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Research Article

RESEARCH ARTICLE

The N-Methyl-D-Aspartate Receptor as a Neurobiological Intersection Between Bipolar Disorder and Alcohol Use: A Longitudinal Mismatch Negativity Study

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Abstract

Background: Comorbid risky alcohol use in bipolar disorder (BD) is recognized for its high prevalence and clinical relevance, though understanding of its neurobiological underpinning is limited. The N-methyl-D-aspartate (NMDA) receptor has recognized alterations in BD and is a major site of ethanol's effects in the brain. The present study aimed to examine the NMDA receptor system in adolescents and young adults with BD by evaluating the longitudinal changes in a robust marker of NMDA function, mismatch negativity (MMN), in relation to changes in alcohol use patterns.
Methods: Forty-six BD patients (aged 16–30) were recruited at baseline and 59% (n = 27) returned for follow-up 17.9 +/- 7.3 months later. At both time-points a two-tone, passive, duration-deviant MMN paradigm was conducted and alcohol measures were collected. Pearson's correlations were performed between changes in MMN amplitudes and changes in alcohol use. Multiple regression was used to assess whether MMN amplitudes at baseline could predict alcohol use at follow-up.
Results: Reduction in risky drinking patterns was associated with increased temporal MMN and decreased fronto-central MMN. Larger temporal MMN at baseline was a significant predictor of greater alcohol use at follow-up.
Conclusions: Results suggest risky alcohol use in BD may further compound pre-existing NMDA receptor abnormalities and, importantly, reducing alcohol use early in stages of illness is associated with changes in MMN. This highlights the importance of monitoring alcohol use from first presentation. In addition, preliminary results present an exciting potential for utility of MMN as a neurobiological marker used to determine risk for alcohol misuse in BD.

Keywords: alcohol, bipolar disorder, longitudinal, mismatch negativity, NMDA receptor

Introduction

Despite its high prevalence and clinical impact in those with bipolar disorder (BD), comorbid risky alcohol use is the "elephant in the room" when we consider illness trajectory, treatment response, service access, and healthcare expenditure. A recent meta-analysis included 31 epidemiological studies that unanimously reported an increased likelihood of alcohol use disorders in BD compared with the general population (Di Florio et al., 2014). The literature also comprises numerous studies that

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have identified the serious and adverse consequences of this comorbidity for patients, including increased severity and rates of mood episodes (Salloum et al., 2002; Rakofsky and Dunlop, 2013), worsened general functioning (Cardoso et al., 2008), and increased risk of suicide (Oquendo et al., 2010). These effects are not only confined to heavy drinkers, with a study of patients consuming just 1–4 standard drinks a week showing negative clinical consequences as a result of their alcohol consumption (Goldstein et al., 2006), highlighting the importance of promoting any reduction of alcohol consumption in this population.

Despite such research, understanding of the neurobiological effects of alcohol use in BD is limited. Going forward, such investigations are necessary in order to define the neural interaction between alcohol use and the disorder and how it contributes to poorer outcomes for patients, as well as to identify neurobiological risk factors responsible for the heightened susceptibility of risky drinking in this population.

The N-methyl-D-aspartate (NMDA) glutamate (Glu) receptor is a neural system with recognized alterations in BD (Mundo et al., 2003; Scarr et al., 2003; Nudmamud-Thanoi and Reynolds, 2004; Woo et al., 2004; McCullumsmith et al., 2007; Sanacora et al., 2008) and as a major site of ethanol's effects in the brain (Grant and Lovinger, 1995), both acutely (Lovinger et al., 1989; Ren et al., 2012) and chronically (for review see Krystal et al., 2003a). Furthermore, alterations in genes encoding the NMDA receptor subunit, GluN2a, are associated with susceptibility for risky drinking during adolescence (Schumann et al., 2008) and an altered NMDA receptor response is evident in people with a positive family history of alcohol dependence (FHP; Petrakis et al., 2004). Agents that block Glu release (e.g. lamotrigine) or block NMDA Glu receptors (e.g. memantine) have been shown to be efficacious in treating alcohol withdrawal (Krupitsky et al., 2007) and, similarly, these same agents have also shown promise in treating BD (Sanacora et al., 2008). It has been hypothesized that mutations that modify NMDA-receptor mediated responses to ethanol are present in those vulnerable to alcohol dependence (Krystal et al., 2003a), and we suggest that this is the case in BD: a population with a propensity to alcohol misuse and dependence (Di Florio et al., 2014), high levels of family history of alcohol dependence (Johnson and Leeman, 1977; Todd et al., 1996), reduced subjective responses to alcohol (Yip et al., 2012), and impairments in the NMDA receptor (Sanacora et al., 2008). Thus, we present the NMDA receptor as a critical area of investigation toward elucidating the neurobiological underpinnings of this comorbidity.

Mismatch negativity (MMN), an event-related potential reliant on efficient Glu signaling via the NMDA receptor (Javitt et al., 1995, 1996, 2011), is consisdered a robust marker for detecting NMDA receptor disturbances (Javitt et al., 2011). As such, MMN abnormalities have been associated with BD (Andersson et al., 2008; Jahshan et al., 2012; Kaur et al., 2012; Chitty et al., 2013), acute and chronic alcohol use (Jaaskelainen, Lehtokoski, et al., 1995; Jaaskelainen, Pekkonen, et al., 1995; Jaaskelainen et al., 1996; Ahveninen et al., 2000; Kenemans et al., 2010; He et al., 2013), and risk for alcohol dependence (Zhang et al., 2001). Our recent investigation revealed that adolescents and young adults with BD who participate in risky drinking have impaired temporal MMN amplitude compared to low-risk drinkers with BD and controls (Chitty et al., 2014). These noted impairments in temporal MMN may be a result of the high-risk drinking (i.e. an additive effect of alcohol on a pre-existing perturbed glutamatergic/NMDA system) or may represent a heightened predisposition for risky drinking.

MMN is thought to index formation of memory and cortical plasticity (Baldeweg and Hirsh, 2014), both of which are neural processes reliant on intact NMDA receptor functioning (Bennett, 2000). Indeed, the effects of alcohol on MMN have been hypothesized to index impairments in passive attention (Jaaskelainen et al., 1996), and studies from our lab have demonstrated reduced MMN in psychiatric populations is associated with poorer verbal learning and working memory (Kaur et al., 2011), psychomotor slowing, and attention difficulties (Hermens et al., 2010).

The aim of the present study is to further probe the NMDA receptor system and thus better understand the intersection of alcohol and BD comorbidity by examining the longitudinal changes in MMN and its relation to changes in alcohol use patterns. We aim to shed light on our previous findings of impaired MMN in risky-drinking patients with BD (Chitty et al., 2014) by investigating the longer-term effects of alcohol consumption. Firstly, we hypothesize that changes in alcohol use will be associated with changes in MMN. Secondly, we hypothesize that MMN at baseline may be a predictor of alcohol use at follow-up. It is essential to investigate these hypotheses in order to assess whether continued risky drinking or, more importantly, a reduction in risky drinking in adolescents and young adults with BD has corresponding effects on their neurobiology.

Methods

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 42 BD participants from our cross-sectional study (Chitty et al., 2014) plus additional recruitment of four patients, giving a total of 46 participants in the study. All participants were invited for follow-up.

Participants aged between 16–30 were recruited as part of a wider Youth Mental Health cohort study (Hermens et al., 2011; Lee et al., 2013; Scott et al., 2013), as referred by a psychiatrist who made a diagnosis of a bipolar illness using DSM-IV criteria (APA, 2000) as follows: bipolar I (n = 19), bipolar II (n = 21), bipolar not otherwise specified (n = 4), or bipolar spectrum with family history of BD (n = 2), defined as an illness pattern consisting of periods of both elevated and depressed mood consistent with a bipolar spectrum disorder (Angst, 2007). Twenty-seven of these patients returned for follow-up and all measures were repeated.

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 hours prior to testing and informed that they might be asked to undertake 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' normal psychotropic medication regimens were not interrupted in any way.

Measures

Clinical and Self-Report Measures

Participants underwent a clinical interview that included 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). Current self-reported symptoms were assessed using the depression anxiety stress scale (DASS; Lovibond and Lovibond, 1995) and the Kessler-10, a psychological distress scale (Kessler et al., 2002). The first time patients engaged a mental health

service was recorded and used as a proxy to determine duration of illness. Patients were asked to report any known first-degree family history of alcohol abuse or dependence.

Participants completed the Alcohol Use Disorders Identification Test (AUDIT) in self-report format. The AUDIT was developed from a World Health Organization collaboration as a screening instrument for hazardous and harmful alcohol consumption (Saunders et al., 1993). The tool differs from other screening tests, as it emphasizes identification of hazardous drinking rather than long-term dependence and focuses primarily on recent symptoms and behaviors (Babor et al., 2001), making it more appropriate for adolescent and young adult 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 above zero on the problems sub-score is indicative of problem drinking.

Frequency of tobacco use was assessed using baseline and follow-up answers from the World Health Organization alcohol, smoking, and substance involvement screening test (ASSIST; Edwards et al., 2003), in which participants were asked to indicate how often in the previous three months they had used tobacco products using ordinal options of never, once or twice, monthly, weekly, or daily/almost daily.

Neurophysiological Measures

Participants were fitted with a 64-channel Quik-Cap (Neuroscan) and headphones and told they would be watching a silent movie for 20 minutes and would be asked to report back the storyline at the end of the task. A different movie was used at each time point. Participants were then presented with 2 500 binaural pure tones (1 000 Hz, 75 dBSPL, 10 ms rise/fall) with stimulus onset asynchrony of 500 ms. Two hundred of these tones were duration-deviant tones (100 ms) presented pseudo-randomly within 2 300 standard tones (50 ms).

Continuous electroencephalography activity was recorded from sites according to the standard 10–20 International system (including mastoids), referenced to a nose electrode. Activity was sampled and digitized at 500 Hz (SynAmps2, Scan 4.3.1 software) and filtered using a band pass filter (0.1–30Hz). Data were processed offline using Neuroscan Scan 4.3.1 (Compumedics) software. Epochs were constructed at -100 to 450 ms relative to stimulus onset and were baseline corrected. MMN was derived from fronto-central and temporal sites as follows: Fz (frontal site), Cz (central site), M1 (left temporal site), and M2 (right temporal site). Epochs that contained activity ±100 μV at these sites were rejected. Additional electrodes were placed above and below the left eye and at the outer canthi of both eyes to monitor for eye-blink artifacts, and contaminated data was corrected using established algorithms (Semlitsch et al., 1986). MMN difference waveforms were obtained by subtracting waveforms elicited by standards from those elicited by duration-deviant stimuli. Peak amplitude was chosen as the primary outcome measure to maintain consistency with our previous MMN studies, and was determined using automated peak picking within an established epoch window of 135–205 ms (Hermens et al., 2010; Kaur et al., 2011, 2012).

It should be noted that MMN inverts its polarity when recorded at the mastoids and referenced to the nose (Naatanen et al., 2007). Therefore, for ease of comparison between fronto-central sites and temporal sites, we inverted fronto-central amplitudes so that positive amplitudes for all electrodes correspond to an increased MMN.

Statistical Analyses

Statistical analyses were carried out using SPSS for Windows 21.0 (SPSS Inc.). Differences in symptoms, alcohol, tobacco, and medications and in MMN amplitudes between baseline and follow-up were determined using paired t-tests or McNemar tests where relevant. Differences in MMN amplitudes and alcohol use between FHP and those with no family history of alcohol abuse/dependence (family history negative; FHN) were conducted using paired t-tests.

In order to test the primary hypothesis that decreased drinking will be associated with a positive change in MMN, we calculated change scores for AUDIT total and sub-scores, ASSIST tobacco frequency, and MMN variables.

Positive values for change-M1, change-M2, change-Fz, and change-Cz represent increased MMN amplitudes at follow-up. A positive value for change-AUDIT sub-scores represents an increase in drinking from baseline to follow-up and a positive value for change-tobacco use indicates a higher frequency of tobacco use at follow-up. All change scores were converted to z-scores to inspect for outliers (a z-score of +/- 3.00). Outliers were then removed from subsequent analyses to reduce the impact of influential cases.

Pearson's correlations were performed between change-MMN amplitudes with change-AUDIT and change-tobacco use.

We then conducted robust forced-entry multiple regression to assess predictors of alcohol use at follow-up. The outcome variable was AUDIT total score at follow-up. Predictors were chosen based on the results from the correlations, where the most strongly correlated fronto-central site and temporal site were chosen as predictors, along with the baseline AUDIT total score, FHP (0 = no, 1 = yes), and date difference between baseline and follow-up. Multicollinearity of predictors was assessed by the variance inflation factor. Cook's distance was used to assess the impact of influential cases and standardized residuals were inspected to identify outliers.

For all analyses, a simple bootstrapping method based on 1 000 samples was used to obtain bias-corrected and accelerated (BCa) 95% confidence intervals. Alpha was set to 0.05.

Results

Baseline Sample Characteristics

At baseline (n = 46), participants were aged 22.2 +/- 3.5 years, with duration of illness 6.93 +/- 3.5 years and 12.7 +/- 2.1 years of education. There were no significant differences between those who were included in the follow-up analysis (n = 27) versus those in the baseline-only sample (n = 19) in their demographic characteristics at baseline: age [$t(44) = 1.29$, $p = 0.20$], gender [χ^2 (1) = 0.77, $p = 0.38$], duration of illness [$t(44) = 0.19$, $p = 0.85$], or years of education [$t(44) = 1.20$, $p = 0.24$]. Additionally, there were no differences in clinical ratings at baseline: DASS stress [$t(44) = 0.34$, $p = 0.81$], DASS anxiety [$t(44) = 0.51$, $p = 0.62$],

DASS depression [t(44) = 0.15, p = 0.88], BPRS total [t(43) = 0.88, p = 0.38], HDRS total [t(43) = 0.14, p = 0.89], or YMRS [t(41) = 0.56, p = 0.58].

There were also no differences in baseline measures of substance use: AUDIT-total [t(44) = 1.56, p = 0.13], AUDIT-consumption sub-score [t(44) = 1.37, p = 0.18], AUDIT-problems sub-score [t(44) = 1.64, p = 0.11], AUDIT-dependence sub-score [t(44) = 1.18, p = 0.25], or proportion of smokers [$\chi^2(1) = 2.49$, p = 0.12]. There was, however, a trend toward a higher proportion of high-risk drinkers in the baseline-only sample [$\chi^2(1) = 3.68$, p = 0.055].

The baseline-only sample had significantly decreased MMN amplitude at M1 [t(44) = 2.29, p = 0.027], M2 [t(44) = 2.63, p = 0.012], and Fz [t(44) = 2.50, p = 0.016] compared to their peers who returned for follow-up. There was also a trend toward decreased Cz amplitude [t(44) = 1.79, p = 0.08] in the baseline sample.

Eleven (23.9%) of the baseline sample reported FHP. There were no differences in MMN amplitudes at Fz [t(44) = 0.97, p = 0.34], Cz [t(44) = 0.67, p = 0.51], M1 [t(44) = 1.59, p = 0.12] or M2 [t(44) = 0.72, p = 0.48]; in AUDIT scores: total [t(44) = 0.72, p = 0.48], consumption [t(44) = 0.02, p = 0.98], problems [t(44) = 0.97, p = 0.34]; or in dependence [t(44) = 0.99, p = 0.33] between FHP and FHN.

Follow-Up Sample Characteristics

Participants in the follow-up analysis (n = 27) included 19 (70.4%) females, aged 22.8 +/- 3.4 years; illness duration was 6.89 +/- 3.6 years and 13.1 +/- 2.3 years of education. Ten patients (37.0%) reported FHP. The mean time between baseline and follow-up was 17.9 +/- 7.3 months (min: 10 months; max: 38 months).

Clinical scores for participants at baseline and follow-up are shown in Table 1. Stress and anxiety, as measured by the DASS and the BPRS, were significantly improved at follow-up. There were no other significant changes in clinical measures.

Changes in Alcohol, Tobacco, and Medication Use

Table 2 shows the mean scores (and standard deviation) in alcohol, tobacco, and medication use over time. At the group level, there were no significant changes in alcohol use (as measured by AUDIT scores), tobacco use, or medications between baseline and follow-up.

There were no outliers in terms of change-AUDIT total (z-score range: -2.61, 2.67), change-AUDIT consumption (-2.87, 2.82), or change-AUDIT dependence (-1.88, 2.24). There was one change-AUDIT problems outlier (z-score = 4.19), which was then removed from subsequent analyses (z-score range once outlier was removed: -1.29, 1.27).

Table 1. Demographic and Symptoms Scores at Baseline and Follow-Up.

	Baseline (n = 27)	Follow-up (n = 27)	t
K-10 (SD)	25.8 (8.9)	22.9 (8.1)	t(25) = 1.64
DASS – Stress (SD)	19.7 (11.9)	13.9 (10.2)	t(25) = 2.77*
DASS – Anxiety (SD)	12.3 (9.0)	7.08 (7.0)	t(25) = 3.06**
DASS – Depression (SD)	16.1 (14.3)	14.5 (11.6)	t(25) = 0.59
HDRS – Total (SD)	10.0 (8.4)	8.91 (6.9)	t(23) = 0.74
BPRS – Total (SD)	37.3 (11.1)	32.8 (5.7)	t(23) = 2.42*
YMRS – Total (SD)	5.78 (6.6)	3.61 (3.6)	t(22) = 1.37

Tested using paired t-test. *p < 0.05, **p < 0.01. DASS and K-10 scores were missing from one patient, BPRS and HDRS missing for three patients, and YMRS missing from four patients.

AUDIT, alcohol use disorder identification test; BPRS, Brief Psychiatric Rating Scale; DASS, depression anxiety stress scales; HDRS, Hamilton Depression Rating Scale; K-10, Kessler-10 psychological distress scale; SD, standard deviation; YMRS, Young Mania Rating Scale.

Longitudinal MMN

At the group level, there were no significant differences between MMN at any site recorded at baseline compared with follow-up (Table 3).

Baseline and follow-up MMN amplitudes were highly correlated at M1 (r = 0.670, p < 0.001, BCa 95%, confidence interval [CI]: 0.32, 0.85), M2 (r = 0.57, p < 0.01, BCa 95%, CI: 0.18, 0.80), Fz (r = 0.521, p < 0.01, BCa 95%, CI: 0.28, 0.79), and Cz (r=0.578, p < 0.01, BCa 95%, CI: 0.31, 0.79).

There were no change-MMN outliers at M1 (z-score range: -1.96, 2.13), M2 (-1.73, 1.64), Fz (-2.25, 2.20), or Cz (-2.53, 1.07).

Correlations Between Change Scores

The correlation matrix is shown in Table 4. Change in MMN amplitudes versus change in AUDIT total for all four sites are depicted in scatterplots in Figure 1.

Changes in temporal MMN amplitudes showed negative associations with change-AUDIT scores, such that decreased MMN was associated with increased drinking. Specifically, the change-AUDIT total was significantly negatively associated with change-M1 and change-M2 (see Figure 1). Additionally, change-AUDIT dependence was significantly associated with change-M2. There were trend-level negative associations between change-AUDIT consumption and change-M1.

Table 2. Alcohol, Tobacco, and Medication Use

	Baseline (n = 27)	Follow-up (n = 27)	t/McNemar test
AUDIT total (SD)	8.00 (7.0)	8.33 (6.6)	t(26) = 0.32
AUDIT consumption (SD)	4.56 (2.9)	4.63 (3.1)	t(26) = 0.12
AUDIT problems (SD)	2.33 (3.3)	2.85 (3.5)	t(26) = 0.98
AUDIT dependence (SD)	1.11 (1.9)	0.85 (1.6)	t(26) =0.93
Lithium (%)	5 (18.5)	5 (18.5)	ns
Anti-depressant (%)	16 (59.3)	15 (51.7)	ns
Anti-psychotic (%)	15 (51.7)	14 (48.2)	ns
Anti-convulsant (%)	12 (41.4)	11 (40.7)	ns
Benzodiazepine (%)	1 (3.7)	1 (3.7)	ns
Medication free (%)	2 (7.4)	6 (22.2)	ns
Tobacco use (%)	15 (51.7)	11 (40.7)	ns
Cannabis use (%)	9 (33.3)	10 (37.0)	ns

Tested using t-test or McNemar's test. *p < 0.05, **p < 0.01, ***p <0.001.
AUDIT, alcohol use disorder identification test; MMN, mismatch negativity; ns, not significant; SD, standard deviation.

Table 3. Mismatch Negativity Changes Over Time

	Baseline (n = 27)	Follow-up (n = 27)	t	BCa 95% CI
Mismatch negativity				
M1 amplitude μV	2.52 (1.1)	2.30 (1.3)	t(26) = 1.13	-0.17, 0.63
M2 amplitude μV	2.57 (1.1)	2.60 (1.5)	t(26) = 0.19	-0.52, 0.41
Fz amplitude μV	-5.52 (2.5)	-5.30 (2.5)	t(26) = 0.92	-1.18, 0.66
Cz amplitude μV	-4.96 (2.5)	-4.59 (2.0)	t(26) = 0.48	-1.19, 0.36

*p < 0.05. Parentheses indicate standard deviations.
BCa 95% CI, bias-corrected and accelerated 95% confidence interval; Cz, central electrode; Fz, frontal electrode; M1, left temporal electrode; M2, right temporal electrode; μV, microvolts.

Table 4. Correlation Matrix

	Change-AUDIT total		Change-AUDIT consumption		Change-AUDIT problems^		Change-AUDIT dependence		Change-tobacco use	
	r	BCa 95% C.I	r	BCa 95% C.I	r	BCa 95% C.I	r	BCa 95% C.I	r	BCa 95% C.I
Change-M1	-0.426*	-0.72, -0.05	-0.324#	-0.63, 0.09	-0.283	-0.62, 0.18	-0.242	-0.63, 0.25	-0.029	-0.52, 0.36
Change-M2	-0.434*	-0.71, -0.04	-0.244	-0.54, 0.22	-0.245	-0.62, 0.23	-0.393*	-0.72, 0.10	0.218	-0.44, 0.63
Change-Fz	0.388*	-0.003, 0.67	0.318	-0.19, 0.61	0.265	-0.13, 0.62	0.364#	-0.04, -0.74	0.067	-0.20, 0.28
Change-Cz	0.351#	-0.11, 0.64	0.394*	-0.11, 0.66	0.229	-0.23, 0.59	0.331#	-0.01, 0.64	0.058	-0.24, 0.26

#$p < 0.10$, *$p < 0.05$.

One outlier was excluded from change-AUDIT problems analysis. Tobacco use refers to frequency of cigarette smoking.

AUDIT, Alcohol Use Disorders Identification Test; BCa 95% C.I, bias-corrected and accelerated 95% confidence intervals; Cz, central mismatch negativity peak amplitude; Fz, frontal mismath negaivity peak amplitude; M1, left temporal mismatch negativity peak amplitude; M2, right temporal mismatch negativity peak amplitude.

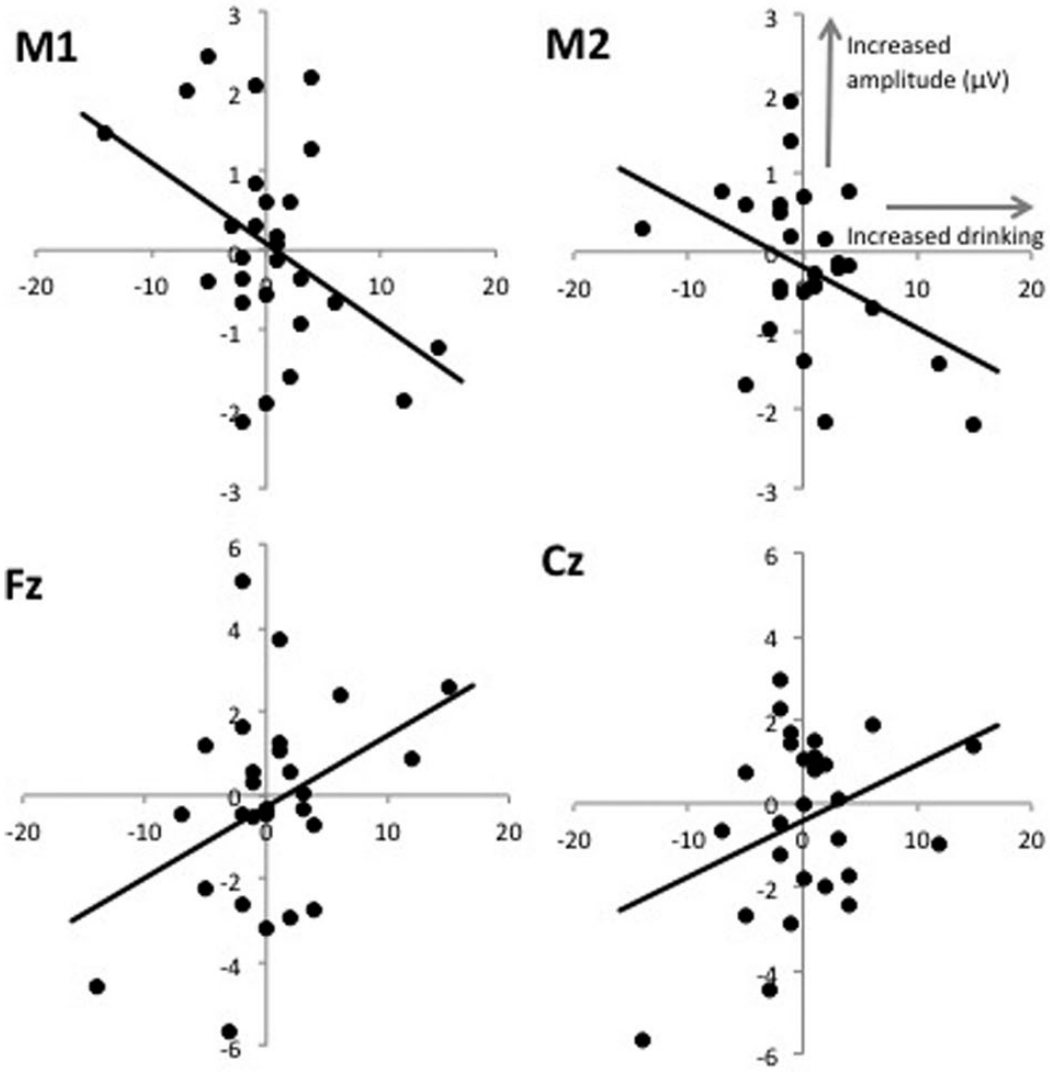

Figure 1. Scatterplots depicting relationships between changes in peak MMN amplitudes (μV, vertical axes) versus change in alcohol use patterns as measured by change in total AUDIT score (horizontal axes).Note: Scales of axes are oriented so an increased MMN is represented by a positive direction on the vertical axes.AUDIT, Alcohol Use Disorders Identification Test; Cz, central electrode; Fz, frontal electrode; M1, left mastoid electrode; M2, right mastoid electrode; MMN, mismatch negativity.

Changes in fronto-central electrodes showed positive associations with changes in AUDIT sub-scores, such that decreased MMN was associated with decreased drinking. The change-AUDIT total was significantly positively associated with change-Fz, with a trend-level positive association with change-Cz (see Figure 1). Change-AUDIT consumption was positively associated with change-Cz. Trend-level positive associations were seen between change-AUDIT dependence and both change-Fz and change-Cz.

There were no associations between change in frequency of tobacco use and any MMN variable.

Predicting Drinking Patterns at Follow Up

The regression model was significant [$F(5, 22) = 5.78$, $p = 0.001$], explaining 57.0% of the variance in alcohol use at follow-up. Both total AUDIT value at baseline and baseline M2 amplitude were significant predictors (see Table 5), whereby larger baseline AUDIT totals and larger baseline M2 amplitudes predicted larger AUDIT totals at follow-up. No other predictors contributed significantly to the model. All variance inflation factor values were between 1 and 1.2. Cook's distance for all variables was less than 1 and standardized residuals were all within three standard deviations.

Discussion

The current study uncovered some interesting results that highlight a potential key role for the NMDA receptor in the comorbidity between alcohol use and BD. Firstly, we confirmed our hypothesis that a decrease in drinking behavior (as indicated by a decrease in total AUDIT score) is associated with an increase in temporal MMN. Secondly, we discovered that an increase in drinking behavior is associated with increased fronto-central MMN amplitudes. Thirdly, temporal MMN amplitude at baseline was a significant predictor of AUDIT total score at follow-up. These findings emphasize three main points. Firstly, impaired temporal MMN in adolescent and young adults with BD and high risky drinking, as seen in our cross-sectional study (Chitty et al., 2014), appears to be modifiable, as observed here, with a concomitant decrease in drinking in this follow-up sample. Secondly, the effects of alcohol use patterns on frontal and temporal MMN appear to have opposing associations (see Figure 1), highlighting the utility of MMN as a tool for measuring the complicated effects of alcohol on the brain. Thirdly, preliminary results suggest that MMN may be utilized as a predictor of future risky alcohol use.

We found that increased fronto-central MMN amplitude was associated with increases in overall AUDIT scores, alcohol consumption scores, and alcohol dependence patterns, indicated by the AUDIT consumption and dependence sub-scores. These findings are interesting and are in line with previous research that has found that people with alcohol dependence display increased frontal MMN (Ahveninen et al., 1999), as do children of parents with alcohol dependence (Zhang et al., 2001). The interpretation of these two studies are related, with the former suggested to be due to compensatory upregulation of NMDA receptors and increased extrasynaptic Glu release as a result of chronic alcohol use (Ahveninen et al., 2000; Strelnikov, 2007) and the latter reflecting elevated levels of excitatory glutamatergic transmission relating to susceptibility of developing dependence (Zhang et al., 2001). Indeed, this neural hyperexcitability is hypothesized to be central to the development and risk for alcohol dependence (Zhang et al., 2001; Krystal et al., 2003a, 2003b), which is in line with the present findings. That is, neurobiologically speaking, a reduction in drinking results in a relaxation of the compensatory NMDA receptor excitability, and hence a reduction in MMN.

Conversely, an increase in peak temporal MMN was associated with a decrease in total AUDIT score as well as AUDIT dependence sub-scores, suggesting that an overall decrease in alcohol consumption and patterns of dependence is associated with an increased temporal MMN. In our cross-sectional study, risky-drinking adolescent and young adults with BD had the most impaired temporal MMN compared to their non-risky-drinking peers and controls (Chitty et al., 2014). The negative association seen with change scores in the present study suggests that the previously-noted impairment may be modified by the decrease in drinking, and hence highlights the importance of limiting alcohol use in adolescent and young adults with BD as a first step to counter additional negative effects on the NMDA receptor system.

It is noteworthy that the vast majority of alcohol and psychiatric MMN studies that have informed our present line of inquiry have investigated Fz and Cz, rather than temporal MMN measured at M1 and M2. Hence, the current findings in temporal MMN are quite novel. It is very interesting that the effects of alcohol in the present study appear to be disparate in frontal versus temporal MMN, as has also been noted in a study which looked at the acute effects of alcohol on MMN (Jaaskelainen et al., 1996). These findings may relate to the two distinct sources generating these event-related potentials, which are proposed to have different neuropsychological correlates (Giard et al., 1990; Rinne et al., 2000; Naatanen et al., 2007). Temporal MMN originates from the auditory cortex and is hypothesized to reflect the pre-perceptual change detection of the deviant stimulus using sensory-memory (Naatanen et al., 1978), whereas frontal MMN is thought to be related to the involuntary attention-switch caused by the deviant stimulus (Giard et al., 1990; Jaaskelainen et al., 1996; Naatanen et al., 2007). While speculative at this stage, the current results may show that MMN can be used as a tool to investigate the distinct sites and actions of ethanol, both from an NMDA receptor and a neuropsychological perspective. Temporal MMN may reflect the direct effect of alcohol on NMDA receptors (for example, ethanol's antagonist action at the receptor) and be related to alcohol-induced memory impairments (such as alcohol-induced blackouts; Chitty et al., 2014). On the other hand, frontal MMN may reflect the compensatory effects on NMDA receptors as a result of longer-term or chronic alcohol use (for example, may be related to density of NMDA receptors) and be related to attention difficulties associated with alcohol use (which may contribute toward risk of alcohol-related injury; Jaaskelainen et al., 1996).

Our preliminary analysis into the utility of MMN in predicting those who may be at a greater risk of heavy drinking revealed that larger M2 amplitude at baseline was associated with a larger AUDIT total score at follow-up. This result took into account baseline alcohol use, which was the most significant predictor of follow-up drinking patterns. A higher MMN amplitude at baseline may reflect higher NMDA receptor hyperexcitability, and hence a greater tolerance to the effects of alcohol. This again is consistent

Table 5. Results of Forced-Entry Regression Analysis

	B	SE B		
Constant	-0.56	4.25	β	BCa 95% CI
AUDIT total baseline	0.69	0.13	0.74**	0.01, 3.06
M2 amplitude baseline	1.59	0.75	0.27*	0.37, 0.92
Cz amplitude baseline	-0.63	0.40	-0.24	-1.58, 0.09
FHP	-0.90	1.92	-0.07	-4.58, 3.54
Date difference	0.15	0.20	0.16	-0.33, 0.34

*$p < 0.05$, **$p < 0.01$

n = 27

AUDIT, alcohol use disorder identification test; BCa 95% CI, bias-corrected and accelerated 95% confidence interval; Cz, central mismatch negativity peak amplitude; FHP, positive family history of alcohol abuse/dependence (no = 0, yes = 1); M2, right temporal mismatch negativity peak amplitude. Date difference refers to the difference between baseline and follow-up mismatch negativity acquisitions in months

with the predominant NMDA receptor theory regarding susceptibility for alcohol dependence (Zhang et al., 2001; Krystal et al., 2003a, 2003b). These results require replication with a larger cohort, but present a promising line of enquiry for utility of MMN as a neurobiological marker that may be used to determine risk for alcohol dependence in adolescent and young adults with BD.

Limitations

There are several limitations to consider when interpreting these study results. Firstly, due to the sample size of the study our regression analysis is limited and should be viewed as preliminary and in need of replication.

There were significant differences in baseline MMN amplitudes, whereby those who did not return for follow-up displayed significantly lower amplitudes at M1, M2, and Fz, with a trend in the same direction at Cz, compared to their peers who did return for follow-up. This was noted in another longitudinal study from our lab, with authors suggesting the worse underlying pathophysiology may have increased the likelihood of being lost to follow-up (Kaur et al., 2013). In the present case, the baseline-only sample also had trend-level higher rates of risky drinking. Thus, it is fitting to speculate that maintenance of risky drinking in those that were lost to follow-up may be associated with even greater MMN impairments.

We did not find any differences between FHP and FHN in terms of MMN or alcohol use within the study, which is contrary to previous evidence. This may be a result of our relatively low sample size, and the self-report collection of FHP data. This is an area that requires more rigorous future evaluation.

Participants were on an array of medications. Although there was no significant difference in patients that remained on or off medications, there is the possibility that some medications may have influenced the neurobiological measures. Of particular relevance are those medications that have an effect on the NMDA/glutamatergic system, such as lamotrigine, lithium, and valproate (Sanacora et al., 2008). Along with concurrent medications, almost 40% of participants also engaged in some form of cannabis use. In our cross-sectional study, cannabis use was not a significant predictor of impaired MMN (Chitty et al., 2014) and therefore was not covaried for in the present analysis. However, readers should bear in mind that use of cannabis, along with other illicit substances, is highly prevalent in BD. Future studies with larger sample sizes should examine the potential effect of cannabis.

Conclusions

The present study has highlighted a role of the NMDA receptor in this common and debilitating comorbidity of alcohol use and bipolar disorder. While the present study has not allowed us to make any firm conclusions about whether it is the NMDA receptor disturbance that is triggering the predisposition for alcohol use or whether alcohol use is compounding pre-existing disturbances, it has provided a basis for future research. We suggest that potentially both these theories are in play, and can be investigated looking at different components of MMN. The key message from the current study is that reducing alcohol use early in stages of illness is associated with changes in MMN, which may suggest that alcohol-induced NMDA impairments are modifiable. This supports the utility of targeted alcohol prevention strategies in adolescent and young adults with BD.

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Dr Hickie is a Senior Principal Research Fellow of the Australian National Health & Medical Research Council (AppID 1046899). He is the executive director of the Brain and Mind Research Institute at the University of Sydney, which operates two early-intervention youth services under contract to headspace. He is a commissioner of the Australian National Mental Health commission and was previously the CEO of beyondblue: the national depression initiative and a director of headspace: the national youth mental health foundation until January 2012. Previously, he has led a range of community-based and pharmaceutical industry–supported depression awareness and education and training programs. He has led depression and other mental health research service evaluation or investigator-initiated research projects that have been supported by a variety of pharmaceutical partners. Current investigator-initiated studies are supported by Servier (manufacturers of agomelatine) and Pfizer. He has received honoraria for his contributions to professional educational seminars related to depression, youth mental health, and circadian-rhythms research. He has received travel support from Servier to attend scientific meetings related specifically to circadian-rhythm disorders.

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