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Elucidating the glutamatergic processes underlying mismatch negativity deficits in early stage bipolar disorder and schizophrenia: A combined ^{1}H-MRS and EEG study

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A B S T R A C T

Impairments in mismatch negativity (MMN) in schizophrenia are well-established; these findings have been extended to show impairments at early illness stages and in bipolar disorder. A substantial literature supports MMN as an index of NMDA receptor output, however, few studies have conducted *in vivo* assessments to elucidate the neurochemical underpinnings of MMN. Sixty young (16–33 years) participants with bipolar disorder (n = 47) or schizophrenia (n = 13) underwent ^{1}H-MRS and MMN assessment. Glutamate over creatine (Glu/Cr) levels in the anterior cingulate cortex (ACC) and hippocampus were determined and MMN was measured frontally and temporally. Correlational analyses assessed the relationship between MMN amplitudes and Glu/Cr. Any significant relationships were assessed for specificity with a follow up correlation analysis of MMN and n-acetyleaspartate (NAA/Cr). No associations between frontal or temporal MMN and ACC or hippocampal Glu/Cr were noted in the bipolar group. In the schizophrenia group, frontal and right temporal MMN amplitudes corresponded with increased ACC Glu/Cr at the trend-level. Right temporal MMN was similarly significantly associated with NAA/Cr. MMN was not associated with hippocampal Glu/Cr. This work provides *in vivo* evidence that glutamatergic processes may underlie MMN generation in early stage schizophrenia but not in early stage bipolar disorder suggesting differences in the MMN mechanism in these groups. The negative association between ACC Glu/Cr and MMN is consistent with findings of reduced MMN and increased *in vivo* glutamatergic neurometabolite levels in early stage schizophrenia. Furthermore, these results indicate that examining *in vivo* NAA/Cr may have provide additional insights into the MMN mechanism in schizophrenia.

1. Introduction

Mismatch negativity (MMN) is the difference event-related potential reflecting the brain's detection of a perceptual deviance in the environment (Hermens et al., 2018). With a plethora of investigations reporting marked MMN impairments in schizophrenia, it is one of the most replicable findings in the psychophysiological literature (Erickson et al., 2016; Naatanen and Kahkonen, 2009; Umbricht and Krljes, 2005). There was a general consensus that MMN deficits are exclusive to patients with schizophrenia (Catts, 1995; Hall, 2009) and occur in chronic stages of the disease (Umbricht, 2003; Salisbury, 2007). The literature has now expanded to show impairments at early stages of psychotic disorders such as, high-risk for psychosis (Bodatsch et al., 2011) and first-episode psychosis (Hermens et al., 2010; Kaur et al., 2011) as well as in affective-spectrum psychoses (Kaur et al., 2011) and bipolar disorder (Andersson et al., 2008; Kaur et al., 2012). MMN was touted as a biomarker of intermediate effect in bipolar disorder (Hermens et al., 2018), in light of reports of MMN deficits (compared with healthy samples) but which are moderate compared to MMN deficits in schizophrenia (Chitty et al., 2013; Kaur et al., 2012).

Several animal and human studies have shown that administration of antagonists of n-methyl-*d*-aspartate receptor (NMDAr) attenuates MMN amplitude, providing compelling support for the specific role of NMDAr in MMN generation (Kenemans and Kahkonen, 2011). Additionally, dopaminergic (Kahkonen et al., 2001; Korostenskaja et al., 2005; Pekkonen et al., 2002; Umbricht et al., 1998, 1999) or serotonergic (Leung et al., 2010; Umbricht et al., 2002) neurotransmitter receptor agents do not modulated MMN. While MMN recorded at the scalp is thought to index NMDAr output, the combination of EEG and proton magnetic resonance spectroscopy (^{1}H-MRS) allows for the quantification of key neurometabolite concentrations *in vivo* thereby providing the opportunity for a more integrated understanding of the

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glutamatergic system underlying MMN generation. Three studies have reported on the relationship between MMN and ^{1}H-MRS-derived glutamatergic neurometabolite concentrations. The first showed that smaller frontal MMN amplitudes corresponded with lower thalamic Glx (the overlapping resonance of glutamate and its precursor, glutamine) levels in at-risk for psychosis participants (Stone et al., 2010). This study was limited by small sample size (N = 11) and the long length of time between MMN and ^{1}H-MRS assessments (645 ± 475 days). Rowland et al. (2016) similarly found a positive association between *in vivo* glutamate (Glu) in the anterior cingulate cortex (ACC) and frontally recorded MMN in n = 45 schizophrenia-spectrum patients. The only investigation of MMN and ^{1}H-MRS in bipolar disorder by our group observed no association between MMN amplitudes and Glu/Cr (glutamate over creatine ratio) levels, however, the MMN data reported were at temporal sites and Glu/Cr levels were derived from a hippocampal voxel (Chitty et al., 2015a).

The limited number of studies on the *in vivo* neurochemical underpinnings of MMN described above have focused exclusively on either frontal or temporal brain regions. Source localisation studies provide strong evidence that MMN initially emerges from a temporal generator with subsequent influence from a frontal generator (Naatanen et al., 2007). The bilateral supratemporal plane is the most commonly implicated region for the temporal generator although the thalamus and hippocampus may contribute to MMN elicitation (Alho, 1995). The ACC and right inferior frontal cortex are commonly implicated frontal MMN sources (Jemel et al., 2003). While the early MMN and ^{1}H-MRS literature provides some pertinent insights into the relationship between MMN and *in vivo* glutamatergic neurometabolites, given key methodological differences among the studies (i.e. ^{1}H-MRS measures and samples characteristics), further work is required to more comprehensively elucidate the *in vivo* glutamatergic processes underpinning MMN elicitation.

The current study will provide a more comprehensive view of the neurochemical underpinnings of MMN in key brain regions by determining whether frontal and temporal MMN amplitude is significantly associated with *in vivo* Glu/Cr concentrations from both frontal and temporal voxels in a sample of early stage bipolar disorder and schizophrenia groups. Given that MMN has been proposed as an index of NMDAr output (Kenemans and Kahkonen, 2011) we hypothesise that frontal and temporal MMN will be associated with *in vivo* Glu/Cr concentrations in frontal and temporal regions.

2. Experimental procedures

2.1. Sample

Sixty patients with schizophrenia or bipolar disorder (aged 16–33) were recruited from a specialised referral service (Scott et al., 2012). Trained research psychologists (MK, KMC) conducted structured interviews using the Structured Clinical Interview for DSM-IV (First et al., 2007) to confirm referring psychiatrists' diagnoses of a bipolar (n = 47, bipolar disorder I with psychotic features n = 10, a bipolar disorder I or II without psychotic features n = 37) or schizophrenia-spectrum disorder (n = 13, schizophrenia, schizoaffective disorder, schizophreniform disorder). For the bipolar group, the mean duration since onset of any psychiatric symptoms was 8.0 ± 3.5 and, 36 were right-handed, 9 were left handed and 2 were ambidextrous. For the schizophrenia group, the mean duration since onset of any psychiatric symptoms was 6.1 ± 2.7 and, 12 were right-handed and 1 was left handed. Exclusion criteria were being too unwell for assessments or a history of neurological illness impacting brain function, intellectual disability (IQ < 70) and insufficient English for assessments. Participants were required to abstain from using any substances (apart from prescribed medication) for 48 h before testing. On indication of intoxication during testing, alcohol breath testing or saliva drug screening (for cannabis, cocaine, amphetamine, methamphetamine, opioids, benzodiazepines) were undertaken and if positive, assessments were rescheduled. Caffeine and tobacco use were not restricted. Additional information on mood state and, nicotine and substance use is provided in supplementary materials. Patients were tested under treatment-as-usual conditions. For the bipolar group, 22 (46.8%) were on antidepressants, 23 (48.9%) were taking anti-convulsants or mood-stabilisers, 20 (42.6%) were on antipsychotics, three were on benzodiazepines, a simulant or fish oil supplements (6.4% each) and 10 (21.3%) were medication free. For the schizophrenia group, 12 (92.3%) were on antipsychotics, 4 (30.8%) were taking anti-convulsants or mood-stabilisers, 4 (30.8%) were on antidepressants and 1 (7.7%) was medication free.

This study was approved by the University of Sydney ethics committee, written informed consent was obtained from all participants prior to participation and the study was conducted in accordance with the Declaration of Helsinki.

2.2. Procedure and clinical assessment

Participants were recruited as part of our longitudinal study (Kaur et al., 2013) and underwent clinical assessment, neurophysiological assessment and ^{1}H-MRS. ^{1}H-MRS was recorded within 3 months of the clinical and neurophysiological assessment. To quantify current symptoms, clinical ratings were made using the expanded version of the Brief Psychiatric Rating Scale (BPRS) (Ventura et al., 1993).

2.3. 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 min and that they will be asked to report back the storyline at the end of the task. Participants then underwent an auditory duration deviant MMN paradigm. They were 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 EEG activity was recorded from sites according to the standard 10–20 International system (including mastoids), referenced to a nose electrode. Peak amplitude was the primary outcome measure and MMN was derived from Fz, M1 and M2. A detailed description of the EEG acquisition and analyses are described in our previous studies (Hermens et al., 2010; Kaur et al., 2011, 2012, 2013).

2.4. ^{1}H-MRS data acquisition and processing

Participants were scanned on a 3 T GE Discovery MR750 MRI (GE Medical Systems, Milwaukee, WI). Following acquisition of a 3D sagittal whole brain scout and T1 weighted sagittal slices, a 2 x 2 × 2 cm^{3} single voxel was placed midline on the ACC (Chitty et al., 2015c; Duffy et al., 2015, 2016; Hermens et al., 2012) and a 1.5 x 3.0 × 1.0 cm^{3} voxel was placed in the left hippocampus (Chitty et al., 2014, 2015a; Hermens et al., 2015a, 2015b). 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 prior to any post processing, visually inspected by independent raters, to ensure the consistency of the data. Poorly fitted neurometabolite peaks as reflected by large (> 20) Cramer–Rao Lower Bounds (CRLB) were excluded from further analysis. Post processing of data was offline using the LCModel software package (Provencher, 1993) and all spectra were quantified using a GAMMA-simulated PRESS TE 35 basis set of 15 metabolites and incorporated macromolecule and baseline fitting routines. The spectra were visually inspected separately by two different raters to ensure consistent spectra, and poorly fitted metabolite peaks. See our published protocols for: a detailed description of spectroscopy data acquisition and processing (Chitty et al., 2014); localisation of ACC and associated offline processing (Duffy

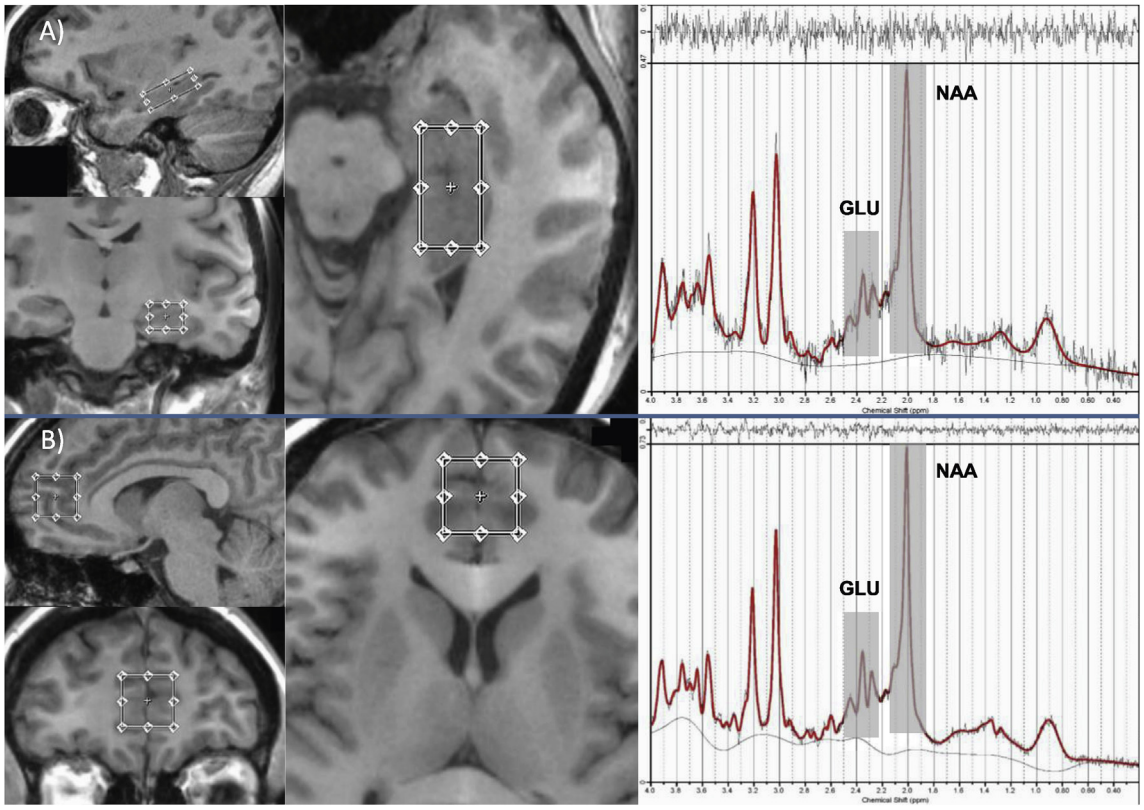

Fig. 1. *Left panel* T1-weighted images illustrating the axial, sagittal and coronal views of voxel placement for the left hippocampus (A) and ACC (B). *Right panel* sample spectra sampled from the left hippocampus (A) and ACC (B) processed using LCModel from a single representative participant. *Note*: Glu = glutamate over creatine ratio; NAA = N-acetylaspartate; ACC = anterior cingulate cortex.

Table 1
Mean scores (± standard deviation) and demographic, clinical and neurobiological (i.e. MMN and Glu/Cr) characteristics for the bipolar and schizophrenia groups with corresponding results for #chi-squared and independent samples comparison statistics. *Note*: BPRS = Brief Psychiatric Rating Scale; Glu/Cr = glutamate over creatine ratio; ACC = anterior cingulate cortex; Hipp = hippocampus; NAA/Cr = n-acetylaspartate over creatine ratio.

	Bipolar (n = 47)	Schizophrenia (n = 13)	Between group significance test [p]
Gender (F/M)[#]	37/10	4/9	χ^2 (1) = 10.8 [p < .01]**
Age	23.5 ± 4.2	24.2 ± 3.1	t (1,58) = 0.60 [P > .05]
Time between MMN and MRS	5.3 ± 16.9	14.5 ± 39.4	t (1,58) = −1.25 [P > .05]
BPRS total	39.9 ± 10.0	42.0 ± 11.6	t (1,56) = 0.64 [p < .05]
BPRS positive	10.1 ± 3.6	12.6 ± 5.8	t (1,56) = 1.91 [p = .06]*
BPRS negative	6.5 ± 2.2	8.7 ± 3.4	t (1,56) = 2.80 [p < .01]**
BPRS depression	14.4 ± 5.1	13.2 ± 4.7	t (1,56) = −0.71 [p > .05]
MMN Fz	−4.7 ± 1.9	−4.4 ± 2.0	U = 279, z = −0.25 [p > .05]
MMN M1	2.3 ± 1.2	2.1 ± 1.1	U = 281, z = −0.44 [p > .05]
MMN M2	2.3 ± 1.2	2.3 ± 1.2	U = 282, z = −0.31 [p > .05]
ACC Glu/Cr	1.8 ± 0.4	1.7 ± 0.2	U = 187, z = −1.51 [p > .05]
Hipp Glu/Cr	1.6 ± 0.3	1.4 ± 0.2	U = 113, z = −1.19 [p > .05]
ACC NAA/Cr	1.3 ± 0.2	1.3 ± 0.1	U = 260, z = < 0.01 [p > .05]
Hipp NAA/Cr	1.3 ± 0.2	1.2 ± 0.1	U = 114, z = −1.27 [p > .05]

et al., 2014); and, left hippocampus regions and associated offline processing (Chitty et al., 2014). Glu and n-acetylaspartate (NAA) were analysed for this study and was determined as a relative ratio to creatine-phosphocreatine (Cr; i.e. Glu/Cr and NAA/Cr). The example spectra and voxel placement figures are shown in Fig. 1. Following this, the coordinates of the acquired ACC voxels for each participant were obtained using the SAGE (Spectroscopy Analysis GE) software package and the reconstructed acquisition voxels for all participants were corrected for grey matter (GM) content. GM correction was achieved by segmenting each participant's structural image into GM, white matter (WM) and CSF using the FAST4 algorithm as implemented in FSL (Zhang et al., 2001) and volume fractions were calculated. Hippocampal data could not be GM-corrected due to the angulation of the acquisition voxel used. However, since hippocampal tissue composition is predominantly GM, left hippocampal volumes were calculated and used as a proxy for individual differences. The FWHM and signal-to-noise ratio mean and standard deviations for each group at each region are provided in supplementary materials. For the bipolar group, 85.1% (n = 40) and 72.3% (n = 34) had valid spectroscopy data for the ACC and the left hippocampus, respectively. For the schizophrenia group, all participants (n = 13) had valid ACC data and 69.2% (n = 9) had valid left hippocampus data. An independent samples *t*-test confirmed no significant differences between bipolar and schizophrenia groups in *in vivo* creatine in the ACC [t (51) = −1.1, p = .27] and hippocampus [t (39) 0.9, p = .39].

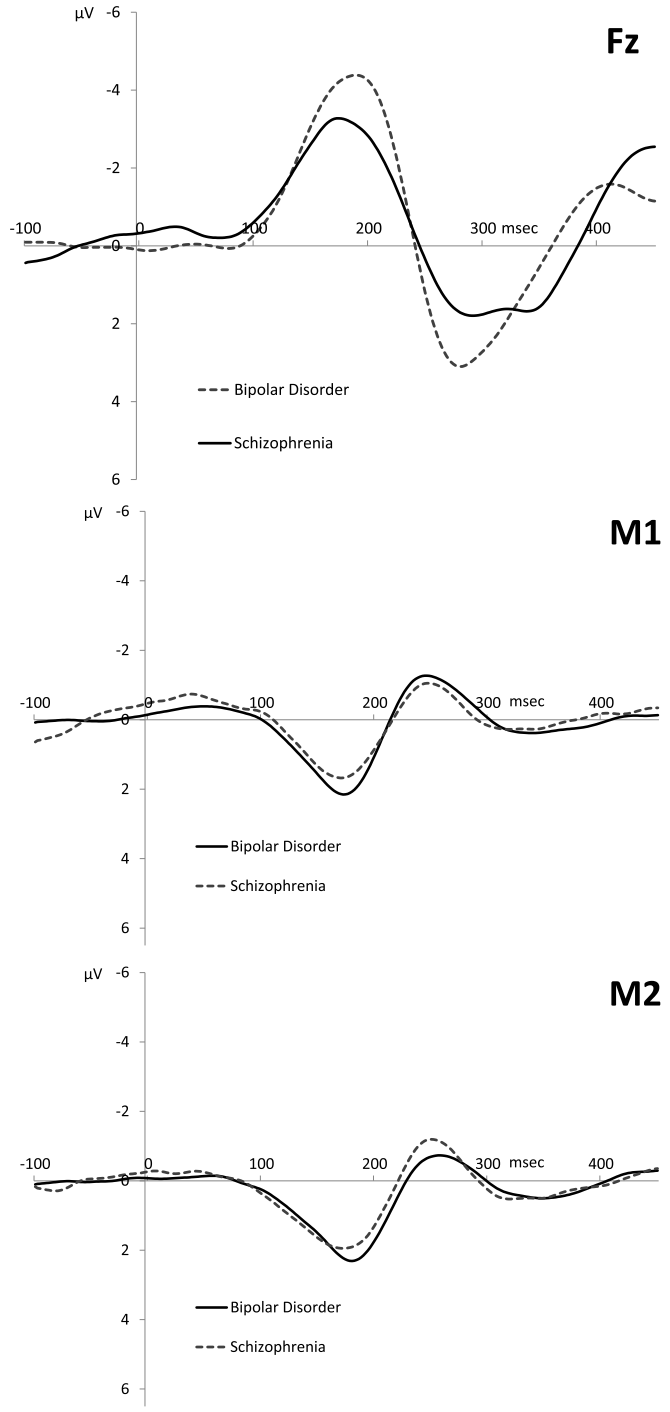

Fig. 2. MMN waveforms at EEG sites, Fz, M1 and M2 for bipolar disorder and schizophrenia groups.

2.5. Statistical analyses

SPSS 23.0 (SPSS Inc., Chicago, Illinois, USA) for Windows was used to perform statistical analyses. For between group differences, data were inspected for normality using the Kolmogorov-Smirnov test and non-normal variables were transformed where possible. To determine differences between the groups, independent samples t-tests (for normally distributed and transformed data) and the Mann-Whitney *U* test was used. Spearman's rho correlational analyses were performed to assess the relationship between MMN amplitude at each of the electrode sites (i.e. Fz, M1 and M2) and Glu/Cr (in ACC and hippocampus). For any significant/trend-level associations, the relationship between MMN and NAA/Cr was determined using correlational analysis to assess the specificity of MMN and Glu/Cr relationships.

Table 2
Spearman's Rho correlation coefficients between Glu/Cr levels in the ACC and Hipp and MMN at Fz, M1 and M2 for the bipolar and schizophrenia groups. *Note*: Glu/Cr = glutamate over creatine ratio; ACC = anterior cingulate cortex; Hipp = hippocampus; NAA/Cr = n-acetylaspartate over creatine ratio; * denotes $p < .05$.

		MMN peak amplitude		
		Fz	M1	M2
Bipolar	ACC Glu/Cr	.15	-.18	-.19
	Hipp Glu/Cr	.14	-.18	.10
Schizophrenia	ACC Glu/Cr	.54#	-.14	-.53#
	Hipp Glu/Cr	-.42	-.60	-.58

3. Results

3.1. Clinical, neurophysiology and spectroscopy characteristics

The demographic, clinical, neurophysiology and spectroscopy characteristics of the bipolar and schizophrenia groups in demographic, clinical, neurophysiological and spectroscopy measures are presented in Table 1. Overall, the schizophrenia group had significantly more severe negative ($p < .01$) and at the trend-level ($p = .06$), positive symptoms compared with the bipolar group. Groups did not differ significantly on time between gender, age MMN and ^{1}H-MRS, total psychiatric symptoms, depressive symptoms, MMN (at Fz, M1 or M2), Glu/Cr (in ACC or hippocampus) or NAA/Cr (at ACC or hippocampus) (all $p > .05$). See Fig. 2 for the MMN waveforms for bipolar and schizophrenia groups. Frontal MMN waveforms for schizophrenia and bipolar subgroups (bipolar disorder with psychotic features and bipolar disorder without psychotic features) are presented in supplementary materials.

3.2. Neurophysiology and spectroscopy correlational findings

The correlational analyses results for MMN and Glu/Cr are presented in Table 2. For the bipolar group, there were no significant associations between MMN at Fz, M1 or M2 and ACC Glu/Cr or hippocampal Glu/Cr (all $p > .05$). For the schizophrenia group, ACC Glu/Cr was positively associated with MMN at Fz ($p = .06$) and negatively associated with MMN at M1 ($p = .06$) at the trend-level, however, there was no significant association for MMN at M2 ($p > .05$) (note: MMN is a negative potential however at temporal sites, polarity is inversed due to recording techniques). Furthermore, a negative relationship was observed between ACC NAA/Cr and MMN at M2 ($r = -0.70$; $p < .01$) but not at Fz ($r = 0.16$; $p > .05$) or M1 ($r = -0.37$; $p > .05$). Fig. 3 depicts the associations between MMN at Fz and ACC Glu/Cr in the schizophrenia group, as well as the bipolar group for comparison.

4. Discussion

This study is the first to investigate the association between both frontal and temporal MMN amplitudes and *in vivo* ACC and hippocampal Glu/Cr concentrations in early stage bipolar disorder and schizophrenia groups. While no significant associations between MMN and Glu/Cr were noted in the bipolar group, reduced frontal and right temporal MMN amplitudes corresponded with increased ACC Glu/Cr in the schizophrenia group. However, MMN amplitudes at frontal or temporal sites were not related to hippocampal Glu/Cr levels in the schizophrenia group. Right temporal MMN was also associated with ACC NAA/Cr in the schizophrenia group whereby reduced MMN amplitudes corresponded with increased NAA/Cr levels.

The results for MMN and Glu/Cr in bipolar disorder failed to

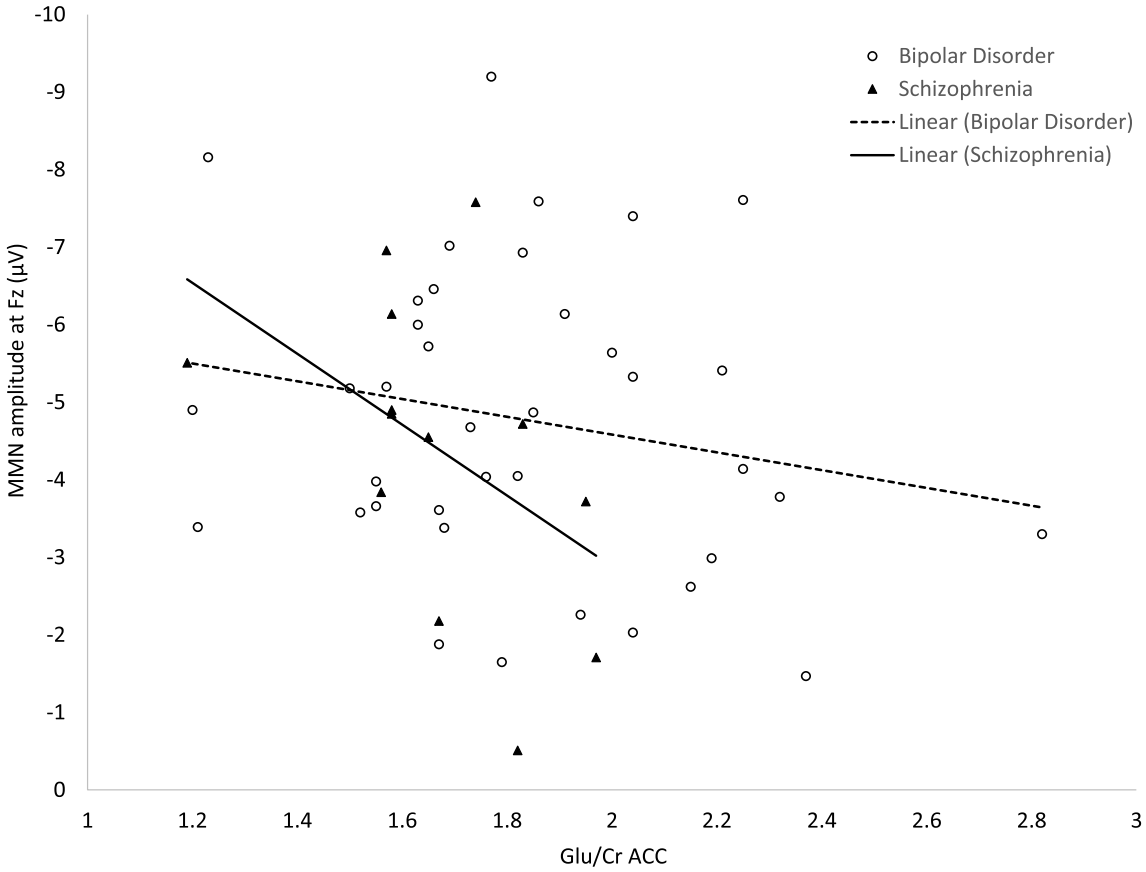

Fig. 3. Scatter plot showing the Glu/Cr concentrations in the ACC and MMN amplitude at Fz for the bipolar and schizophrenia groups. *Note*: Glu/Cr = glutamate over creatine ratio; ACC = anterior cingulate cortex.

provide support for the NMDAr output theory of MMN generation (Kenemans and Kahkonen, 2011). However, these findings are in keeping with the only other study on MMN and *in vivo* glutamatergic measures in bipolar disorder (Chitty et al., 2015a). Different patterns of association between MMN and *in vivo* Glu/Cr and glutathione (another NMDAr modulatory chemical) have been reported in bipolar disorder and healthy people. Specifically, MMN was associated with both *in vivo* Glu/Cr (Chitty et al., 2015a) and glutathione (Chitty et al., 2015b) in healthy people but not in bipolar disorder. Further, studies show that MMN amplitude is related to glutathione (Chitty et al., 2015b) in healthy people and its precursor, n-acetyl-cysteine (Lavoie et al., 2008) in schizophrenia. To this end, the lack of association between MMN and Glu/Cr in bipolar disorder could suggest that different neurobiological processes influence MMN generation in this clinical group compared to schizophrenia and healthy people. The current research and this broader literature lends to the complexity of the NMDAr mechanism involved in MMN generation and highlights the importance of considering differences in glutamatergic function and pathology in MMN and ^{1}H-MRS studies.

The association between frontal and right temporal MMN amplitudes and ACC Glu/Cr concentration in schizophrenia is in keeping with the extant literature suggesting that MMN is driven by NMDAr output (Kenemans and Kahkonen, 2011). For the first time in the literature, right temporal MMN amplitude was associated NAA/Cr. As NAA is a precursor of the neuropeptide, n-acetylaspartylglutamate, that modulates neuronal release of glutamate (Jessen et al., 2013), this association might suggest that the synthesis of n-acetylaspartylglutamate contributes to the MMN mechanism in schizophrenia. It was unexpected that MMN amplitudes and ACC Glu/Cr were negatively related given the positive association between MMN amplitudes and *in vivo* glutamatergic measures previously documented (Rowland et al., 2016; Stone et al., 2010). Several methodological differences in the MMN and ^{1}H-MRS studies provide insight into interpreting the difference in results; that is, across this literature, findings of *in vivo* Glu specifically and MMN varied and, different clinical samples were included. In the 'at-risk' for psychosis study, reduced Glx corresponded with reduced MMN amplitudes, however, Glu itself was not related to MMN (Stone et al., 2010). Contrastingly, reduced Glu was related to reduced MMN amplitudes and increased Gln/Glu was associated with reduced MMN amplitude in a chronic schizophrenia cohort (Rowland et al., 2016). In schizophrenia, patterns of variability in frontal *in vivo* glutamatergic neurometabolites levels appear to relate to illness stage. In chronic schizophrenia, unaltered or *reduced* Glu and Glx is observed whereas, in first-episode psychosis, *increased* Gln has been consistently found as well as reports of *increased* Glu/Cr and Gln/Glu ratio (Wijtenburg et al., 2015). This evidence might explain the divergent patterns of association between MMN and *in vivo* glutamatergic neurometabolites levels in the early stage schizophrenia sample in the current study and in chronic schizophrenia (Rowland et al., 2016). However, such interpretation of the current findings warrants caution since any differences in MMN and ACC Glu/Cr compared to healthy controls could not be determined and due to the small schizophrenia sample.

Given that *in vivo* Glx was measured in the thalamus in the study by Stone et al. (2010), it is not possible to directly compare to the current study or the aforementioned investigation on chronic schizophrenia. Notwithstanding, in contrast to the association of frontal MMN and thalamic Glx found in 'at risk' for psychosis (Stone et al., 2010), here we did not observe a relationship between MMN and hippocampal Glu/Cr. A potential reason for the difference is that thalamic glutamatergic disturbances appear in 'at risk' for psychosis and may precede glutamatergic disturbances in other brain regions (Wijtenburg et al., 2015).

It is also possible that any relationship could not be detected due to differences in tissue homogeneity between the ACC and hippocampus and the reduced number of cases that had valid hippocampal data in this study.

A limitation of this study is the lack of a healthy control group and thus, any differences between the clinical groups and a healthy sample in MMN or Glu/Cr variables, as would be expected, could not be determined. *In vivo* neurometabolite levels have shown to be related to mood state and medications, however, due to sample size restrictions, these factors were not co-varied for (Chitty et al., 2013). Further, the duration between MMN and ^{1}H-MRS assessments (up to 3 months) may have limited this study. It is also important to recognise that ^{1}H-MRS is a measure of the net concentration of neurometabolites within a voxel that does not encompass the dynamicity of neurochemical activity. Thus, inferences from assessing *in vivo* neurometabolite concentrations cannot be made on neurometabolite concentration distributions across intracellular vs extracellular spaces.

In conclusion, this work forms a part of an emerging literature combining EEG with ^{1}H-MRS techniques to inform the relationship between a proposed neurophysiological index of NMDAr output and *in vivo* glutamatergic neurometabolite concentrations. This work thereby provides additional neurochemical insights into the glutamatergic system underlying MMN at early stages of bipolar disorder and schizophrenia.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpsychires.2019.03.018.

Conflicts of interest

We have no conflicts of interest to declare.

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