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Risky alcohol use predicts temporal mismatch negativity impairments in young people with bipolar disorder

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ABSTRACT

Alcohol misuse in bipolar disorder (BD) has a negative impact on illness progression. The NMDA/glutamatergic system is implicated in BD pathophysiology and is critically involved in the effects of alcohol on the brain. Mismatch negativity (MMN) is purported to reflect NMDA receptor output, providing a measure for investigating this association. Forty-two patients and 34 controls (16–30 years) were split into low and high-risk drinkers (based on the Alcohol Use Disorders Identification Test) and underwent a two-tone passive auditory oddball, duration deviant MMN paradigm. Multiple regression models revealed risky drinking and BD diagnosis were predictors of impaired temporal MMN. Potentially reflecting an additive effect of alcohol on a perturbed NMDA/glutamatergic system in BD, these findings highlight alcohol as both a modifiable risk factor of neurobiological impairments and as a potential confounder in MMN studies. Given the increasing use of glutamatergic agents for BD treatment, this finding is important clinically.

1. Introduction

Rates of up to 70% of lifetime alcohol misuse have been reported in youth with bipolar disorder (BD) (Cassidy, Ahearn, & Carroll, 2001). In a recent study, 20–30 year old males with BD were identified as one of the most likely groups in a young psychiatric cohort to participate in weekly substance use (Hermens et al., 2013). Alcohol misuse in BD destabilises the course of illness, with documented increases in rates of mood episode recurrences, switching and cycling (Rakofsky & Dunlop, 2013). Despite the high prevalence and clinical relevance, very little is known about the underlying neurobiology of the comorbidity.

The event-related potential, mismatch negativity (MMN), has received substantial attention in both psychiatric and alcohol literature. MMN is elicited approximately 200 ms after a deviant stimulus is presented within a set of standard tones. Multichannel magnetoencephalography and electroencephalography (EEG) studies have identified multiple sources of MMN including generators in the frontal and temporal cortex (Giard et al., 1995; Giard, Perrin, Pernier, & Bouchet, 1990; Rinne, Alho, Ilmoniemi, Virtanen, & Naatanen, 2000). MMN is maximal over fronto-central electrodes, and it reverses polarity (i.e. a positive mismatch potential) over the mastoid electrodes, which are reflective of the temporal MMN component. Temporally generated MMN, originating from the auditory cortex, purportedly reflects the pre-perceptual change detection of the deviant stimulus (Naatanen, Gaillard, & Mantysalo, 1978), which is hypothesised to be resultant of matching incoming stimuli to the sensory memory trace (Giard et al., 1990). Frontal MMN is proposed to be involved in the attention switch, after the deviant stimulus has been analysed in the temporal lobes (Rinne et al., 2000). Previous studies have shown these components can be separable, such that one can be impaired whereas the other can remain relatively intact (Baldeweg, Klugman, Gruzelier, & Hirsch, 2002; Corbera, Corral, Escera, & Idiazabal, 2005), and MMN in one hemisphere can be significantly more impaired than the other (Corbera et al., 2005).

There are a number of theories proposing relationships between different neurotransmitter systems and MMN generation (see Garrido, Kilner, Stephan, & Friston, 2009). The most robust and current of these is the hypothesis that MMN represents current flow through the glutamatergic, N-methyl-D-aspartate (NMDA) receptor channels (Javitt et al., 1995; Javitt, Steinschneider, Schroeder, & Arezzo, 1996). Intra-cortical MMN is reduced following microinfusion of NMDA antagonists into the primary cortex of monkeys (Javitt et al., 1996) and significant reductions in MMN amplitude have been found following acute administration of the NMDA antagonist ketamine in healthy human adults (Heekeren et al., 2008; Umbricht et al., 2000). Ethanol, a partial NMDA receptor antagonist (Izumi, Nagashima, Murayama, & Zorumski, 2005), has

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also been shown to dose-dependently decrease NMDA receptor current flow, as measured by patch clamping in the hippocampus (Lovinger, White, & Weight, 1989). In this aforementioned study the strength of inhibition of the receptor was linearly related to several alcohols (i.e. methanol, 1-butanol and isopentanol) intoxicating potency, leading authors to suggest that alcohol-induced inhibition of NMDA receptor activation may contribute to the neural impairments associated with intoxication. Ethanol administration also effects glutamate concentration, the primary neurotransmitter for NMDA receptor activation, with results from rat studies showing dysregulated glutamate transmission in the hippocampus after acute (Moghaddam & Bolinao, 1994) and repeated (Chefer et al., 2011) ethanol treatment.

Indeed many studies have investigated both the acute and chronic effects of alcohol on MMN, though the results are inconsistent. Acutely, alcohol decreases MMN amplitude (He et al., 2013; Jaaskelainen, Lehtokoski, et al., 1995; Jaaskelainen, Pekkonen, et al., 1995; Jaaskelainen, Pekkonen, Hirvonen, Sillanaukee, & Naatanen, 1996; Kenemans, Hebly, van den Heuvel, & Grent, 2010), supporting its known antagonist action at NMDA receptors. Chronically, however, the effects of alcohol on the brain are a result of multiple neural compensatory mechanisms and differs depending on whether participants are currently drinking, in withdrawal or abstinent. For example, as a result of chronic exposure to NMDA receptor antagonism by alcohol, receptor density (Gulya, Grant, Valverius, Hoffman, & Tabakoff, 1991) and sensitisation (Chandler, Newsom, Sumners, & Crews, 1993) is up regulated, hence creating susceptibility to NMDA receptor hyperexcitation during abstinence. In terms of the electrophysiological findings, increased MMN amplitude and shorter latencies have been reported in alcohol dependent patients who are abstinent (Ahveninen et al., 1999), though other studies have reported no differences in MMN between controls and abstinent patients (Fein, Whitlow, & Finn, 2004; Marco-Pallares et al., 2007) or active-drinking patients (Fein, McGillivray, & Finn, 2004). One study reported that while there were no significant differences between MMN in terms of peak amplitude or latency, there was reduced scalp density activity in frontal and temporal areas in abstinent alcoholics, indicating that chronic alcohol use contributes to a reorganisation of the neurodynamics of auditory change detection (Marco-Pallares et al., 2007). Another study noted that while there were no overall group differences between abstinent patients and controls, there was an effect of age, whereby the older patients (mean 40 years) showed decreased MMN amplitude (Polo, Escera, Gual, & Grau, 1999). MMN has also been investigated in children of parents with alcohol dependence (i.e. those with a genetic predisposition), with a finding of increased frontal MMN (Zhang, Cohen, Porjesz, & Begleiter, 2001). The authors of this study concluded this might reflect elevated levels of excitatory glutamatergic transmission and relate to their susceptibility of developing dependence.

In adolescence and young adulthood alcohol dependence is not common, although it is during this time that risky drinking patterns develop. This is especially relevant in psychiatric cohorts at risk of alcohol misuse. Our previous study revealed that among young patients with an early psychotic disorder, self-identified risky drinkers had a decreased left and right temporal MMN, compared to patients with low alcohol use and healthy controls (Chitty, Kaur, Lagopoulos, Hickie, & Hermens, 2011). We also found a significant negative relationship between drinking level and MMN amplitude in patients. Interestingly in this study, the findings were specific to temporal MMN, with no significant effects on frontal MMN. These results suggested that alcohol's antagonistic actions on NMDA receptors might act in an additive manner in people who may already have a compromised glutamatergic/NMDA system.

Recently, there has been much attention on glutamatergic/NMDA disturbances in BD. Abnormal levels of glutamate have been reported in cerebrospinal fluid, serum and plasma of patients with BD (Sanacora, Zarate, Krystal, & Manji, 2008). Post-mortem studies have reported elevated brain glutamate and decreased levels of the glutamatergic NMDA receptor subunits in the frontal cortex (Hashimoto, Sawa, & Iyo, 2007; Rao, Harry, Rapoport, & Kim, 2010). Accordingly, recent studies have shown that people with BD of various ages exhibit decreased frontal MMN (Andersson, Barder, Hellvin, Lovdahl, & Malt, 2008; Jahshan et al., 2012; Kaur, Battisti, et al., 2012), which was supported by our recent meta-analysis (Chitty, Lagopoulos, Lee, Hickie, & Hermens, 2013). Given this accumulating evidence it is not surprising that the use of glutamatergic agents for the treatment of BD is increasing (Krystal et al., 2002).

The aim of this study was to investigate the effects of alcohol use on MMN in young people with BD compared to controls. We hypothesised that high risk drinkers would have decreased temporal MMN amplitudes due to higher level of NMDA receptor antagonism without reaching a stage of dependence-related compensatory receptor up-regulation. Furthermore, due to an existing perturbed glutamatergic/NMDA system we expected these abnormalities to be more pronounced in people with BD.

2. Methods

2.1. Sample

Forty-two patients with BD and 34 controls (aged 16–30 years) were recruited from a specialised tertiary referral service (Scott et al., 2012) or the community, respectively. Diagnoses were determined by a psychiatrist using DSM-IV criteria for bipolar I ($n = 19$) or bipolar II ($n = 23$) disorder (APA, 2000). To confirm diagnosis, a research psychologist subsequently conducted a structured interview including the Hamilton Depression Rating Scale (HDRS; (Hamilton, 1967)), the Brief Psychiatric Rating Scale (BPRS; (Overall & Gorham, 1962)) and the Young Mania Rating Scale (Young, Biggs, Ziegler, & Meyer, 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, Martinez, Young, Chelminski, & Dalrymple, 2013). Mood states were defined as follows: euthymic, YMRS total score <12 (Young et al., 1978) and HDRS <17; hypomanic, YMRS >11 and HDRS <17; depressed, YMRS <12 and HDRS >16; and mixed mood state, YMRS was >11 and HDRS >16. Patients' normal psychotropic medication regimens were not interrupted in any way.

Exclusion criteria for patients and controls were medical instability (i.e. not medically or mentally well enough to complete the assessment), 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 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, Aasland, Babor, de la Fuente, & Grant, 1993). The tool was developed using a conceptual–statistical rationale and 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, Higgins-Biddle, Saunders, & Monteiro, 2001), which makes 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. We used the sex-specific cut-off scores for detecting risky alcohol use in psychosis (as it has not yet been established specifically in BD); a total AUDIT score of 10 or more for men and eight for women (Nesvag et al., 2010). Both the BD group and the control group were then split into low-risk drinkers (BD-low, control-low) and high-risk drinkers (BD-high, control-high) according to these cut-offs.

The AUDIT can be further broken down into sub-scores, which were also calculated for each group. The consumption sub-score assesses hazardous alcohol use (e.g. frequency and amount of drinking), the dependence sub-score is comprised of