Journal of Affective Disorders 186 (2015) 95–98

Contents lists available at ScienceDirect

Journal of Affective Disorders

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

Short communication

# Hippocampal glutamate is increased and associated with risky drinking in young adults with major depression

Daniel F. Hermens [a,*], Kate M. Chitty [a], Rico SC Lee [a], Ashleigh Tickell [a], Paul S. Haber [b,c], Sharon L. Naismith [a], Ian B. Hickie [a], Jim Lagopoulos [a]

[a] Clinical Research Unit, Brain and Mind Research Institute, University of Sydney, Camperdown, Australia
[b] Drug Health Services, Royal Prince Alfred Hospital, Camperdown, Australia
[c] Sydney Medical School, University of Sydney, Camperdown, Australia

ARTICLE INFO

*Article history:*
Received 10 April 2015
Received in revised form
2 July 2015
Accepted 6 July 2015
Available online 26 July 2015

*Keywords:*
Hippocampus
Depression
Alcohol
Glutamate
Magnetic resonance spectroscopy

ABSTRACT

*Background:* Risky drinking in young people is harmful, highly prevalent and often complicated by co-morbid mental health problems that compound alcohol-induced impairment. The hippocampus and the glutamate system have been implicated in the pathophysiology of alcoholism and depression. This study aimed to determine whether risky drinking is associated with glutamate levels recorded within the hippocampus of young adults with major depression.
*Methods:* Sixty-three young persons with major depression (22.1 ± 3.1 years; 65% female) and 38 healthy controls were recruited. Participants completed the alcohol use disorder identification test and underwent proton magnetic resonance spectroscopy to measure *in vivo* glutamate levels within the hippocampus following a period of at least 48 h of abstinence.
*Results:* Young adults with depression had significantly increased hippocampal glutamate levels and a positive association between the level of alcohol use and glutamate. Regression analysis revealed that higher levels of hippocampal glutamate were predicted by having increased levels of risky drinking and depression.
*Limitations:* Small sample sizes for testing diagnosis by risky drinking interaction and use of creatine ratios rather than the absolute concentrations of glutamate.
*Discussion:* The hippocampus is a critical region; given its role in learning and memory as well as mood regulation, and the neurochemical changes observed in this study may precede structural changes, which are commonly observed in both depression and alcohol misuse. These findings suggest that young adults with major depression who engage in risky drinking may be at increased risk of glutamate excitotoxicity.


## 1. Introduction

Beyond determining the high prevalence of comorbid depression and risky drinking, little is known about the early neurobiological changes associated with this comorbidity. Importantly, the hippocampus has been implicated in the pathogenesis of both depression (Mannie et al., 2014) and alcohol use disorders (White and Swartzwelder, 2004). Acute alcohol exposure inhibits glutamate binding and reduces the transmission efficacy of cortical neurons via the suppression of N-methyl-D-aspartate receptor (NMDAr) activity (Strelnikov, 2007). With chronic alcohol use, NMDAr binding sites increase in number and level of functioning; as demonstrated in rodents who show increased glutamate transmission in the hippocampus after repeated ethanol administration (Chefer et al., 2011). Moreover, converging evidence indicates that aberrations in glutamate homoeostasis and neurotransmission have a significant role in the development of depression. Post mortem investigation of glutamate derived from depressed patients has revealed elevated glutamate in the frontal cortex (Hashimoto et al., 2007) and studies on brain tissue from depressed patients have found down-regulation of genes that code for the excitatory amino acid transporters which reside on the glia and are responsible for clearing glutamate from the synapse (Beart and O'Shea, 2007). As a consequence of altered sensitivity, glutamate may accumulate at the synapse resulting in excitotoxicity (Meyerhoff et al., 2013).

As a means to assess *in vivo* neurochemistry, proton magnetic resonance spectroscopy ($^1$H-MRS) has provided important neurobiological insights into both depression and alcohol use. In terms of glutamate, $^1$H-MRS studies of depression samples have been mixed with evidence of decreased frontal (Hasler et al., 2007), normal frontal (Taylor et al., 2009), normal occipital (Godlewska

* Corresponding author. Fax: +61 2 93510652.
*E-mail address:* daniel.hermens@sydney.edu.au (D.F. Hermens).

http://dx.doi.org/10.1016/j.jad.2015.07.009
0165-0327/

et al., 2015) and increased occipital (Sanacora et al., 2004) levels. Of note, increased hippocampal glutamate has been reported in young people with a family history of depression (Mannie et al., 2014). In $^{1}$H-MRS studies of alcohol misuse, increased frontal glutamate has been reported in dependant humans (Hermann et al., 2012; Lee et al., 2007) and rats (Hermann et al., 2012). Similarly, treatment-seeking heavy drinkers show increased frontal glutamate; associated with duration of drinking (Yeo et al., 2013). In contrast, decreased glutamate levels have been found in the visual cortex of alcohol-dependent (Bagga et al., 2014) and frontal regions of binge (Silveri et al., 2014) and heavy (Ende et al., 2013) drinkers. Overall, the variability in the aforementioned $^{1}$H-MRS findings may be explained by key factors such as region of interest and duration of exposure/illness. In this study, we hypothesised that young adult outpatients with major depressive disorder (MDD) would show increased levels of *in vivo* hippocampal glutamate levels and this would be associated with their levels of alcohol use.

## 2. Methods

Sixty-three outpatients (aged 18–30 years) with a primary DSM-IV diagnosis of MDD were recruited from a specialised service for young people with mental health problems (Scott et al., 2012). At the time of assessment, all patients were receiving clinician-based case management and their psychotropic medication regimens were as follows: 27% (17/63) were not taking psychotropic medications; 63% (40/63) were taking a third-generation anti-depressant; 17% (11/63) an atypical antipsychotic medication; and 9% (6/63) were taking a mood stabiliser. Healthy controls ($N=38$; aged 18–29 years) were recruited from the community and screened to ensure they had no history of a mental disorder. Exclusion criteria for all participants were medical instability, history of neurological disease, medical illness known to impact cognitive and brain function, intellectual and/or developmental disability, current substance dependence (not including alcohol) and insufficient English for assessment. All participants were asked to abstain from drug or alcohol use for 48 h prior to testing and informed that they may be asked to under-take an alcohol breath test and/or a saliva drug screen. The University of Sydney Human Research Ethics Committee approved the study and all participants gave written informed consent.

A trained research psychologist conducted the BMRI Structured Interview for Neurobiological Studies (Lee et al., 2013) to determine the nature and history of any mental health problems. The interview included the Hamilton Depression Rating Scale (HDRS, 17-item) to quantify mood symptoms at the time of assessment; the Brief Psychiatric Rating Scale (BPRS) to quantify general psychiatric symptoms at the time of assessment; and, the Social and Occupational Functioning Assessment Scale (SOFAS); where a patient's functioning is rated from 0 to 100, with lower scores suggesting more severe impairment. As part of a self-report questionnaire, participants completed: the Kessler-10 (K-10), as a measure of psychological distress; the first two items of the World Health Organisation's (WHO) 'alcohol, smoking and substance involvement screening test' to assess lifetime and current substance use; and the WHO Alcohol Use Disorders Identification Test (AUDIT) to assess level of risky drinking in the past year, as well lifetime familiarity.

$^{1}$H-MRS data was acquired on a 3Tesla GE Discovery MR750 MRI scanner (GE Medical Systems, Milwaukee, WI), using an 8-channel phased array headcoil. The protocol comprised of a 3D sagittal whole-brain scout (TR=50 ms; TE=4 ms; matrix=256; no averaging, $z=5$ mm thickness), a T1-weighted MPRAGE sequence for anatomical localisation (TR=7.2 ms; TE=2.8 ms; flip angle=10°; matrix $256\times256$; 0.9 mm isotropic voxels, 196 slices) and single-voxel $^{1}$H-MRS using PRESS acquired from a $1.5\times3.0\times1.0$ cm$^3$ voxel placed in the left hippocampus. Unsuppressed water scans (acquired from the same voxel) were collected prior to acquisition of the metabolite scans. Eddy current correction as implemented by LCModel package (Provencher, 1993) was undertaken on the metabolite data using the unsuppressed water FIDs as reference. Spectra were then quantified with LCModel, using a PRESS TE=35 basis set of 15 metabolites. Anatomical localisation of voxel placement was based on the Talaraich brain atlas and positioning was guided by the MPRAGE image. All spectra were shimmed to achieve full-width half maximum $<13$ Hz. Poorly fitted metabolite peaks as reflected by Cramer–Rao lower bounds $>20$ were excluded from further analysis. Statistical analyses were then conducted on glutamate (GLU) level as a ratio over water-scaled creatine (Cr) concentration. Segmentation of left hippocampal volumes was also undertaken as per our previously published methods (Hermens et al., 2015).

Two-tailed independent *t*-tests were used to assess group differences for demographic, clinical and spectroscopic variables. If homogeneity of variance was violated Welch's corrected degrees of freedom and p-values were reported. Analysis of Covariance (ANCOVA) was employed to control for the potential effects of age. Pearson product moment correlations were used to examine for significant associations between total AUDIT scores and GLU levels, with partial correlations controlling for age. In order to further analyse the relationships between alcohol use (AUDIT total score), diagnosis, demographics (sex, age, family history) and glutamate, we performed multiple linear regression analyses with six predictor variables ('enter' method) in the model. Current nicotine smoking status was included as a predictor as this has been shown to affect $^{1}$H-MRS variables (Meyerhoff et al., 2013).

## 3. Results

Table 1 summarises between-group comparisons across variables. There was no difference in gender ratio among groups; however, there was a significant difference in age ($p<.05$; control group older). Furthermore, the groups differed significantly in years of education but did not differ in predicted IQ scores. In terms of alcohol-related variables, there were no group differences in age of first alcoholic drink or AUDIT total score, however the depression group had a significantly ($p<.05$) higher proportion of individuals with a family history of alcoholism. Controls had significantly higher social and occupational functioning (SOFAS) as well as lower self-reported psychological distress (K-10), current depressive (HDRS) symptoms and general psychiatric (BPRS) clinical ratings (all $p<.001$). The groups did not differ in the proportion of daily nicotine smokers.

The groups did not differ in terms of creatine levels or hippocampal volumes; however, they were significantly ($p<.05$) different in GLU/Cr, with the depression group having increased levels (Table 1). ANCOVA confirmed this main effect remained significant when controlling for age ($p<.05$), years of education ($p<.05$), family history of alcoholism ($p<.05$) or hippocampal volume ($p<.05$). For the depression group, total AUDIT score was positively associated with GLU/Cr levels ($r=0.429$, $n=62$, $p<0.001$), and remained significant ($p<.001$) after controlling for age or hippocampal volume. The controls showed no significant correlations between these measures. Fig. 1 depicts the associations between GLU/Cr levels and AUDIT scores for each group.

The multiple linear regression model for hippocampal GLU/Cr level was significant [$F(6, 97)=3.3$, $p<.01$] and explained 18.1% of the variance (adjusted $R^2=0.126$) with three significant predictors: