



# The impact of alcohol and tobacco use on in vivo glutathione in youth with bipolar disorder: An exploratory study



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## ABSTRACT

Risky alcohol consumption and tobacco smoking is highly prevalent in bipolar disorder (BD) and is associated with increased formation of neural reactive oxygen species. Proton magnetic resonance spectroscopy ( $^1\text{H-MRS}$ ) is an in vivo imaging modality that allows quantification of glutathione (GSH) concentration, the brain's primary antioxidant. Sixty-four patients with BD and 49 controls (18–30 years) completed self-report questionnaires regarding alcohol and tobacco use and underwent  $^1\text{H-MRS}$ . Levels of GSH in the hippocampus and anterior cingulate cortex (ACC) were determined. Within-group Pearson's correlations were used to explore the relationship between alcohol use and GSH concentration for BD and controls, covarying for age, gender, family history of alcohol dependence and smoking status. Relationships between GSH and presence/severity of alcohol-induced blackouts were determined using Spearman's correlations. In BD, reduced hippocampal-GSH associated with higher alcohol use ( $R = -0.489, p < 0.021$ ). Reduction of ACC-GSH with increased drinking was non-significant when controlling for tobacco use. Independent samples  $t$ -test revealed a significantly decreased ACC-GSH in smokers with BD ( $t(53) = 4.162, p < 0.001$ ). In controls, alcohol use was not correlated to GSH in either region. In both patients and controls, reduced hippocampal-GSH was associated with blackout presence/severity, supporting a role for the hippocampus in the continuum of alcohol-induced memory impairments. Our preliminary findings suggest that in youth with BD reduced hippocampal-GSH is associated with risky alcohol use and alcohol and tobacco use is associated with reduced ACC-GSH, highlighting the role of these substances as modifiable risk factors for decreased anti-oxidant capacity in BD.

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## 1. Introduction

Alcohol misuse and tobacco smoking is highly prevalent in bipolar disorder (BD). A recent meta-analysis identified the pooled lifetime prevalence of alcohol use disorders in BD to be 35.1% (Di Florio et al., 2014), and a study in young people with BD reported rates of up to 70% of lifetime misuse (Cassidy et al., 2001). Alcohol misuse and dependence in BD has been associated with a significant negative impact on illness progression (Frye and Salloum, 2006), with documented increases in rates of mood episode recurrences, switching and cycling (Rakofsky and Dunlop, 2013), increased risk of suicide and increased comorbid nicotine dependence (Oquendo et al., 2010). The latter of which is reflected in our Youth Mental Health sample, with 12–30 year olds with BD being the most likely patients to participate in weekly alcohol and

nicotine use (Hermens et al., 2013a). Smoking has also been found to be associated with poorer mental health outcomes in BD; with worse outcomes reported for treating mania (Berk et al., 2008), identified associations with increased mood episode recurrences and severity (Waxmonsky et al., 2005) and prospective data indicating that patients who smoked daily had poorer scores on clinical ratings of depression and lengthier stays in hospital (Dodd et al., 2010). Despite the high prevalence, clinical relevance and economic burden, very little is known about the underlying neurobiology of the comorbidity between alcohol and/or tobacco use and BD.

Previously we have investigated the effects of risky alcohol use in young people with BD on the in vivo level of the brain's most potent anti-oxidant, glutathione (GSH), using proton resonance imaging spectroscopy ( $^1\text{H-MRS}$ ). Our preliminary findings showed that reduced GSH in the anterior cingulate cortex (ACC) was associated with higher levels of alcohol use in youth with emerging BD (Chitty et al., 2013). Neural tissue is especially prone to oxidation due to its high content of oxygen and easily oxidisable substrates, paired with its relatively low activity of anti-oxidant defence

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molecules. With evidence from animal studies suggesting that young brains are more susceptible to oxidative stress due to inadequate compensatory mechanisms to increase anti-oxidant capacity (Sommavilla et al., 2012) together with ethanol's demonstrated propensity to stimulate the formation of reactive oxygen species (ROS), and resultant oxidative stress (Nordmann et al., 1990), examining the neurochemistry associated with cortical anti-oxidant capacity in a young group of risky drinkers is of significant interest. The *in vivo* quantification of GSH is a recent development and its quantification in human  $^1\text{H}$ -MRS alcohol research has not yet been investigated, to date the vast accumulation of evidence to support a relationship between alcohol use and depletion of GSH and the subsequent increase in oxidative stress is currently provided by rodent studies (Agar et al., 1999; El-Sokkary et al., 1999; Patten et al., 2013; Reyes et al., 1993; Sommavilla et al., 2012; Uysal et al., 1989; Zhong et al., 2012).

An extensive array of evidence exists, which implicates the role of the hippocampus as a region mediating the effects and receiving direct insult as a result of alcohol use (Hermens et al., 2013b), and therefore is a clear brain region of interest in  $^1\text{H}$ -MRS alcohol studies. The hippocampus is documented to have heightened susceptibility to oxidative stress and is closely associated to other brain regions affected by necrotic degeneration resulting from alcohol-induced oxidative stress (Obernier et al., 2002). The hippocampus has also been proposed to play an important role in the continuum of alcohol-mediated memory impairments, given its central role in memory processing (Ryabinin, 1998; Sommavilla et al., 2012). Alcohol-induced blackouts, which are defined as episodes of memory loss of conscious time during acute alcohol intoxication (White, 2003), are one amnesic effect of alcohol hypothesized to be related to hippocampus dependent long-term potentiation (LTP) (Izumi et al., 2005; Tokuda et al., 2011).

The ACC has also been implicated in the neurological effects of alcohol use (Meyerhoff et al., 2013) as well as in the pathophysiology of BD, with separate neuroimaging investigations involving structural, functional and spectroscopic analyses consistently ACC abnormalities in the disorder (Fornito et al., 2008, 2007; Haldane and Frangou, 2004; Lagopoulos and Malhi, 2007). These neuroimaging findings corroborate an existing neuropsychological literature that has consistently reported frontal lobe-mediated impairments in BD (Olley et al., 2005).

Previous  $^1\text{H}$ -MRS studies have shown that chronic cigarette smoking compounds regional neurobiological abnormalities in people with alcohol use disorders (Meyerhoff et al., 2013). Given cigarette smoke is associated with increased oxidative stress in the brain (Mendez-Alvarez et al., 1998; Li and Wang, 2004; Zhang et al., 2007), and has been linked to the inflammatory response in depression (Berk et al., 2013) investigating its relationship with GSH is also of significant interest.

Models of oxidative stress have also been described as potential pathophysiological processes associated with BD (Andreazza et al., 2008; Berk et al., 2011). Lagopoulos et al. (2013), found no difference in the levels of *in vivo* GSH in the ACC between controls and people with BD, a finding that has also been found in the occipital lobe and medial prefrontal cortex (Godlewska et al., 2014). However, given the evidence that alcohol use is associated with increased oxidative stress and our preliminary findings showing young patients with emerging BD appear to be more susceptible to alcohol-induced oxidative stress (Chitty et al., 2013), we sought to further explore the relationship between GSH and risky levels of alcohol use, extending this investigation to include the hippocampus and exploring whether the relationship between GSH and alcohol use exists in controls. We then sought to explore a relationship between GSH and alcohol-induced blackouts as well as GSH levels resulting from tobacco use.

## 2. Methods

### 2.1. Participants

Sixty-four patients with BD and 49 controls (18–30 years) were recruited from a specialized tertiary referral service (Scott et al., 2012) and the wider community, respectively. Participants for the study were recruited by referral from psychiatrists, with a diagnosed bipolar illness using DSM-IV criteria (APA, 2000) as follows: bipolar I ( $n = 15$ ), bipolar II ( $n = 31$ ) or bipolar spectrum with family history of BD ( $n = 18$ ), defined as an illness pattern consisting of periods of both elevated and depressed mood consistent with a bipolar spectrum disorder (Angst, 2007). To confirm diagnosis and current symptoms, a research psychologist subsequently conducted a structured interview including the Hamilton Depression Rating Scale (HDRS; Hamilton, 1967), the Brief Psychiatric Rating Scale (BPRS; Overall and Gorham, 1962) and the Young Mania Rating Scale (Young et al., 1978). Mood state at time of testing was determined based on an algorithm using patients YMRS and HDRS scores, with a YMRS total score greater than 12 suggestive of elevated mood (Young et al., 1978) and a HDRS score greater than 16 suggestive of moderate depression (Zimmerman et al., 2013). Mood states were defined as follows: euthymic, YMRS total score less than 12 (Young et al., 1978) and HDRS less than 17; hypomanic, YMRS greater than 11 and HDRS less than 17; depressed, YMRS less than 12 and HDRS greater than 16; and mixed mood state, YMRS was greater than 11 and HDRS greater than 16. Patients' normal psychotropic medication regimens were not interrupted in any way.

Exclusion criteria for all participants were use of fish oil supplementation or medications containing N-acetyl cysteine (which act as cysteine donor for synthesis of GSH), medical instability, history of neurological disease, medical illness known to impact cognitive and brain function, intellectual disability 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 if the researcher had reason to believe the participant was under the influence or intoxicated.

The study was carried out in accordance with the Declaration of Helsinki, and approved by the University of Sydney ethics committee. Participants gave written informed consent before participation.

### 2.2. Self-report measures

All participants completed the Alcohol Use Disorders Identification Test (AUDIT) in self-report format. The AUDIT was developed from a World Health Organisation collaboration as a screening instrument for hazardous and harmful alcohol consumption (Saunders et al., 1993). The tool was developed using a conceptual-statistical rationale and differs from other screening tests as it emphasizes identification of hazardous drinking rather than long-term dependence and focuses primarily on recent symptoms and behaviours (Babor et al., 2001), making it more appropriate for youth cohorts many of whom will be initiating their drinking habits or will be risky drinkers rather than alcohol dependent. The AUDIT is made up of 10 questions, with possible scores ranging from zero to 40.

The AUDIT can be further broken down into sub-scores, which were also calculated for each group and used to further assess the drinking patterns of the cohort. The consumption sub-score assesses hazardous alcohol use (e.g. frequency and amount of drinking), the dependence sub-score is comprised of symptoms associated with dependence (e.g. morning drinking and impaired

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