Psychiatry Research: Neuroimaging 250 (2016) 42–49

Contents lists available at ScienceDirect

Psychiatry Research: Neuroimaging

journal homepage: www.elsevier.com/locate/psychresns

# Brain metabolite levels in recently sober individuals with alcohol use disorder: Relation to drinking variables and relapse

Natalie M. Zahr [a,b,*], Rebecca A. Carr [b], Torsten Rohlfing [b,1], Dirk Mayer [b,c], Edith V. Sullivan [a], Ian M. Colrain [b], Adolf Pfefferbaum [a,b]

[a] Psychiatry & Behavioral Sciences, Stanford University School of Medicine, 401 Quarry Road, Stanford, CA 94305, USA
[b] Center for Health Sciences, SRI International, Menlo Park, CA 94025, USA
[c] Diagnostic Radiology and Nuclear Medicine, University of Maryland, School of Medicine, Baltimore, MD 21201, USA

ARTICLE INFO

*Article history:*
Received 25 June 2015
Received in revised form
5 January 2016
Accepted 14 January 2016
Available online 18 February 2016

*Keywords:*
Sobriety
Relapse
MR spectroscopy
N-acetylaspartate
Choline-containing compounds

ABSTRACT

Magnetic resonance spectroscopy (MRS) studies in alcohol use disorder (AUD) typically report lower levels of N-acetylaspartate (NAA) and choline-containing compounds (Cho) in several brain regions. Metabolite levels, however, are labile and can be affected by several competing factors, some related to drinking variables.. This in vivo MRS study included 20 recently sober (19.6 ± 12.6 days) individuals with AUD and 15 controls. MRS was performed in single voxels placed in frontal white matter and thalamic regions using Constant-Time Point Resolved Spectroscopy (CT-PRESS) for absolute quantification of NAA, Cho, total creatine (tCr), and glutamate (Glu). A trend toward a thalamic NAA deficit in the total AUD group compared with controls was attributable to the subgroup of alcoholics who relapsed 3 or so months after scanning. In the total AUD group, frontal and thalamic NAA and Cho levels were lower with more recent drinking; frontal and thalamic Cho levels were also lower in AUD individuals with past stimulant abuse. Thalamic Cho levels were higher in binge-drinking AUD individuals and in those with longer length of alcohol dependence. MRS-visible metabolite peaks appear to be modulated by variables related to drinking behaviors, suggesting a sensitivity of MRS in tracking and predicting the dynamic course of alcoholism.

© 2016 Elsevier Ireland Ltd. All rights reserved.

## 1. Introduction

Most magnetic resonance spectroscopy (MRS) studies report lower levels of N-acetylaspartate (NAA) in recently sober subjects with alcohol use disorders (AUD) relative to healthy controls in several brain regions including frontal areas (Bendszus et al., 2001; Durazzo et al., 2004, 2010; Fein et al., 1994; Jagannathan et al., 1996; Schweinsburg et al., 2003) and cerebellum (Bendszus et al., 2001; Durazzo et al., 2010; Jagannathan et al., 1996; Parks et al., 2002; Seitz et al., 1999). Levels of NAA, which when compromised can, in certain cases, reflect neuronal loss or damage (Moffett et al., 2007), and are useful in determining regions of the brain that are particularly susceptible to the untoward effects of alcohol. Similarly, below control levels of choline-containing compounds (Cho) in AUD patients shortly following detoxification are also reported in frontal (Durazzo et al., 2004; Ende et al., 2005; Fein et al., 1994) and cerebellar (Bendszus et al., 2001; Ende et al., 2005; Parks et al., 2002; Seitz et al., 1999) regions (but see, Hermann et al., 2012; Modi et al., 2011). Together with changes in NAA levels, changes in Cho levels can be used, theoretically, to distinguish neuronal from glial targets of brain pathology (Fein et al., 1994). MRS studies suggest that both NAA (e.g., Bartsch et al., 2007; Bendszus et al., 2001; Parks et al., 2002), particularly in frontal (Bartsch et al., 2007; Bendszus et al., 2001; Durazzo et al., 2006) and cerebellar (Bendszus et al., 2001; Fein et al., 1994; Parks et al., 2002) regions, and Cho (e.g., Bartsch et al., 2007; Bendszus et al., 2001; Durazzo et al., 2006; Ende et al., 2005; Martin et al., 1995) levels show normalization (i.e., increase) with abstinence. By contrast, elevated levels of Cho have been noted in non-abstinent chronic heavy drinkers (Meyerhoff et al., 2004), social and moderate drinkers (Ende et al., 2006), and rodents exposed to binge alcohol (e.g., Zahr et al., 2010, 2009).

At least two-thirds of AUD individuals return to drinking within months of initiating recovery (e.g., Sinha, 2007). Using in vivo MR imaging (MRI) results, the neural correlates of relapse risk have begun to be explored. The most substantial evidence thus far supports the integrity of frontal regions in the maintenance of sobriety (e.g., Sorg et al., 2012). The volume of the orbitofrontal cortex was smaller in AUD individuals that relapse than in those

* Corresponding author at: Psychiatry & Behavioral Sciences, Stanford University School of Medicine, 401 Quarry Road, Stanford, CA 94305, USA.
*E-mail address:* nzahr@stanford.edu (N.M. Zahr).
[1] Dr. Rohlfing's current affiliation is Google, Inc.

http://dx.doi.org/10.1016/j.pscychresns.2016.01.015
0925-4927/© 2016 Elsevier Ireland Ltd. All rights reserved.

that remained sober at 3-month (Beck et al., 2012) and 12-month (Durazzo et al., 2011) follow-up time points (also see, Cardenas et al., 2011), and smaller medial-frontal gray matter volumes predicted relapse to heavy drinking at 3-month follow-up (Rando et al., 2011).

Another perspective on AUD relapse risk derives from the sleep literature. Sleep disturbances are highly prevalent in AUD (for review, Colrain et al., 2014; Jia et al., 2007) and may be associated with relapse (Conroy, 2015). The thalamus, a key region of arousal modulation, is responsible for producing sleep-specific electroencephalogram (EEG) phenomena such as sleep spindles (Steriade, 1993), which are compromised in AUD (Colrain et al., 2014). Another study, using tissue from the lateral geniculate nucleus of the thalamus of monkey model of chronic alcohol drinking by self-administration, found reduced calcium currents in thalamic relay cells known to contribute to normal sleep patterns (Carden et al., 2006). In humans, an MRI study reported that AUD subjects with smaller thalamic volumes at treatment entry tended to resume heavy alcohol consumption at 6-month follow-up (Segobin et al., 2014).

The current MRS study was conducted in individuals with AUD and demographically-matched control subjects to evaluate frontal white matter and thalamic metabolite levels. Because of the preponderance of evidence in support of frontal integrity as a requirement for sustained abstinence and for the role of thalamic integrity in sleep maintenance, it was hypothesized that NAA levels in frontal white matter and in thalamic tissue of AUD subjects at study entry would be lower than those of controls and be associated with relapse, thereby providing a potential marker for relapse risk. Further, we tested the hypothesis that high Cho levels in either voxel would be predictive of relapse. Exploratory correlations examined relations between metabolite levels and alcohol consumption variables, notably, that greater amount of alcohol drunk, recency of drinking, and binge-style drinking would be associated with lower NAA levels in either voxel.

## 2. Methods

### 2.1. Participants

AUD patients ($n=20$, $44.35 \pm 9.89$ years, age range=28–64 years, sober for $19.55 \pm 12.61$ days) were recruited from residential treatment centers around the San Francisco Bay Area. Demographically-matched healthy controls (Ctrl, $n=15$, $46.13 \pm 8.84$ years, age range=30–62 years) were recruited through community fliers (Table 1). All participants provided written, informed consent to participate in this study, approved by the Institutional Review Boards of Stanford University and SRI International. Participants underwent a thorough psychiatric interview by a trained research psychologist using the Structured Clinical Interview for the Diagnostic and Statistical Manual (DSM) IV-TR to diagnose alcohol dependence and to exclude other diagnoses or medical conditions before study entry that can affect brain functioning (e.g., diabetes, head injury, epilepsy, uncontrolled hypertension, radiation, chemotherapy, HIV infection) or preclude MR study (e.g., pacemakers).

Control and AUD groups were not significantly different with respect to age, blood pressure (systolic or diastolic), body mass index (BMI), or performance on the Mini-Mental State Exam (MMSE) (Folstein et al., 1975) or the National Adult Reading Test (NART) (Nelson, 1982). Based on a quantitative handedness questionnaire (Crovitz and Zener, 1962), 2 control and 3 AUD subjects were left-handed; 2 AUD subjects were ambidextrous. AUD relative to control subjects had higher lifetime alcohol consumption ($p<0.0001$), elevated heart rate ($p=0.017$), lower socio-economic status (SES) (Hollingshead, 1975) ($p<0.0001$), less education ($p<0.0001$), poorer global assessment of functioning (GAF) scores ($p<0.0001$) (First, 2000), and worse performance on the American-NART ($p=0.0184$). Five AUD men and 3 AUD women were current smokers; an additional 4 AUD men and 1 AUD woman were past smokers. Out of 20 AUD subjects, 7 met criteria for current anxiety diagnoses (including generalized anxiety ($n=1$), anxiety disorder not otherwise specified ($n=5$), or social phobia ($n=1$)); 5 for major depressive episode (3/5 substance induced); and 5 for past dependence on other drugs of abuse (cocaine ($n=1$), amphetamine ($n=2$), methamphetamine ($n=2$). One of the methamphetamine users was also one of the individuals with anxiety disorder (not otherwise specified); there were no other co-morbidities for affective disorders and substance use.

All subjects were contacted within 3 months of study participation for follow-up phone interviews to determine drinking behavior. Of the 20 AUD subjects included in the study, 5 had remained abstinent (AUD-A, 4 men, 1 woman), 10 had relapsed (AUD-R, 5 men, 5 women), and 5 were lost to follow up (AUD-lost, 3 men, 2 women) (Table 2).

**Table 1**
Participant demographics at baseline (at MRS scan, mean ± SD).

| | Ctrl ($n=15$) | AUD ($n=20$) | $p$-Value |
|---|---|---|---|
| **M/F**[a] | 9/6 | 12/8 | 0.99 |
| **Age** | 46.13 ± 8.84<br>30–62 | 44.35 ± 9.89<br>28–64 | 0.58 |
| **Systolic BP** | 121.62 ± 16.47<br>103–162 | 129.15 ± 17.77<br>100–160 | 0.27 |
| **Diastolic BP** | 73.54 ± 8.55<br>62–88 | 75.85 ± 13.78<br>45–100 | 0.61 |
| **Heart rate** | 67.77 ± 10.74<br>51–88 | 79.69 ± 12.87<br>60–109 | **0.02** |
| **Right/left-handed**[a,b] | 13/2 | 15/3 | 0.67 |
| **Education** | 17.00 ± 2.10<br>12–21 | 12.35 ± 2.01<br>8–15 | < **0.0001** |
| **Body mass index** | 24.38 ± 3.52<br>19–30 | 25.47 ± 2.38<br>21–30 | 0.31 |
| **Hepatitis C**[a] | 0 | 2 | 0.50 |
| **SES** | 20.67 ± 9.73<br>11–44 | 39.29 ± 8.45<br>19–58 | < **0.0001** |
| **GAF** | 88.21 ± 3.04<br>80–92 | 63.90 ± 8.35<br>45–82 | < **0.0001** |
| **Length of dependence (yrs)** | – | 14.90 ± 7.43<br>3.8-33.4 | – |
| **Lifetime EtOH (kg)** | 52.21 ± 112.21<br>1–435 | 1189.85 ± 795.45<br>250–2975 | < **0.0001** |
| **Last drink (days)**[c] | 14.77 ± 17.69<br>1–55 | 19.55 ± 12.61<br>9–63 | 0.37 |
| **Binge drinking pattern (y/n)** | – | 9/11 | – |
| **Smoker**[a] | 0 | 8/12 | **0.01** |
| **Stimulant abuse**[a,d] | – | 11/9 | – |
| **MMSE** | 28.38 ± 1.39<br>25–30 | 27.39 ± 1.69<br>25–30 | 0.09 |
| **DRS** | 139.82 ± 3.49<br>132–144 | 136.22 ± 9.78<br>103–144 | 0.25 |
| **NART IQ** | 115.73 ± 5.39<br>105–123 | 112.33 ± 7.84<br>94–123 | 0.22 |
| **ANART IQ** | 118.77 ± 6.18<br>105–125 | 111.01 ± 9.01<br>86–123 | **0.02** |

SES: socio-economic status, low score=good; GAF: global assessment of functioning; EtOH: alcohol; MMSE: mini-mental state exam; DRS: dementia rating scale; NART: National Adult Reading Test; ANART: American National Adult Reading Test.

[a] Fisher's exact test.
[b] 2 AUD subjects ambidextrous.
[c] 2 Ctrl subjects with no alcohol consumption (>10 years) not included in calculation.
[d] *past* stimulant abuse or dependence; stimulants include cocaine, amphetamine, other undesignated stimulant.

Download English Version:

https://daneshyari.com/en/article/334408

Download Persian Version:

https://daneshyari.com/article/334408

Daneshyari.com