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Research report

A longitudinal proton magnetic resonance spectroscopy study investigating oxidative stress as a result of alcohol and tobacco use in youth with bipolar disorder

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ABSTRACT

Alcohol and tobacco have been suggested to be "aggravating factors" for neuroprogression in bipolar disorder (BD), however the impact of these substances on the underlying neurobiology is limited. Oxidative stress is a key target for research into neuroprogression in BD and in accordance with this model, our previous cross-sectional studies have found that risky alcohol and tobacco use in BD is associated with increased oxidative stress, investigated via in vivo glutathione (GSH) measured by proton magnetic resonance spectroscopy (^{1}H-MRS) in the anterior cingulate cortex (ACC). What remains unknown is whether the negative impact on GSH levels can be modified as a result of limiting alcohol and tobacco use.

Thirty BD patients were included in the study. ^{1}H-MRS and tobacco and alcohol measures were conducted at baseline and follow-up assessments (15.5 ± 4.6 months apart). Pearson's correlations were performed between percentage change in GSH concentration and changes in alcohol/tobacco use. Regression analyses were then conducted to further explore the significant correlations. An increase in GSH was associated with a decrease in alcohol consumption ($r = -0.381$, $p < 0.05$) and frequency of tobacco use (-0.367, $p = 0.05$). Change in alcohol consumption, tobacco use and age were significant predictors of change in GSH concentration (F (3, 26) = 3.69, $p < 0.05$). Due to the high comorbidity of alcohol and tobacco use in the sample, the individual effects of these substances on GSH levels could not be determined.

This study offers longitudinal evidence that changing risky drinking patterns and tobacco use early in the course of BD is associated with improvements in antioxidant capacity, and therefore may be specific targets for early intervention and prevention of neuroprogression in BD.

1. Introduction

Substances of abuse, such as alcohol and tobacco are suggested to be aggravating factors for neuroprogression of bipolar disorder (BD) (Berk, 2009; Kapczinski et al., 2008). Accordingly, both substances are found to significantly impact illness trajectory, with increased rates of mood episode recurrence and severity (Rakofsky and Dunlop, 2013; Salloum et al., 2002; Waxmonsky et al., 2005), worsening general function (Cardoso et al., 2008), increased morbidity (Farren et al., 2012), poorer response to treatment (Berk et al., 2008), lengthier stays in hospital (Dodd et al., 2010) and increased risk of suicide (Oquendo et al., 2010). Despite the increased understanding of the clinical impact of these modifiable environmental exposures (Berk et al., 2011, 2013) knowledge of the neural interaction between alcohol/tobacco and BD pathophysiology remains limited. Thus, research in this area is necessary to enable a better understanding of how these factors contribute to poorer outcomes for patients and to help identify neurobiological risk factors responsible for the heightened susceptibility of risky drinking and tobacco use in this population.

Oxidative stress is a key target for research into the neuroprogression of BD (Berk et al., 2011). Accordingly, ethanol and cigarette smoke have a demonstrated propensity to stimulate the formation of reactive oxygen species (ROS) resulting in oxidative stress (Li and Wang, 2004; Mendez-Alvarez et al., 1998; Nordmann et al., 1990; Zhang et al., 2007). Neural tissue is especially prone to such stress due to its high consumption of oxygen and resultant production of ROS, easily oxidisable substrates such as lipids with unsaturated fatty acids and relatively low activity of antioxidant defence molecules (Halliwell, 1992, 2006; Dringen, 2000). Previously, we have addressed the impact of alcohol and tobacco use

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on oxidative stress in BD by cross-sectionally examining the brain's primary antioxidant, glutathione (GSH), measured in vivo via proton magnetic resonance spectroscopy (^{1}H-MRS) (Chitty et al., 2013, 2014b). We found that increased/more frequent alcohol and tobacco use were both negatively associated with GSH levels in the anterior cingulate cortex (ACC), and that this effect was specific to BD and not to matched controls. Although we were unable to untangle the individual effects of alcohol and tobacco use on GSH levels due to high comorbidity of their use in our sample, these findings support the notion that people with BD have an increased propensity for oxidative stress when consuming tobacco and risky levels of alcohol, highlighting the importance of the early identification and treatment of BD patients who may be susceptible to their use. It is unknown whether these initial negative impacts on GSH levels can be modified as a result of limiting alcohol and tobacco use, and hence whether these aggravating factors should be specific targets of early intervention and prevention of neuroprogression in BD.

The aim of the present study was to examine longitudinal changes in GSH and its relation to self-reported changes in alcohol use patterns and tobacco use among BD patients. We examined different components of risky drinking behaviour (e.g. alcohol consumption, problem use or the development of dependence) in order to investigate the specific aspects of alcohol use that are associated with any corresponding changes in GSH levels. In addition, we assessed the impact of tobacco use on these relationships. We hypothesised that a reduction in risky drinking and smoking would be associated with an increase in GSH concentration, reflecting a relaxation of oxidative stress.

2. Patients and methods

2.1. Participants

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. The sample consisted of the 57 BD participants from our cross-sectional study (Chitty et al., 2014b) plus an additional recruitment/inclusion of 20 patients, giving a total of 77 participants in the study.

Participants were recruited as part of a wider Youth Mental Health cohort study (Hermens et al., 2011; Lee et al., 2013; Scott et al., 2013), with referral from psychiatrists with a diagnosed bipolar illness using DSM-IV criteria (APA, 2000) as follows: bipolar I ($n=19$), bipolar II ($n=30$) or bipolar spectrum with family history of BD ($n=21$) or bipolar NOS ($n=7$), defined as an illness pattern consisting of periods of both elevated and depressed mood consistent with a bipolar spectrum disorder (Angst, 2007). Participants were asked at baseline whether they would be interested in being contacted for a follow-up assessment. Thirty-six of these patients were followed up after 11 months and all measures were repeated. Researchers gave no instruction regarding alcohol or tobacco use before or during the follow-up period. Recorded changes at follow-up reflect changes in patients' self-reported alcohol and tobacco habits. Likewise, researchers did not enquire about reasons for any change in substance use at follow-up.

Exclusion criteria for all participants were 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. Patients' usual psychotropic medication regimens were not interrupted in any way.

2.2. Measures

2.2.1. Clinical and self-report measures

Participants underwent a clinical 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 (YMRS; Young et al., 1978).

Participants completed the Alcohol Use Disorders Identification Test (AUDIT) in self-report format. The AUDIT was developed from a World Health Organisation (WHO) collaboration as a screening instrument for hazardous and harmful alcohol consumption (Saunders et al., 1993). The tool differs from other screening tests as it emphasises 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 (abstinence) to 40.

The AUDIT can be further broken down into sub-scores, which were also calculated at each timepoint. 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 control over drinking) and the problems sub-score addresses harmful alcohol use (e.g. alcohol related injuries, blackouts, guilt after drinking and concerns of others). A score of 6–7 on the consumption sub-score may indicate a risk of self-related harm. The dependence score assesses symptoms associated with dependence, a score of 4 or more in this sub-score plus a total AUDIT score of 20 or more indicates almost certain dependency. Any score on the problems sub-score is indicative of problem drinking.

Frequency of tobacco use was assessed using baseline and follow-up answers from the WHO Alcohol, Smoking and Substance Involvement Screeening Test (WHO-ASSIST) (Edwards et al., 2003), in which participants were asked to indicate how often in the previous three months they had used tobacco products with ordinal options: never, once or twice, monthly, weekly or daily/almost daily.

Current self-reported symptoms were assessed using the depression anxiety stress scale (DASS; Lovibond and Lovibond, 1995) and the Kessler-10 (K-10), a psychological distress scale (Kessler et al., 2002).

2.2.2. ^{1}H-MRS data acquisition and processing

As per previously published protocols (Hermens et al., 2012; Lagopoulos et al., 2013), participants were scanned on a 3 T GE Discovery MR750 MRI (GE Medical Systems, Milwaukee, WI). First, a 3D sagittal whole-brain scout was undertaken for orientation and positioning of scans (TR=50 ms; TE=4 ms; 256matrix; no averaging, $z=5$ mm thickness). Next a T1-weighted Magnetization Prepared RApid Gradient-Echo (MPRAGE) sequence producing 196 sagittal slices (TR=7.2 ms; TE=2.8 ms; flip angle=10°; matrix 256×256; 0.9 mm isotropic voxels) was acquired for the purpose of localisation of the ACC. A $2 \times 2 \times 2$ cm^3 single voxel was placed midline on the ACC (for example spectra and voxel placement please see Chitty et al. (2014a)). Spectroscopy data was acquired using PRESS (TE=35 ms, TR=2000 ms, 128 averages) along with two chemical shift-selective imaging pulses for water suppression. All spectra were shimmed to achieve full-width half maximum (FWHM) of <13 Hz and visually inspected by independent raters. Spectra with the following features were excluded: Cramer–Rao Lower Bound greater than 20%, poor spectral morphology (spectra