BADS. ECF performance of alcoholic participants was impaired across measures other than the figure

position test with deficits on tasks of initiation, cognitive flexibility and attention (large ES between groups).

Davies, Pandit, Feeney, Stevenson, Kerwin, Nutt, Marshall, Boddington and Lingford-Hughes (2005) QR: 79%

This study compared ECF performance of 43 alcohol dependant particaipnts (DSM-IV) (median length of abstinence 5 months), with 58 control participants. ECF was examined using the ROCFT (copy), the TMT B, a letter fluency task and the Symbol Digit Modalities Task. Significant differences between groups (medium ES) were found in tests of cognitive flexibility and attention (TMTB and SDMT).

Šprah and Novak (2008) QR: 79%

This study compared ECF in 33 alcohol dependant participants (DSM-IV) who had been abstinent for an average of 8 weeks with 66 control participants matched for age, gender, education and handedness, using the Stroop task, spatial and verbal n-back tasks. Alcoholic participants were significantly impaired on tasks of inhibition (medium ES) and working memory (small ES) as compared to controls.

Sullivan, Rosenbloom and Pferfferbaum (2000a) QR: 75%

The authors compared ECF in 71 alcoholic dependent participants (DSM-IV) abstinent for 32 days to 67 control participants using the WCST, a self-ordered pointing task, a search task and a recency judgement task. ECF was significantly impaired in alcoholic participants suggesting difficulties

with working memory and cognitive flexibility. It was not possible to calculate effect size differences.

Munro, Saxton and Butters (2000) QR: 71%

This study investigated ECF in 36 abstinent older alcohol dependant participants (DSM-IV). The group was split in half based on the length of abstinence (more/less than 6 months). Groups were compared with 17 control participants matched for age, gender and education. ECF were examined using ROCFT (copy), letter fluency and TMTB and a clock-drawing task. Deficits in ECF were found in both groups of alcoholic dependant participants compared to control participants (small to large effect size differences). This may suggest residual difficulties with working memory and generativity (Suchy 2009).

Dawson and Grant (2000) QR: 66%

The authors examined the impact alcohol misuse on problem solving skills using the ROCFT (copy) and Boston Qualitative Scoring System to assess construction accuracy, organisation strategy and perceptual clustering. Twenty-nine short-term (average 39 days) and 29 long-term (12 years) abstinent alcohol dependent participants were compared with 29 control participants. Alcoholic participants had to have drunk approximately six drinks a day for at least 5 years prior to detoxification and met DSMIV criteria for alcohol dependence. Differences between control participants and recently detoxified alcoholics, but not long term abstinent participants were significant suggesting difficulties deficits in working memory in

recently detoxified alcoholics (large ES difference between recently detoxified group and control group).

- More than 6 months abstinence

Fein and McGillivray (2007) QR: 83%

This study examined the relationship between very long-term abstinence and ECF using the Stroop, ROCFT, TMTB, SDMT, short categories test, letter fluency, the Paced Serial Addition Test and subtests of the MicroCog Assessment (numbers backwards, world lists, analogies, and word match). Ninety-one alcoholic participants (DSM-IV) were divided into three groups based on the age at which they stopped drinking: before 50, between age 50 and 60, after the age of 60. Mean length of abstinence was 14.8 years (minimum 6 months). Participants were compared to 52 control participants matched for age and gender. All three groups were comparable to controls on assessments of ECF. This suggests that all aspects of ECF assessed had recovered after at least 6 months abstinence.

- More than 12 months abstinence

Fein, Torres, Price, and Di Sclafani (2006)QR:79%

ECF was examined after long-term abstinence using the same measures as Fein and McGillivary (2007). Forty-eight alcoholic participants (DSM-IV) abstinent for an average of 6.7 years were compared with 48 age and gender matched controlled participants. They found that alcoholic

participants performed comparably to control participants on all measures of ECF.

Oscar-Berman, Kirkley, Gansler and Couture (2004)QR: 75%

This study examined ECF in people with KS compared with alcoholics dependant participants (DSM-IV) abstinent for an average 7 years, 82 healthy control participants and 6 participants with right hemispheric lesions. ECF impairment was assessed by WCST, TMTB, letter fluency, RFFT and Progressive Planning Test. Performance in the KS group was impaired as compared to both the alcohol (small to large ES) and control groups (large ES). Alcohol dependent participants abstinent for longer than 5 years performed equivalently to controls.

Discussion

The results of this review are affected by the differences in the design of studies. Longitudinal studies enable examination of recovery in the same individuals over time, while cross sectional studies provide insight into recovery at discrete points in abstinence. The outcomes of cross-sectional studies are difficult to assimilate due to differences in participant and control groups, study methodologies and outcome measures used. Longitudinal studies control for such factors and may provide a better basis from which conclusions about the recovery of ECF over time can be drawn. The results from cross-sectional therefore provide evidence supplementary to longitudinal studies when considering the questions this review sought to answer.

To what extent do executive cognitive functions recover during abstinence in people with a history of alcohol dependence?

The outcomes from longitudinal studies show that ECF recovery appears to start very early in abstinence. One study found that observable change had occurred by as few as 14 days of abstinence (Cordovil De Sousa Uva et al, 2010). Overall however deficits in ECF were found in studies in which participants were abstinent for less than 6 months, although some recovery was evident. One longitudinal study was exceptional to this: Dingwall et al (2011) found that ECF performance in alcohol participants was comparable to control participants by four weeks of abstinence. The authors of this study noted however that the improvement they observed may have been due to the resolution of withdrawal symptoms. This is consistent with earlier work examining the rapid restoration of cognitive functions in early abstinence (Emmerson, Dustaman, Heil et al 1988). This emphasises the need for cautious interpretation of any assessment made within the first 30 days of abstinence. While similar recovery of function was not observed in individuals with KS, included in Fujiwara and colleagues' study, abstinence appeared to halt any further deterioration.

The evidence of progressive improvement over time in is not clear when non-longitudinal studies are compared. While deficits in ECF were evident in the majority of studies examining very short-term abstinence (less than 30 days), there did not appear to be an association between time abstinent and decreased severity of ECF impairment between studies if

participants had been abstinent for less than 6 months. Studies including participants abstinent for longer than this time found little evidence of ECF deficits unless indivudlas had been diagnosed with KS. Only Munro et al (2000) contrasts this: participants abstinent for more than 6 months performed no better on assessments of ECF than those abstinent for less than this time as compared to controls.

.

The outcomes of cross sectional studies appear to be consistent with the findings from longitudinal studies. ECF impairments are likely to remain at least until a person has been abstinent for more than 6 months after which time, ECF performance is more likely to be comparable to that of healthy individuals. Cross sectional studies considered in isolation cannot provide information about the 'speed' or patterns of recovery. The evidence gathered from these studies for this review does however enhance a general understanding of the extent to which ECF may be impaired in abstinent alcohol dependant individuals during different stages of their recovery.

Do all aspects of ECF which recover to the same extent?

All studies included in this review, both longitudinal and cross-sectional found deficits in at least one aspect of ECF up until 6 months of abstinence, including inhibition, initiation, working memory, attention, generativity and cognitive flexibility. With the exception of Munro et al (2000) impairments in specific aspects of ECF were not found following 6 months of abstinence, unless participants had been diagnosed with KS.

A minority of studies examined ECF longitudinally. Of those studies that reassessed participant in very early abstinence, Cordovil de Souse Uva et al (2010) found that, difficulties to persist in inhibition, while Manning et al (2008) found residual difficulties in cognitive flexibility and working memory. Each of these studies used different outcome measures to assess participants making results difficult to assimilate. As discussed, Dingwall et al (2011) found no continuing difficulties in very early abstinence, and no deficits were found in studies that included longer term follow up.

Results from cross sectional studies were difficult to understand collectively due to the range of measures used to assess ECF between studies. Where different studies employed similar ECF assessment measures, no consistent pattern was found between length of abstinence and participants' performances. The paucity of longitudinal work employing similar outcome assessments, along with the inherent difficulties of combing the outcomes of cross sectional studies with differing methodologies mean that it is not possible to conclude form this review whether all aspects of ECF recover to the same extent during early abstinence.

Limitations of reviewed studies

Of the studies reviewed here, only one provided justification for the sample size used (Manning et al 2008). Despite this, several authors noted that small samples sizes limited the generalisability of results. As well as this, the majority of studies excluded people with severe comorbid psychiatric disorders, comorbid drug use, physical health difficulties and history of head injury. It is unlikely that such samples would be representative of the general population of people who are dependent on alcohol.

There were also differences between studies in the strategies used to recruit control participants with methods such as public advertisement and recruitment from staff within the research department employed. This means that the control groups in themselves may not be representative of the general population, thus the comparisons they provide to the participants who misused alcohol may not be valid.

The measures used to assess ECF may have also limited the conclusions of some studies. Many of the measures used were designed primarily for general clinical use or have come to be accepted as measure of ECF over time. As such, they may not be the most appropriate tools for research and may not be sensitive to subtle changes in aspects of ECF (Burgess, Alderman, Forbes et al 2006; Suchy 2009).

Limitations of Review

This review is limited by the lack of any standardised method to combine the results of studies. While effect size calculations provide a very broad base from which study findings can be collectively understood, no standardised method, such as meta-analysis was used to assimilate results found between studies. Furthermore, although clinical criteria were used by most studies to define alcohol dependence there is likely to have been some variability between participants and across study in the extent to which people misused alcohol. The potential impact of this was not addressed in this review.

The quality rating system used failed to assess the relative strengths of sampling strategies. The rating system only considered whether authors clearly described the strategy they used. Given that the selection of participants is likely to be a weakness of some studies reviewed, it would have been prudent to examine how this affected the overall quality of the selected articles.

For the purpose of this review, one definition of ECF was used. As such, this review may have excluded papers which examined functions outwith this. Using a definition in this way allowed the parameters of the review to be defined, however this excluded papers which provided relevant information when considering the impact of ECF difficulties for people living with alcohol misuse disorders (for example Brand, Fujiwara,

Borsutzky et al 2005 examining decision making in Korsakoff Syndrome patients in a gambling task). The review also excluded studies that were not published in English. This is likely to have excluded potentially relevant studies from the review (for example Reka, Oguz, Tamas et al 2009).

In considering the second question, non-significant changes between baseline and follow up assessments in longitudinal studies were considered to be evidence of poorer recovery or continued impairment in particular aspects of ECF. Where studies were cross-sectional, significant differences between control groups and alcoholic participants on aspects of ECF were considered to reflect impairment. It is likely that these methods were not robust enough to explore and answer the question in a meaningful manner.

This review used Suchy (2009) as a guide to define which aspects of ECF were assessed by the tools employed by study authors. A single measure is likely to tap into various aspects of ECF. This review however described assessments with reference to only one of the aspects of ECF assessed by each tool. This is a limited interpretation the asp ects of ECF in fact examined by different measures.

Future research

Future research should make wider use of longitudinal naturalistic designs, including participants ranging age with comorbid health needs. This would provide a representative reflection of the extent of recovery in abstinent alcoholics. Future research would also benefit from using large samples and standardised measures of ECF (Suchy 2009).

The implications of deficits in ECF extend to the general wellbeing of people recovering from alcohol misuse. Moriyama et al (2002) found that deficits in ECF were associated with poorer non alcohol specific outcomes e.g. occupation, in abstinent alcoholics. It has been found targeted rehabilitation offered to people who have suffered a head jury and experience with working memory deficits improves cognition and benefits patients' daily lives (Serino, Ciaramelli, Di Santantonio et al 2007). It would be of interest to examine if interventions targeted at particular aspects of ECF in abstinent alcoholics could bring similar benefits that could help to improve their overall quality of life.

Conclusion

Based on the studies reviewed here, there appears to be evidence that up until 6 months of abstinence, ECF remains significantly impaired in people who misuse alcohol. Although some improvements in function do occur before 6 months, this should be interpreted cautiously as it may be difficult to differentiate this from the resolution of withdrawal symptoms. It appears that after 6 months of abstinence people will recovery essentially normal

ECF unless they are experiencing a chronic disorder such as KS. This review was unable to conclude if all aspects of ECF recover to the same extent. These conclusions must be considered in the context of the limitations of this review.

References

Brand, M., Fujiwara, E., Borsutzky, S., Kalbe, E., Kessler, J. and Markowitsch, H.J. (2005) Decision-making deficits of korsakoff patients in a new gambling task with explicit rules: associations with executive functions. *Neuropsychology*, 19(3), pp.267-77

Brokate,B.,Hildebrandt,H., Eling, P., Fichtner, H., Runge, K. and Timm, C.(2003) Frontal lobe dysfunctions in Korsakoff's Syndrome and chronic alcoholism: continuity or discontinuity?. *Neuropsychology*, 17(3), pp. 420–428

Burgess,P.W., Alderman,N.,Forbes,C.,Costello,A,Coates,L.M., Dawson,D. R., Anderson N.D.,Gilbert,S.J.,Dumontheil,I. and Channon,S. (2006) The case for the development and use of "ecologically valid" measures of executive function in experimental and clinical neuropsychology. *The Journal of the International Neuropsychological Society*, 12(2), pp. 194-209

Chanraud, S., Martelli, C., Delain, F., Kostogianni, N., Douaud, G., Aubin, H.J., Reynaud, M. and Martinot, J.L. (2007). Brain morphometry and cognitive performance in detoxified alcohol dependents with preserved psychosocial functioning. *Neuropsychopharmacology*, 32(2),pp. 429-38.

CONSORT (2010) *The Consort Statement* [internet] Available from: <http://www.consort-statement.org/consort-statement/> [Accessed 2 September 2011]

Cordovil De Sousa Uva, M., Luminet, O., Cortesi, M., Constant, E., Derely, M. and de Timary, P. (2010) Distinct effects of protracted withdrawal on affect, craving, selective attention and executive functions among alcohol-dependent patients. *Alcohol and Alcoholism*, 45(3), pp. 241–246

Cox,S., Anderson,I. and McCabe, L. (2004). A Fuller Life: Report of Expert Group on Alcohol Related Brain Damage. Stirling: University Of Stirling.

Daig, I., Mahlberg, R., Schroeder, F., Gudlowski, Y., Wrase, J., Wertenauer, F., Bschor, T., Esser, G., Heinz, A. and Kienast, T. (2010) Low effective organizational strategies in visual memory performance of unmedicated alcoholics during early abstinence. *GMS Psycho-Social-Medicine*, 7, pp.1 -10

Davies,S.J.C.,Pandit,S.A.,Feeney,A.,Stevenson,B.J.,Kerwin, R.W., Nutt, D.J., Marshall, E.J., Boddington, S and Lingford-Hughes, A. (2005) Is there cognitive impairment in clinically healthy abstinent alcohol dependence. *Alcohol and Alcoholism*, 40(6), pp.498–503

Dawson, L.K. and Grant, I. (2000) Alcoholics' initial organizational and problem-solving skills predict learning and memory performance on the Rey–Osterrieth Complex Figure. *Journal of the International Neuropsychological Society*, 6, pp. 12–19.

De Witte, P., Pinto, E., Ansseau, M. and Verbanck, P. (2003) Alcohol and withdrawal: from animal research to clinical issues. *Neuroscience and Biobehavioural Reviews*, 27, pp.189-97

Dingwall, K.M., Maruff, P. and Cairney, S. (2011) Similar profile of cognitive impairment and recovery for Aboriginal Australians in treatment for episodic or chronic alcohol use. *Addiction*, 106, pp.1419–1426

Emmerson,R.Y., Dustman,R.E., Heil,J. and Shearer, D.E. (1988) Neuropsychological performance of young nondrinkers, social drinkers, and long- and short-term sober alcoholics. *Alcoholism: Clinical and Experimental Research*,12(5), pp.625-629

Fein, G., Torres, J., Price, L.J. and Di Sclafani, V. (2006) Cognitive Performance in Long-Term Abstinent Alcoholic Individuals. *Alcoholism: Clinical and Experimental Research*, 30(9), pp.1538- 1544

Fein, G. and McGillivary, S. (2007) Cognitive Performance in Long-Term Abstinent Elderly Alcoholics. *Alcoholism: Clinical and Experimental Research*, 31(11), pp.1788- 1799

Fujiwara, E., Brand, M., Borsutzky, S., Steingass, H-P and Markowitsch, H.J. (2007) Cognitive performance of detoxified alcoholic Korsakoff syndrome patients remains stable over two years. *Journal of Clinical and Experimental Neuropsychology*, I, pp.1-12

Goldstein, R.Z., Leskovjan, A.C., Hoff, A.L., Hitzemann, R., Bashan, F., Khalsa, S.S., Wang, G-J., Fowler, J.S., and Volkow, N.D. (2004) Severity of neuropsychological impairment in cocaine and alcohol addiction: association with metabolism in the prefrontal cortex. *Neuropsychologia*, 42, pp.1447–1458

Hildebrandt,H.,Brokate,B.,Eling,P. and Lanz,M. (2004) response shifting and inhibition, but not working memory, are impaired after long-term heavy alcohol consumption. *Neuropsychology*, 18(2),pp. 203-211

Ihara, H., Berrios, G.E. and London, M. (2000) Group and case study of dysexecutive syndrome in alcoholism without amnesia. *Journal of Neurology, Neurosurgery and Psychiatry*, 68(6),pp. 731-737

Johnson-Greene,D., Adams,K.M., Gilman,S., Koeppe,R.A., Junck,L. ,Kluin, K.J., Martorell, O,S. and Heumann, M. (1997) Effects of abstinence and relapse upon neuropsychological function and cerebral glucose metabolism in severe chronic alcoholism. *Journal of Clinical and Experimental Neuropsychology*, 19 (3), pp. 378-385

Kopelman, M.D., Thomson, A.D., Guerrini, I. and Marshall. E.J. (2009) The Korsakoff Syndrome: clinical aspects, psychology and treatment. *Alcohol and Alcoholism*, 44(2), pp. 148-154

Lezak,M.D. (2004) Basic Concepts. In. Lezak, M.D., Loring, D.W., Hannay, H.J. and Fischer, J.S. ed. *Neuropsychological Assessment*. 4th edition. New York: Oxford University Press

Mann,K., Gunther,A., Stetter F. and Ackermann,K. (1999) Rapid recovery from cognitive deficits in abstinent alcoholics: a controlled test-retest study. *Alcohol and Alcoholism*, 34(4), pp. 567-574

Manning, V., Wanigaratne, S., Best, D., Hill, R.G., Reed, L.J., Ball, D., Marshall,J., Gossop, M. and Strang, J. (2008) Changes in neuropsychological functioning during alcohol detoxification. *European Addiction Research*, 14(4) pp.226-233

McCabe,L. (2005) *Alcohol related brain damage: knowledge and attitudes of frontline care staff* [internet]. Available from: <http://www.aerc.org.uk/documents/pdfs/finalReports/AERC_FinalReport_0011.pdf> [Accessed 21 December 2010]

Miller, B.L. (2007) The Human Frontal Lobes: An Introduction. In: Miller, B.L. and Cummings, J.L. ed. *The Human Frontal Lobe*. 2nd ed. New York: The Guilford Press. pp.3-11

Montagne, B. Kessels, R.P.C., Wester, A.J., De Haan, E.D.F. (2006) Processing of emotional facial expressions in Korsakoff's syndrome. *Cortex*, 42(5), pp. 705-710

Moriyama,Y., Mimura, M.,Kato,M., Yoshino, A., Hara, T., Kashima,H., Kato, A. and Watanabe, A. (2002) Executive Dysfunction and Clinical Outcome in Chronic Alcoholics. *Alcoholism: Clinical and Experimental Research*, 26(8), pp. 1239-1244

Moselhy, H.F., Georgiou, G. and Kahn, A. (2001) Frontal lobe changes in alcoholism: A review of the literature. *Alcohol and Alcoholism*, 36 (5), pp. 357–368

Munro, C.A., Saxton, J. and Butters, M.A. (2000) The Neuropsychological Consequences of Abstinence Among Older Alcoholics: A Cross-Sectional Study. *Alcoholism: Clinical and Experimental Research*, 24(10),pp. 1510-1516

Noël, X., Van der Linden, M., Schmidt, N., Sferrazza, R., Hanak, C., Le Bon, O., De Mol, J., Kornreich, C., Pelc, I. and Verbanck, P. (2001) Supervisory attentional system in nonamnesic alcoholic men. *Archives of General Psychiatry*, 58(12, pp.1152-8.

Noël ,X., Bechara, A., Dan, B., Hanak, C. and Verbanck, P. (2007) Response inhibition deficit is involved in poor decision making under risk in nonamnesic individuals with alcoholism. *Neuropsychology*, 21(6), pp.778-86

Oscar-Berman, M., Hancock, M., Mildworf, B., Hutner, N. and Weber, D. A. (1990), Emotional perception and memory in alcoholism and aging. *Alcoholism: Clinical and Experimental Research*, 14, pp. 383–393

Oscar-Berman, M., Kirkley, S.M., Gansler, D.A., and Couture,A. (2004) Comparisons of korsakoff and non-korsakoff alcoholics on neuropsychological tests of prefrontal brain functioning. *Alcoholism: Clinical and Experimental Research*, 28(4),pp.667-75

Pitel, A.L., Beaunieux, H., Witkowski, T., Vabret, F., Guillery-Girard, B., Quinette, P., Desgranges, B., and Eustache, F. (2007) Genuine episodic memory deficits and executive dysfunctions in alcoholic subjects early in abstinence. *Alcoholism: Clinical and Experimental Research*, 31(7),pp.1169-78

Pitel, A.L., Rivier, J., Beaunieux, H., Vabret, F., Desgranges, B. and Eustache, F. (2009) Changes in the episodic memory and executive functions of abstinent and relapsed alcoholics over a 6-month period. Alcoholism*: Clinical and Experimental Research*,33(3), pp.490-498

Ratti, M.T., Bo, P., Giardini, A. and Soragna, D. (2002), Chronic alcoholism and the frontal lobe: which executive functions are imparied?.*Acta Neurologica Scandinavica*, 10,pp. 276–281

Reka, M., Oguz, K., Tamas, S. and Dezo, N. (2009) Kognitiv funkciok vizsgalata alkoholfuggo betegeknel [Examination of cognitive function in patients with alcohol dependence], *Neuropsychopharmacologia Hungarica.* XI(3),pp.135-139

Schweinsburg, B. C, Taylor, M.J, Alhassoon, O.M, Vindeen, J.S., Brown, G.G., Patterson, T.L., Berger, F.and Grand I. (2001) Chemical pathology in brain white matter of recently detoxified alcoholics: a 1H magnetic

resonance spectroscopy investigation of alcohol-associated frontal lobe injury. *Alcoholism: Cliical and Experimental Research,* 25, pp. 924–934

Serino, A., Ciaramelli, E., Di Santantonio, A., Malagù, S., Servadei, F. and Làdavas, E. (2007) A pilot study for rehabilitation of central executive deficits after traumatic brain injury. *Brain Injury*, 21(1),pp.11-19

SIGN (nd.) SIGN *50: A guideline developers handbook, Case control studies checklist* [internet]. Available from: <http://www.sign.ac.uk/guidelines/fulltext/50/checklist4.html> [Accessed 21 August 2011]

Smith, I. and Hillman, A. (1999) Management of alcohol Korsakoff syndrome. *Advances in Psychiatric Treatment*, 5, pp. 271-27

Šprah,L. and Novak, T. (2008) Neurocognitive Assessment of Alcoholic Inpatients during Recovery from Alcoholism. *Zdravstveni Vestnik*, 77, pp.75–84

Stuss, D. (2007) New Approaches to Prefrontal Lobe Testing . In: Miller, B.L. and Cummings, J.L. ed. *The Human Frontal Lobe*. 2nd ed. New York: The Guilford Press. pp.292-305.

Suchy, Y. (2009). Executive functioning: Overview, assessment, and research issues for non-neuropsychologists. *Annals of Behavioral Medicine*,37, pp.106-116

Sullivan, E.V., Rosenbloom, M.J. and Pfefferbaum, A (2000a) Pattern of Motor and Cognitive Deficits in Detoxified Alcoholic Men. *Alcoholism: Clinical and Experimental Research*, 24(5), pp.611-621

Sullivan, E.V., Rosenbloom, M.J., Lim, K.O. and Pfefferbaum, A. (2000b) Longitudinal changed in cognition, gait and balance in abstinent and relapsed alcoholic men: relationship to changes in brain structure. *Neuropsychology*, 14 (2), pp. 178-188

Swanson, J. (2005) The Delis Kaplan Executive Function System: a review. *Canadian Journal of School Psychology*, 20(1),pp. 117 - 128

Tedstone,D and Coyle, Kieran (2004) Cognitive impairments in sober alcoholics: performance on selective and divided attention tasks. *Drug and Alcohol Dependence*,75(3),pp. 277-286

Zahr,N., Kaufman, K.L. and Harper, C.G. (2011) Clinical and pathological features of alcohol-related brain damage. *Nature Reviews: Neurology*, 7, pp. 284-294

Zimmermann, P. and Fimm, B. (1993) Testbatterie zur Erfassung von Aufmerksamkeitssto rungen. Psytest, Freiburg. Cited in Pitel, A.L., Rivier, J., Beaunieux, H., Vabret, F., Desgranges, B. and Eustache, F. (2009) Changes in the episodic memory and executive functions of abstinent and relapsed alcoholics over a 6-month period. Alcoholism*: Clinical and Experimental Research*,33(3), pp.490-498

Zinn, S., Stein, R. and Swartzwelder, H.S. (2004) Executive functioning early in abstinence from alcohol. *Alcoholism: Clinical and Experimental Research*, 28(9), pp.1338-1346

Chapter 2

Major Research Project

Variables associated with cognitive impairment in adults who misuse alcohol as assessed by the Addenbrooke's Cognitive Examination (revised)

(7065 words inc. lay summary, abstract, tables and references)

Written according to guidelines for submission to the journal *Alcoholism: Clinical and Experimental Research*

(Author's Instructions – see Appendix 1.1)

Address for Correspondence:

Academic Unit of Mental Health and Wellbeing

Centre for Population and Health Sciences

Gartnavel Royal Hospital

1055 Great Western Road

Glasgow, G12 0XH

Lay summary

Long-term alcohol misuse can damage the brain. This causes problems with memory and overall thinking ability. Health professionals need tools to help them to spot 'cognitive' difficulties of this kind. This means that people will get the support they need to help to improve their thinking ability.

The Addenbrooke's Cognitive Examination (Revised version) is a short test of memory and other thinking skills. It is widely used with people who might have Dementia. The Scottish Government have said that the ACE-R should be used to detect thinking problems in people who misuse alcohol, but no one has yet looked at whether it actually picks up the thinking difficulties these people might have.

This study looked at how well people who misuse alcohol did on the ACE-R compared to a group of healthy people. It also looked at whether different things about a person's drinking history (how much they drink, whether they had tried to stop drinking before and the length of time they had been using alcohol) were connected to their ACE-R score.

The study suggests that the length of time attendees at an alcohol service have been drinking or, if they have suffered effects of alcohol withdrawal is not strongly related to their scores on the ACE-R. In more general terms the ACE-R detects thinking problems in people who misuse alcohol.

Abstract

Background

The Addenbrooke's Cognitive Examination-Revised (ACER) is a widely used screening tool for Dementia. Although it is recommended for use in detecting cognitive impairment in people who misuse alcohol (Scottish Government 2007), the ACE-R has not been validated with this population. This study compared the performance of a group of people who misuse alcohol on the ACE-R with published normative data. The study examines whether deficits in ACE-R performance are associated with previous experience of a withdrawal from alcohol, duration of alcohol use and units consumed per week.

Methods

Data from 77 attendees at the Alcohol Liaison Service in NHS Ayrshire and Arran who had completed the ACE-R was extracted from an existing database and included in the study. The ALS group ACE-R total and domain scores were compared to those of the original validation control group used by Mioshi et al (2006). Using independent t–tests, differences in overall ACE-R performance and domain performance were examined. Independent t-tests were also used to determine the impact of previous withdrawal on ACE-R scores. Correlation analyses and multiple regression were used to examine relationships between aspects of drinking history (previous withdrawal, duration of use and units consumed per week) and ACE-R outcome.

Results

Total ACE-R scores, memory and fluency domain scores were significantly lower in the ALS group compared to normative data ($p<0.001$) It was not possible compare attention, language and visuospatial domain scores between groups as parametric assumptions were not met and only mean control group data was available. Attendees with a history of alcohol withdrawal had significantly poorer scores on the domain of attention compared to those who had not ($p=0.009$). They appeared to have lower overall ACE-R scores although this differnce was not significant ($p=0.128$). This analysis was underpowered.

Longer duration of alcohol drinking was associated with lower verbal fluency ($r=-0.362$), lower memory ($r=-0.239$) and lower visuospatial ($r_s=-0.234$) domain scores. Units consumed weekly were not significantly associated with any ACE-R domain score or total score. Longer duration of alcohol use and previous withdrawal experience together accounted for 10% of the variance in ACE-R total scores ($p=0.02$).

Conclusion

It is likely that most people who chronically and hazardously misuse alcohol will experience persisting cognitive impairment. The ACE-R appears to be a good measure for the assessment such difficulties in this population. This study suggests that it is not possible to accurately judge the severity of cognitive impairment in people who drink hazardously on the basis of duration of alcohol use and previous withdrawal experience alone. The study has methodological limitations and more rigorous

research examining the use of the ACE-R with this population is necessary.

Introduction

It is estimated that up to 50% of Scottish men and 30% of Scottish women drink alcohol in excess of weekly recommended limits (The Scottish Government 2009). Alcohol is a contributory factor in many health problems (e.g. cancer and stroke) however, it is central to understanding the aetiology of particular disorders. Alcohol Related Brain Damage (ARBD) is primarily caused by the chronic misuse of alcohol (Cox, Anderson and McCabe, 2004, Zahr, Kaufman and Harper 2011). While there is no set clinical definition of ARBD, it is a term that broadly encapsulates a range of cognitive impairments and disorders, such a Korsakoff Syndrome, that are associated chronic alcohol misuse (Cox et al 2004, Scottish Government 2007). People who experience ARBD may present with a number of problems including memory impairment, confusion, and impaired attention which may affect their ability to live independently (Smith and Hillman 1999).

- *Factors affecting cognitive impairment*

Particular drinking variables may be associated with the severity of cognitive impairment caused by alcohol misuse (Sullivan, Rosenbloom and Pfefferbaum, 2000). Cognitive deficits in alcoholic individuals have been found to be associated with the amount of alcohol consumed in the six months to twelve months prior to assessment (Errico, King, Lavallo and Parsons 2002). This may suggest that recent alcohol use has an impact upon cognition (Beatty, Tivis, Stott, et al 2000). As well as this, people with shorter drinking careers tend to show fewer cognitive impairments and

better recovery during abstinence (Pitel, Rivier, Beaunieux et al 2009). Greater lifetime consumption has been found to be associated with changes in brain structure in alcohol dependent individuals (Fein, Di Sclafani, Cardenas et al 2002).

There is evidence that those people who have previously experienced alcohol withdrawal will have greater cognitive impairment (Duka, Townshend, Collier and Stephens 2003, Loeber, Duka, Welzel et al 2009, Loeber, Duka, Welzel Marquez et al 2010). Alcohol misuse disrupts the molecular functioning of the brain. Chronic alcohol misuse reduces the sensitivity of N-methyl-D-aspartate (NMDA) receptors. This is a type of glutamate receptor. Because receptor function is inhibited, the brain maintains a homeostatic state by increasing glutamate secretion, however following cessation of alcohol use, the increased levels of glutamate causes excitotoxicity (De Witte, Pinto, Ansseau and Verbanck 2003, Loeber et al 2010). Repeated withdrawals are also associated with increased cortisol secretion, elevated levels of which are associated with poorer cognitive function (Errico et al 2002).

Understanding how aspects of a person's drinking history have an impact on cognitive function would make it easier to identify who is most at risk of impairment at an earlier stage in their contact with services. Appreciation of the factors that lead to increased cognitive impairment is however, different from establishing the presence of such impairment.

- *Assessment need*

The Mental Welfare Commission (MWC) in 2010 highlighted that people with ARBD can adapt to cognitive difficulties and may not immediately appear as having any impairment during clinical interview (Cox et al 2004, MWC 2010). Cognitive impairment may therefore be difficult to detect without using a standard cognitive assessment (Green, Garrick, Sheedy et al 2010). In reporting on the care of Mr H, a gentleman with ARBD, the Mental Welfare Commission highlighted that early opportunities to examine his cognitive function beyond a basic mental state exam were missed. The report highlights that unidentified cognitive impairments may have affected Mr H's ability to care for himself.

The need for timely and accurate identification of alcohol related cognitive impairment is crucial to promote chances of recovery. Seventy five percent of people with cognitive impairment caused by alcohol misuse will make some recovery if they receive appropriate treatment and maintain abstinence (Smith and Hillman 1999). The Scottish Government (2007) has stated that the Addenbrooke's Cognitive Examination Revised (ACE-R) can be useful in screening for cognitive impairments in people who are at risk of developing ARBD. Despite the government's recommendation, the use of the ACE-R with people who misuse alcohol has not been examined.

The ACE-R is a screening tool validated for Dementia and Mild Cognitive Impairment (Mioshi, Dawson, and Mitchell et al 2006). The measure assesses five domains of functioning: attention and orientation, memory,

verbal fluency, language and visuospatial abilities. The ACE-R and the original verson of the ACE are also known to be valid screening measures for deteting cognitive impairment in people who have experienced a head injury or have Parkinson's disease (Gaber, 2008; Reyes, Lloret, Gerscovich et al 2009). The ACE-R is designed for bedside use and takes around twenty minutes to administer. It requires no additional resoucres to complete and although it is copywritten it is a currently a free to use measure. This makes it ideal for use within the health service.

Green et al (2010) examined the use of the Repeatable Battery for Assessment of Neuropsychological Status (RBANS) in an Australian sample of people who misused alcohol. They found that on tasks of memory, new learning, visuospatial function and verbal fluency people who chronically misused alcohol were impaired as compared to healthy control participants. It may be that similar deficits in performance will be evident on the ACE-R.

Aims and hypotheses

The main aim of this study was to examine ACE-R performance in a sample of people who had been in contact with the Alcohol Liaison Service (ALS) in NHS Ayrshire and Arran as compared to normative data published by Mioshi et al (2006). The second aim was to examine associations between variables related to drinking (recent and historical consumption; previous withdrawal attempts) and ACE-R scores.

Hypotheses:

1. Scores of ALS attendees on the ACE-R are poorer than normative data.
2. ACE-R total and domain scores will differ significantly between attendees who have experienced a previous alcohol withdrawal and those who have not.
3. Current alcohol use, lifetime duration of use and previous withdrawal experience are associated with ACE-R performance in people who drink hazardously.

Methods

Design

This study used a retrospective design to examine between and within subject variables.

Participants

Data for this study was gathered from an existing database of people who had attended the ALS in NHS Ayrshire and Arran. Referral criteria for this service are: admission to a general hospital with physical complaints that appear to be associated with alcohol; patients undergoing medical detoxification from alcohol (the ACE-R is completed following resolution of withdrawal symptoms) and patients requesting help to achieve responsible drinking prior to discharge (Mason 2009). Data from all attendees with whom an ACE-R had been completed between January 2010 and March 2012 was made available for the study.

Attendees' data were included in the study if they had an Alcohol Use Disorder Identification Test (AUDIT) score greater than seven (indicative of a hazardous level of alcohol consumption) and information was available relating to all variables of interest.

Data published by Moishi et al (2006) on a healthy control group was used as a comparator with the ALS group. Making a comparison to this control group replicated a procedure employed by Gaber (2008).

Sample Size

Sample size calculations were completed using G*power software. There is no research available examining the ACE-R with community dwelling adults who misuse alcohol.

Hypothesis 1: Green et al (2010) found a large difference (d= 1.08) between people who misused alcohol and healthy control participants on the RBANS (total scores and memory, visuospatial and attention subscores). Assuming a large effect size (d=0.8), a sample size of 26 for each group was necessary (based on two tailed t-test for independent groups, error = 0.05, power = 0.8).

Hypothesis 2: The sample size required to detect a difference between those people with and without a withdrawal history was estimated using results from Loeber et al (2010) (d = 0.59). A sample size of 74 (37 in each group) was found to be necessary (two tailed t-test for independent groups, error = 0.05, power = 0.8).

Hypothesis 3: Recent use and chronicity of alcohol use have been found to have a large effect on cognition (recent use: Beatty, Tivis, Scott et al 2000 f^2 = 0.3; duration of use: Pitel et al 2009 r =0.67). Given the preliminary nature of this study, a medium effect size was assumed. A sample size of 80 was necessary to perform a multiple regression analysis including 3 variables (previous withdrawal, length of use and units consumed per week).

Ethical Issues

All data included were retrospective and anonymous to the researcher. No patients were approached for the purpose of this study. The National Research Ethics Committee London City and East approved the study via proportionate review (appendix 2.1). NHS Ayrshire and Arran Research and Development Department also approved study procedures (appendix 2.2).

Procedure

ALS staff administer the ACE-R to attendees if they suspect a person has a cognitive impairment. Information about attendee age, historic and recent alcohol use, and past withdrawal attempts is collected routinely with all attendees during initial assessment using a standardised assessment care pathway form. This information, including ACE-R total and subscores, is then entered onto an Excel database by ALS nurses.

For this study, a member of the ALS staff accessed this database and identified attendees with whom an ACE-R had been completed. The member of staff extracted information relating to attendees' gender, age (not date of birth), ACE-R total and domain scores, AUDIT score, previous withdrawal experience (yes/no) and current alcohol use. They also provided details of the age at which the person reported they had started drinking. Years of use was calculated from this. Anonymous data was transferred to the researcher using an encrypted USB stick belonging to a member of the ALS. Data was stored on a password protected Excel spreadsheet on an encrypted laptop owned by the University of Glasgow, held by the trainee for the duration of the study. No personal identifiable data was given to the trainee. The trainee had no access patient records.

Measures

Addenbrooke's Cognitive Examination – revised version (Mioshi et al 2006): This screening measure has been found to detect cognitive impairment in a number of populations. It has five sub- scores.

- *Attention and Orientation (maximum score 18)*

Orientation: participants are asked provide details of day, date, month, year, season and place.

Attention: subjects are asked to subtract 7 from 100 continuing in a serial manner for 5 subtractions. Subjects are then asked to spell 'WORLD' backwards. Points are given only for the task on which they perform best.

- *Memory (maximum score 26)*

Recall: subjects are given three words and asked to recall these after a short delay.

Anterograde memory: Subjects are asked to register a name and address. They are then asked to recall this after all other items of the ACE-R have been completed

Reterograde memory: subjects are asked to provide the names of current and past Prime Minister's and American Presidents.

- *Fluency (maximum score 14)*

Letter: Subjects are asked to provide as many words as possible in one minute beginning with a particular letter.

Category: Subjects are asked to provide the name of as many members of a particular category as possible in one minute.

- *Language (maximum score 26)*

Comprehension: subjects read a short instruction and follow it. They are then asked to follow a three-stage instruction. Later in the assessment, participants are asked to select a picture which matches a description they are given.

Writing: Subjects are asked to write a sentence. This must contain a subject and verb to score.

Repetition: Participants are asked to repeat four words and two short phrases after the examiner.

Naming: Subjects are asked to name 12 pictures.

Reading: Subjects are asked to read a list of five words.

- *Visuospatial (maximum score 16)*

Visuospatial abilities: Subjects are asked to draw two overlapping pentagons, a cube and a clock face.

Perceptual abilities: Subjects are asked to count the number of dots in four boxes without pointing at them. They are then asked to identify four letters printed incompletely.

Alcohol use details

Information about attendess' current use, previous withdrawal experience and age at onset of alcohol was reported to the ALS through self-report. Current daily alcohol use was most often reported to the ALS staff in terms of the type and volume of alcohol consumed. This information was passed to the researcher who calculated units per week consumed using an online calculator (Drinkaware website).

Data Analyses

Statistical analyses were carried out using The Statistical Package for Social Sciences version 18.0 (SPSS 2009) and GraphPad (nd). For the ALS sample, group mean age, mean ACE-R total score and domain scores were calculated where possible. Where data was not normally distributed, median scores were calculated.

H1: Comparisons between the ALS group and the normative data for age and ACE-R scores were made using a t-test (two tailed) for independent samples. Chi squared analysis was used to examine group differences in gender composition.

H2: Examination of the impact of previous withdrawals was made using independent t-tests or Mann Whitney Tests if parametric assumptions were not met.

H3: Examination of the associations between duration of use and units consumed and ACE-R scores was made using Pearson's correlation or Spearman's correlation where parametric assumptions were not met. Drinking variables that had an effect of at least r=0.1 or d=0.2 were entered into a regression model to examine the extent to which drinking variables were predictive of ACE-R total score.

Effects sizes are reported using Cohen's d (t-tests), Cohen's f^2 (regression analysis) and correlation coefficients (Pearson's r and Spearman's r_S).

Results

Demographic data

The ALS team identified 92 attendee records where ACE-R information was available. Three were excluded as the ACE-R data was incomplete. Eight cases were excluded because data was not available relating to variables of interest. Four were excluded as their AUDIT scores were not greater than seven.

The mean age in the ALS group was 51.8 (Standard Deviation = 11). The duration of alcohol use ranged from 3 years to 56 years. Mean duration of use was 33.2 years (SD = 10.7). The units consumed by individual

attendees per week was not normally distributed (Kolmogorov-Smirnov <0.001). The median units of alcohol consumed weekly was 140 (Inter Quartile Range=105 -262.5).

The Mioshi et al (2006) control group consisted of 63 participants (28 men and 35 women) with a mean age of 64.4 years (SD= 5.7). In comparing data between groups on age, equality of variances was not found (Levene's Test <0.001). Welch's unpaired t-test (two tailed) was therefore used to compare groups. The ALS group was significantly younger than the control group (t (118) = 8.7216, p<0.001). The proportion of males and females in each group differed significantly (chi-square (1) =16.633, p< 0.001). Although age differed significantly between groups, Mioshi et al (2006) found that age had no impact on ACE-R scores within their control group. For this reason, age was not used as a covariate.

Table 1: Demographic and ACE-R information: mean (Standard Deviation) or median*(inter quartile range)

Characteristic	ALS group (n=77)	Mioshi et al (2006) Control Group (n=63)	Significant difference	Z score
Gender (male)	60	28	<0.001	-
Age	51.8(11.0)	64.4(5.7)	<0.001	-
Units Consumed weekly	140* (105-262.5)	N/A	-	-
Duration of alcohol use (years)	33.2(10.7)	N/A	-	-
Previous withdrawal (yes)	N=55	N/A	-	-
ACE-R total score (100 points max)	71.6(12.9)	93.7 (4.3)	<0.001	-5.14
Attention and Orientation (18 points max)	15* (13-17)	17.7 (0.5)	Unable to calculate	-
Memory (26 points max)	14.5(5.3)	23.4 (2.7)	<0.001	-3.3
Fluency (14 points max)	7.11(2.92)	11.9 (1.7)	< 0.001	-2.94
Language (26 points max)	24* (21-25)	25.1 (1.5)	Unable to calculate	-
Visuospatial (16 pts max)	13*(11-14)	15.7 (0.7)	Unable to calculate	-

Between group differences: Total ACE-R and domain scores.

Kolmogorov-Smirnov's test was use to determine the normality of the ACE-R total and domain scores in the ALS attendee group. Data relating attention, visuospatial function and language was not normally distributed (attention: skewness = -0.67, kurtosis = -0.413; visuospatial: skewness = -0.23, kurtosis = -0.9; language: skewness = -1.36, kurtosis = 1.48). Median scores for attention, visuospatial function and language were 15 (IQR 13-17), 13 (IQR 11-14) and 24 (IQR 21-25) respectively. Data remained skewed after log and square root transformations. It was not possible to use nonparametric tests to examine the data further as published normative data provided mean group scores only.

Welch's unpaired t-test (two tailed) was used to compare grouped data as equality of variances was not assumed. Total ACE-R score, memory and fluency domain scores in the ALS group were significantly poorer than normative data with large effect size differences (ACE-R: $t(95)=14.12$, $p<0.001$ $d= -2.3$; Memory: $t(117)=12.84$, $p<0.001$, $d=-2.11$; Fluency: $t(118)=11.55$, $p<0.001$, $d=-1.94$). The ALS group z score obtained for ACE-R total was -5.14. For domain scores, these were -2.94 (fluency) and -3.3 (memory) (table 1) indicating significant impairment in the ALS group. Sixty-five attendees' (84.4%) total ACE-R scores were below 85.1 (2 standard deviations below the mean of the control group).

A test of the power of Welch's t-test ' [has] not been specifically discussed in the literature' (Minitab 2010, pg 18), however an 'approximate power

function' can be derived from one-way ANOVA power analysis (Minitab 2010). As such, post hoc power analysis was completed using one-way ANOVA as a model. This indicated that the study was adequately powered to make comparisons using Welch's test (power >0.8) (based on a large effect size difference, group size and error = 0.05)

Previous Withdrawal

ALS attendee data were split into two groups based on whether or not an attendee had previously experienced a withdrawal from alcohol. Fifty-five attendees had experienced a previous alcohol withdrawal and 22 had not (descriptive statistics table 2).

Table 2: Demographic data- previous withdrawal: mean (SD) or median*(inter quartile range)

Characteristic	No previous withdrawal (n=22)	Previous withdrawal (n=55)	Significant difference
Age	51.1(14.1)	51.9 (10.08)	-
Units Consumed weekly	140*(67-237)	150*(105 – 262)	-
Duration of alcohol use (years)	30.5* (19.5 – 41)	34* (28 – 41)	-
ACE-R score (100 pts max)	75.3(12.31)	70.36(12.92)	-
Attention and Orientation (18 points max)	16*(14-18)	15*(12 -17)	P=0.009
Memory (26 points max)	15.7(5.06)	14(5.39)	-
Fluency (14 points max)	7*(5 -11)	7*(4-8)	-
Language (26 points max)	24*(20-25)	24*(21-25)	-
Visuospatial (16 pts max)	12*(10-14)	13*(11-14)	-

Data for overall ACE-R performance and memory domain scores were normally distributed. Using independent t-tests, differences between

groups were found to be small and non-significant (ACE-R t(75)=1.540,p=0.128 d = 0.39, Memory t(75)=1.291, p=0.201, d =0.329).

Mann Whitney tests were used to examine the association between previous withdrawals and all other domains due to violation of parametric assumptions (Kolmogorov-Smirnov <0.05). Attention scores in attendees who had experienced a previous withdrawal differed significantly from those with no previous experience of withdrawal (U=375.5, z =-2.611, p=0.009, r =-0.29) (medium effect size). No other significant differences were found between groups (language U=596.0, z =-1.03, p=0.918; fluency U=461.50, z = -1.626, p=0.104; visuospatial, U=6.35, z= 3.46, p=0729). All effect sizes were small (language r = -0.011, visuospatial r = 0.039, fluency r = -0.19).

The size of the group of ALS attendees who had not experienced a withdrawal was smaller than that deemed necessary in a priori power calculations. Post hoc power analysis was therefore completed (non-parametric independent groups, error = 0.05, effect size r = -0.29). This found that the analysis was underpowered (power = 0.48).

Duration and units: Association with ACE-R outcome

Associations between duration of use, ACE-R total score, fluency and memory domain scores were examined using Pearson's correlation (two-tailed) as parametric assumptions were met. Visuospatial, language and attention scores were not normally distributed (Kolmogorov-Smirnov

<0.001). Spearman's correlation was therefore used to examine the association between these domain scores and duration of use.

A significant correlation was found between duration of use and ACE-R total score (r = -0.251, p=0.028 medium effect size). Significant correlations were also found between duration of use and fluency (r = -0.362, p=0.001, medium effect size) and memory scores (r=-0.239, p=0.036, small effect size). Using Spearman's correlation analysis, a significant association was found between duration of use and visuospatial function (r_S= -0.234, p =0.04). No significant correlations were found between duration, language and attention (table 3).

Table 3: Duration of use – ACE-R total, and domain scores (Spearman's correlation*)

	ACE-R	memory	fluency	attention*	language*	visuospatial*
Correlation Coefficient	-0.251	-0.239	-0.362*	-0.186	0.045	-0.234
Sig. (2-tailed)	0.028	0.036	0.001	0.105	0.697	0.040
N	77	77	77	77	77	77

Data relating to units consumed were not normally distributed therefore Spearman's correlation (two-tailed) was used for all analysis. No significant associations were found between units consumed per week and ACE-R total score (rho=-0.095, p=0.41) or any domain scores.

(table 4)

Table 4: Spearman correlation: units consumed per week ACE-R and domain scores

	ACE-R	Memory	fluency	attention	language	visuospatial
Correlation Coefficient	-0.095	-0.130	-0.073	-0.049	-0.124	0.098
Sig. (2-tailed)	0.410	0.258	0.526	0.672	0.283	0.395
N	77	77	77	77	77	77

- ***Alcohol variables and ACE-R outcome: Regression model***

Linear regression was used to explore those factors related to alcohol use that may predict ACE-R outcome. Units consumed weekly was not included as a variable in this analysis as the association between this factor and ACE-R total outcome was very small (r=-0.095). Duration of use and previous withdrawal were entered into the model as these variables appeared to have a small effect on ACE-R performance (duration: r = - 0.251, previous withdrawal d =0.39). There was not a significant correlation between these variables (r*point-biserial* = 0.127, p=0.272) Homoscedasticity and normality of the residuals was found (appendix 2.3).

A significant model including duration and previous withdrawal experience was found (F = *(1,74)* 4.132, p=0.021) explaining 10% of the variance(f^2 = 0.11, small effect size) (table 5).

Table 5: Regression- duration and previous withdrawal

		Unstandardized Coefficients		Standardized Coefficients
		B	Std. Error	Beta
1	(Constant)	85.392	5.014	
	Duration	-.342	.136	-.278
	Prev.withdraw	-3.415	3.157	-.120

The difference between the r square and adjusted r square values was small (shrinkage = 0.024)(Table 6).

Table 6: Adjusted R square shrinkage

Model	R square	Adjusted R square
1(Duration, p.withdraw)	.100	.076

Discussion

- *ALS group ACE-R performance as compared to normative data*

This study found that a sample of hazardous drinkers were significantly impaired on the ACE-R as compared to normative data. The majority of attendees in this sample scored at least 2 standard deviations below the mean of the control group. As well as total ACE-R score differences, the ALS group performed significantly more poorly on the domains of memory and fluency. This is consistent with previous research examining cognitive deficits in people who misuse alcohol (Green et al 2010, Oscar Berman and Marinkovic 2004). Deficits in memory and executive function have been found to persist in alcoholics even after 4 weeks (30 days) of abstinence (Daig et al 2010, Manning, Wanigaratne, Best et al 2008; Noel, Billieux, van der Linden et al 2009). The majority of people in contact with

the ALS return to community on discharge from hospital (Mason 2009). The ACE-R therefore potentially provides a way of detecting cognitive impairment in people who may not necessarily be in receipt of specialist interventions or care support.

- *Alcohol history factors associated with ACE-R performance*

No association between units consumed weekly and cognitive function was found. This replicates previous research examining the performance of people who misuse alcohol on cognitive screening measures (Green et al 2010).

Duration of alcohol use was associated with memory, visuospaital and fluency scores. Previous research has found that lifetime duration of alcohol use is associated with poorer episodic memory and visuospatial perception (Fama, Pfefferbaum and Sullivan 2004, Pitel et al 2009). Research has also shown that duration of alcohol use has some association with fluency scores, although this was also related to quantity of alcohol consumed (Fernández-Serrano, Pérez-García, Río-Valle et al 2010). Given that the associations found between duration of alcohol use and domain scores in this study were however small, it is therefore possible that other factors affected this outcome.

Attendees who had experienced at least one withdrawal from alcohol performed significantly more poorly on the domain of attention as compared to those without any withdrawal experiences. Total ACE-R score, memory and fluency domain scores were also poorer in attendees

who had experienced a withdrawal as compared to those who had not, however these differences were small and non-significant.

Duration of use and previous withdrawal experience predicted 10% of the variance in ACE-R total score in this sample. The results show that if applied to the general population, this model would explain approximately 8% of variance associated with the ACE-R (Field 2009). This suggests that consideration of only these two factors is unlikely to enable clinicians to judge the severity of cognitive impairment in people who misuse alcohol hazardously.

The small amount of variance explained in this study may be due to a number of factors. Previous research has found that the impact of alcohol withdrawal on cognition is greater when people have had two or more withdrawal attempts (Loeber et al 2009, 2010). The total number of withdrawals experienced by attendees was not considered here; the study may have benefited from more detail regarding this.

There is variability in the literature about the impact of lifetime alcohol consumption on cognitive function (Sullivan et al 2000). Duration of hazardous use has more consistently been found to be associated with cognition than duration of overall lifetime use (Hildebrandt, Brokate, Eling, and Lanz 2004). Although lifetime duration of alcohol use may have some impact on cognition, the unique effect of this will only be understood once delineated from the influence of duration of hazardous drinking behaviour.

While aspects of the study design could therefore account for the small amount variance explained, it is likely that other alcohol and non-alcohol related variables explain the remaining 90% of variance in outcome. Factors not examined in this study, such as premorbid intellectual function, education, the age at which a person stated drinking and familial alcohol history have been found to be associated with cognitive performance in samples of hazardous drinkers, although not to the same extent by all researchers (Daig et al 2010, Goldstein, Leskovjan, Hoff et al 2004, Oscar-Berman and Marinkovic 2004, Schafer, Butters,Smith et al 1991). The association between poor nutrition, alcohol misuse and cognitive impairment is also well established (McCabe 2005). Although it may be that some people who misuse alcohol habitually neglect their own wellbeing, chronic alcohol misuse impairs the ability of the gut to absorb vitamin B1. Deficiency of B1 causes small brain lesions associated with cognitive impairment (Martin, Singleton and Hiller–Sturmhöfel 2003).

Study limitations

This study was limited by the use of retrospective data. This design meant that fidelity to standard guidance for the administration of the ACE –R and the consistency with which the care pathway was used to gain information could not be assessed. Although members of the ALS have considerable experience in administering the ACE-R, no assessment of the accuracy of their scoring was made. There is some evidence that when people have cognitive impairment, health professionals may under score some ACE-R

items (Crawford 2010). Had this study been prospective, the reliability of the ACE-R ratings made by members of staff in the ALS could have been reviewed.

Information relating to the ACE-R and AUDIT were the only data gathered through standard tools although the AUDIT is based on self-report. All other information relating to drinking history and duration was gained through attendee self-report. It is unclear therefore how accurate this information was. As such, the data used in this study may not be a true representation of individuals' alcohol histories.

The ACE-R is not routinely administered with all patients referred to the ALS. The Alcohol Liaison Nurse attending any person referred makes this decision on the basis of their own clinical perception. The sample used in this study is therefore highly likely to be biased and unrepresentative of the population of people in contact with the ALS. This significantly restricts the extent to which the results of this study can be generalised.

In the study analysis, no account was made of the severity of attendees drinking; all data relating to people with an AUDIT score of more than 7 were treated as one group. This prevented any examination of the way in which severity of use could impact ACE-R outcome (for example hazardous use as compared to alcohol dependence).

While this study provides a preliminary examination of how people with alcohol misuse difficulties perform on the ACE-R, the methodological

limitations mean that these results are highly tentative. More rigorous studies are necessary to examine further the implications for use of this measure with this population.

Future research

Future research examining the ACE-R with people who drink hazardously would benefit from the use of prospective designs, recruiting large samples. Given the many variables that are likely to influence the extent of cognitive impairment in people who misuse alcohol, controlling for age, gender, education and premorbid IQ will be necessary. Furthermore, it will be necessary for future research to control for other health factors that may be associated with cognitive impairment, for example, traumatic head injury.

Age was not included as a variable in this study. As described, Mioshi et al (2006) found that age did not affect ACE-R performance in their control group. In alcohol research there is some evidence that older brains may be more vulnerable to the effects of alcohol misuse (Oscar –Berman and Marinkovic 2004). Fein et al (2002) found that lifetime duration of alcohol use and age are highly confounded. As this study primarily examined factors associated with ACE-R performance and alcohol use, lifetime duration of use was identified as a variable of interest to the exclusion of age. Further research may benefit from examining the way in which age and duration of use interact to affect ACE-R outcome. Furthermore, at present there is no research examining how early and late onset drinking may affect cognitive functioning as assessed by the ACE-R. Exploring this

may highlight particular vulnerabilities in older people to the effects of alcohol misuse.

In order to determine the clinical utility of the ACE-R, future research should seek to establish if the current cut- off scores used when assessing people with suspected Dementia are sensitive and specific when applied to a population of people who misuse alcohol. Although the ACE-R includes items that assess verbal and categorical fluency, it does not make a comprehensive assessment of executive function. Executive function may be particularly affected by chronic alcohol misuse (Oscar-Berman, Hancock, and Mildworf et al 1990). The original version of the ACE has been found to differentiate between people with Alzheimer's Disease and Frontotemporal Dementia (Mathuranath, Nestor, Berrios et al 2000). Further work is required to assess whether the ACE-R is sensitive to impairments in executive function in people who misuse alcohol.

Cognitive deficits often improve in people who misuse alcohol if abstinence is maintained. Repeated use of screening tools at short intervals can monitor this change. Practice effects may mimic improvement in cognitive function. The ACE-R already is available in three different versions. It would be useful to determine whether employing different versions of the measure entirely avoids practice effects with this population.

Conclusion

The majority of people who chronically misuse alcohol at a hazardous level are likely to be cognitively impaired to some extent. The extent of such impairment may be dependent on various alcohol and non-alcohol related factors, such as nutrition, and will differ between individuals. The ACE-R can detect cognitive impairment in this population and is likely to be an extremely useful tool for professionals in the health service who may encounter people who are using alcohol hazardously. It provides a short, standard way in which impairment can be assessed avoiding dependence on clinical judgement alone. This is particularly relevant with a population of community dwelling individuals. The use of standard assessment may identify needs which would otherwise be missed, as with the case of Mr H. Identification of cognitive impairment at an early stage using this tool could enable intervention to prevent further deterioration in function.

People who misuse alcohol are a highly heterogeneous group. Routine use of screening tools such as the ACE-R with people who are misusing alcohol may provide an objective way in which cognitive impairments can be detected without assumptions about the influence of individuals' drinking histories having to be made.

References

Beatty,W.W., Tivis, R., Stott,H.D., Nixon, S.J. and Parsons, O.A. (2000) Neuropsychological Deficits in Sober Alcoholics: Influences of Chronicity and Recent Alcohol Consumption. *Alcoholism: Clinical and Experimental Research*, 24(2),pp.149-154

Cox,S.,Anderson,I. and McCabe, L. (2004). A Fuller Life: Report of Expert Group on Alcohol Related Brain Damage. Stirling: University Of Stirling.

Crawford, S. (2010) *An investigation of the reliability of the Addenbrooke's Cognitive Examination – revised (ACE-R) and clinical research portfolio*. D Clin Psy thesis, University of Glasgow.

Daig, I., Mahlberg, R., Schroeder, F., Gudlowski, Y., Wrase, J., Wertenauer, F., Bschor, T., Esser, G., Heinz, A. and Kienast, T. (2010) Low effective organizational strategies in visual memory performance of unmedicated alcoholics during early abstinence. *GMS Psycho-Social-Medicine*,7.pp.1 -10

De Witte, P., Pinto, E., Ansseau, M. and Verbanck, P. (2003) Alcohol and withdrawal: from animal research to clinical issues. *Neuroscience and Biobehavioural Reviews*, 27(3), pp.189-97

Drinkaware, *Unit calculator* [internet]. Available from: <http://www.drinkaware.co.uk/tips-and-tools/drink-diary/#> [accessed 11th June 2012]

Duka T., Townshend J.M.,Collier K. and Stephens, D.M. (2003) Impairment in cognitive functions after multiple detoxifications in alcoholic inpatients. *Alcoholism, Clinical and Experimental Research*, 27(10),pp.1563-72

Errico, A.L.,King, A.C., Lovallo, W.R. and Parsons, O.A. (2002) Cortisol Dysregulation and Cognitive Impairment in Abstinent Males. Alcoholics. *Alcoholism, Clinical and Experimental Research,* 26(8), pp. 1198-1204

Fama, R., Pfefferbaum,A. and Sullivan, E.V (2004) Perceptual learning in detoxified alcoholic men: contributions from explicit memory, executive function, and age. *Alcoholism: Clinical and Experimental Research*, 28(11),pp.1657 - 1665

Fernandez-Serrano, M.J., Perez-Garcia, M. Rio-Valle, J.S. and Verdejo-Garcia, A. (2010) Neuropsychological consequences of alcohol and drug abuse on different
components of executive functions. *Journal of Psychopharmacology,* 24(9),pp. 1317–1332

Field, A. (2009) *Discovering Statistics Using SPSS*. 3rd ed. London:SAGE publications Ltd

Fein, G., Di Sclafani, V., Cardenas, V. A., Goldmann, H., Tolou-Shams, M. and Meyerhoff, D. J. (2002) Cortical Gray Matter Loss in Treatment-Naïve Alcohol Dependent Individuals. *Alcoholism: Clinical and Experimental Research*, 26, pp. 558–564

G*Power, version 3.1.2 [internet]. Available from: < http://www.psycho.uni-duesseldorf.de/abteilungen/aap/gpower3/download-and-register>. [accessed 28th May 2011]

Gaber, T. A.-Z. (2008). Evaluation of the Addenbrooke's Cogntive Examination's validity in a brain injury rehabilitation setting. *Brain Injury* , 22 (7-8), pp. 589-593

Goldstein, R.Z., Leskovjan, A.C., Hoff, A.L., Hitzemann, R., Bashan, F., Khalsa, S.S., Wang, G-J., Fowler, J.S., and Volkow, N.D. (2004) Severity of neuropsychological impairment in cocaine and alcohol addiction: association with metabolism in the prefrontal cortex. *Neuropsychologia* , 42, pp.1447–1458

GraphPad (nd.) *T-test calculator* [internet] Available from: <http://www.graphpad.com/quickcalcs/ttest1.cfm?Format=SD>. [accessed 9th June 2012]

Green, A., Garrick, T., Sheedy, D., Blake, H., Shores, E.A. and Harper, C. (2010) The effect of moderate to heavy alcohol consumption on neuropsychological performance as measured by the Repeatable Battery for the Assessment of Neuropsychological Status. *Alcoholism: Clinical and Experimental Research*, 34(3), pp. 443 - 450

Hildebrandt,H.,Brokate,B.,Eling,P. and Lanz,M. (2004) response shifting and inhibition, but not working memory, are impaired after long-term heavy alcohol consumption. *Neuropsychology*, 18(2),pp. 203-211

Loeber,S.,Duka,T.,Welzel,H.,Nakovics,H.,Heinz,A,,Flor,H. and Mann, K. (2009) Impairment of cognitive abilities and decision making after chronic use of alcohol: the impact of multiple detoxifications. *Alcohol and Alcoholism*, 44(2),pp.372-881

Loeber,S., Duka, T., Welzel Márquez, H.,Nakovics, H., Heinz,A. Mann,K. and Flor,H. (2010) Effects of repeated withdrawal from alcohol on recovery of cognitive impairment under abstinence and rate of relapse. *Alcohol and Alcoholism*, 45(6), pp. 541-547

McCabe,L. (2005) *Alcohol related brain damage: knowledge and attitudes of frontline care staff* [internet]. Available from: <http://www.aerc.org.uk/documents/pdfs/finalReports/AERC_FinalReport_0011.pdf> [Accessed 21 December 2010]

Manning, V., Wanigaratne, S., Best, D., Hill, R.G., Reed, L.J., Ball, D., Marshall,J., Gossop, M. and Strang, J. (2008) Changes in neuropsychological functioning during alcohol detoxification. *European Addiction Research*, 14(4) pp.226-233

Martin,P.R., Singleton, C.K. and Hiller–Sturmhöfel, S. **(**2003) The role of thiamine deficiency in alcohol brain disease. *Alcohol Research and Health*,27(2), pp.134-142

Mason, F. (2009) *Unique approach to alcohol liaison services in Scotland* [internet]. Available from: <http://www.piramhids.com/case-studies/view-casestudy?resid=666> [Accessed 6 May 2011]

Mathuranath, P., Nestor, P., Berrios, G., Rakowicz, W., and Hodges, J. (2000). A Breif Cogntive Test Bettery to Differentiate Alzheimer's Disease and Frontotemporal Dementia. *Neurology* , 55, pp. 1613-1620.

Mental Welfare Commission (2010) *Missed Opportunities: Findings from our visits to people with Acquired Brain Injury and Alcohol Related Brain Damage* [internet] <http://reports.mwcscot.org.uk/web/FILES/Visiting_Monitoring/Missed_opportunities.pdf> [Accessed 28 April 2012]

Minitab (2010) *2-sample t-test: Overview.* [internet]. Available from: <http://www.minitab.com/en-US/support/documentation/Answers/Assistant%20White%20Papers/2SampleT_MtbAsstMenuWhitePaper.pdf> [Accessed 22 June 2012}

Mioshi, E., Dawson, K., Mitchell, J., Arnold, R., and Hodges, J. R. (2006). The Addensbrooke's Cogntive Examination Revised (ACE-R): a brief cognitive test battery for dementia screening. *International Journal of Geriatric Psychiatry*, 21, pp. 1078 - 1085.

Noel, X., Billieux, J.,Van der Linden, M.,Dan, B.,Hanak,C.,de Bournonville,S., Baurain,C. and Verbanck,P. (2009) Impaired inhibition of proactive interference in abstinent individuals with alcoholism. *Journal of Clinical and Experimental Neuropsychology*, 31(1),pp.57-64

Oscar-Berman, M., Hancock, M., Mildworf, B., Hutner, N. and Weber, D. A. (1990), Emotional Perception and Memory in Alcoholism and Aging. *Alcoholism: Clinical and Experimental Research*, 14, pp. 383–393

Oscar-Berman, M. and Marinkovic, K. (2004) *Alcoholism and the brain: An Overview, NIAAA* [internet]. Available from: <http://pubs.niaaa.nih.gov/publications/arh27-2/125-133.htm> [Accessed 6 May 2011]

Pitel, A.L., Rivier, J., Beaunieux, H., Vabret, F., Desgranges, B. and Eustache, F. (2009) Changes in the episodic memory and executive functions of abstinent and relapsed alcoholics over a 6-month period. *Alcoholism:Clinical and Experimental Research*,33(3),pp.490-498

Reyes, M.A., Lloret, S.P., Gerscovich, E.R., Martin, M.E., Leiguarda, R. and Merello, M. (2009) Addenbrooke's Cognitive Examination validation in Parkinson's disease. *European Journal of Neurology*, 16 (1), pp. 142-147

Schafer, K., Butters, N., Smith, T., Irwin, M., Brown, S., Hanger, P., Grant, I. and Schuckit, M. (1991) Cognitive performance of alcoholics: a longitudinal evaluation of the role of drinking history, depression, liver function, nutrition, and family history. *Alcoholism: Clinical and Experimental Research,* 15(4), pp.653-660

Smith, I. and Hillman, A. (1999) Management of alcohol Korsakoff syndrome. *Advances in Psychiatric Treatment,* 5, pp. 271-27

SPSS (2009). PASW Statistics 18, Released. 30 July 2009. Chicago: SPSS Inc.

Sullivan,E.V., Rosenbloom, M.J. and Pfefferbaum, A (2000) Pattern of Motor and Cognitive Deficits in Detoxified Alcoholic Men. *Alcoholism: Clinical and Experimental Research*, 24(5), pp.611-621

The Scottish Government (2007) *Mental Health in Scotland: Closing the Gaps – Making a Difference – Commitment 13,* [internet]. Available from: < http://www.scotland.gov.uk/Publications/2007/12/10141643/9> [Accessed 8th July 2011]

The Scottish Government (2009) *Changing Scotland Relationship with Alcohol: A Framework for Action* [internet]. Available from: <http://www.scotland.gov.uk/Resource/Doc/262905/0078610.pdf> [Accessed 25th June 2012]

Zahr,N., Kaufman, K.L. and Harper, C.G. (2011) Clinical and pathological features of alcohol-related brain damage. *Nature Reviews: Neurology*, 7, pp. 284-294

Chapter 3

Advanced Clinical Practice

Reflective Account I

Lessons from direct therapeutic and MDT working (abstract only)

Full account bound separately (volume 2)

Address for Correspondence:

Academic Unit of Mental Health and Wellbeing

Centre for Population and Health Sciences

Gartnavel Royal Hospital

1055 Great Western Road

Glasgow, G12 0XH

Abstract

Working as a reflective practitioner is essential if psychologists are to identify future learning needs and ensure their own professional development. During training and beyond qualification, reflection on difficult or novel experiences can help provide further insight into such situations that may elicit new learning or highlight further development needs. In this reflective account I discuss two experiences I have had during placement which have made me feel challenged: one working with a client individually and the other in working with a multidisciplinary team. I use Boud et al's (1985) model to describe each experience as well as considering how this model is relevant as part of a meta-reflective process i.e. returning to earlier reflections and considering the new perspectives developed from this. Engaging in this process made it possible to consider these experiences together which highlighted three main themes in my reflection: the impact of lacking confidence in the ability to apply psychological theory competently, the frustration which can emerge from practice and the importance of addressing these to aid communication and build good working alliances. This account also briefly describes how these experiences and themes are relevant in the context of National Occupational Standards for Psychologists (British Psychological Society 2006) as well as developing policy regarding the Psychologists' role in NHS Scotland.

Chapter 4

Advanced Clinical Practice

Reflective Account II

Promoting service delivery: A reflective account on the necessity of teamwork and leadership

(abstract only)

Full account bound separately (volume 2)

Address for Correspondence:

Academic Unit of Mental Health and Wellbeing

Centre for Population and Health Sciences

Gartnavel Royal Hospital

1055 Great Western Road

Glasgow, G12 0XH

Abstract

The Well's report (2011) defines how Applied Psychologists working in the NHS are integral to managing and leading services. Within organisations, a transformational style of leadership has been found to aid companies and services in difficult times whilst providing a satisfactory product to customers. The NHS is increasingly facing tightening of resources in parallel to increasing demands for access. I have been working in a team which has recently faced a large increase in the demands made of team members in terms of the size of the population they are expected to deliver a service to. In this review, I have considered how these top down demands have placed pressures on team members and how the team has coped with these. I use Rolfe and colleagues' (2001) model of reflection to support my reflection on this experience as well as link my experience to broader theories of transformational leadership and systems theory. I consider how in the context of the National Occupational Standards for Psychologists (British Psychological Society 2006) my experience of working in the team is relevant to the roles I will undertake post qualification.

Appendix 1.1: Instructions for submission to *Alcoholism-Clinical and Experimental Research*

WILEY-BLACKWELL

ALCOHOLISM
CLINICAL & EXPERIMENTAL RESEARCH

Alcoholism

Clinical and Experimental Research

Published on behalf of the Research Society on Alcoholism and the International Society for Biomedical Research on Alcoholism

Edited by:
Ivan Diamond, Editor-in-Chief, and Harriet de Wit, Deputy Editor

Print ISSN: 0145-6008
Online ISSN: 1530-0277
Frequency: Monthly
Current Volume: 36 / 2012
ISI Journal Citation Reports® Ranking: 2010: Substance Abuse: 3 / 14
Impact Factor: 3.468

Author Guidelines

Alcoholism: Clinical and Experimental Research is the official publication of the Research Society on Alcoholism and the International Society for Biomedical Research on Alcoholism. It is a peer-reviewed, multidisciplinary journal that publishes papers based on original research that make substantial contributions to the understanding of the etiology, treatment, and prevention of alcohol-related disorders. Two kinds of papers may be submitted, full-length papers and critical reviews. Papers that the editors consider to have cross-disciplinary interest and significance may be highlighted as Feature Articles. The journal will also publish invited mini reviews and editorial commentaries.

Ethical/Legal Considerations

Note to NIH Grantees: Pursuant to NIH mandate, Wiley-Blackwell will post the accepted version of contributions authored by NIH grant-holders to PubMed Central upon acceptance. This accepted version will be made publicly available 12 months after publication. For further information, see www.wiley.com/go/nihmandate.

A submitted manuscript must be an original contribution not previously published (except as an abstract or a preliminary report), must not be under consideration for publication elsewhere, and, if accepted, must not be published elsewhere in similar form, in any language, without the consent of Wiley-Blackwell. Each person listed as an author is expected to have participated in the study to a significant extent. Although the editors and referees make every effort to ensure the validity of published manuscripts, the final responsibility rests with the authors, not with the Journal, its editors, or the publisher. **All manuscripts must be submitted on-line through the journal's Web site at** http://mc.manuscriptcentral.com/acer. **See submission instructions under 'On-line manuscript submission.'**

Patient anonymity and informed consent: It is the author's responsibility to ensure that a patient's anonymity be carefully protected and to verify that any experimental investigation with human subjects reported in the manuscript was performed with informed consent and following all the guidelines for experimental investigation with human subjects required by the institution(s) with which all the authors are affiliated. Authors should mask patients' eyes and remove patients' names from figures unless they obtain written consent from the patients and submit written consent with the manuscript.

Research ethics. You will be asked during online submission to confirm that your study has been approved by relevant bodies (e.g. institutional review boards, research ethics committees) and that appropriate consent was obtained for studies involving human or animal participants.

Copyright: All authors must sign a copy of the Journal's 'Copyright Transfer Agreement' and submit it at the time of manuscript submission. The copyright transfer agreement is available here.

Permissions: Authors must submit written permission from the copyright owner (usually the publisher) to use direct quotations, tables, or illustrations that have appeared in copyrighted form elsewhere, along with complete details about the source. Any permissions fees that might be required by the copyright owner are the responsibility of the authors requesting use of the borrowed material, not the responsibility of Wiley-Blackwell.

Manuscript Submission

On-line manuscript submission: All manuscripts must be submitted on-line through the journal's Web site at http://mc.manuscriptcentral.com/acer. First-time users: Please click the Register button from the menu and enter the requested information. On successful registration, you will be sent an e-mail indicating your user name and password. Print a copy of this information for future reference. Note: If you have received an e-mail from us with an assigned user ID and password, or if you are a repeat user, do not register again; just log in. Once you have an assigned ID and password, you do not need to re-register, even if your status changes (that is, author, reviewer, or editor). Authors: Please click the log-in button from the menu at the top of the page and log into the system as an Author. Submit your manuscript according to the author instructions. You will be able to track the progress of your manuscript through the system. If you experience any problems, please contact Mary Newcomb, Acerjournal@earthlink.net, or by calling (317) 375-0819. You may also contact Lisa Daitch, Associate Managing Editor, LDaitchACER@gmail.com, or by calling (925) 915-0271. Requests for help and other questions will be addressed in the order received.

Authors who submit a manuscript do so with the understanding that if it is accepted for publication, copyright in the article, including the right to reproduce the article in all forms and media, shall be assigned exclusively to the Research Society on Alcoholism.

Articles, editorials, letters to the editor, and other text material in the journal *Alcoholism: Clinical and Experimental Research* represent the opinions of the authors and do not reflect the opinions of the Research Society on Alcoholism, the International Society for Biomedical Research on Alcoholism, the publisher, or the institution with which the author is affiliated, unless the contrary is clearly specified. All papers are subject to peer review by a Review Editor (member of the Board of Review Editors, the Editor, and the Associate Editors) and one or two referees. Authors may suggest up to four, and disqualify two, potential referees.

A cover letter signed by all authors must accompany the manuscript. The letter should state that: a) the submitted manuscript has been read and approved by all signatories, b) all authors acknowledge that they have exercised due care in ensuring the integrity of the work, and c) none of the original material contained in the manuscript has been submitted for consideration nor will any of it be published elsewhere except in abstract form in connection with scientific meetings.

Requirements for authorship are: (1) substantial contribution to conception, design, gathering, analysis and/or interpretation of data and (2) contribution to the writing and intellectual content of the article.

Page Charges

Manuscripts accepted for publication in *Alcoholism: Clinical and Experimental Research* will be assessed a page charge of $60.00 (U.S.) per printed page to cover, in part, the cost of publication. Color pages will be assessed a page charge of $650. Editorial consideration of a manuscript is in no way related to the author's ability to assume the page charge, but it is expected that this charge will be paid by the author's research funds that supported the research. Requests for waiver of page charges will be considered at the time of acceptance, if rationale can be provided.

OnlineOpen

OnlineOpen is available to authors of primary research articles who wish to make their article available to non-subscribers on publication, or whose funding agency requires grantees to archive the final version of their article. With OnlineOpen, the

Appendix 1.1: Instructions for submission to *Alcoholism-Clinical and Experimental Research* (continued)

author, the author's funding agency, or the author's institution pays a fee to ensure that the article is made available to non-subscribers upon publication via Wiley Online Library, as well as deposited in the funding agency's preferred archive. For the full list of terms and conditions, see: http://wileyonlinelibrary.com/onlineopen#OnlineOpen_Terms.

Any authors wishing to send their paper OnlineOpen will be required to complete the payment form available from our website here.

Prior to acceptance there is no requirement to inform an Editorial Office that you intend to publish your paper OnlineOpen if you do not wish to. All OnlineOpen articles are treated in the same way as any other article. They go through the journal's standard peer-review process and will be accepted or rejected based on their own merit.

Types of Papers

The following types of articles may be submitted for publication in the journal.

Manuscripts exceeding the word and reference limitations will be returned without review.

- Critical Review articles **are not to** exceed 4500 words (excluding title page, abstract, references, figure legends, tables, and figures.) **References are not to exceed 50.**

- Original Research **are not to** exceed 4500 words (excluding title page, abstract, references, figure legends, tables, and figures.) **References are not to exceed 50.** It should be noted that Alcoholism: Clinical & Experimental Research does not impose a minimum length on original research articles.

-Commentaries **are not to exceed** 2500 words (excluding title page, abstract, references, figure legends, tables and figures) and 20 references.

Preparation of Manuscript

Please ensure that all text (including abstract, body of manuscript, figure legends, and references) is submitted as double-spaced type. **We also require all text be line-numbered.** Manuscripts that do not adhere to the following instructions will be returned to the corresponding author for technical revision before undergoing peer review.

Title page:

The title page should include:

- The complete manuscript title
- The full names of all authors, their highest academic degrees, and affiliations
- Name and address for correspondence, including fax number, telephone number, and e-mail address
- All sources of support, including pharmaceutical and industry support, that require acknowledgement

Manuscripts that do not adhere to the following instructions will be returned to the corresponding author for technical revision before undergoing peer review.

Structured abstract and key words: The article should be briefly summarized or abstracted in a short paragraph (approximately 300 words) at the beginning of the text on a separate page. It should contain 4 elements labeled: Background, Methods, Results, and Conclusions. At the end of the paragraph, provide no more than 5 key words or phrases.

Text: Organize the manuscript into four main headings: Introduction, Materials and Methods, Results, and Discussion. Define abbreviations at first mention in text and in each table and figure. If a brand name is cited, supply the manufacturer's name and address (city and state/country).
Abbreviations: For a list of standard abbreviations, consult the Council of Biology Editors Style Guide (available from the Council of Science Editors, 9650 Rockville Pike, Bethesda, MD 20814) or other standard sources. Write out the full term for each abbreviation at its first use unless it is a standard unit of measure.

References: The authors are responsible for the accuracy and completeness of information contained in the references. The journal uses **Harvard Style for Referencing**.

-Citation

Cite references in the text by name and year in parentheses. Several publications by the same author or group should be listed in chronological order; those that appeared in the same year should be distinguished by a,b,c, etc. Where there are two authors, both should be named, but with three or more only the first author's name plus "et al." should be given.

-Reference List

The list of references should only include works that are cited in the text and have been published or accepted for publication. Personal communications and unpublished works should only be mentioned in the text. Do not use footnotes or endnotes as a substitute for a reference list. Reference list entries should be alphabetized by the last names of the first author of each work. References should be compiled **(double-spaced)** at the end of the article in alphabetical order. Identify multiple authors published in the same year with an a,b,c, etc. after the year. In-text citations should be listed by author name(s) and year of publication in parentheses.

*Journal article, list **all** authors*
1. Aragon CMG, Spivak K, Amit Z (1991a) Effect of 3-amino-1,2,4-triazole on ethanol-induced narcosis, lethality and hypothermia in rats. Pharmacol Biochem Behav 39:55-59.
Aragon CMG, Stotland LM, Amit Z (1991b) Studies on ethanol-brain catalase interaction: evidence for central ethanol oxidation. Alcohol Clin Exp Res 15:165-169.

Book chapter
2. Holtzman SG (1990) Discriminative stimulus effects of drugs: relationship to potential for abuse, in Modern Methods in Pharmacology, Vol. 6, Testing and Evaluation of Drugs of Abuse (Adler M, Cowan A eds), pp 193-210. Wiley-Liss, New York.

Entire book
3. Julien RM (1985) A Primer of Drug Action. 4th ed. WH Freeman, New York.

Software
4. Epi Info [computer program]. Version 6. Atlanta, GA: Centers for Disease Control and Prevention; 1994.

Online journals
5. Friedman SA. Preeclampsia: a review of the role of prostaglandins. Obstet Gynecol [serial online]. January 1988;71:22-37. Available from: BRS Information Technologies, McLean, VA. Accessed December 15, 1990.

Database
6. CANCERNET-PDQ [database online]. Bethesda, MD: National Cancer Institute; 1996. Updated March 29, 1996.

World Wide Web
7. Gostin LO. Drug use and HIV/AIDS [JAMA HIV/AIDS Web site]. June 1, 1996. Available at: http://www.ama-assn.org/special/hiv/ethics. Accessed June 26, 1997.

Figures: There are three preferred formats for digital artwork submission: Encapsulated PostScript (EPS), Portable Document Format (PDF), and Tagged Image Format (TIFF). We suggest that line art be saved as EPS files. Alternately, these may be saved as PDF files at 600 dots per inch (dpi) or better at final size. Tone art, or photographic images, should be saved as TIFF files with a resolution of 300 dpi at final size. For combination figures, or artwork that contains both photographs and labeling, we recommend saving figures as EPS files, or as PDF files with a resolution of 600 dpi or better at final size. More detailed information on the submission of electronic artwork can be found at http://authorservices.wiley.com/bauthor/illustration.asp

Each figure should be submitted individually - one file per figure.

Figure legends: Include legends for all figures. They should be brief and specific, and they should appear on a separate manuscript page after the references. Use scale markers in the image for electron micrographs, and indicate the type of stain used.

Color figures: The journal accepts for publication color figures that will enhance an article. Authors who submit color figures will be assessed a charge of $650 per color page to cover the cost for color reproduction. If they decide not to pay for color reproduction, they can request that the figures be converted to black and white at no charge.

Tables: Create tables using the table creating and editing feature of your word processing software (eg, Word, WordPerfect). Do not use Excel or comparable spreadsheet programs. Each table should include the table title, appropriate column heads, and explanatory legends (including definitions of any abbreviations used). Tables should be self-explanatory and should supplement, rather than duplicate, the material in the text. Cite tables consecutively in the text, and number them in that order. Tables may be submitted at the end of the manuscript text file. Table legends should appear on a separate page, labeled 'Table Legends'.

Appendix 1.2 :Quality Rating Scale: Systematic Review

	Yes =1 point
1. The study context is clear	
2. Hypotheses/aims/objectives are clearly stated	
PARTICIPANTS	
3. Sampling strategy is clearly defined	
4. It is made clear how 'caseness' of participants has been defined	
5. Control group included	
6. Eligibility criteria are clear and (if applicable)equally applied to each group	
7. Prior matching completed	
8. Prior sample size calculation described/size justified	
ASSESSMENT	
9. Methods described to allow replication	
10. Measures clearly described	
11. Two or more methods of EF assessment used	
12. Length of abstinence reported	
13. Longitudinal analysis conducted	
ANALYSIS	
14. Descriptive statistics are presented	
15. Analysis is appropriate	
16. Potential confounds are controlled for	
RESULTS	
17. Participant flow is clearly described	
18. Effect sizes are reported for measures of executive function	
19. Confidence intervals are stated	
CONCLUSION	
20. Results are clearly related to aims and hypotheses	
21. Conclusions are appropriate related to results	
22. Generalisability and implications of study discussed	
23. Limitations of study acknowledged	
24. Ethical considerations described (including informed consent and/or details of ethics application)	
TOTAL	**/24**

Appendix 1.3 Systematic Review- data extraction table

Table 1: Studies up to 30 days abstinence (*longitudinal studies)

	Quality score	**AL: alcohol group N; diagnostic assessment; length of abstinence CG: control group N; variables matched for**	**Measure of Executive Function**	**Main finding related to executive function**	**Impaired ECF aspects /not improved from t1 to t2**	**Effect size (differences between groups/ time 1 vs time 2) Significant difference***
*Cordovil De Sousa Uva et al (2010)**	88% No prior sample size (SS) calculation described Potential confounds not controlled CI not stated	AL:35, DMS-IV, t1 = onset of abstinence t2 = 3 week abstinent CG:22; age, gender and education.	D2 Cancellation Test Trail Making Test part B Stroop Task (colour and words)	ECF remained impaired at end of 3 weeks. AL performance improved at t2 as compared to t1 on D2 and TMTB. Improvement was not observed on Stroop.	Inhibition (Stroop)	**D2 Test** ALt1 vs t2 d = 1.53 (speed)* ALt1 vs t2 d=0.67(error)* **TMTB** Alt1 vs t2 d = 0.53 * **Stroop** AL vs CG d= 0.55* T1 vs t2 d=0.16
Noel et al (2001)	83% No prior SS calculation described No longitudinal analysis ES not reported No CI stated	Al: 30; DSM-III;, 3-4 week abstinence CG: 30;age, gender, education and vocabulary skills	Tower of London (ToL) Brixton test Hayling test Letter, alternate & category fluency TMTB Stroop Object alternate use test Alpha span task	AL in early abstinence show deficits in ECF.	Initiation (Hayling) Inhibition (Stroop, alternate fluency) Cognitive Flexibility (Brixton,alternate use, TMTB) Working memory (ToL, alpha span)	**Hayling speed** AL vs CG d=0.92* **Brixton error** AL vs CG d= 0.42* **Alternate Fluency** Al vs CG d=-1.36* **Letter fluency** AL vs CG d=-0.37 **Category fluency** AL vs CG d=-0.51 **Alternate object use** AL vs CG d= -0.45* **Stroop** AL vs CG d= -0.97* **TMTB** AL vs CG d=-0.82* **ToL moves to correct error** AL vs CG d=1.86*

						Alpha task (alphabetical recall) Unable to calculate EF
Noel et al (2007)	83% No prior SS calculation described No longitudinal analysis Recruitment /follow up unclear No CI stated	AL: 30 ;DSM-IV; 18 to 21 days abstinent CG: 30 ; age, gender, education	Brixton test Hayling test Alpha span task	AL group impaired on all aspects of ECF.	Working memory (alpha span) Initiation (Hayling) Cognitive Flexibility (Brixton)	**Hayling speed*** AL vs CG d =0.97(speed) **Brixton*** AL vs CG d = -1.53 **Alpha error*** AL vs CG d = 1.85
*Manning et al (2008)**	83% No control group No prior matching Potential confounds not controlled Confidence Interval (CI) not stated	AL :30; ICD-10; t1=4days, t2 = 26 days No control group	Letter-number sequencing Letter and category fluency Hayling test Set shifting Stockings of Cambridge Test (towers)	After 4 weeks of abstinence there were significant improvements on measures of verbal ECF but not in non-verbal ECF . Impairment in cognitive flexibility and working memory remained between t1and 2.	Cognitive flexibility (set shifting) Working memory (towers)	**Letter-number sequencing** T1 vs t2 d = 0.3* **Letter fluency** T1 vs t2 d = 0.31* **Category fluency** T1 vs t2 d =0.33* **Hayling *** T1 vs t2 d = 0.33 **Set shifting** T1 vs t2 d=0.13 **Towers** T1 vs t2 d=0.2

Daig et al (2010)	83% No prior SS calculation described Fewer than 2 measures of ECF used No longitudinal analysis No CI reported	AL: 25; DSM-IV;7-10 day abstinent CG:15; age, gender and education	Rey Complex Figure (ROCFT) (Copy) rated using ROCFT handbook	No differences between groups were found .	N/A	**Unable to calculate for copy strategy**
*Dingwall et al (2011)**	83% No prior matching No prior SS calculation ES not reported No CI stated	AL Chronic:40 ; >6 drinks per occasion> 4days/week; AL Episodic :26; >6 drinks per occasion <4days/week; 10days (baseline) – 4 weeks, 8week, 11 months (follow up times) CG: 24 (>6 drinks/occasion)	CogState battery subtests: Groton Maze Learning Test Visual working memory task Attention task	Significant improvement observed between baseline and 4 week follow up in both groups. No differences between chronic and episodic users as compared to controls on measures of ECF at 4 weeks abstinence	N/A	**Unable to calculate effect size**
Zinn et al (2004)	79% No prior SS calculation No longitudinal analysis ES not reported No CI stated Limitations not acknowledged	AL: 27; DSM-IV; average abstinence 21.7 days CG:18; age	ROCFT Letter fluency Ruff Figural Fluency Test (RFFT) TMT B	Deficits in ECF remain in early abstinence.	Generativity (RFFT) Cognitive Flexibility (TMTB)	**RFFT (unique designs)** AL vs CG d = -0.95* **TMTB** AL vs CG d = 0.89* **Letter fluency** AL vs CG d =-0.46 **ROCFT** AL vs CG d=-0.45

Ratti et al (2002)	75% No prior SS calculation described No longitudinal analysis Recruitment/follow up unclear ES not reported No CI stated Limitations not acknowledged	AL: 22; DSM-IV abstinent for 3 weeks CG: 22; age, education, IQ	Symbol Digit Modalities Test (SDMT) TMTB Stroop Digit cancellation Wisconsin Card Sorting Test (WCST)	AL participants performed poorly on all ECF tasks as compared to CG.	Attention (SDMT, cancellation) Inhibition (Stroop, WCST errors) Cognitive flexibility (WCST categories, errors, TMTB)	**SDMT** AL vs CG d = -1.24* **TMT B** AL vs CG d = -1.17* **Stroop** AL vs CG d=- 0.74* **Digit cancellation** AL vs CG d= -1.58* **WCST (categories)** AL vs CG d=-1.3* **WCST (preservative error)** AL vs CG d = 0.9*
Brokate et al (2003)	75% No prior matching No prior SS calculation described No longitudinal analysis ES not reported No CI stated Ethical considerations not described	AL :23; ICD10; 14-21days abstinent AL KS 17; ICD10 CG:21; not matched	Letter and categoy fluency WCST N- back task Alternate response task	KS group scored significantly poorer on nearly all ECF tasks compared AL group. AL participants were only poorer than CG on alternate response task.	**KS:** Working memory (nback) inhibition (alternate response task) **AL:** Inhibtion (alternate response task)	**Fluency (letter- category)** Unable to calculate **WCST** Unable to calculate **N-back (error)** KS vs CG d=1.17* KS vs AL d =1.05* ALvs CG d=0.34 **Alternate response (hit)** KS vs CG d=-5.55* AL vs CG d = -0.68* KS vs AL d= -1.35*

Goldstein et al (2004)	75% Hypotheses not clear No prior matching No prior SS calculation described No longitudinal analysis Recruitment/follow up unclear No CI stated	AL: 40; DSM-III; avg 16.9 days abstinent Cocaine users: 42 CG: 72; not matched	Cancellation TMT B WCST(errors) SDMT *(measures were assimilated by authors into a unitary assessment of ECF based on their own examination of assessments)*	AL impaired performance of ECF as compared to CG (no significance level for individual tests provided).	Attention (cancellation task, SDMT) Cognitive flexibility (TMTB) Inhibition (WCST errpe)	**Cancellation Test** CG vs AL d = 0.53 **TMTB** CG vs AL d = 0.41 **Symbol Digit Modality Test** CG vs AL d = 0.63 **WCST (error)** AL vs CG d = 0.27
Pitel et al (2007)	75% No prior SS calculation described No longitudinal analysis Potential confounds not controlled Effect Size (ES) not reported No CI stated Limitations not acknowledged	AL: 40; DSMIV; avg 11.5 days abstinence CG:55; age and education	Letter and category fluency Stroop Alternate response task 2N- Back task Integration task	AL impaired on all aspects of ECF.	Generativity (fluency) Working memory (2nback) Inhibition (Stroop, alternate response) Integration (integration task)	**Total fluency** AL vs CG: d = -0.70* **Stroop test:** AL vs CG d =-0.89* **Alternate response task:** AL vs CG d =-0.65* **2n-back task** AL vs CG d=-0.96* **Integration task** AL vs CG d =-0.79*

Ihara et al (2000)	71% No prior SS calculation described No longitudinal analysis Potential confounds not controlled Recruitment/follow up unclear ES not reported No CI stated Limitations not acknowledged	AL: 17; DSM-IV; 3 weeks CG:17; age and premorbid IQ	Cognitive Estimation Test TMTB Verbal Fluency WCST Stroop *Behavioural Assessment of Dysexecutive Syndrome (BADS) (dysexecutive syndrome: aspects of test outside Stuss's definition)*	Impaired performance by AL on Stroop, WCST, TMT, *BADS*	Cognitive Flexibility (TMTB, WCST categories) Inhibition (Stroop**)** *Initiation (BADS)*	**TMTB** AL vs CG d = - 0.81* **WCST** (categories achieved): AL vs CG d= -0.6* **Stroop** AL vs CG d= -0.94* **Verbal Fluency** AL vs CG d=-0.37 **CET** AL vs CG d=-0.53 ***BADS*** *AL vs CG d= -1.06**
Tedstone and Coyle (2004)	71% No prior SS calculation described Length of abstinence not reported Caseness not made clear No longitudinal analysis Potential confounds not controlled Recruitment /follow up unclear Ethical considerations not described	AL: 98;unclear how diagnosis made; 57% abstinent less than 30 days CG: 30 ;age, education	Eriksen task Stroop Divided attention task	Significant impairment was evident on all tasks.	Attention (DA task) Inhibition (Stroop and Eriksen)	**Divided Attention (errors made)** AL vs CG d= -0.69* **Stroop** AL vs CG d**=** -2.14* **Eriksen** AL vs CG d = -0.73 *

Hildebrandt et al (2004)	63% No prior matching No prior SS calculation described No longitudinal analysis Potential confounds not controlled Recruitment/follow up unclear ES not reported No CI stated Limitations not acknowledged Ethical considerations not described	AL: 24; ICD-10; abstinence 14 to21 days KS: 12; ICD-10; abstinence 14 to21 days CG: 40; not matched	Category and letter fluency Alternate response task 2n-back task	AL impaired in alternative response and fluency but not 2n-back KS impaired on all tasks . KS were impaired on tasks of 2Nback task relative to AL participants.	**KS**: inhibition (alternate response task) Working memory (2N- back) **AL**: Inhibition (alternate response task)	**Fluency (letter-category)** Unable to calulate **Alternate resp. (error)** KS vs CG d= 0.95* KS vs AL d= 0.82* AL vs CG d= 0.87* **2n-back (error)** KS vs CG d= 1.55* KS vs AL d=1.21* AL vs CG d= 0.44

(Appendix 1.3 continued)

Table 2: Abstinence form 30 days up to 6 months(*longitudinal studies)

	Quality score	**AL: alcohol group N; diagnostic assessment; length of abstinence CG: control group N; variables matched for**	**Measure of Executive Function**	**Main finding related to executive function**	**Impaired ECF aspects /not improved from t1 to t2**	**Effect size (differences between groups/ time 1 vs time 2) Significant difference***
Moriyama et al (2002)	83% No prior SS calculation descried No longitudinal analysis ES not reported No CI stated	AL:22 ; DSM-III; avg 7 week abstinence CG:15; education and age	Symbol Digit Modalities task Figure Position TMTB *BADS subtests*	Most aspects of ECF in the AL group were impaired.	Attention (SMDT) Cognitive Flexibility (TMTB) *Initiation (BADS)*	**SDMT** AL vs CG d= -1.04* **FP** AL vs CG d= -0.17 **TMTB** AL vs CG d = 0.82 ***BADS*** *AL vs CG d = -1.7**
Davies et al (2005)	79% No prior matching No prior SS calculation described No longitudinal analysis No CI stated Limitations not acknowledged	AL:43; DSM-IV; 5 months. CG:58 ; not matched	ROCFT (copy) TMT B Letter Fluency Symbol Digit Modalities Test	Impairment was found on TMTB and SDMT.	Cognitive Flexibility (TMTB) Attention (SDMT)	**ROCFT** AL vs CG d=-0.15 **TMTB** AL vs CG d=-0.53 * **Fluency** AL vs CG d= -0.02 **SDMT** AL vs CG d=- 0.61*

Sprah and Novak (2008)	79% No prior SS calculation described No longitudinal analysis ES not reported No CI stated Ethical considerations not described	AL: 33; DSM-IV ; 8 weeks avg. CG:36;age, sex, education and handedness	Stroop Spatial and verbal N-back tasks	Alcohol abstainers compared to healthy controls showed impairment on Stroop task . Only error score in spatial 1n back task was higher than controls.	Inhibition (Stroop) Working memory (spatial nback)	**Stroop** AL vs CG d= -0.61* **Spatial N back (1-back)** AL vs CG d= 0.40*
*Sullivan et al (2000b)**	79% No prior matching No prior SS calculation described ES not reported No CI stated Limitations not acknowledged	AL: T1: 42; DSM-IV; 32 days abstinent T2: 20abstained, 22 relapse; 2-12 month follow up	WCST Brown Petersen distracter task (nonverbal/verbal) Digit Span reversed Wechsler Memory Scale Copy figure (immediate)	Abstainers improved to a greater extent than relapsers. Relapsers' score decreased where abstainers did not.	N/A	**WCST (categories completed)** abst t1 vs t2 d=0.5* relapse t1 vs t2 d=0.3* **WCST (preservative errors)** abst t1 vs t2 d=0.35* relapse t1 vs t2 d=0.17 **BP task verbal** abst t1 vs t2 d=0.14 relapse t1 vs t2 d=0.11 **BP task nonverbal** abst t1 vs t2 d=0.08 relapse t1 vs t2 d=-0.27* **DS backward** abst t1 vs t2 d=0 relapse t1 vs t2 d= -0.2* **WMS copy** abst t1 vs t2 d=0 relapse t1 vs t2 d= -0.9*

Sullivan et al (2000a)	75% No prior matching No prior SS calculation described No longitudinal analysis ES not reported No CI stated Limitations not acknowledged	AL: 71 DSM-IV; 32 days abstinent CG: 67; not matched	WCST Pointing task (verbal/nonverbal) Search task Recency Judgement	ECF significantly impaired in AL vs CG.	Cognitive Flexibility (WCST categories) Working memory (self ordered pointing task, recency judgement, search task)	**Executive function** CG vs AL: unable to calculate effect size
Munro et al (2000)	71% No prior SS calculation described No longitudinal analysis Potential confounds not controlled Recruitment /follow up unclear ES not reported No CI stated Ethical considerations not described	AL: 36; DSMIV; split into 2 groups G1:18; less than 6 months abstinent (4-24 wks. ab.) G2:18; more than 6 abstinent(26 wk to 4yr ab.) CG:17; age, gender, education	ROCFT(copy) Letter fluency TMT B Clock drawing	Deficits remain in ECF impaired for older alcoholics who had been abstinent for more than 6 months (G2).	Working memory (ROCFT, clock drawing) Generativity (fluency)	**ROCFT copy** G1 vs CG d = -0.99* G2 vs CG d=-0.58 **Fluency** G1 vs CG d = -0.97* G2 vs CG d= -0.98* **Clock Drawing** G1 vs CG d= -0.6 G2 vs CG d= -1.15* **TMTB** G1 vs CG d=- 0.01 G2 vs CG d=-0.2

Dawson and Grant (2000)	66% No prior matching Fewer than 2 measures of ECF used No prior SS calculation No longitudinal analysis Recruitment /follow up unclear ES not reported No CI stated Limitations not acknowledged Ethical considerations not described	AL1: 29; DSMIV, average 39 days AL2:29; DSMIV, average 12 yr CG: 29; not matched	ROCFT (copy) rated using Boston Qualitative Scoring System	Both the AL2 and CG groups performed better than the AL1 group on constructional accuracy, organisation score, and perceptual clustering index.	Working memory	**Construction** AL1 vs CG d= -1.35 * AL1 vs AL2 d= -0.93* **Organisation** AL1 vs CG d= -1.15* AL1 vs AL2 d = -0.68* **Perceptual** AL1 vs CG d = -0.69 * AL2 vs CG d = -0.66*

(Appendix 1.3 continued)

Table 3: Abstinence longer than 6 months(*longitudinal studies)

	Quality score	**AL: alcohol group N; diagnostic assessment; length of abstinence CG: control group N; variables matched for**	**Measure of Executive Function**	**Main finding related to executive function**	**Impaired ECF aspects /not improved from t1 to t2**	**Effect size (differences between groups/ time 1 vs time 2) Significant difference***
Fein and McGillvary (2007)	83% No prior SS calculation described No longitudinal analysis No CI stated Limitations not acknowledged	AL:91, DSMIV Divided into 3 groups: age stopped drinking EAA1 before age 50 EAA2 between age 50 and 60 EAA3 after age 60 Abstinent avg. 14.8 years (range 6 months to 45 years). CG: 52;age and gender	Stroop ROCFT TMTB SDMT Short categories test Letter fluency Paced Auditory Serial Addtion Test Microcog subtests: numbers forward/backward, word lists, analogies, word match	All groups comparable to CG on all measures of executive function.	N/A	No differences significant (unable to calculate group ES)
*Pitel et al (2009)**	83% No prior SS calculation described Potential confounds not controlled ES not reported No CI stated	AL: T1:44; DSM-1V; avg 11.5 days abstinence T2: 34 (14 abstainers, 20 relapsers); avg 6.39 months abstinence CG: 50; gender, age, education	Letter and category fluency Stroop Alternate response task 2N- Back task Integration task Verbal span Spatial Multimodal span Sustained and Divided attention task	AL ECF comparable to CG in abstainers at 6 months; for abstainers to return to normal ECF but pre-existing executive impairments to worsen in relapsers	N/A	**Stroop** Relapser t1 vs t2 d = 0.009 **Alt.resp** Relaps. t1vs.t2 d =-0.69* **2n-back** Relaps. t1vs.t2 d =-0.14 Unable to calculate other ES difference

(Appendix 1.3 continued)

Table 4: Abstinence longer than 12 months(*longitudinal studies)

	Quality score	**AL: alcohol group N; diagnostic assessment; length of abstinence CG: control group N; variables matched for**	**Measure of Executive Function**	**Main finding related to executive function**	**Impaired ECF aspects /not improved from t1 to t2**	**Effect size (differences between groups/ time 1 vs time 2) Significant difference***
*Fujiwara et al (2007)**	83% No prior matching No prior SS calculation described Measures not clearly described Confounds not controlled	AL: Korsakoff syndrome (ICD-10, DSM-IV) t1:41; baseline t2:20; (2years later) avg 10.25 year abstinent CG: 20 ; not matched	Stroop Digit Span reversed ROCFT (copy) Letter Fluency	At both test sessions, KS performance was inferior to CG although differences were not significant on all measures . Cognitive abilities of detoxified KS remain stable over two years and did not decline but remained poorer than CG.	Working memory (digit span reversed) Generativity (Fluency)	**Stroop** T2 vs CG unable to calculate T1 vs t2 d=0.15 **DS reversed**: T2 vs CG d= -0.83* T1 vs t2 d= 0.15 **ROCFT** T2 vs CG d = -0.26 T1 vs T2 d = -0.09 **Fluency:** T2 vs CG d = -1.14* T1 vs T2 d = 0.61*

Fein et al (2006)	79% No prior SS calculation described No longitudinal analysis ES not reported No CI stated Limitations not acknowledged	AL: 48; DSM-IV; avg 6.7 years abstinent CG :48 ; gender and age	Stroop ROCFT TMTB SDMT Short categories test Letter fluency Paced Auditory Serial Addtion Test Microcog subtests: numbers forward/backward, word lists, analogies, word match	Alcoholic participants performed comparably to control participants on all measures of ECF.	N/A	No EF differences significant (unable to calculate effect size differences)
Oscar-Berman et al (2004)	75% No prior matching No prior SS calculation described No longitudinal analysis ES not reported No CI stated Limitations not acknowledged	AL: 50, DSMIV; 7.1 yr KS AL: 6, DSM IV; No information re abstinence RH lesion patients: 6 CG: 82; not matched	WCST Letter Fluency RFFT Progressive Planning test TMT B	KS ECF impairment on all tasks. Evidence of impairment in AL group but not significant When abstinent for at least 5 years the performance of AL group was comparable to control group.	KS: Cognitive Flexibility (TMTB) Generativity (verbal fluency, RFFT) Inhibition (WCST error) Initiation (progressive planning)	**WCST preservative error** AL vs CG d=0.84 KS vs CG d = 1.5* KS vs AL d=0.27* **Fluency** AL vs CG d = -0.23 KS vs CG d= -1.87* KS vs AL d= -1.58* **TMT B** AL vs CG d = -0.001 KSvs CG d= -1.5* KS vs AL d= 1.37 * **RFFT unique designs** AL vs CG d=-0.08 KS vs AL d=-1.94* KS vs CG d = -2.38* ***Progressive planning test*** *AL vs CG d= -0.14* *KS vs CG d=-1.61** *KS vs AL d= -1.22**

Appendix 2.1: Research Ethics Committee approval letter

NHS
Health Research Authority

NRES Committee London - City & East
South West REC Centre
Whitefriars
Level 3, Block B
Lewins Mead
Bristol
BS1 2NT

Telephone: 01173421386
Facsimile: 01173420445

25 June 2012

Prof Tom McMillan
Professor of Clinical Neuropsychology,
Mental Health and Wellbeing
MVLS, University of Glasgow
Gartnavel Royal Hospital, 1055 Great Western Road,
Glasgow
G12 0XH

Dear Prof McMillan,

Full title of study: **Variables associated with cognitive impairment in adults who misuse alcohol as assessed by the Addenbrooke's Cognitive Examination (revised)**
REC reference number: **12/LO/0932**

Thank you for your letter of 11th June 2012. I can confirm the REC has received the documents listed below as evidence of compliance with the approval conditions detailed in our letter dated 28 May 2012. Please note these documents are for information only and have not been reviewed by the committee.

I can confirm that all the conditions of the favourable opinion have now been met.

Documents received

The documents received were as follows:

Document	*Version*	*Date*
Other: Letter from Consultants		11 June 2012

You should ensure that the sponsor has a copy of the final documentation for the study. It is the sponsor's responsibility to ensure that the documentation is made available to R&D offices at all participating sites.

12/LO/0932 **Please quote this number on all correspondence**

Yours sincerely,

Mr Rajat Khullar
Committee Co-ordinator
E-mail: Ubh-tr.CityandEastREC@nhs.net

Appendix 2.2 Research and Development Department approval letter

NHS Ayrshire & Arran

Healthcare Quality, Governance & Standards Unit
Research, Development & Evaluation Office
58 Lister Street
Crosshouse Hospital
Kilmarnock
KA2 0BB

Professor Tom McMillan
Mental Health & Wellbeing
Gartnavel Royal Hospital
1055 Great Western Road
Glasgow
G12 0XH

Date 28 June 2012
Your Ref
Our Ref CAW/KLB/AMK 2012AA040

Enquiries to Karen Bell
Extension 25850
Direct line 01563 825850
Fax 01563 825806
Email Karen.bell@aaaht.scot.nhs.uk

Dear Professor McMillan

Variables associated with cognitive impairment in adults who misuse alcohol as assessed by the Addenbrooke's Cognitive Examination (revised)

I confirm that NHS Ayrshire and Arran have reviewed the undernoted documents and grant R&D Management approval for the above study.

Approved documents:

Document	Version	Date
IRAS R&D Form	3.4	21 May 2012
SSI Form	3.4	18 May 2012
Protocol	2.0	18 May 2012

The terms of approval state that the investigator authorised to undertake this study within NHS Ayrshire & Arran is: -

- Ms Sarah Macdonald, Gartnavel Royal Hospital

With additional investigator: -

- Dr Sharon Mulhern, NHS Ayrshire & Arran.

The sponsors for this study are NHS Ayrshire & Arran.

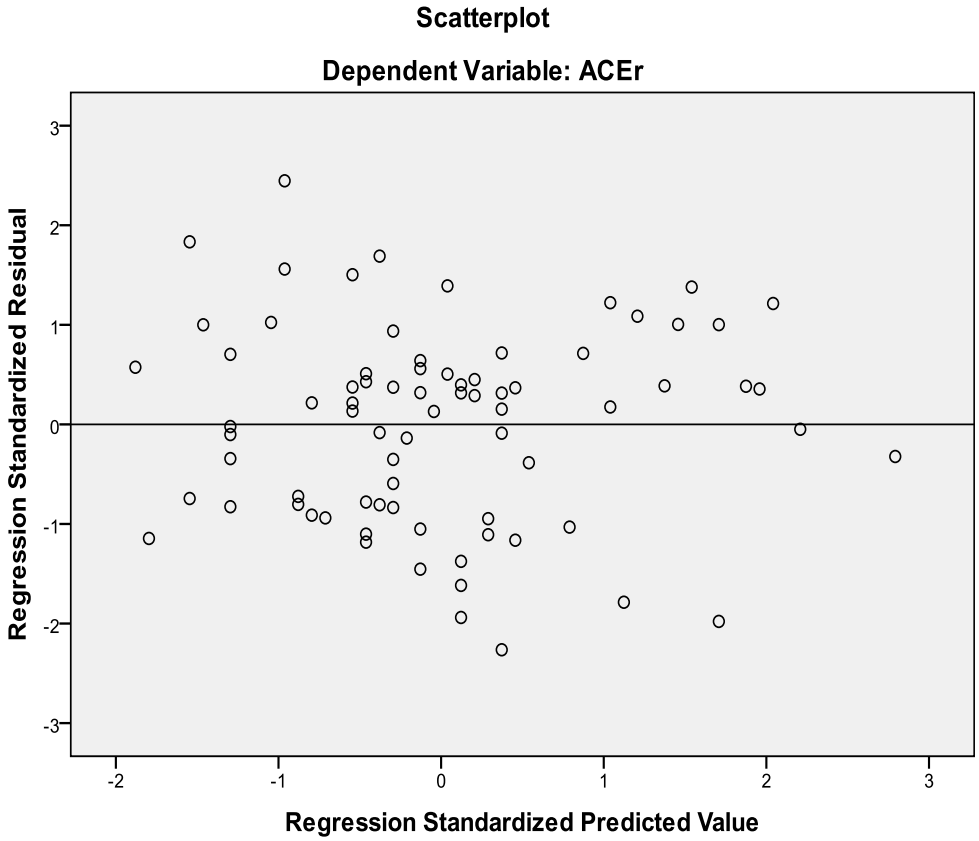
This approval letter is valid until 28 January 2013.

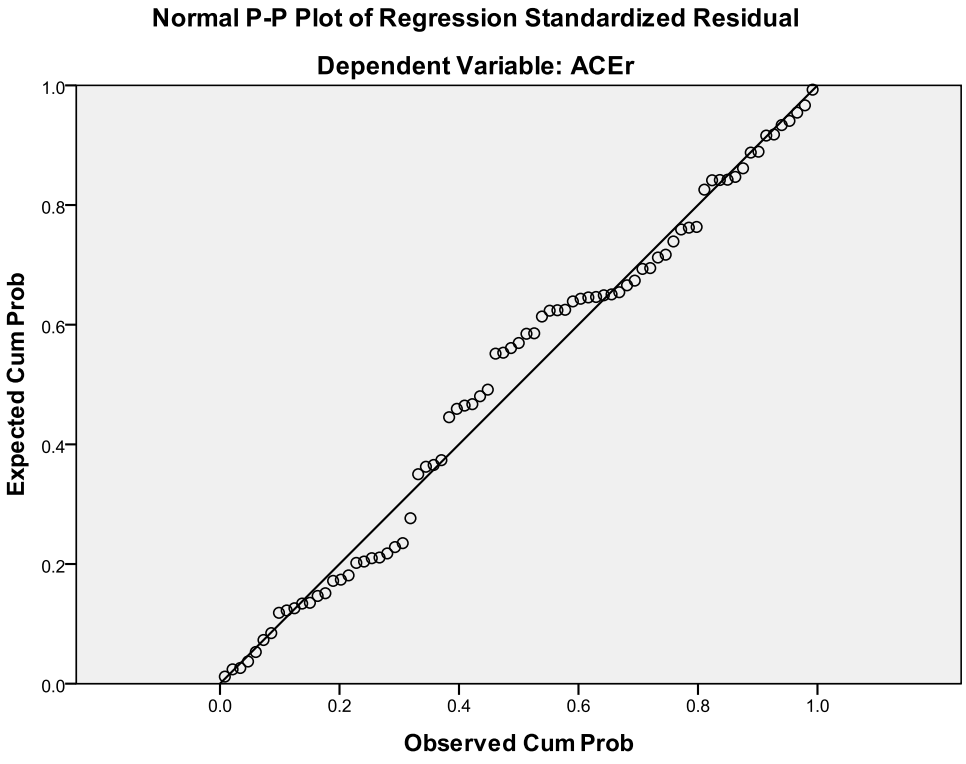
Yours sincerely

Prof Craig White
Assistant Director (Healthcare Quality) & Caldicott Guardian

c.c. Libby Prentice, NHS Ayrshire & ArranSPONSOR contact
Lesley Douglas, Finance, Ailsa Hospital
Information Governance, Ailsa Hospital
Peter MacArthur, Service Manager, NHS Ayrshire & Arran

Appendix 2.3: Homoscedasticity and normality P-P plots for regression analysis





Appendix 2.4 : MRP Proposal 18th May 2012

Study Protocol

Version No 2

Study Code

Date 18th May 2012

Variables associated with cognitive impairment in adults who misuse alcohol as assessed by the Addenbrooke's Cognitive Examination (revised)

Correspondence to

Prof Tom McMillan

University of Glasgow

Mental Health and Wellbeing

Gartnavel Royal Hospital

Administration Building

1055 Great Western Rd

G12 0XH

Sarah Macdonald

Trainee Clinical Psychologist

Mental Health and Wellbeing

Gartnavel Royal Hospital

Administration Building

1055 Great Western Rd

G12 0XH

Title

Variables associated with cognitive impairment in adults who misuse alcohol as assessed by the Addenbrooke's Cognitive Examination (revised)

Chief Investigator

Prof Tom McMillan

University of Glasgow

Mental Health and Wellbeing

Gartnavel Royal Hospital

Administration Building

Trust HQ, 1st floor

1055 Great Western Rd

G12 0XH

Investigators

Dr. Sharon Mulhern

Consultant Clinical Lead Neuropsychology

Ayrshire Central Hospital

Pavilion 7

Kilwinning Road

Irvine

KA12 8SS

Sarah Macdonald

Trainee Clinical Psychologist

Mental Health and Wellbeing

Gartnavel Royal Hospital

Administration Building

1055 Great Western Rd

G12 0XH

Study Sponsor:

NHS Ayrshire and Arran

Funder

N/A

1. PROTOCOL SYNOPSIS

Title: **Variables associated with cognitive impairment in adults who misuse alcohol as assessed by the Addenbrooke's Cognitive Examination (revised)**

Study Design: Retrospective; within and between subject

Study Population: Adult using alcohol hazardously

Sample Size: 80

Study Duration: 1 month

Intervention(s): Extraction of anonymous data relating to ACE-R total and domain scores, age, duration of total alcohol use, current use and experience of withdrawals. Data will be compared to a healthy control group included in previously published research.

Intervention Duration: 1 month

Primary Research Objective:

The purpose of this study is to provide a preliminary investigation of the utility of the ACE-R with people who misuse alcohol. The aims of the study are to examine whether the ACE-R can identify cognitive impairment in people who misuse alcohol and explore the associations between individual factors and outcome.

Study Endpoints: when all relevant anonymised data has been extracted and examined.

Statistical methods:

Descriptive statistics, two tailed t-test, multiple linear regression.

ABBREVIATIONS

ALS : Alcohol Liaison Service

ACE-R: Addenbrooke's Cognitive Examination – Revised

MWC: Mental Welfare Commission

PID: Personal Identifiable Data

BACKGROUND AND RATIONALE

The Mental Welfare Commission (MWC) when reviewing the care and treatment of Mr.H raised concerns regarding the appropriate identification and treatment of ARBD by health and social care professionals. People with ARBD are also likely to experience complex comorbid health difficulties which may make identification difficult (MWC 2010). The Mental Welfare Commission in 2010 highlighted that people with ARBD are often able to adapt to cognitive difficulties they experience and can often appear articulate, without impairment at interview. This may mean that cognitive impairment is not detected without a standardised assessment of function (Green, Garrick, Sheedy et al 2010).

The need for timely and accurate identification of alcohol related cognitive impairment is crucial so that appropriate treatment can be given, promoting chances of recovery. It has been found that 75% of people with ARBD who are treated will make some recovery in contrast to degenerative neurological disorders (Smith and Hillman 1999). The Scottish Government (2007) has stated that the Addenbrooke's Cognitive Examination Revised (ACE-R) can be useful in screening for cognitive impairments in people who are at risk of developing ARBD; this measure is also favourable to the MMSE which may not adequately assess the deficits particular to ARBD (MWC 2010). Despite the Scottish Government's recommendation, no formal assessment of the ACE-R has been with people who misuse alcohol.

Although it is not a comprehensive assessment of cognitive functioning the ACE-R is a well established screening measure for Dementia and mild cognitive impairment (Mioshi et al 2006). The measure assesses five domains of functioning: attention and orientation, memory, verbal fluency, language and visuospatial abilities. The ACE and ACE-R are also known to be valid screening measures in brain injury settings and in the evaluation of Parkinson's disease (Gaber, 2008; Reyes et al 2009). The original version of the ACE has also been found to be sensitive in detecting differences between Frontal Lobe Dementia (FLD) and Alzheimer's Disease (AD) based on differences in domain scores between populations (Mathurunuth et al 2000). The measure is designed for bedside use, and takes around 20 minutes to administer. No additional equipment is required to complete the ACE-R and although it is copywritten it is currently a free to use measure.

Green, et al (2010) examined the use of the Repeatable Battery for Assessment of Neuropsychological Status (RNANS) in an Australian sample of moderate and heavy drinkers. They found that people misusing alcohol were impaired on tasks of memory, new learning, visuospatial function and executive functions as compared to healthy control participants. It may be that the ACE-R will detect similar deficits of impairment. This may enable a profile of impairment associated with alcohol misuse to be identified. Such a profile, if compared to that found with healthy individuals and other clinical populations, may aid earlier identification of alcohol related cognitive impairment and support further assessment.

In order to identify cognitive impairment in people misusing alcohol, widespread general screening could help to overcome some of the complexity associated with identification. This however would not be practical in all services and is unlikely to be clinically necessary for all people misusing alcohol. Understanding the variables which are likely to be associated with cognitive impairment in people who misuse alcohol may enable health and social services to more readily identify people at risk of these difficulties.

STUDY OBJECTIVES

Aim: The purpose of this study is to provide a preliminary investigation of the utility of the ACE-R with people who misuse alcohol. The aims of the study are to examine whether the ACE-R can identify cognitive impairment in people who misuse alcohol and explore the associations between individual factors and outcome.

6.1 The primary hypothesis is:

Performance on tasks of visuospatial ability, memory and fluency will be significantly poorer in people with hazardous alcohol drinking (AUDIT scores >8) compared to control participants.

6.2 Secondarily, it is hypothesised that

Older age, higher current alcohol use and longer duration of use with be predictive of poorer ACE-R scores in people who drink hazardously.

Experience of previous withdrawal from alcohol will be associated with worse ACE-R total scores.

7. STUDY PLAN AND PROCEDURES

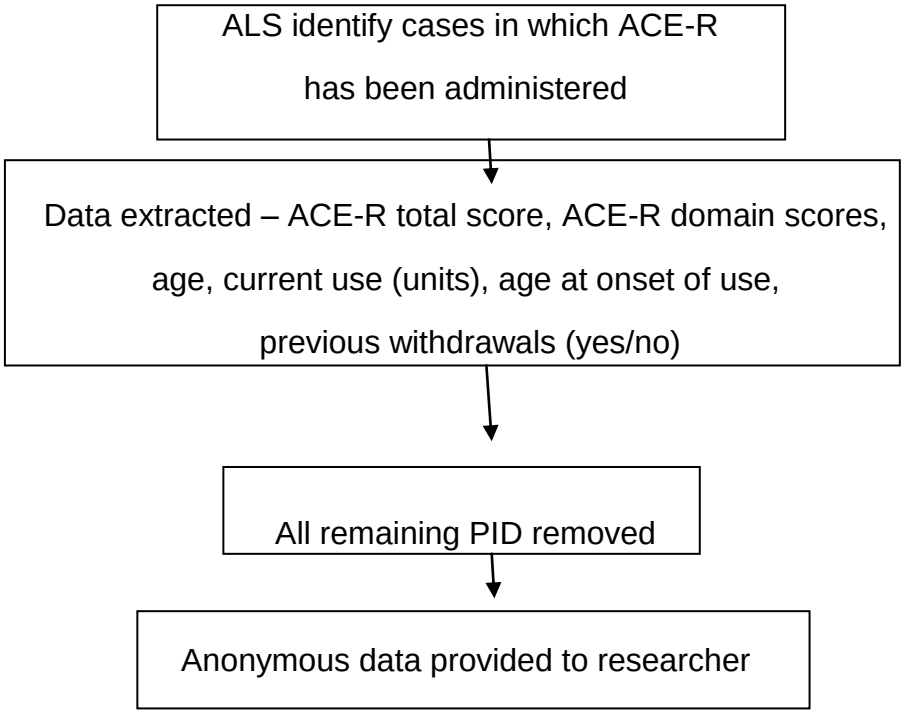
7.1 Overall study design(s) and flow chart

To evaluate the use of the ACE-R a retrospective design examining both within and between subject factors will be used. Anonymised data already held by the Alcohol Liaison Service (ALS) in NHS Ayrshire and Arran will be compared with data from healthy control participants obtained by Mioshi et al (2006). It will not be possible to match groups; however, comparisons will be made between the age and gender composition of the ALS group and Mioshi's control group. Using this published control data replicates the procedure employed in a previous study examining the ACE-R (Gaber 2008). Data will also be examined to explore the associations between ACE-R score and patient age, current alcohol use, duration of alcohol use and previous experiences of withdrawal.

The ALS team member will extract information related to research variables and remove any personal identifiable data including date of birth and CHI numbers. Anonymised data will be transferred to the researcher electronically using an encrypted flash drive belonging to the ALS team member and stored on a password protected database on an encrypted laptop owned by the University of Glasgow.

The anonymous data held by the researcher will contain: ACE-R total and domain scores, patient age in years (not date of birth), current alcohol use (units consumed per week), duration of alcohol use (years) and whether

the person had previously experienced an alcohol withdrawal (yes/no). At no time during the analysis or reporting of the data will it be presented in a way which would enable identification of an individual.



7.2 Selection of study population

All cases between January 2010 and April 2012 will be examined by a member of the ALS.

7.2.1 Inclusion criteria

- Referrals accepted by the ALS. Referral criteria for this service are: patients who have been admitted to a general hospital with physical complaints and alcohol appears to be having a detrimental effect on their wellbeing; patients who are undergoing medical detoxification from alcohol; patients who

request help to achieve responsible drinking prior to discharge (Mason 2009).

- Cases where an ACE-R was administered to patients

7.2.2 Exclusion criteria

- Data from patients with a AUDIT score of more than 8
- Cases in which data relating to all variables of interest is not available

7.2.3 Subject information and consent

Data used in this study will include people who have been discharged from the ALS. No participants will be prospectively recruited. Patient files and personal identifiable data will not be accessible to the researcher.

7.2.4 Discontinuation/ Withdrawal of participants from study

Cases that do not include all variables of interest will excluded from the study.

8. STUDY INTERVENTION/TREATMENT

8.1 Description of Study Intervention/Treatment

A member of the ALS will identify cases seen by the ALS between January 2010 and April 2012 with whom an ACE-R was completed using an electronic log held by the service. Data relating to variables of interest will be provided anonymously to the researcher.

8.2 Compliance with Study Intervention/Treatment

All data included in the study is retrospective. No action will be taken to check ALS team members' compliance with published administration guidance. As the members of the ALS have a great deal of experience in administering the ACE-R compliance is assumed.

9. STUDY MEASUREMENTS AND ENDPOINTS

9.1 Research procedures will end once enough data (based on sample size calculation) has been collected.

10. DATA MANAGEMENT

The ALS team member will remove any personal identifiable data including date of birth and CHI numbers. The researcher will have no access to patient files or identifiable information. Anonymised data will be transferred to the researcher electronically using an encrypted flash drive belonging to the ALS team member and stored on a password protected database on an encrypted laptop owned by the University of Glasgow. This laptop will be held by the researcher for the duration of the study.

11. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

11.1 Determination of sample size

Sample size calculations were complete using G*power software. Green et al (2010) found a significant and large effect size difference between people misusing alcohol and healthy control participants on the RBANS (total scores and memory, visuospatial and attention subscores). Based on this effect size, a sample size of 26 for each group will be necessary

(based on two tailed t-test for independent groups, error = 0.05, power = 0.8).

It is of interest to examine participant variables influence performance on the ACE-R in a population of people misusing alcohol. In a study of the association between scores on the Mini Mental State Examination and alcohol use in older adults, heavy alcohol use (>400g per week) was associated with increased risk of cognitive impairment (Odds Ratio: 4.99) (Chan, Chiu and Chu 2010). Duration of alcohol use and previous withdrawal experiences are thought to have some impact on cognitive function (Duka et al 2003, Fein and McGillivary 2007). Assuming a medium effect size, (error =0.05, power = 0.8) a sample size of 80 will be necessary to perform a multiple regression analysis including three variables (age, length of use and current use). Using the same parameters, a sample size of 64 will be necessary for point biserial correlation analysis. Based on these calculations, a minimum of 80 cases will be included in this study.

11.2 Statistical evaluation

Statistical analyses will carried out using The Statistical Package for Social Sciences (SPSSv18).

11.3 Methods of statistical analysis

For the ALS group, means and standard deviations will be calculated for ACE-R total score and domain scores. Two tailed t-tests will be used to

compare the ALS sample group mean age and gender composition to the control sample used by Mioshi et al (2006) and the population of people seen by the ALS between 2010 and 2012. Two tailed t-tests will also be used to examine differences between the ALS sample ACE-R total and domain scores with Mioshi et al (2006) control data.

Multiple linear regression will be used to examine associations between ACE-R scores and age, units consumed weekly and length of alcohol abuse. Point bi-serial correlations will be used to examine the association between previous withdrawals and total ACE-R scores. Effects sizes were reposed using Cohen's d (t-tests) and Cohen's f^2 (regression analysis).

11.4 Criteria for termination of the Study

The study will end once a minimum number of cases (based on sample size calculation) have been identified.

11.5 Procedures for Accounting for Missing, Unused and Spurious data

Only data relating to all variables of interest will be included in the study. If more than 67 cases are identified this data will be included in the study.

12. SAFETY AND RISK ASSESSMENT

12.1 Definitions of Adverse Events, Serious Adverse Events, and Serious Unexpected Serious Adverse Events (SUSAEs)

As this is a non-interventional study, no adverse events are anticipated.

12.2 Recording and reporting of Adverse Events

As this is a non-interventional study no adverse events are anticipated . If any adverse events occur the research team will report the incident to NHS Ayrshire and Arran Health Board's R&D Office within 24 hours and this will be followed up as per the R&D policies and procedures.

12.3 Reporting and reporting of Serious Adverse Events Serious Unexpected Serious Adverse Events (SUSAEs)

As this is a non-interventional study no serious adverse events (SAEs) or suspected unexpected serious adverse events (SUSAEs) are anticipated. If any SAEs or SUSAEs events occur the research team will report the incident to NHS Ayrshire and Arran Health Board's R&D Office within 24 hours and this will be followed up as per the R&D policies and procedures.

13. STUDY MANAGEMENT

13.1 Ethics

13.1.1 Ethical conduct of the study

An application will be made to the West of Scotland Research and Ethics Committee.

13.1.2. Ethics Review

The researcher has been advised that as the study only includes anonymised data, a proportionate review will be made.

13.2 R&D Management Approval

An application for R&D approval will be made to NHS Ayrshire and Arran R&D team.

13.3 Finance and Indemnity

This study is not funded.

It is anticipated that insurance provision will be provided by the study sponsor. The process of application to NHS Ayrshire and Arran for sponsorship is ongoing.

13.4 Monitoring and Auditing

Pending approval for sponsorship, NHS Ayrshire and Arran R&D team will monitor the study. The researcher will also receive ongoing supervision form Prof. McMillan and Dr Mulhern.

13.5 Training of staff

No additional training of staff will be made. The research will discuss which variables are of interest with the ALS team member before they extract the data.

13.6 Study agreements

Dr Mulhern has discussed the project with Dr Malcolm Cameron (Consultant Psychiatrist) Karen McDowell (Nurse Manager), Frances Mason (Charge Nurse) and Gail Sabatini (Services Manger Mental Health), who are all supportive of this study.

13.7 Study timetable

Obtain R&D and ethical approval: June 2012

Data Collection: June 2012

Analysis and first draft: June 2012

Submission for examination: Late July 2012

13.8 Dissemination

This study will be made available to the Alcohol Liaison Service for local distribution. The study forms part of the researcher's portfolio necessary for completion of training in the Doctorate of Clinical Psychology. As such, the portfolio will be accessible through the University of Glasgow library website.

14. REFERENCES

G*Power, version 3.1.2 [internet]. Available from: < http://www.psycho.uni-duesseldorf.de/abteilungen/aap/gpower3/download-and-register>. [accessed 28th May 2011]

Green, A., Garrick, T., Sheedy, D., Blake, H., Shores, E.A. and Harper, C. (2010) The effect of moderate to heavy alcohol consumption on neuropsychological performance as measured by the Repeatable Battery for the Assessment of Neuropsychological Status. *Alcoholism: Clinical and Experimental Research*, 34(3),pp. 443 - 450

Gaber, T. A.-Z. (2008). Evaluation of the Addenbrooke's Cogntive Examination's Validity in a Brain Injury Rehabilitation Setting. *Brain Injury* , 22 (7-8), pp. 589-593

Loeber,S., Duka, T., Welzel Márquez, H.,Nakovics, H., Heinz,A. Mann,K. and Flor,H. (2010) Effects of repeated withdrawal from alcohol on recovery of cognitive impairment under abstinence and rate of relapse. *Alcohol and Alcoholism*, 45(6), pp. 541-547

Mason, F. (2009) *Unique approach to alcohol liaison services in Scotland* [internet]. Available from: <http://www.piramhids.com/case-studies/view-casestudy?resid=666> [Accessed 6 May 2011]

Mathurunuth, P., Nestor, P., Berrios, G., Rakowicz, W., & Hodges, J. (2000). A Breif Cogntive Test Bettery to Differentiate Alzheimer's Disease and Frontotemporal Dementia. *Neurology* , 55, pp. 1613-1620.

Mental Welfare Commission (2010) *Missed Opportunities: Findings from our visits to people with Acquired Brain Injury and Alcohol Related Brain damage.* [internet] Available from:< http://reports.mwcscot.org.uk/web/FILES/Visiting_Monitoring/Missed_opportunities.pdf> [Accessed 28 April 2012]

Mioshi, E., Dawson, K., Mitchell, J., Arnold, R., & Hodges, J. R. (2006). The Addensbrooke's Cogntive Examination Revised (ACE-R): a brief

cognitive test battery for dementia screening. *International Journal of Geriatric Psychiatry*, 21, pp. 1078 - 1085.

Pitel, A.L., Rivier, J., Beaunieux, H., Vabret, F., Desgranges, B. and Eustache, F. (2009) Changes in the episodic memory and executive functions of abstinent and relapsed alcoholics over a 6-month period. *Alcoholism:Clinical and Experimental Research*, 33(3),pp.490-498

Reyes, M.A., Lloret, S.P., Gerscovich, E.R., Martin, M.E., Leiguarda, R. and Merello, M. (2009) Addenbrooke's Cognitive Examination validation in Parkinson's disease. *European Journal of Neurology*, 16 (1), pp. 142-147

Smith, I. and Hillman, A. (1999) Management of alcohol Korsakoff syndrome. *Advances in Psychiatric Treatment,* 5, pp. 271-27

The Scottish Government (2007) Mental Health in Scotland: Closing the Gaps – Making a Difference – Commitment 13, [internet]. Available from: < http://www.scotland.gov.uk/Publications/2007/12/10141643/9> [Accessed 8th July 2011]

Appendix: 2.5 Amendments to proposal

1. Previous research has found that age and duration of alcohol use are highly confounded (Fein et al 2002 cited in MRP reference). As such, it was decided that age would be excluded from analysis as this study was principally examined the influence of drinking variables on cognitive outcome.

2. The impact of previous alcohol withdrawal was examined using group comparisons rather than point biserial correlation as this was more appropriate to explore between group differences.