Research Paper

Visual sensory processing deficits in patients with bipolar disorder revealed through high-density electrical mapping

Sherlyn Yeap, MRCPsych; Simon P. Kelly, PhD ; Richard B. Reilly, PhD; Jogin H. Thakore, MD, PhD; John J. Foxe, PhD

Yeap, Kelly, Reilly, Thakore, Foxe — The Cognitive Neurophysiology Laboratory, St. Vincent's Hospital, Richmond Road, Fairview, Dublin, Republic of Ireland; Kelly, Foxe — The Cognitive Neurophysiology Laboratory, Nathan S. Kline Institute for Psychiatric Research, Program in Cognitive Neuroscience and Schizophrenia, Orangeburg, NY; Reilly — School of Engineering and School of Medicine, Trinity College, University of Dublin, Dublin, Republic of Ireland; Foxe — Program in Cognitive Neuroscience, Departments of Psychology and Biology, City College of the City University of New York, New York, NY

Background: Etiological commonalities are apparent between bipolar disorder and schizophrenia. For example, it is becoming clear that both populations show similar electrophysiological deficits in the auditory domain. Recent studies have also shown robust visual sensory processing deficits in patients with schizophrenia using the event-related potential technique, but this has not been formally tested in those with bipolar disorder. Our goal here was to assess whether early visual sensory processing in patients with bipolar disorder, as indexed by decreased amplitude of the P1 component of the visual evoked potential (VEP), would show a similar deficit to that seen in those with schizophrenia. Since the P1 deficit has already been established as an endophenotype in schizophrenia, a finding of commonality between disorders would raise the possibility that it represents a measure of common genetic liability. **Methods:** We visually presented isolated-check stimuli to euthymic patients with a diagnosis of bipolar disorder and age-matched healthy controls within a simple go/no-go task and recorded VEPs using high-density (72-channel) electroencephalography. **Results:** The P1 VEP amplitude was substantially reduced in patients with bipolar disorder, with an effect size of $f = 0.56$ (large according to Cohen's criteria). **Limitations:** Our sample size was relatively small and as such, did not allow for an examination of potential relations between the physiologic measures and clinical measures. **Conclusion:** This reduction in P1 amplitude among patients with bipolar disorder represents a dysfunction in early visual processing that is highly similar to that found repeatedly in patients with schizophrenia and their healthy first-degree relatives. Since the P1 deficit has been related to susceptibility genes for schizophrenia, our results raise the possibility that the deficit may in fact be more broadly related to the development of psychosis and that it merits further investigation as a candidate endophenotype for bipolar disorder.

Introduction

There is mounting evidence that at least partial common genetic liability exists between schizophrenia and bipolar disorder[1–3] and that the 2 disorders may be more closely related than was previously believed. Not only do bipolar disorder and schizophrenia cosegregate in families, there is now evidence that they also share common genetic loci (see Bramon and Sham,[1] Table 1). The borders between these illnesses are increasingly blurred, and current psychiatric nosology, dividing the 2 into entirely separate, categorically distinct entities, may need some reconsideration. With overlapping symptoms, presentations of either disorder can often be challenging for clinicians to differentiate. Establishing both common and separable neurobiological markers is one means by which we can begin to understand the commonalities between these 2 disorders and what distinguishes them.

Efforts along these lines have already established that evoked potential measures of auditory function such as P50 suppression, P300 and prepulse inhibition can potentially be used as endophenotypes in both schizophrenia and bipolar disorder.[4] Although it is increasingly clear that some of these auditory deficits are common in both populations,[5,6] to our knowledge, potential visual dysfunction has yet to be

Correspondence to: Professor J.J. Foxe, Director, Program in Cognitive Neuroscience, Department of Psychology, City College of the City University of New York, 138th St. and Convent Ave., New York, NY 10031; fax 845 398-6545; foxe@nki.rfmh.org

J Psychiatry Neurosci 2009;34(6):459-64.

Submitted Jul. 27, 2008; Revised Sept. 8, 2008; Jul. 7, Aug. 3, 10, 2009; Accepted Aug. 25, 2009.

assessed in patients with bipolar disorder. In a series of studies, our group has employed visual evoked potentials to investigate early sensory processing in patients with schizophrenia, and we have consistently found a reduction in amplitude of the extrastriate-generated P1 component,[7–11] a finding that has been replicated by many others[12,13] (see Yeap and colleagues,[14] Table 1). This deficit is not only found in patients with chronic schizophrenia, but also in their first-degree unaffected relatives,[15] and more recently this deficit was also found in patients with first-episode schizophrenia at the initial onset of psychosis.[16] Its presence in first-degree unaffected relatives in particular suggests that the P1 deficit may serve as a genetic marker for schizophrenia and that it may constitute a risk factor for the development of psychosis. We have also related the P1 deficit to a specific risk haplotype for schizophrenia on the dysbindin gene, which has been associated with increased risk for schizophrenia in numerous independent samples,[17] further underlining its capacity as an endophenotypic marker for the disease.

Given that certain auditory processing deficits have been found to be common across both schizophrenia and bipolar disorder and given the demonstrated power of electrophysiological indices in inferring genetic liability, the question of whether the visual P1 deficit marks a common genetic risk factor for both disorders is one of clear and immediate priority. A logical first step is to determine whether the visual P1 deficit is present in patients with diagnoses of bipolar disorder. We address this directly in the present study by employing the same paradigm and methods in a group of patients with bipolar disorder as those used in our previous studies of patients with schizophrenia and their relatives.

Methods

Participants

Our study population included patients from St. Vincent's Psychiatric Hospital in Fairview, Dublin, Ireland, who met DSM-IV criteria for bipolar disorder. We used the Young Mania Rating Scale[18] and the Hamilton Depression Rating Scale[19] to assess the level of severity of their current illnesses. We recruited controls from the local community and hospital staff, and they were paid for volunteering. We assessed handedness in both groups using the Edinburgh Handedness Inventory.[20] Controls self-reported any psychiatric illness or symptoms as well as medication use based on criteria from the nonpatient version of the Structured Clinical Interview for DSM-III-R.[21] The ethics committee at St. Vincent's Hospital approved all procedures, and all participants provided written informed consent after the details of the study were fully explained to them and before participating in the study.

Stimuli and experimental design

In each experimental block, we presented participants with about 100 isolated-check images (grey on a white background, 4° × 4° visual angle, 64% contrast) and 40 line drawings of 2 kinds of animals (on a white background, 2.4° × 1.8°). The line drawings of the animals were interleaved between the check images. We chose a different animal pair for each block from a possible 22 animals. On average, participants completed 13.5 (10–15) blocks, each lasting 3 minutes. We presented stimuli centrally on a cathode ray tube computer monitor in random order, with the monitor located 160 cm directly in front of the seated participant.

The timing of stimulus presentation was such that each image appeared for 60 ms with a variable interstimulus interval between 740 and 1540 ms (randomly in steps of 200 ms) during which there was a blank white screen. The target animal was displayed at the start of the task, and we asked participants to respond each time this animal was presented by pressing a button with their right thumb. We asked them to respond only to target animals and to withhold responses to any other animal presented. The target and nontarget animals appeared with equal probability, ensuring that an observer could not rely on the exogenous alerting nature of any noncheck stimulus. Furthermore, we made the task of discrimination difficult by pairing similar-looking animals (e.g., a hippopotamus and an elephant; Fig. 1). The use of this task ensured that participants were actively observing the stimuli. We analyzed only event-related potentials to the standard check stimuli.

Electrophysiological recording and analysis

We acquired continuous electroencephalographic (EEG) data through the ActiveTwo Biosemi (Biosemi) electrode system from 72 scalp electrodes, digitized at 512 Hz with an open pass-band from direct current to 150 Hz. We filtered data with a 0-phase shift 45 Hz low-pass filter (24 dB/octave) and re-referenced them to the nasion after acquisition. No high-pass filter was applied.

We analyzed the data using Brain Electric Source Analysis version 5.08 software (www.besa.de). Using a time-window from 200 ms prestimulus to 500 ms poststimulus, we extracted epochs and baseline-corrected them relative to the interval –80 to 20 milliseconds. Then we subjected epochs to an artifact

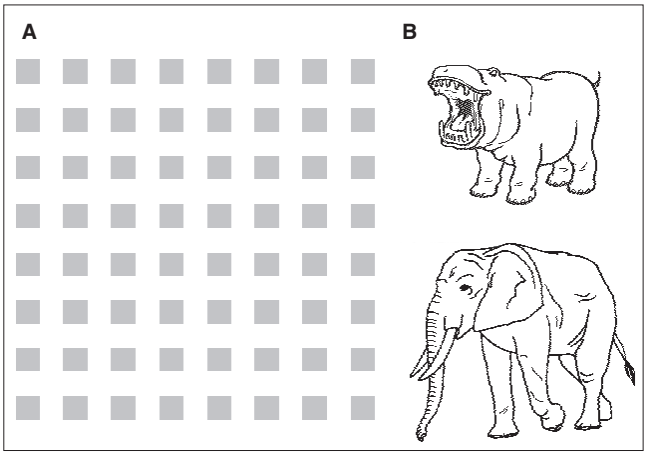

Fig. 1: The centrally presented visual stimuli used in the task. (**A**) We derived event-related potential waveforms for the isolated-check nontarget stimulus, (**B**) whereas target discrimination was based on infrequently presented animal line drawings.

criterion of ±120 μV applied across all channels to reject trials with excessive electromyography or other noise transients. We also visually inspected the vertical and horizontal electrooculograms for blinks and large eye movements. Accepted trials were averaged for the isolated check stimuli only.

As our primary dependent measure, guided by our previous work in schizophrenia populations, we defined an estimate of P1 amplitude as the area under the curve (v. the 0 μV baseline) in the interval 80–100 ms, spanning the P1 component and chosen based on grand average waveforms collapsed across groups. We then submitted these integrated amplitude measures to a mixed-design analysis of variance (ANOVA) using SPSS software (SPSS Inc.) with the between-subject factor of group (patients v. controls) and within-subject factors of region (left, midline, right) and electrode (O1, PO7, PO3; Oz, POz, Pz; O2, PO4, PO8). These regions covered the left lateral occipital, midline dorsal and right lateral occipital visual scalp regions, respectively.

Following our primary analysis of P1 amplitude, it was of interest to further investigate spatiotemporal properties of any potential differences among groups using the statistical cluster plot method. This procedure has been used effectively in post-hoc analyses to fully explore complex data sets and generate pointed follow-up hypotheses.[22] Point-wise 2-tailed *t* tests (here between controls and patients with bipolar disorder) are calculated at each time point for all electrodes, and a colour map is subsequently generated marking time points on each electrode for which the *t* value exceeds that corresponding to a *p* value of 0.05. Here we plot positive and negative *t* values in separate colour scales (green and gold), to distinguish differences in opposite directions. All nonsignificant points are represented as white.

Results

Participants

Our sample included 12 patients with bipolar disorder (6 women and 6 men) aged 19 to 63 years (mean 47.8, standard deviation [SD] 12.0 yr). All 12 patients met DSM-IV criteria for bipolar disorder, and all but 2 were outpatients. Also, all 12 patients were in remission and euthymic at the time of testing. The patients' demographic and clinical characteristics are outlined in Table 1. All patients were medicated, with medications comprising combinations of mood stabilizers and typical and atypical antipsychotics. Note that we have repeatedly found no correlation between the P1 measure and antipsychotic dose in studies where our samples were large enough to adequately assess this issue.[8,14] The control group comprised 12 paid volunteers (5 women and 7 men) aged 21–64 years, (mean 46.0, SD 12.7 yr). The mean age of patients and controls did not differ significantly ($p = 0.72$). All but 2 participants from each group were right-handed, as assessed using the Edinburgh Handedness Inventory.[20] All participants reported normal or corrected-to-normal vision. Controls were medication-free and free of any psychiatric illness or symptoms and reported no history of alcohol or substance abuse and no family history of psychiatric disorders. Regarding the EEG data, patients and controls did not differ significantly ($p = 0.42$) in terms of hit rate (mean percentage of correct responses 91.1%, SD 7.7% among patients v. 94.2%, SD 10.4% among controls).

Our results show the P1 peak latency occurring between 80 and 100 ms, as is entirely typical for stimulation of this type (Fig. 2A). An ANOVA (2 groups × 3 regions × 3 electrodes) on P1 amplitude showed a significant main effect of group ($F_{1,22} = 7.25$, $p = 0.010$), driven by the fact that the amplitude of the P1 was significantly smaller in patients with bipolar disorder. There was also a main effect of region ($F_{2,44} = 26.36$, $p = 0.010$) but no interaction of group with region. The main effect of region simply indicates that the P1 was of greater amplitude over the lateral regions than over the central region, and the lack of a region × group interaction indicates that there was no difference in topographies between groups. There was no main effect of electrode ($F_{2,44} = 1.28$, $p = 0.28$), nor was there a group × electrode interaction ($F_{2,44} = 0.65$, $p = 0.49$). Using results from this ANOVA, we calculated an effect size of $f = 0.54$ for the main effect of group, which is a large effect size (i.e., > 0.35) according to Cohen's criterion.[23] In keeping with previous studies in patients with schizophrenia,[14–16] we observed the distribution of the P1 component to be bilateral over the parieto-occipital scalp (Fig. 2B). The statistical cluster map (Fig. 2C) illustrates the group difference at posterior electrode sites within the time range of the P1. Differences between groups are also evident during the N1 processing period (about 150 ms) and during a later positive component occurring at about 300 ms. As the focus of the present study was on the P1 component, these latter effects will not be further discussed here but may be the subject of future investigations.

Discussion

In this study, we found that the amplitude of the P1 component of the visual evoked potential was significantly reduced

Table 1: Characteristics of outpatients of St. Vincent's Psychiatric Hospital, Dublin, Ireland, with bipolar disorder

Patient no.	Sex	Age, yr	Test score		Bipolar I or II	Age at onset, yr	Duration, yr	No. admissions*
			YMRS	HAMD				
1	M	57	3	3	I	14	43	> 20
2†	M	33	0	0	II	13	20	1
3	M	53	5	5	I	33	20	1
4	M	49	14	4	I	26	23	> 20
5	M	59	3	8	I	30	29	4
6	M	43	2	6	I	21	23	10
7	F	53	6	3	I	16	37	> 20
8†	F	46	0	2	II	18	28	3
9†	F	19	9	2	II	17	2	1
10	F	63	0	0	I	18	45	5
11	F	49	2	10	I	15.5	33.5	1
12	F	50	0	1	I	14	36	> 20
Average		47.8	3.7	3.7	I = 9 II = 3	19.6	28.3	

F = female; HAMD = Hamilton Depression Rating Scale;[19] M = male; YMRS = Young Mania Rating Scale.[18]
*Number of acute admissions, not necessarily of a psychotic nature.
†Denotes patients who have never had any psychotic episodes.

in patients with bipolar disorder. This amplitude reduction was highly similar to deficits that we have previously described in patients with schizophrenia using an identical paradigm,[15] which suggests that visual sensory processing deficits are common to both conditions. Since a weight of evidence suggests that the P1 deficit is endophenotypic for schizophrenia, it will be important in future investigations to establish whether this marker of visual dysfunction indexes shared genetic liability between schizophrenia and bipolar disorder.

These findings for visual processing build on work by other groups in auditory sensory processing that has demonstrated common deficits in a number of auditory evoked potential components known to be endophenotypic for schizophrenia. For example, significantly diminished auditory P50 sensory gating[24] and latency prolongation and amplitude reduction of the auditory evoked P300[25] have been reported, suggesting a disturbance of the temporoparietal generators of these components in patients with bipolar disorder similar to that typically seen in those with schizophrenia. Delayed auditory P300 latency has also been found in euthymic patients with bipolar disorder,[26] and it has been shown that unaffected relatives of such patients also exhibit significantly delayed P300 latency — though not amplitude deficits — over the central parietal scalp.[27] In contrast, however, abnormal mismatch negativity (MMN) generation, a highly robust finding in patients with chronic schizophrenia, does not appear to be present in patients with bipolar disorder.[28] Although this latter finding might appear to cast doubt on the extent of overlap between these 2 disorders in terms of their underlying neurophysiology, these results are actually quite consistent with some recent findings regarding the endophenotype of MMN in patients with schizophrenia.[29,30] Magno and colleagues[29] showed that although chronic schizophrenia patients did indeed show MMN deficits, as had been found by many others previously,[31,32] their first-degree biological relatives showed no such deficit, nor did a group of first-episode patients. Other groups[33–35] also found no evidence of MMN impairment in first-episode patients. Taken together, the implication of these studies is that the greatest part of the MMN deficit in patients with schizophrenia results from the active expression of the disease state itself rather than the underlying genetic risk for the disorder. As such, it is perhaps not surprising that MMN does not appear to be affected in patients with bipolar disorder.

Increasingly, evidence from family[36] and twin studies[37] suggests that a strong overlap exists in familial susceptibility to schizophrenia and bipolar disorder. The heritability of the 2 disorders is not only significant, but also strikingly similar.[1] Nonetheless, despite the evidence for similar patterns of brain electrophysiology, there is also clear evidence that

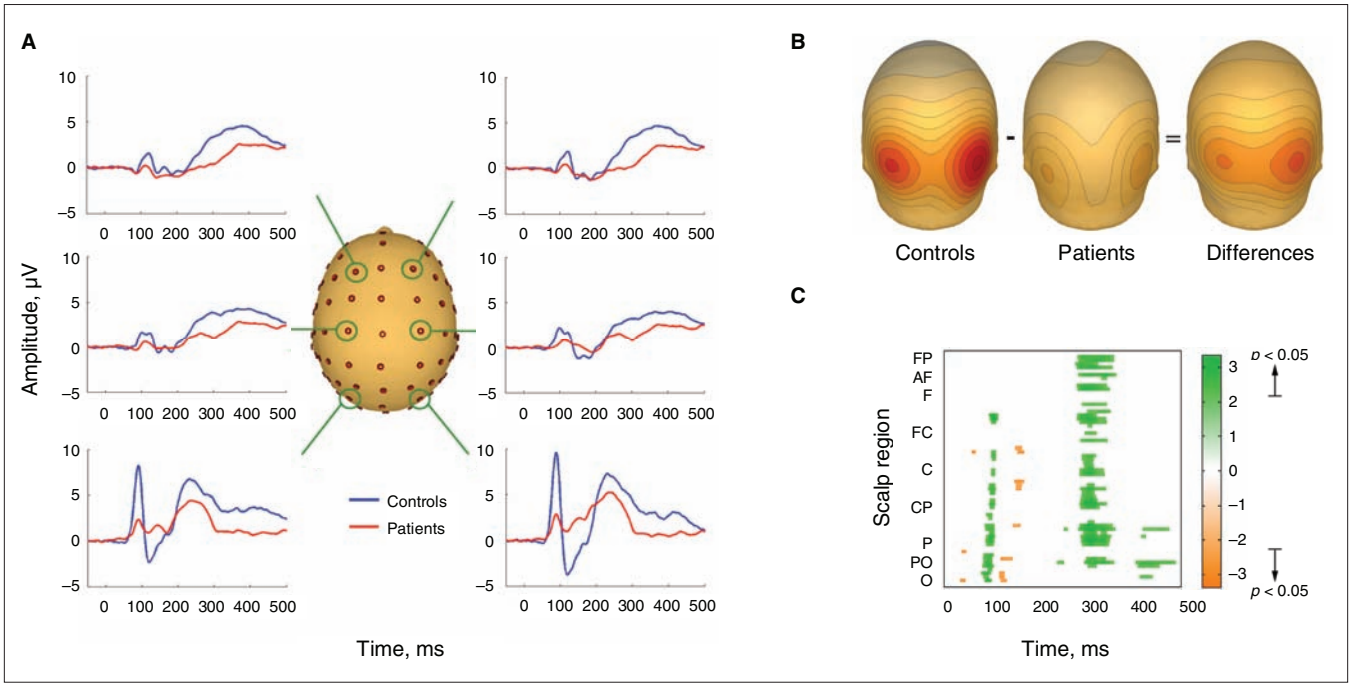

Fig. 2: (**A**) An overview of the event-related potential waveforms across the scalp with 6 representative channels over the time interval of –100 ms to 500 ms. The P1 component (about 90 ms) is strongest over the posterior sites where contrasting responses to the isolated-check stimuli are best observed for the 2 groups. (**B**) Topographic maps showing the voltage distribution on the scalp at 90 ms. There is a bilateral parieto-occipital distribution of the P1 amplitude evident in both the bipolar and control groups. A difference map is plotted in the right panel. (**C**) A statistical cluster plot is shown to illustrate all time points and scalp sites at which the event-related potential differed significantly between groups on the basis of 2-tailed *t* tests at an α level of 0.05. White denotes nonsignificance. Positive *t* values are displayed in green and negative *t* values are displayed in gold. The 72-channel electrode array is arranged on this plot with the most posterior electrodes displayed at the bottom and the most anterior at the top. This leads to the following progression: occipital (O), parieto-occipital (PO), parietal (P), centroparietal (CP), central (C), frontocentral (FC), frontal (F) and anteriofrontal (AF).

important distinctions exist between the 2 psychotic illnesses. For example, magnetic resonance imaging studies have confirmed brain volumetric changes in patients with schizophrenia but not in those with bipolar disorder; only those with schizophrenia showed increased lateral and third ventricles and reduced hippocampus volumes.[38] Again, the question may be raised whether these differences are more attributable to disease progression as opposed to shared genetic liability. Salisbury and colleagues[6] found a unilateral abnormality in the P300 in the left temporal lobe in patients with schizophrenia, whereas their patients with bipolar disorder showed more anterior frontal abnormalities. Other (potential) endophenotypic measures like the auditory P50 ratios and the frequency of leading saccades during smooth pursuit eye movements have been used to good effect to distinguish between patients with schizophrenia and those with bipolar disorder.[2]

In summary, our study provides evidence that a commonly observed visual processing deficit in patients with schizophrenia is also apparent in patients with bipolar disorder. That this deficit has been shown to be endophenotypic for schizophrenia highlights the possibility that its presence in patients with bipolar disorder may result from shared underlying genetic liability for psychotic disorders. It is provocative that this deficit has been linked to a specific risk haplotype for schizophrenia on the dysbindin gene,[17] since a number of recent studies now point to an association between specific dysbindin gene variants and bipolar disorder.[39–41] An obvious next step will be to test for this deficit in healthy first-degree biological relatives of patients with bipolar disorder to confirm whether the visual P1 deficit also represents an endophenotype for this disorder.

Acknowledgements: This work was supported in part by a grant from the National Institute of Mental Health (MH65350) to Professor John Foxe. Dr. Yeap was supported by a fellowship from the Irish Health Research Board. The authors thank the Chief Executive Officer at St. Vincent's Hospital, Mr. Edward Byrne and the Director of Nursing, Mrs. Phil Burke, for their support of the Cognitive Neurophysiology Laboratory (CNL). Thanks also to Mícheál Mac an tSionnaigh and Máire Nic an tSionnaigh for their essential help in establishing and maintaining the CNL facilities at St. Vincent's.

Competing interests: None declared for Drs. Kelly, Thakore and Foxe. Dr. Yeap has received speaker fees and travel assistance from the Irish Health Research Board. Dr. Reilly has received travel assistance from Unilever.

Contributors: Dr. Foxe designed the study. Drs. Yeap and Thakore acquired the data, which Drs. Yeap, Kelly, Reilly and Foxe analyzed. Drs. Yeap, Kelly and Foxe wrote the article, which all authors reviewed and approved for publication.

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