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Neurological, Nutritional, and Alcohol Consumption Factors Underlie Cognitive and Motor Deficits in Chronic Alcoholism

Rosemary Fama, PhD^{1,2,*}, Anne-Pascale Le Berre, PhD¹, Cheshire Hardcastle, BA^{1,2}, Stephanie A. Sassoon, PhD², Adolf Pfefferbaum, MD^{1,2}, Edith V. Sullivan, PhD¹, and Natalie M. Zahr, PhD^{1,2}

¹Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Stanford, CA

²Neuroscience Program, SRI International, Menlo Park, CA

Abstract

Variations in pattern and extent of cognitive and motor impairment occur in alcoholism (ALC). Causes of such heterogeneity are elusive and inconsistently accounted for by demographic or alcohol consumption differences. We examined neurological and nutritional factors as possible contributors to heterogeneity in impairment. Participants with ALC (n=96) and a comparison group (n=41) were examined on tests assessing 6 cognitive and motor domains. Signs of historically-determined subclinical Wernicke's encephalopathy were detected using the Caine et al. criteria, which were based on postmortem examination and chart review of antemortem data of alcoholic cases with postmortem evidence for Wernicke's encephalopathy. Herein, four Caine criteria provided quantification of dietary deficiency, cerebellar dysfunction, low general cognitive functioning, and oculomotor abnormalities in 86 of the 96 ALC participants. Subgrouping by number of Caine criteria met yielded a graded effect, where those meeting more criteria exhibited greater impairment than those meeting no to fewer criteria. These results could not be accounted for by history of drug dependence. Multiple regression indicated that compromised performance on an ataxia battery, indicative of cerebellar dysfunction, predicted nonmnemonic and upper motor deficits, whereas low whole blood thiamine level, consistent with limbic circuit dysfunction, predicted mnemonic deficits. This double dissociation indicates biological markers that contribute to heterogeneity in expression of functional impairment in ALC. That nonmnemonic and mnemonic deficits are subserved by the dissociable neural systems of frontocerebellar and limbic circuitry, both commonly disrupted in ALC, suggests neural mechanisms that can differentially affect selective functions, thereby contributing to heterogeneity in pattern and extent of dysfunction in ALC.

*Corresponding author, Rosemary Fama, Ph.D., Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine (MC5723), 401 Quarry Road, Stanford, CA 94305-5723, Phone: (650) 859-5064, FAX: (650) 859-2743, rfama@stanford.edu.

Author Contributions

RF, EVS, NMZ, APL and AP were responsible for the study concept and design. SAS, NMZ, and CH contributed to the acquisition of data. RF, EVS, CH, SAS, and NMZ assisted with data analyses and collection. RF, EVS, SAS, and AP interpreted the findings. RF and EVS drafted the manuscript. EVS, SAS, NMZ, APL, and AP provided critical revision of the manuscript for important intellectual content. All authors critically reviewed content and approved final version for publication.

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Keywords

alcohol; ataxia; Caine criteria; memory; thiamine; Wernicke's encephalopathy

INTRODUCTION

Alcoholism is associated with deficits in a number of cognitive and motor domains including executive functioning (e.g., selective attention, working memory, and information processing speed), memory (e.g., episodic memory), visuospatial abilities (e.g., visuoconstruction and visuo-perceptual processing), and motor dexterity and speed (e.g., Beatty, Tivis, Stott, Nixon, & Parsons, 2000; Davies et al., 2005; Pitel et al., 2009; Stavro, Pelletier, & Potvin, 2012; for reviews see Le Berre, Fama, & Sullivan, 2017; Oscar-Berman et al., 2014). Neural correlates associated with these deficits in chronic alcoholics include frontal, limbic, and cerebellar systems (for a review see Oscar-Berman & Marinkovic, 2007).

Although cognitive and motor deficits have been observed in upwards of 50% of alcoholics, not all alcoholics demonstrate measurable cognitive impairment (Fein, Torres, Price, & Di Sclafani, 2006). Furthermore, severity of cognitive deficits in alcoholics range from mild, often referred to as "uncomplicated alcoholism," to severe including alcohol-related dementia when accompanied by impairment in 2 or more cognitive domains with functional compromise (DSM-IV) or the profound anterograde amnesia characteristic of Korsakoff's syndrome (for reviews see Fama, Pitel, and Sullivan, 2012; Kopelman, 1995). It has been debated whether the severity of alcohol-related cognitive impairment is best viewed on a continuum or whether different patterns of impairment are categorically distinct (Bowden, 1990; Pitel et al., 2007; Ryback, 1971).

The heterogeneity in the extent and severity of neuropsychological deficits in chronic alcoholics is often marked (Ritz et al., 2016) but has not consistently been associated with any one demographic or alcohol-related variable. Factors that can moderate cognitive deficits include age, sex, medical and psychiatric co-morbidities, family history of alcoholism, number of withdrawals and relapses, length of abstinence, lifetime alcohol consumption, and nutrition (cf., Fama & Sullivan, 2013; Oscar-Berman, 2000).

Some alcohol-related cognitive deficits, in particular memory and learning problems, have been quantitatively associated with poor nutrition (Albert, Butters, Rogers, Pressman, & Geller, 1982; Guthrie & Elliott, 1980). Indeed, thiamine deficiency is estimated in upwards of 80% of alcoholics (Galvin et al., 2010; Thomson, 2000) and can result in Wernicke's encephalopathy (WE), an acute neurological condition, characterized by a clinical triad of symptoms: oculomotor disturbances, gait and balance instability, and altered mental state (Victor, Adams, & Collins, 1989). If left untreated or undertreated, WE can progress to Korsakoff's syndrome (KS), with its hallmark symptom of profound anterograde amnesia (Kopelman, 1995; Victor et al., 1989).

In the late 1990's Caine and colleagues noted that neuropathological signs associated with WE were observed upon autopsy in alcoholics who had not been diagnosed in life with WE (Caine, Halliday, Kril, & Harper, 1997). The result was a modification of the historical triad

used in clinical settings to diagnosis WE by adding a dietary deficiency criterion and suggested that individuals need only to meet 2 of the 4 criteria to be classified as showing signs of Wernicke's encephalopathy. A study that examined the utility of antemortem Caine criteria (Pitel et al., 2011) reported graded deficits in the alcohol groups categorized by number of criteria met. The most pronounced deficits occurred in the group of alcoholics who met 2 or more Caine criteria. Further, Pitel and colleagues reported that lower thiamine levels were selectively associated with lower memory scores. Additionally, a recent study (Ritz et al., 2016) reported that malnutrition, liver dysfunction, and thiamine metabolism partially explained the heterogeneity of alcohol-related neuropsychological impairments observed in a group of 30 alcoholics, with the most severe cognitive impairments associated with malnutrition, defined as "at least 30-missed meal days" over the lifetime concurrent with heavy drinking.

The study presented here examined currently abstinent alcoholics (ALC) and age-matched comparison volunteers on cognitive and motor abilities, with a focus on the associations between the pattern and severity of cognitive and upper motor deficits and Caine-related neurological and nutritional criteria. We tested three primary hypotheses: 1) the total group of ALC men and women compared with comparison participants would show mild to moderate deficits on selective cognitive (e.g., executive functions, episodic memory, and visuospatial construction) and motor (e.g., upper limb motor speed and dexterity) measures; 2) categorizing the ALC group by Caine criteria would reveal a stepwise deficit severity, where ALCs meeting 2 or more criteria would show the greatest and most widespread cognitive deficits, pronounced in memory impairment; and 3) cognitive and motor scores in the ALC group would be differentially associated with factors related to alcohol consumption, neurological function, and dietary variables, with executive functioning and motor speed associated with cerebellar dysfunction assessed with balance and gait tasks and episodic memory associated with dietary factors assessed here as thiamine levels.

MATERIAL AND METHODS

Participants

This study was carried out in accordance with protocols approved by the Institutional Review Boards of Stanford University and SRI International. Written informed consent was obtained from all participants in accordance with the Declaration of Helsinki. Study participants included 96 individuals with alcohol dependence (ALC; 73 men and 23 women) recruited from local substance abuse treatment programs and 41 normal comparison participants (NC; 22 men, 19 women), recruited from the local community. A subgroup of participants included herein was part of a study published by our laboratory that examined the nature of cognitive impairment in alcoholism related to Caine criteria (Pitel et al., 2011). The current study includes more than twice the number of subjects and serves to extend the previously published observations.

All participants were screened using the Structured Clinical Interview for DSM-IV (SCID) (First, Spitzer, Gibbon, & Williams, 1998) and structured health questionnaires. Upon initial assessment, subjects were excluded if they had fewer than 8 years of education, a significant history of medical (e.g., epilepsy, stroke, multiple sclerosis, uncontrolled diabetes, or loss of

consciousness > 30 minutes), psychiatric (i.e., schizophrenia or bipolar I disorder) or neurological disorder (e.g., neurodegenerative disease). Other exclusionary criteria were recent (i.e., past 3 months) substance dependence other than alcohol in the ALC group or any DSM-IV Axis I disorder in the NC group. Severity of depression symptoms was assessed with the Beck Depression Inventory-II (Beck, Steer, & Brown, 1996) in both groups. All participants underwent a semi-structured timeline follow-back interview (Skinner, 1982; Skinner & Sheu, 1982) to quantify lifetime alcohol consumption.

Among the 96 alcoholics, the average age of onset of alcoholism was 24.2 ± 8.7 years (range = 12 to 48 years) and the average length of alcoholism was 23.6 ± 11.6 years (range = 3 to 51 years). Alcoholics drank an average of 1318 ± 1007 kg of alcohol over their lifetimes (range = 176 to 4711 kg), whereas controls drank significantly less, at an average of 24 ± 33 kg of alcohol over their lifetimes (range 0 to 136 kg). Duration of abstinence was 16 weeks (sd= 16 weeks, range 1 to 746 days). No ALC participant reported ever being diagnosed with Wernicke's encephalopathy or met criteria for alcohol-induced persisting amnesic disorder.

All 96 alcoholics met DSM-IV criteria for Alcohol Dependence. Regarding DSM-IV alcohol dependence remission criteria at the time of visit, 13 of 96 (14%) were in sustained remission, 76 of 96 (79%) were in early remission, and 7 of 96 (7%) had current alcohol dependence. Per DSM-5 diagnostic criteria, 86 of the 96 alcoholics (90%) met criteria for severe AUD (Alcohol Use Disorder), 7 (7%) met at least moderate AUD, and 3 (3%) met at least mild AUD. Regarding DSM-5 AUD remission criteria at the time of visit, 13 of the 96 (14%) had AUD in sustained remission, 44 (46%) had AUD that was in early remission, 39 (41%) had current AUD.

Of the 96 alcoholics, 30 (32%) met DSM-IV criteria for cannabis abuse or dependence and 52 (54%) met DSM-IV criteria for abuse/dependence on other drugs including: 44 ALC participants (46%) for cocaine, 18 (19%) for amphetamine, 14 (15%) for opioid, 5 (5%) for sedative, 5 (5%) for hallucinogen, and 2 (2%) for other. No control participant met DSM-IV criteria for substance abuse or dependence. For nicotine, 53 (55%) of the 96 ALC participants were current smokers and 14 (15%) were past smokers, whereas 3 of 41 (7%) controls were current smokers and 2 (5%) were past smokers.

Demographics for the ALC and NC groups are presented in Table 1. The ALC and NC groups did not differ in age, but ALC had fewer years of formal education than NC. NART scores [National Adult Reading Test; (Nelson, 1982)] were available for a subset of participants and showed a modestly lower estimated premorbid IQ for ALC than NC. ALC endorsed a greater number of depressive symptoms (Beck et al., 1996), scored lower on a general cognitive screening test (Mattis, 2004), and had lower socioeconomic status (Hollingshead, 1975) than NC. As expected, the ALC group had higher lifetime alcohol consumption.

Neuropsychological test measures

Six functional domains were assessed: Attention/Working Memory, Production (ability to initiate, plan, and strategize), Immediate Memory, Delayed Memory, Visuospatial Construction, Upper Limb Motor Speed and Dexterity.

Attention/Working Memory—The Trail Making Test (Trails A and B, Reitan, 1958) required participants to sequence numbers from 1 to 25 and then sequence numbers and letters in alternating fashion (1-A-2-B-3-C...). Time to completion for each condition was the dependent measure.

Production Ability—The Controlled Oral Word Association Test (COWAT, Borkowski, Benton, & Spreen, 1967) required participants to generate as many words as they could beginning with the letters F, A, and S. Each trial was 60-sec. The total number of correct words produced across the three trials was calculated.

Ruff Figural Fluency Test (RFFT, Ruff, 1988), often referred to as a visual analog of the COWAT, required participants to generate as many different designs as possible by using straight lines to connect at least 2 of the 5 dots in each array. The test consists of five conditions, some with distractors, each with a 1-min time limit. The total number of correct unique designs was summed across the five conditions.

Immediate Memory—Logical Memory - I (WMS-R, Wechsler, 1987) required participants to recall two short narratives immediately after each story was read to them. Number of details (max=50) recalled from both stories was calculated.

Rey-Osterrieth Complex Figure –Immediate Recall (Rey, 1942) required participants to draw a complex figure from memory immediately after having copied it. The number of details (max=36) recalled according to standardized scoring instructions was calculated.

Delayed Memory—Logical Memory - II (WMS-R, Wechsler, 1987) had participants recall the short narratives presented after a 30-min delay.

Rey-Osterrieth Complex Figure – Delayed Recall (Rey, 1942) required participants to draw from memory the complex figure after a 30-min delay.

Visuospatial Construction—Rey-Osterrieth Complex Figure – Copy Condition required participants to copy the complex figure as accurately as possible. Scoring was according to standardized criteria.

Upper Limb Motor—Fine Finger Movement (FFT, Corkin, Growdon, Sullivan, Nissen, & Huff, 1986) required participants to turn a knurled rod with their forefinger and thumb, unimanually and then bimanually. Three, 30-second trials for each condition were administered with the unimanual and bimanual scores reflecting the average number of rotations across trials.

Grooved Pegboard (Matthews & Kløve, 1964) required participants to insert grooved pegs into a 5 × 5 pegboard. The time to completion with each hand was averaged.

Caine criteria and thiamine measurement

The four Caine criteria were quantified as previously described (Pitel et al., 2011): (1) *Dietary Deficiency* – reporting, in a clinical interview based on a timeline follow-back format, at least 30 days in their lifetime when they went the entire day without eating because of their active drinking, (2) *Oculomotor Disturbance* - exhibiting nystagmus on neurological examination, (3) *Cerebellar Dysfunction* - scoring at least 1.5 standard deviations below the mean for age- and sex-matched controls on at least 2 of the 4 balance and ataxia measures with eyes open (standing heel-to-toe on a line for 60 sec (Romberg), walking 10 steps on a line, balancing on the right leg for 30 sec, and balancing on the left leg for 30 sec) (Fregly, Smith, & Graybiel, 1973), and (4) *Altered Mental State or Mild Cognitive Impairment* - scoring below 124 out of 144 points on the Dementia Rating Scale (Mattis, 2004).

Thiamine status was assessed by ARUP Laboratories (Salt Lake City, UT) via measurement of thiamin diphosphate (TDP, nmol/L) in whole blood samples. Red blood cell quantification of TDP, the biologically active form of thiamine, is thought to reflect total body stores: approximately 80% of thiamine in whole blood is found in the red blood cells and approximately 90% of thiamine in whole blood is in the form of TDP (Guerrini et al., 2009).

Statistical analyses

Test scores were statistically corrected for age and education and standardized on the NC group [mean and standard deviation for NC group: $Z=0\pm1$], allowing direct comparisons across groups and across tests. Where higher raw scores indicated worse performance, scores were multiplied by -1 , so that lower Z scores always indicated worse performance. Theoretically-derived composite scores were then calculated as the mean of all Z-scores of tests comprising each of 6 functional domains: Attention/Working Memory, Production, Immediate Memory, Delayed Memory, Visuospatial Construction, and Upper Limb Motor Function. Analysis of variance (MANOVA and ANOVA) tested group differences on the composite scores between ALC and NC and among the 3 alcohol-related Caine subgroups. Follow-up t-tests examined 2 group comparisons for significant omnibus results. Correlational analyses tested relations between composite scores and demographic, alcohol consumption, neurological, and dietary variables in the ALC group. Multiple regression analyses sought unique predictors of cognitive and motor composites.

RESULTS

Between Group Analyses: ALC vs. NC

Composite scores—MANOVA between the two diagnostic groups (ALC, NC) and across the 6 functional domains was significant ($F(1,125)=12.25$, $p=.0006$). Follow-up analyses indicated that ALC scored lower than NC on all age- and education-corrected cognitive composite scores and modestly below NC on the motor composite score (Figure 1). Alcoholic men and alcoholic women did not differ on any of the composite scores.

Individual Test Scores—ALC scored significantly lower than NC on 8 measures: Trails B, FAS, Logical Memory (Immediate and Delayed), Rey-Osterrieth Complex Figure (Immediate, Delayed, and Copy), and Grooved Pegboard (Table 2). A modest group difference was observed for Ruff Figural Fluency. ALC and NC did not differ on Trails A or Fine Finger Movement.

Within Group Analyses: ALC

ALC subgroups by Caine criteria—Of the 96 alcoholic participants, 86 had Caine criteria scores (Table 3): 21 ALC participants did not meet any of the Caine criterion (Caine 0), 39 met 1 criterion (Caine 1), 24 met 2 criteria (Caine 2), 2 met 3 criteria (Caine 3), and no one met all 4 criteria. Given this distribution, Caine groups 2 and 3 were combined and categorized as the Caine 2+ group. Groups differed on age, total alcohol consumption, and DRS score, with Caine 1 younger than Caine 0 and Caine 2+, Caine 2+ having a higher lifetime alcohol consumption than Caine 1, and Caine 2+ scoring lower on the DRS than Caine 0 or Caine 1.

MANOVA among the 3 Caine groups and across the 6 functional domains was significant ($F(2,118)=10.30$, $p<.0001$). Differences among the Caine groups were observed for Production ($F(2,83)=4.87$, $p=.01$), Immediate Memory ($F(2,82)=7.40$, $p=.001$), Delayed Memory ($F(2,82)=6.98$, $p=.002$), and Upper Limb Motor ($F(2,83)=5.08$, $p=.008$) composite scores. Caine groups did not differ on Attention/Working Memory ($F(2,80)=1.36$, $p=.26$) or Visuospatial ($F(2,83)=1.41$, $p=.25$) composite scores (Figure 2). Follow-up analyses indicated that for the 4 composites with group differences, Caine 2+ demonstrated the most severe deficits, scoring lower than Caine 0 or Caine 1.

When these analyses were repeated excluding the 3 participants in the Caine 2+ group with the highest alcohol consumption, Caine 2+ continued to score lower than Caine 0 and Caine 1 on Immediate Memory and Delayed Memory, but the group effects were no longer significant for Production or Upper Limb Motor composite scores.

ALC subgroups by individual Caine criteria—The 2 Caine criteria with the highest frequency in this study sample were dietary deficiency (self-reported) and cerebellar dysfunction (based on ataxia scores), with 51 ALC (59.3%) reporting 30 or more days of missed meals in their lifetime due to drinking and 37 ALC (43%) demonstrating balance/gait deficits. Only 2 alcoholics had oculomotor disturbances and 3 alcoholics scored below 124 on the Dementia Rating Scale.

To determine the relative utility of the dietary and ataxia criteria in identifying alcohol-related cognitive and motor impairment we compared 4 alcoholic subgroups: (1) ALCs who met neither diet deficiency nor ataxia criteria ($n=21$), (2) ALCs who met only the dietary criterion ($n=27$), (3) ALCs who met only the ataxia criterion ($n=12$), and (4) ALCs who met both criteria ($n=21$). Groups differed on Production ($F(3,77)=3.30$, $p=.025$), Immediate Memory ($F(3,76)=2.89$, $p=.041$), and Upper Limb Motor ($F(3,77)=3.00$, $p=.036$) composite scores (Figure 3), with modest differences noted on Attention/Working Memory ($F(3,76)=2.40$, $p=.074$) and Delayed Memory ($F(3,76)=2.64$, $p=.057$) composite scores. Groups did not differ on Visuospatial Construction composite score ($F(3,77)=.306$, $p=.821$).

Two-group, follow-up analyses indicated that ALC meeting both the dietary deficiency and ataxia criteria scored lower on Production and Immediate Memory than ALC who met only dietary deficiency or neither criterion. ALC meeting both criteria also scored lower than those who met neither criterion on Delayed Memory.

ALC meeting only the ataxia criterion scored lower on Attention/Working Memory and Production than ALC meeting only the dietary deficiency criterion or neither criterion. ALC meeting the ataxia criteria and ALC meeting both criteria scored lower than ALC meeting only the dietary deficiency criteria on Upper Limb Motor.

Ataxia scores and thiamine (TDP) levels—The ALC group was impaired on all 4 balance and gait conditions [Romberg $t(128)=2.93$, $p=.004$; Line walking $t(128)=2.13$, $p=.035$; Balance on left leg $t(128)=4.50$, $p<.0001$; Balance on right leg $t(128)=4.24$, $p<.0001$] (Figure 4) compared with NC.

Whole blood TDP levels were available for 72 of the ALC participants (111.85 ± 32.15 nmol/L, 38 to 199 nmol/L, normal range being 74–222 nmol/L), with 9 ALC participants having whole blood thiamine levels under the clinical cutoff of 74 nmol/L. The total group of ALC did not differ from NC ($n=31$) on TDP levels $t(101)=.64$, $p=.52$). Caine categorized groups differed on TDP levels ($F(2,62)=3.29$, $p=.04$), with Caine 2+ having a significantly lower TDP level (100 ± 31 nmol/L, 38 to 148 nmol/L) compared with Caine 0 (126 ± 35 nmol/L, 83 to 199 nmol/L).

Correlations in the ALC group

Greater lifetime alcohol consumption was correlated with poorer performance on the 6 cognitive and motor composite scores in the ALC group (Table 4). Within the ALC group, older age was correlated with lower scores on the Production, Visuospatial Construction, and Upper Limb Motor composites corrected for age and education. Lower TDP levels were correlated with worse performance on Immediate Memory and Delayed Memory composite scores. Lower ataxia scores were correlated with lower scores on 5 of the composites: Attention/Working Memory, Production, Immediate Memory, Delayed Memory, and Upper Limb Motor.

Thiamine was not correlated with age ($r=-.09$), total alcohol ($r=.04$), or ataxia score ($r=.20$). Lower ataxia scores were related to higher total alcohol consumption ($r=-.36$) and older age ($r=-.53$).

Multiple regression analyses identified uniquely contributing factors to the prediction of each composite (Table 5). When examining the relative contribution of all significant factors to the prediction of Attention/Working Memory, Production, and Upper Limb Motor Composite scores, it was the ataxia score that consistently accounted for a significant amount of variance (Figure 5). By contrast, total lifetime alcohol and TDP levels were independent and significant predictors of Immediate Memory and Delayed Memory scores (Figure 6). These results did not change when age was added to the prediction model.

To identify the relative contribution of significant factors, namely TDP level and ataxia, to the prediction of mnemonic and nonmnemonic scores in ALC, we calculated a Memory composite (average of Immediate Memory and Delayed Memory scores) and an Executive Function composite (average of Attention/Working Memory and Production scores). TDP level accounted for 12.6% of the variance of the Memory composite score over and above the contribution of total lifetime alcohol, and total lifetime alcohol accounted for 24.2% of the variance over and above the contribution of TDP level. By contrast, total lifetime alcohol accounted for only 1.1% of the variance of the Executive Function composite score over and above the contribution of ataxia score, which accounted for 10.2% of the variance over and above total lifetime alcohol.

ALC with and without history of drug dependence—To assess whether these results were influenced by drug dependence reported by 54 of our 96 alcoholics, we reanalyzed the data to include only the 42 ALCs (36 of which had Caine data) with no history of drug (i.e., cocaine, opioid, amphetamine, cannabis) dependence. As was found in the entire ALC group, these analyses revealed a group difference among Caine subgroups on Immediate Memory ($F(2,34)=5.69$, $p=.007$) and Delayed Memory ($F(2,34)=6.38$, $p=.004$). Specifically, Caine 2+ was impaired compared with Caine 0 and Caine 1 on Immediate Memory and impaired compared with Caine 0 on Delayed Memory. Caine 1 was impaired compared with Caine 0 on Immediate Memory and Delayed Memory. In addition, a group difference was reported on the Upper Motor composite ($F(2,34)=3.37$, $p=.046$), with Caine 2+ having lower scores than Caine 1 and Caine 0 (Figure 8).

Post-hoc analyses also revealed that the ALCs with a history of drug dependence did not differ from the ALCs without a history of drug dependence on any composite score when examined within the entire group or within Caine-related subcategories, with the exception that within Caine 0, ALCs with a history of drug dependence scored lower than ALCs without a history of drug dependence on Delayed Memory. Comparing ALCs with and without cocaine dependence, with and without amphetamine, with and without opioid, and with and without cannabis dependence yielded no group differences on any of the cognitive or motor composite scores. ALCs with a history of dependence on more than 1 drug ($n=25$) did not differ from ALCs with no history of any drug dependence on any of the composite scores.

Multiple regression analyses, including only ALCs with no history of drug dependence, continued to show that thiamine and total alcohol consumption were unique predictors of Immediate Memory and Delayed Memory.

DISCUSSION

These results provide additional evidence for dissociable alcohol, nutritional, and neurological factors that are predictive of selective cognitive and motor deficits in currently sober alcoholics. Specifically, these data demonstrate a double dissociation, where lower thiamine levels and higher lifetime alcohol consumption selectively predicted episodic memory deficits, whereas ataxia selectively predicted executive and upper motor deficits.

The pattern of cognitive impairment in our alcoholics involving executive functions, episodic memory, and visuospatial construction and the graded effect observed related to number of Caine criteria met are consistent with earlier reports (e.g., Beatty et al., 2000; Oscar-Berman & Marinkovic, 2007; Parsons & Nixon, 1993; Pitel et al., 2011; Sullivan, Fama, Rosenbloom & Pfefferbaum, 2002; Sullivan, Rosenbloom & Pfefferbaum, 2000) and provide support for assuming that our alcoholics are representative of other samples. This study replicates and extends previous work (e.g., Pitel et al., 2011; Ritz et al., 2016) addressing the heterogeneity of cognitive and motor deficits in alcoholism and demonstrating that alcohol-related factors and not a history of drug dependency likely underlie these impairments. Here, we identified that dietary deficiency and signs of cerebellar dysfunction, the two most frequently met criteria, significantly predicted cognitive and motor performance. Cerebellar signs of ataxia, more so than dietary deficiency, were associated with deficits in attention/working memory, production, and upper limb motor function, consistent with evidence for an association between higher-order cognitive function and cerebellar integrity (cf., Fitzpatrick and Crowe, 2013). These data also support the position that thiamine plays a role in the presence of episodic memory deficits in alcoholism (cf., Vedder, Hall, Jabrouin, & Savage, 2015); it was the subgroup of alcoholics who met criteria purported to reflect both cerebellar dysfunction and dietary deficiency who demonstrated the most pronounced memory impairment.

A relation between thiamine level and ataxia was not observed in our alcoholics, although thiamine deficiency has been associated with cerebellar compromise (cf., Mulholland, 2006). This may be due to the fact that the thiamine measure used in this study assessed current level of TDP and is not necessarily reflective of past levels of deficiencies. Additionally, the role of genetics in the understanding of differences among alcoholics related to absorption and utilization of thiamine in the central nervous system and the differential susceptibility of brain structures are not yet well understood (Hazell, Faim, Wertheimer, Silva, & Marques, 2011; Thomson, 2000).

These results highlight the importance of the revised criteria for the diagnosis of a subclinical form of Wernicke's encephalopathy proposed by Caine and colleagues (Caine et al., 1997) and operationalized by Pitel and colleagues (Pitel et al., 2011) for identifying factors contributing to cognitive and motor deficits in non-KS chronic alcoholism, particularly the criteria of cerebellar dysfunction and dietary deficiencies in abstinent alcoholics. Indeed, application of these criteria may aid in identifying individuals who are at heightened risk of developing cognitive and motor deficits. Further, the Caine criteria may contribute to the understanding of the underlying nature of the heterogeneity in functional deficits in chronic alcoholism and inconsistencies reported among studies.

Additional studies with a larger number of participants in each Caine subgroup may unveil relationships among neurological, nutritional, and cognitive factors that were not observed in this study for lack of statistical power when examining subgroups. In addition, a historical signature or biomarker of thiamine deficiency over the lifespan would enable further investigation of the relation between thiamine and susceptibility of impairment of diencephalic, medial temporal, and cerebellar structures and associated cognitive and motor deficits.

Taken together, these results suggest nonmnemonic and mnemonic deficits in chronic alcoholism are associated with dysfunction in dissociable neural systems, including the frontocerebellar and Papez circuits, both of which are affected in chronic alcoholism (Le Berre et al., 2014; Oscar-Berman & Hutner, 1993; Pitel et al., 2007). To the extent that ataxia measures reflect cerebellar integrity and their relation with executive functions of attention, working memory, and production, these results implicate underlying dysfunction in frontocerebellar systems (cf., E, Chen, Ho, & Desmond, 2014; Sullivan, 2003). And to the extent that the thiamine measure assesses dietary status (Guerrini & Thomson, 2009), with its known relevance to neural structures included in Papez circuit (Thomson & Marshall, 2006) and its selective relation to mnemonic ability (cf., Le Berre et al., 2014; Pitel et al., 2007), these results suggest underlying limbic-diencephalon system dysfunction.

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References

- Albert M, Butters N, Rogers S, Pressman J, Geller A. 1982; A preliminary report: nutritional levels and cognitive performance in chronic alcohol abusers. *Drug and Alcohol Dependence*. 9:131–142. [PubMed: 7094836]
- Beatty W, Tivis R, Stott H, Nixon S, Parsons O. 2000; Neuropsychological deficits in sober alcoholics: Influences of chronicity and recent alcohol consumption. *Alcoholism: Clinical and Experimental Research*. 24(2):149–154.
- Beck, AT, Steer, RA, Brown, GK. Manual for the Beck Depression Inventory-II. San Antonio, TX: Psychological Corporation; 1996.
- Borkowski JG, Benton AL, Spreen O. 1967; Word fluency and brain damage. *Neuropsychologia*. 5:135–140.
- Bowden SC. 1990; Separating cognitive impairment in neurologically asymptomatic alcoholism from Wernicke-Korsakoff Syndrome: Is the neuropsychological distinction justified. *Psychological Bulletin*. 107(3):355–366. [PubMed: 2190253]
- Caine D, Halliday GM, Kril JJ, Harper CG. 1997; Operational criteria for the classification of chronic alcoholics: Identification of Wernicke's encephalopathy. *Journal of Neurology Neurosurgery and Psychiatry*. 62(1):51–60.
- Corkin, S, Growdon, JH, Sullivan, EV, Nissen, MJ, Huff, FJ. Assessing treatment effects from a neuropsychological perspective. In: Poon, L, editor *Handbook of Clinical Memory Assessment in Older Adults*. Washington DC: American Psychological Association; 1986. 156–167.
- Davies SJ, Pandit SA, Feeney A, Stevenson BJ, Kerwin RW, Nutt DJ, Lingford-Hughes A. 2005; Is there cognitive impairment in clinically 'healthy' abstinent alcohol dependence? *Alcohol and Alcoholism*. 40(6):498–503. [PubMed: 16186142]
- E K-H, Chen S-HA, Ho M-HR, Desmond J. 2014; A meta-analysis of cerebellar contributions to higher cognition from PET and fMRI studies. *Human Brain Mapping*. 35:593–615. [PubMed: 23125108]
- Fama R, Pitel A-L, Sullivan EV. 2012; Anterograde episodic memory in Korsakoff syndrome. *Neuropsychology Review*. 22(2):93–104. [PubMed: 22644546]
- Fama, R, Sullivan, E. Alcohol. In: DA, A, SP, W, editors *Neuropsychological Aspects of Substance Abuse*. Oxford: 2013. (pp. Chapter 6)

- Fein G, Torres J, Price LJ, Di Sclafani V. 2006; Cognitive performance in long-term abstinent alcoholic individuals. *Alcoholism: Clinical and Experimental Research*. 30(9):1538–1544.
- First, MB, Spitzer, RL, Gibbon, M, Williams, JBW. Structured Clinical Interview for DSM-IV Axis I Disorders (SCID) Version 2.0. New York, NY: Biometrics Research Department, New York State Psychiatric Institute; 1998.
- Fregly AR, Smith MJ, Graybiel A. 1973; Revised normative standards of performance of men on a quantitative ataxia test battery. *Acta Otolaryngology*. 75:10–16.
- Galvin R, Brathen G, Ivashynka A, Hillbom M, Tanasescu R, Leone M. 2010; EFNS guidelines for diagnosis, therapy and prevention of Wernicke encephalopathy. *European Journal of Neurology*. 17:1408–1418. [PubMed: 20642790]
- Guerrini I, Thomson A. 2009; Molecular genetics of alcohol-related brain damage. *Alcohol and Alcoholism*. 44:166–170. [PubMed: 19096015]
- Guthrie A, Elliott W. 1980; The nature and reversibility of cerebral impairment in alcoholism. *Journal of Studies on Alcohol*. 41(1):147–155. [PubMed: 7366209]
- Hazell AS, Faim S, Wertheimer G, Silva VR, Marques CS. 2013; The impact of oxidative stress in thiamine deficiency: a multifactorial targeting issue. *Neurochemistry International*. 62:796–802. [PubMed: 23333339]
- Hollingshead, A. Four-Factor Index of Social Status. New Haven, CT: Yale University, Department of Sociology; 1975.
- Kopelman MD. 1995; The Korsakoff Syndrome. *British Journal of Psychiatry*. 166:154–173. [PubMed: 7728359]
- Le Berre A, Fama R, Sullivan EV. 2017; Executive functions, memory, and social cognition deficits and recovery in chronic alcoholism: a critical review to inform future research. *Alcoholism: Clinical and Experimental Research*. 41(8):1432–1443.
- Le Berre A, Pitel A, Chanraud S, Beaunieux H, Eustache F, Martinot J, Pfefferbaum A. 2014; Chronic alcohol consumption and its effects on nodes of frontocerebellar and limbic circuitry: comparison of effects in France and the United States. *Human Brain Mapping*. 35:4635–4653. [PubMed: 24639416]
- Makris N, Oscar-Berman M, Jaffin SK, Hodge SM, Kennedy DN, Caviness VS, Harris GJ. 2008; Decreased volume of the brain reward system in alcoholism. *Biological Psychiatry*. 64(3):192–202. [PubMed: 18374900]
- Matthews, CG, Kløve, H. Instruction manual for the Adult Neuropsychology Test Battery. Madison, WI: University of Wisconsin Medical School; 1964.
- Mattis, S. Dementia Rating Scale (DRS) Professional Manual. Odessa, FL: Psychological Assessment Resources, Inc; 2004.
- Mulholland PJ. 2006; Susceptibility of the cerebellum to thiamine deficiency. *The Cerebellum*. 5:55–63. [PubMed: 16527765]
- Nelson, HE. The National Adult Reading Test (NART). Windsor, Canada: Nelson Publishing Company; 1982.
- Oscar-Berman, M. Neuropsychological vulnerabilities in chronic alcoholism. In: Noronha, A, Eckardt, M, Warren, K, editors *Review of NIAAA's Neuroscience and Behavioral Research Portfolio*, NIAAA Research Monograph. Vol. 34. Bethesda, MD: National Institutes of Health; 2000. 437–472.
- Oscar-Berman, M, Hutner, N. Frontal lobe changes after chronic alcohol ingestion. In: Hunt, WA, Nixon, SJ, editors *Alcohol-Induced Brain Damage*, NIAAA Research Monographs. Vol. 22. Rockville, MD: National Institutes of Health; 1993. 121–156.
- Oscar-Berman M, Marinkovic K. 2007; Alcohol: effects on neurobehavioral functions and the brain. *Neuropsychol Rev*. 17(3):239–257. [PubMed: 17874302]
- Oscar-Berman, M, Valmas, M, Sawyer, K, Ruiz, S, Luhr, R, Gravitz, Z. Profiles of impaired, spared, and recovered neuropsychologic processes in alcoholism. In: Pfefferbaum, EVSaA, editor *Handbook of Clinical Neurology: Alcohol and the Nervous System*. Vol. 125. Elsevier; 2014. 183–210.
- Parsons OA, Nixon SJ. 1993; Neurobehavioral sequelae of alcoholism. *Neurologic Clinics*. 11(1):205–218. [PubMed: 8441371]

- Pitel A, Rivier J, Beaunieux H, Vabret F, Desgranges B, 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):490–498.
- Pitel A-L, Zahr NM, Jackson K, Sassoon S, Rosenbloom M, Pfefferbaum A, Sullivan E. 2011; Signs of preclinical Wernicke's Encephalopathy and thiamine levels as predictors of neuropsychological deficits in alcoholism without Korsakoff's syndrome. *Neuropsychopharmacology*. 36(3):580–588. DOI: 10.1038/npp.2010.189 [PubMed: 20962766]
- Pitel AL, Beaunieux H, Witkowski T, Vabret F, Guillery-Girard B, Quinette P, Eustache F. 2007; Genuine episodic memory deficits and executive dysfunctions in alcoholic subjects early in abstinence. *Alcoholism: Clinical and Experimental Research*. 31(7):1169–1178.
- Reitan RM. 1958; Validity of the Trail Making Test as an indicator of organic brain damage. *Perceptual and Motor Skills*. 8:271–276.
- Rey A. 1942; L'examen psychologique dans les cas d'encephalopathie traumatique. *Archives de Psychologie*. 28:286–340.
- Ritz L, Coulbault L, Lannuzel C, Boudehent C, Segobin S, Eustache F, Beaunieux H. 2016; Clinical and biological risk factors for neuropsychological impairment in alcohol use disorder. *PLOS ONE*. doi: 10.371/journal.pone.0159616
- Ruff, R. Ruff Figural Fluency Test: Administration Manual. San Diego, CA: Neuropsychological Resources; 1988.
- Ryback R. 1971; The continuum and specificity of the effects of alcohol on memory: A review. *Quarterly Journal of Studies on Alcohol*. 32:995–1016. [PubMed: 4944697]
- Skinner, HA. Development and Validation of a Lifetime Alcohol Consumption Assessment Procedure. Toronto, Canada: Addiction Research Foundation; 1982.
- Skinner HA, Sheu WJ. 1982; Reliability of alcohol use indices: The lifetime drinking history and the MAST. *Journal of Studies on Alcohol*. 43:1157–1170. [PubMed: 7182675]
- Stavro K, Pelletier J, Potvin S. 2012; Widespread and sustained cognitive deficits in alcoholism: a meta-analysis. *Addiction Biology*. 18:203–213. [PubMed: 22264351]
- Sullivan EV. 2003; Compromised pontocerebellar and cerebellothalamocortical systems: speculations on their contributions to cognitive and motor impairment in nonamnestic alcoholism. *Alcoholism: Clinical and Experimental Research*. 27(9):1409–1419.
- Sullivan EV, Fama R, Rosenbloom MJ, Pfefferbaum A. 2002; A profile of neuropsychological deficits in alcoholic women. *Neuropsychology*. 16:74–83. [PubMed: 11853359]
- Sullivan EV, Rosenbloom MJ, Pfefferbaum A. 2000; Pattern of motor and cognitive deficits in detoxified alcoholic men. *Alcoholism: Clinical and Experimental Research*. 24(5):611–621.
- Thomson AD. 2000; Mechanisms of vitamin deficiency in chronic alcohol misusers and the development of the Wernicke-Korsakoff syndrome. *Alcohol and Alcoholism Suppl*. 35(1):2–7.
- Thomson AD, Marshall EJ. 2006; The natural history and pathophysiology of Wernicke's Encephalopathy and Korsakoff's Psychosis. *Alcohol and Alcoholism*. 41(2):151–158. [PubMed: 16384871]
- Vedder L, Hall J, Jabrouin K, Savage L. 2015; Interactions between chronic ethanol consumption and thiamine deficiency on neural plasticity, spatial memory, and cognitive flexibility. *Alcoholism: Clinical and Experimental Research*. 39(11):2143–2153.
- Victor, M, Adams, RD, Collins, GH. The Wernicke-Korsakoff Syndrome and Related Neurologic Disorders Due to Alcoholism and Malnutrition. 2. Philadelphia: F.A. Davis Co; 1989.
- Wechsler, D. Wechsler Memory Scale - Revised. San Antonio, TX: The Psychological Corporation; 1987.

Figure 1.

Bar graphs depicting age- and education-corrected scores on the cognitive and motor composites for the ALC and NC groups.

ANOVAs: Attention/Working Memory (Att/WM) $t(132)=2.66$, $p=.0087$; Production (Prod) $t(131)=2.67$, $p=.0085$; Immediate Memory (ImmMem) $t(131)=3.90$, $p=.0002$; Delayed Memory (DelMem) $t(131)=3.54$, $p=.0006$; Visuospatial Construction (Visuosp) $t(135)=2.32$, $p=.02$; Upper Limb Motor (UppMot) $t(131)=1.89$, $p=.06$.

Figure 2.

Bar graphs depicting the alcohol Caine-categorized subgroups in comparison with the ALC group as a whole and the NC group. Att/WM - Attention/Working Memory; Prod - Production; ImmMem - Immediate Memory; DelMem - Delayed Memory; Visuosp - Visuospatial Construction; UppMot - Upper Limb Motor.

Figure 3.

Bar graphs depicting the ALC group divided into subgroups based on the dietary deficiency and cerebellar dysfunction criteria. Attention/Working Memory: ALCs meeting only the ataxia criterion scored lower than ALCs meeting neither criterion ($t=2.24$, $p=.028$) or ALCs who met only the diet criterion ($t=2.48$, $p=.016$). Production: ALCs meeting only the ataxia criterion and ALCs meeting both criteria scored lower than ALCs meeting neither criterion ($t=2.19$, $p=.032$; $t=2.28$, $p=.025$) and ALCs meeting only the diet criterion ($t=2.14$, $p=.035$; $t=2.25$, $p=.027$). Immediate Memory: ALCs meeting both criteria scored lower than ALCs meeting neither criterion ($t=2.75$, $p=.007$) and ALCs meeting only the diet criterion ($t=2.29$, $p=.025$). Delayed Memory: ALCs meeting both criteria were impaired compared with ALCs who met neither criteria ($t=2.78$, $p=.007$). Upper Limb Motor: ALCs meeting only the ataxia criterion and ALCs meeting both criteria scored lower than ALCs meeting only the diet criterion ($t=2.29$, $p=.025$; $t=2.45$, $p=.017$).

Figure 4.

Bar graphs showing age-corrected scores for the 4 gait and balance tasks for ALC and NC.

Figure 5. Scatterplots showing the relationship between age-corrected ataxia score (average of the 4 balance and gait measures) and the attention/working memory, production, and upper limb composite scores for ALC.

Figure 6. Scatterplots showing the relationship between thiamine levels and total lifetime alcohol consumption and immediate memory and delayed memory scores for ALC.

Double dissociation: Factors involving alcohol, nutritional, and cerebellar signs selectively predict cognitive and motor deficits

Figure 7.

Model showing a double dissociation between factors predicting mnemonic and nonmnemonic abilities in ALC. Total lifetime alcohol and thiamine level were each independent and unique predictors of episodic memory in ALC, whereas ataxia predicted nonmnemonic functions.

Figure 8.

Table 1

Demographic characteristics of subjects (mean, standard deviation, range)

Group	Age (yrs)	Education (yrs)	NART IQ [†]	Lifetime Alcohol Consumption (kg)	Beck Depression Inventory-II	Dementia Rating Scale
Alcoholic (ALC n=96)	48.3 (10.7) 21 to 69	12.9 (2.3) 9 to 21	106.6 (8.9) 91 to 124	1318.0 (1007.0) 176 to 4711	9.9 (6.9) 0 to 38	135.9 (5.2) 121 to 144
Comparison (NC n=41)	45.6 (13.8) 21 to 73	15.5 (2.5) 11 to 21	110.6 (8.9) 92 to 126	24.0 (33.0) 0 to 136	3.2 (3.7) 0 to 16	139.1 (2.6) 130 to 144

Table 2

Individual Test Age- and Education-Corrected Z-scores: Means (standard deviation)

	ALC	NC	t-test	P
Trails A [†]	-.245 (.98)	.000 (.15)	1.341	.185
Trails B [†]	-1.251 (2.75)	.000 (.15)	2.833	.005
FAS Total	-489 (.97)	.000 (.16)	2.670	.009
Ruff Figural Fluency Total	-.398 (1.17)	.000 (.15)	1.903	.059
Logical Memory - Immediate	-.662 (1.15)	.000 (.15)	3.199	.002
Rey-Osterrieth - Immediate	-.596 (.91)	.000 (.15)	3.424	.001
Logical Memory - Delayed	-.691 (1.15)	.000 (.15)	3.330	.001
Rey-Osterrieth - Delayed	-.441 (.83)	.000 (.15)	2.694	.008
Rey-Osterrieth - Copy	-.597 (1.52)	.000 (.15)	2.316	.022
Grooved Pegboardt	-.717 (1.69)	.000 (.16)	2.502	.014
Fine Finger Movement	-.085 (1.04)	.000 (.15)	.442	.659

[†] test scores were inverted to have higher scores reflect better performance

Table 3

Demographic characteristics of ALC subgroups (mean, standard deviation, range)

Group	Age (yrs)	Education (yrs)	Lifetime Alcohol Consumption (kg)	Beck Depression Inventory-II	Dementia Rating Scale
Caine 0(n=21) (C0)	49.9 (10.5)	13.9 (2.5)	1150.0 (776.0)	9.5 (5.1)	138.8 (3.8)
Caine 1 (n=39) (C1)	43.5 (11.6)	12.9 (2.1)	1076.0 (929.0)	8.4 (5.1)	136.6 (4.6)
Caine2+(n=26) (C2)	53.8 (7.7)	12.6 (2.1)	1716.0 (1233.0)	10.9 (8.4)	133.6 (6.1)
Group differences (ANOVA) Follow-up t-tests	p=.0005 C1<C0,C2	p=.12	p=.04 C1<C2	p=.30	p=.002 C2<C0,C1

Alcoholics n=86 (10 ALC participants did not have Caine criteria data)

Table 4
Correlations between Composite Scores and Thiamine Level, Total Lifetime Alcohol Consumption, Age, and Ataxia Score in ALC

Test	Age		Lifetime Total Alcohol		Thiamine [†]		Ataxia	
	r	p	r	p	r	p	r	p
Attention/Working Memory	-.188	.071	-.229	.027 *	.051	.676	.310	.004 **
Production	-.257	.013 *	-.296	.004 **	.064	.599	.466	.000 ***
Immediate Memory	-.163	.121	-.438	.000 ***	.271	.023 *	.340	.001 ***
Delayed Memory	-.145	.168	-.415	.000 ***	.261	.029 *	.299	.005 ***
Visuospatial Construction	-.226	.027 *	-.257	.012 *	.125	.295	.186	.181
Upper Limb Motor	-.300	.004 **	-.310	.003 **	.124	.308	.444	.000 ***

[†]Thiamine levels were available for 72 of the ALC subjects

* p<.05

** p<.01

*** p<.0001

Table 5

Multiple regressions predicting Composite Scores in ALC

Dependent Measure	Predictors	t Ratio	p value
Attention/Working Memory	Total Alcohol	-1.16	.249
	Ataxia	2.42	.018 *
Production	Total Alcohol	-1.20	.231
	Age	0.12	.907
	Ataxia	3.72	.000 ***
Immediate Memory	Thiamine	2.69	.009 **
	Total Alcohol	-3.60	.001 **
	Ataxia	1.21	.230
Delayed Memory	Thiamine	2.68	.009 **
	Total Alcohol	-3.89	.000 ***
	Ataxia	0.74	.461
Visuospatial Construction	Total Alcohol	-1.82	.072
	Age	-1.35	.179
Upper Limb Motor	Total Alcohol	-1.65	.104
	Age	-0.37	.715
	Ataxia	3.10	.003 **

*
p<.05**
p<.01***
p<.0001