Schizophrenia Research xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Schizophrenia Research

journal homepage: www.elsevier.com/locate/schres

Dissociable auditory mismatch response and connectivity patterns in adolescents with schizophrenia and adolescents with bipolar disorder with psychosis: A magnetoencephalography study

Sven Braeutigam [a,*], Danai Dima [b,c,d], Sophia Frangou [d], Anthony James [e,f]

[a] Oxford Human Brain Activity Center, Department of Psychiatry, University of Oxford, OX3 7JX, UK
[b] Department of Psychology, School of Arts and Social Sciences, City, University of London, London, UK
[c] Department of Neuroimaging, Institute of Psychiatry, Psychology and Neuroscience, King's College London, UK
[d] Department of Psychiatry, Icahn School of Medicine at Mount Sinai, USA
[e] Department of Psychiatry, University of Oxford, UK
[f] Highfield Unit, Warneford Hospital, Oxford, UK

ARTICLE INFO

Article history:
Received 6 March 2017
Received in revised form 21 July 2017
Accepted 23 July 2017
Available online xxxx

Keywords:
Schizophrenia
Bipolar disorder
First episode
Mismatch negativity
Connectivity
Biomarker

ABSTRACT

Background: There is overlap between schizophrenia and bipolar disorder regarding genetic risk as well as neuropsychological and structural brain deficits. Finding common and distinct event-response potential (ERP) responses and connectivity patterns may offer potential biomarkers to distinguish the disorders.
Objective: To examine the neuronal auditory response elicited by a roving mismatch negativity (MMN) paradigm using magnetoencephalography (MEG).
Participants: 15 Adolescents with schizophrenia (ASZ), 16 adolescents with bipolar disorder with psychosis (ABP), and 14 typically developing individuals (TD)
Methods: The data were analysed using time-series techniques and dynamic causal modelling (DCM).
Outcome measures: MEG difference wave (deviant – standard) at primary auditory (~90 ms), MMN (~180 ms) and long latency (~300 ms).
Results: The amplitude of difference wave showed specific patterns at all latencies. Most notably, it was significantly reduced ABP compared to both controls and ASZ at early latencies. In contrast, the amplitude was significantly reduced in ASZ compared to both controls and ABP. The DCM analysis showed differential connectivity patterns in all three groups. Most notably, inter-hemispheric connections were strongly dominated by the right side in ASZ only.
Conclusions: Dissociable patterns of the primary auditory response and MMN response indicate possible developmentally sensitive, but separate biomarkers for schizophrenia and bipolar disorder.

1. 1. Introduction

A shared aetiology between schizophrenia and bipolar disorder with psychosis is supported by findings from genetic (Lee et al., 2012), neuropsychological (Hill et al., 2013), phenomenological (Tamminga et al., 2013), structural (Ivleva et al., 2012) and functional neuroimaging studies (Li et al., 2017). It is important to see if any shared aetiology is reflected in similar, or related patterns of pathophysiology in adolescent–onset cases, where neurodevelopmental processes are likely to operate.

Electrophysiological techniques (Thibaut et al., 2015) can help determine biomarkers at the neuronal level. Of particular relevance are passive event related potentials (ERPs) in response to auditory oddball paradigms. The N100, a late, attention-sensitive auditory evoked potential (AEP) (McCarley et al., 1991) and the mismatched negativity (MMN) a neurophysiological index of the disturbed automatic and pre-attentive detection of deviant information, evoked by either a change in duration, frequency, loudness, or spatial locus of origin (Näätänen et al., 1978). MMN is a highly reproducible neurophysiological marker in schizophrenia and has been shown to follow a progressive course, with reduced MMN amplitude associated with a loss of grey matter in the left superior temporal gyrus (STG) (Salisbury et al., 2007).

However, ERP measures alone appear less than clear-cut in differentiating the disorders (Näätänen et al., 2012). Reduced amplitude of early auditory ERP components (N100, P200, and N200) are seen in schizophrenia (O'Donnell et al., 2004), some report similar reductions in bipolar disorder (Wang et al., 2014), but others do not (Johannesen et al., 2013). Likewise, some studies have found common neurobiological

* Corresponding author.
E-mail address: sven.braeutigam@psych.ox.ac.uk (S. Braeutigam).

http://dx.doi.org/10.1016/j.schres.2017.07.048
0920-9964/

disturbances in deviance detection/orienting processes (Kaur et al., 2011), others have reported deficits in pre-attentive auditory processing, and MMN deficits that are less severe in bipolar disorder (Jahshan et al., 2012a). Hermens et al. (2017) recently concluded that MMN was not a diagnosis specific biomarker.

Adolescence through to early adulthood is a period of intense brain re-organization. The cortical network generating MMN continues to develop in adolescence into to adulthood (Cooray et al., 2016). Cortical regions in the temporal and frontal lobes, involved in auditory processing, mature with increasing fronto-temporal connectivity together with increased sensitivity in the temporal regions for changes in sound stimuli (Cooray et al., 2016). It is thought that at a neuronal population level this reflects a maturation of the excitatory inhibitory balance in the temporal regions. Mapping changes in adolescence may, therefore, represent a uniquely sensitive way to understand the MMN response in schizophrenia and bipolar disorder against the developmental course of adolescence (e.g., Arango et al., 2014).

Following our previous work (Dima et al., 2012) we used magnetoencephalography (MEG) to quantify the MMN neuronal response in adolescents with schizophrenia (ASZ), in adolescents with bipolar disorder with psychosis (ABP) and in normally developing adolescents. MEG is able to image the brain at high temporal resolution, where the spatial resolution is typically better than EEG, thereby offering the potential to better delineate neural correlates of these disorders. We aimed to examine whether there are differences in early latency deviance detection/orienting processes and the MMN in the early phase between the two disorders reflecting differing neurobiological processes. In order to fully exploit the MEG data and in line with a wealth of studies suggesting schizophrenia specific effects at post-MMN latencies (e.g., Salisbury et al., 1999), we analysed an extended latency range compared to typical MMN studies.

2. Methods

2.1. Subjects

Fifteen adolescents with first episode schizophrenia and 16 adolescents with bipolar disorder with psychosis were recruited. All patients met DSM-IV criteria (APA, 1994) for schizophrenia or bipolar disorder with psychosis, using the Kiddie Schedule for Affective Disorders and Schizophrenia (Kaufman et al., 1997). Exclusion criteria included moderate mental impairment (IQ < 70), a history of pervasive developmental disorder, substance misuse disorder, significant head injury, neurological disorder or major medical disorder (demographics see Table 1).

Table 1
Demographic details of adolescents with schizophrenia (ASZ), adolescent with bipolar disorder with psychosis (ABP) and healthy controls (TD). Age in years. Disease duration in years at time of scanning. R/L: handedness, Edinburgh Inventory. ±PANSS: Positive and Negative Syndrome Scale, positive/negative scores (Kay et al., 1987). CPZ-Eq: chlorpromazine equivalent (Leucht et al., 2015). FSIQ: Wechsler full scale IQ. BDI: Beck Depression Inventory. Y-MRS: Young Mania Rating Scale. Where applicable, ⟨mean⟩ ± ⟨standard deviation of mean⟩ are specified.

	ASZ N = 15	ABP N = 16	TD N = 14	Statistic	p
Male/female	9/6	10/6	6/8	$\chi^2 = 1.7$	0.49
Age	17.0 ± 1.0	16.8 ± 1.1	16.7 ± 1.9	$F_{2,44} = 0.16$	0.89
Duration	0.9 ± 0.9	1.2 ± 1.3		$\chi^2 = 0.19$	0.65
R/L	15/0	14/2	12/1	$\chi^2 = 1.9$	0.38
+PANSS	21.3 ± 3.0	19.5 ± 6.1		$t_{1,30} = 1.0$	0.32
−PANSS	13.5 ± 5.1	7.5 ± 0.8		$t_{1,30} = 18.5$	<0.001
CPZ-Eq	251 ± 140	172 ± 176		$t_{1,30} = 1.7$	0.2
FSIQ	91.6 ± 13.9	99.3 ± 11.8	113.4 ± 8.5	$F_{2,38} = 9.7$	<0.001
BDI	4.2 ± 1.6	6.4 ± 1.4		$t_{53} = 4.3$	<0.001
Y-MRS	0.4 ± 0.4	1.4 ± 0.8		$t_{53} = 5.3$	<0.001
Medication					
Olanzapine			5		7
Quetiapine			0		2
Risperidone			8		4
Fluoxetine			1		2
Sodium			2		3
Lithium			0		2
Clozapine			2		0
Aripiprazole			1		1

2.2. Roving mismatch negativity paradigm

Sinusoidal tones (duration: 70 ms; 10 ms rise/fall; inter-tone interval: 500 ms) were presented binaurally in trains of length 1 to 11 t (for an illustration see S1; Supplementary materials). The trains differed in sound frequency (500–800 Hz in steps of 50 Hz). Both train length and frequency were pseudo-randomly chosen, but only tone trains of lengths 6 to 11 entered the analysis. The subjects were asked to respond to a visually displayed cross changing grey-scale every 2–5 s by pressing a button while passively attending the tones. The experiment lasted for 15 min. On average, 194 ± 8 tone trains entered the analysis, each providing one standard (=6th tone; STD) and one deviant (=1st tone; DEV) stimulus. The paradigm is same as previously employed (Dima et al., 2012). For further details, the reader is referred to the work by Garrido et al. (2009c).

2.3. Data acquisition

Measurements were performed on the Elekta-Neuromag VectorView™ system at the Oxford Centre for Human Brain Activity. The system provides 204 gradiometer channels that are most sensitive to nearby (cortical) sources, where the local root-mean-square (rms) value calculated over the two channels at each detector site and the global rms value calculated over all channels are measures of the local and global brain activity, respectively. Because of the strength (rms) property of gradiometers, the notions of ERP amplitude and neuronal activity will be used interchangeably in the following wherever possible. The data were pre-processed using signal space separation (Taulu et al., 2004) and standard projection methods to remove ocular and cardiac artefacts (e.g., Gonzalez-Moreno et al., 2014). A small number of trials (<0.5%) were excluded because of other artefacts (muscle tension, sensor jumps, etc.) not amenable to pre-processing.

2.4. Data analysis

All epochs between −100 ms to 700 ms peri-stimulus were classified as either standard (STD) or deviant (DEV). Prior to analysis, the epochs were band-pass filtered between 0.5 and 40 Hz and normalized to pre-stimulus variance.

The epochs were examined using two approaches. First, an analysis of evoked amplitudes using a measure P(t) yielding significance as a function of time. P(t) is a robust measure of the differences between evoked responses in signal space and is calculated as follows. Individually for each channel, a local measure f(t) of the significance of differences between evoked responses across subjects is obtained, where f denotes a paired Wilcoxon test of matched samples applied separately to STD and DEV epochs (within group; denoted w in the following), or a Mann-Whitney U test applied to DEV-STD difference curves (across groups; u). Then, a global measure of significance across subjects is obtained according to

$$\mathrm{P(t)} = \text{probability } (\chi^2) \quad (\chi^2) = -2\sum_{i=1}^{N} \ln[f_1(1)]$$

where N denotes the number of channels, and probability is the significance level of the quantity in brackets (Braeutigam et al., 2004;

Please cite this article as: Braeutigam, S., et al., Dissociable auditory mismatch response and connectivity patterns in adolescents with schizophrenia and adolescents with bipolar di..., Schizophr. Res. (2017), http://dx.doi.org/10.1016/j.schres.2017.07.048