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ORIGINAL PAPER

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Visual sensory processing deficits in Schizophrenia and their relationship to disease state

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Abstract *Context* Visual Evoked Potential (VEP) abnormalities have been a fairly consistent finding in patients with schizophrenia, and it has been suggested that electrophysiological markers of early sensory processing may be useful as trait markers for the illness, and for development as potential diagnostic measures. *Objective* Clear amplitude reductions in the occipital P1 component of the VEP (~100 ms), have been repeatedly demonstrated in patients with schizophrenia. Here, we investigated whether the extent of this deficit was related to age, clinical symptoms, medication status and length of illness, in a large cohort of ethnically homogenous patients. *Design, setting and participants* VEP responses to simple isolated-check stimuli were examined in 52 DSM-IV diagnosed patients with schizophrenia, and compared with responses from 26 healthy age-matched control subjects. Using high-density electrical scalp recordings, we assessed the integrity of the visual P1 component across the two groups. This study was conducted at St.Vincent's Psychiatric Hospital in Fairview, Dublin, Ireland. *Results* Substantially reduced P1 amplitude was demonstrated in the patient group compared to controls. The deficit was not linked to age, length of illness or medication status. A small positive correlation, accounting for about 11% of the variance, was found between P1 amplitude and clinical symptoms scales (BPRS and SANS). In addition, we found that a slightly later (~110 ms) fronto-central component was relatively increased in the patient group, and was inversely correlated with the occipital P1 amplitude in the patients, but not in the healthy control subjects. *Conclusions* Our findings clearly demonstrate a deficit in early visual processing in patients with schizophrenia (with a large effect size; Cohen's $d = 0.7$) that is unrelated to chronicity. The results are consistent with recent findings showing that the P1 deficit is endophenotypic of the disorder and related to genetic risk factors rather than the disease process itself.

Key words visual-evoked potential · VEP · ERP · P1 deficit · schizophrenia · Ireland · hyperfrontality

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Introduction

The P1 component of the VEP, with a peak latency typically varying between 75 and 110 ms, is considered an index of early visual sensory processing [50]. It is topographically distributed over the midline and lateral occipital scalp regions, and is widely considered to arise from extrastriate visual areas [25, 44]. The P1 is robustly observable across individuals and easily and quickly measured non-invasively in just a

matter of minutes [38]. Because it reflects relatively automatic basic sensory processing, the P1 can be measured during a wide variety of tasks, and is not susceptible to motivational issues. It has consistently been described in patients with schizophrenia and, in the vast majority of cases, the amplitude of the P1 in patients has been found to be less than half the strength seen in healthy control subjects. More recently, a similar deficit has been demonstrated in non-psychotic first-degree relatives (see Table 1B).

An association between the reduced P1 amplitude and impairment in the magnocellular (M) pathway has also been drawn [8, 10, 24] and evidence from behavioural studies has also pointed to impairments in this system [35, 58]. The M pathway is the part of the visual system responsible for the rapid conduction of low-resolution visual information to the cortex and is involved in processing of overall stimulus organization [47, 63, 67]. Looking at the underlying processes involved in generating the deficit allows better understanding of the mechanisms of early stage visual processing and their putative relationship to subsequent higher-order cognitive processes in schizophrenia.

There are, to our knowledge, a total of twenty-six studies to date that have recorded the visual P1 in chronic patients with schizophrenia (see Table 1A). A large majority of these studies have also shown P1 deficits although eight of the twenty-six did not. The finding of the P1 deficit has been most consistent in our group of studies in chronic patients in New York [8–10, 22, 24, 27, 57] although more recently, a number of other groups have shown similar deficits [16, 28, 59]. However, only a few of these studies have examined the relationship between these early processing deficits and disease state. The present study uses the technique of high-density electrical mapping to record the visual evoked potential (VEP) in a large Irish cohort of patients with chronic schizophrenia ($N = 52$). Our main goal here was to record from a large enough sample to test for correlations of the P1 component with variables such as age, length of illness, medication and symptom scales. This study was carried out in Ireland, which has the advantage of a relatively homogeneous population compared with other countries in Europe.

In this study, we defined length of illness as the date of first presentation to the psychiatric services until the time of testing. This was standardised for all the patients via detailed examination of existing medical records. This measure does not, of course, take into account the duration of untreated psychosis (DUP) [15, 16], which is defined as the time from manifestation of the first psychotic symptoms to ini-

Table 1 Studies investigating the P1 deficit in (A) patients with schizophrenia and (B) unaffected first-degree relatives

Authors	Journal	Year	Patients	Controls	P1 deficit found
(A)					
Mukundan	Biol Psychiatry	Sep-1986	29	29	✔
Romani et al.	Acta Psychiatr Scand	May-1986	18	35	✔
Matsuoka et al.	Electroencep Clin Neurophys	Jan-1996	15	15	✔
Basinska et al.	Acta Neurobiol Exp (Wars)	Nov-1998	50	50	✔
Foxe et al.	Neuroreport	Dec-2001	14	16	✔
Doniger et al.	ArchGen Psych	Nov-2002	16	16	✔
Spencer et al.	J Neurosci	Aug-2003	12	12	✔
Schecter et al.	Schizophr Res	Nov-2003	20	18	✔
Clementz et al.	Cognitive Brain Res	Jan-2004	12	12	✔
Spencer et al.	Proc Natl Acad Sci U S A	Dec-2006	20	20	✔
Butler et al.	Arch Gen Psych	May-2005	33	21	✔
Kim et al.	Schizophr Res	Jul-2005	26	22	✔
Schecter et al.	Clin Neurophysiol	Sep-2005	74	59	✔
Foxe et al.	Cereb Cortex	Dec-2005	16	17	✔
Butler et al.	Brain	Sep-2006	23	19	✔
Yeap et al.	Arch Gen Psych	Nov-2006	15	26	✔
Haenschel et al.	Arch Gen Psych	Nov-2007	12	12	✔
Lalor EC et al.	Schizophr Res	Jan-2008	13	11	✔
Strandburg et al.	Psychophysiology	May-1994	18	19	×
Katsanis et al.	Psychophysiology	May-1996	43	113	×
Van Sweden et al.	Acta Neurol Belg	Mar-1998	38	NA	×
Bruder et al.	J Abnorm Psychol	Aug-1998	28	28	×
Alain et al.	Biol Psychiatry	Dec-1998	15	15	×
van der Stelt et al.	Archives of Gen Psych	Mar-2004	22	22	×
Johnston et al.	Eur J Nuerosci	Sep-2005	11	15	×
Sponheim et al.	Biol Psychiatry	Aug-2006	23	23	×

Authors	Journal	Year	Relatives	Controls	P1 deficit found
(B)					
Katsanis et al	Psychophysiology	May-1996	50	113	×
Sponheim et al	Biol Psychiatry	Aug-2006	28	23	×
Yeap et al	Arch Gen Psych	Nov-2006	25	26	✔

tiation of adequate treatment. Adequate treatment is defined as the taking of antipsychotic medication for a period of 1 month or until significant response was achieved or whichever came first [43]. It is worth noting here that DUP measures are notoriously difficult to obtain and standardise and it was simply not possible to include accurate estimates of this measure in our calculations.

With few studies actually correlating VEP measures to symptom and functional outcome scales [17, 57], we also sought to examine the relationship between the P1 deficit and clinical features of schizophrenia as measured by the brief psychiatric rating scale (BPRS) [52] and the scale for the assessment of negative symptoms (SANS) [2].

Materials and methods

Subjects

Written informed consent was obtained from 52 (17 female) patients with schizophrenia, aged 19–64 years (mean ± SD = 41.8 ± 12.8 years), from the St. Vincent's Hospital Catchment Area, Dublin, Ireland. All procedures were conducted in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. All patients were of white Caucasian Celtic extraction. All patients met DSM-IV criteria for schizophrenia. The mean ± SD score in the BPRS [52] and the scale of assessment of negative symptoms (SANS) [2] were 37.84 ± 9.81 and 38.26 ± 26.02, respectively. The mean ± SD chlorpromazine dose was 410 ± 331 mg/day and medications comprised of typical and atypical antipsychotics. The mean ± SD length of illness was 14.4 ± 9.5 years. Control subjects comprised 26 (13 female) paid volunteers aged 21–64 years, (mean ± SD = 38.7 ± 12.6 years) recruited from the St. Vincent's Hospital Staff Community and the local hospital catchment area. The mean age of patients and controls did not differ significantly [$t(75) = 1.38$, $P = 0.37$]. Forty-four of the 52 patients and 21 of the 26 controls were right-handed as assessed by the Edinburgh Handedness Inventory [51]. All subjects reported normal or corrected-to-normal vision. Controls were medication-free and free of any psychiatric illness or symptoms by self-report using criteria from the SCID-NP [61] and reported no history of alcohol or substance abuse. All procedures were approved by the St. Vincent's Hospital Ethics Committee.

Stimuli and task

In each experimental block, subjects were presented with around 100 isolated check images, grey on a white background (4° × 4° visual angle) at 64% contrast, and 40 line drawings of 2 kinds of animal (2.4° wide × 1.8° high) on a white background [69]. Each block contained a different animal pair from a possible 22. The 64% contrast condition was chosen to stimulate both the magnocellular (M) and parvocellular (P) systems. On average, subjects completed 13.5 (10–15) blocks, each lasting 3 min. Stimuli were presented centrally on a CRT computer monitor in random order with the monitor located 160 cm directly in front of the seated subjects.

The timing of the presentations was such that each image appeared for 60 ms with a variable inter-stimulus interval (ISI) 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 the subjects were asked to respond each time this animal was presented by pressing a button with their right thumbs. They were told only to respond to target animals and to try to withhold responses to any other animal presented. The target and non-target animals were presented with equal probability, ensuring that a subject could not rely on the exogenous alerting nature of any non-checkerboard stimulus to respond. Furthermore, the task of discrimination was made difficult by pairing similar-looking animals, e.g. a dolphin and a whale. The primary motivation for using this task rather than simply having subjects passively observe the standard stimuli was to ensure that subjects remained alert and fixated centrally on the screen throughout recording. Only ERPs to the standard check stimuli were included in the analysis.

Data acquisition and statistical analysis

Continuous electroencephalogram (EEG) data were acquired through the ActiveTwo Biosemi electrode system (BioSemi, Amsterdam, the Netherlands) from 72 scalp electrodes, digitised at 512 Hz with an open pass-band from DC to 150 Hz. For analysis and display purposes, data were subsequently filtered with a 45 Hz low-pass filter (24 dB/octave; zero phase shift) after acquisition. All data were re-referenced to the nasion after acquisition for analysis.

Data were analyzed using BESA Version 5.08 (Brain Electric Source Analysis, Gräfelfing, Germany). All electrode channels were subjected to an artifact rejection criterion of ±120 μV from −200 to 500 ms to reject trials with excessive electromyogram (EMG) or other noise transients. The vertical and horizontal electro-oculograms were also visually inspected for blinks and large eye movements. Epochs were extracted with a time-window from 200 ms pre-stimulus to 500 ms post-stimulus, and baseline-corrected relative to the interval −80–0 ms. Accepted trials were then averaged for the isolated-check stimuli only. The mean ± SD epoch acceptance rate for patients was 62.2 ± 12.7% and for the control group it was 63.4 ± 16.8%. The average numbers of accepted trials were 678 for patients and 992 for controls.

A measure of P1 amplitude was defined as the area under the curve (relative to the 0 μV baseline) in the interval 87–97 ms, spanning the P1 component, chosen based on grand average waveforms. These area measures were then submitted to a repeated-measures analysis of variance (ANOVA) with the between-subjects factor of group (patients vs. controls) and within-subjects factors of region (left/midline/right) and electrode (O1/PO7/PO3, Oz/POz/Pz, O2/PO4/PO8), covering the left lateral occipital, midline dorsal and right lateral occipital visual scalp regions respectively. All tests were two-tailed with a preset α-level of $P < 0.05$. Protected follow-up tests were conducted where appropriate.

To investigate whether P1 amplitude varies as a function of age, length of illness, medication status or clinical symptomatology, we conducted Pearson correlations using the data of the patient group only. In these analyses, the P1 was measured from the electrode showing the largest difference between groups, and hence the largest deficit. In this case, it was electrode site PO4.

Following our primary analysis of P1 amplitude, it was of interest to further investigate spatio-temporal properties of any potential differences between groups, using the statistical cluster plot method. This procedure has been used effectively in post-hoc analyses as a means to fully explore complex datasets and generate pointed follow-up hypotheses [48, 68]. Point-wise two tailed t-tests between patients and controls 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 0.05 P value. 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

The mean ± SD target hit rate (the percentage of correct responses) for the patients was 83.2 ± 16.4% and 95.4 ± 7.6% for the controls ($t(76) = 4.46$, $P < 0.001$). The reason for measuring the target hit

rate was to ensure that patients were focusing their attention on the screen. There was also a difference in the percentage of false alarms (i.e. pressing for the non-target animals) where patients scores were 20.3 ± 20.5% versus 6.4 ± 4.5% for controls ($t(76) = 4.73$, $P < 0.001$).

Figure 1 shows the ERP traces plotted for 6 selected electrodes across the scalp for both groups. As is typical, the P1 peak latency occurred around 90 ms, with a bilateral topography over the posterior lateral-occipital scalp.

An omnibus ANOVA (2 groups × 3 regions × 3 electrodes) was used to compare the P1 amplitudes between both groups over the left lateral occipital, midline dorsal and right lateral occipital areas. The results showed a significant main effect of group [$F(1,76) = 6.02$, $P < 0.02$] indicating reduced P1 amplitude in the patient group compared to the controls. There were also significant effects of region [$F(2,76) = 31.63$, $P < 0.001$], electrode [$F(2,76) = 21.71$, $P < 0.001$] and a region × electrode interaction [$F(2,76) = 12.68$, $P < 0.001$], reflecting the topographic specificity of the P1. The interactions of region × group [$F(1,152) = 3.16$, $P < 0.05$] and region × electrode × group [$F(4,304) = 3.24$, $P < 0.02$] were also significant, pointing to significant topographic differences in the distribution of the P1 between groups.

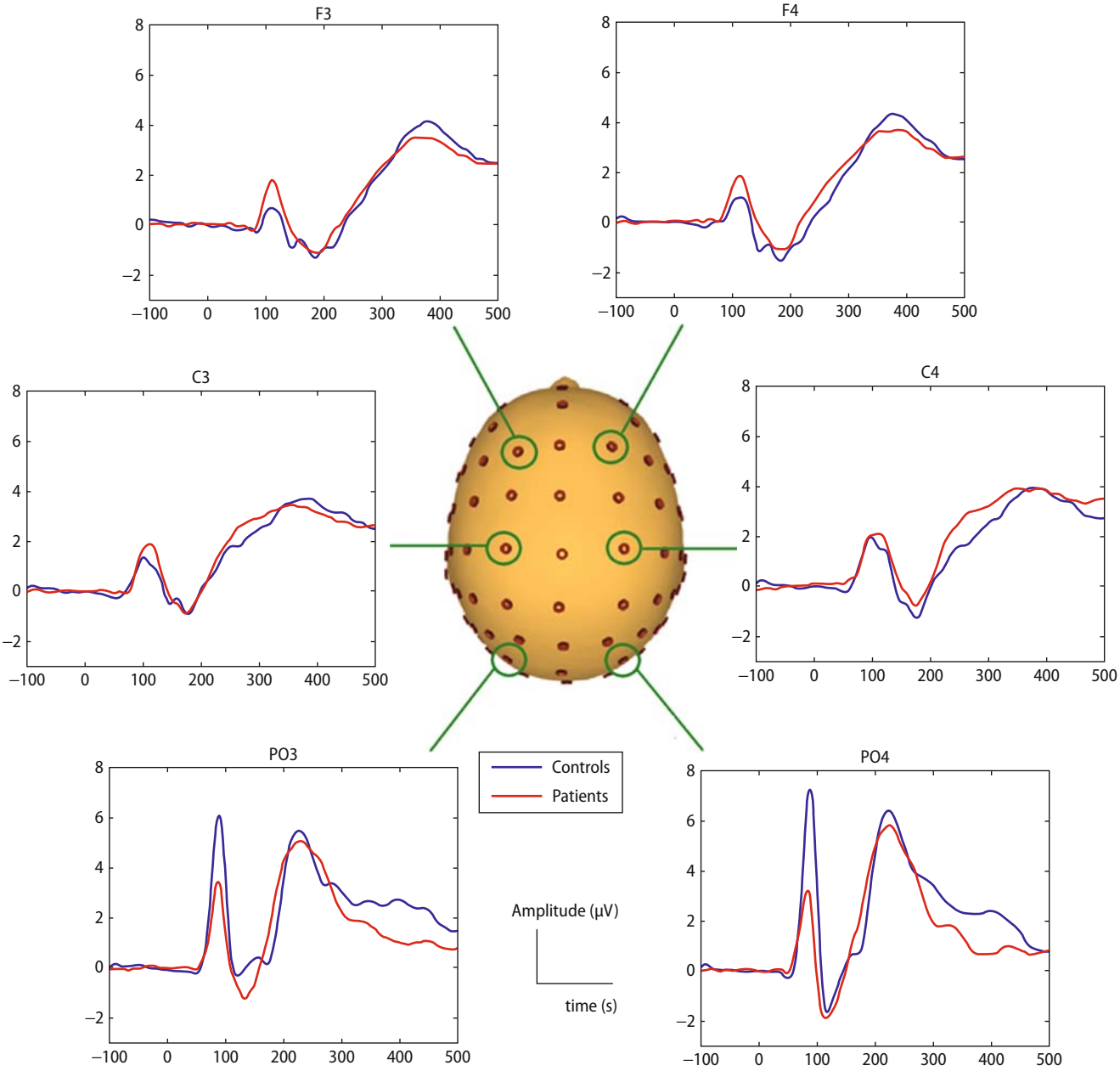
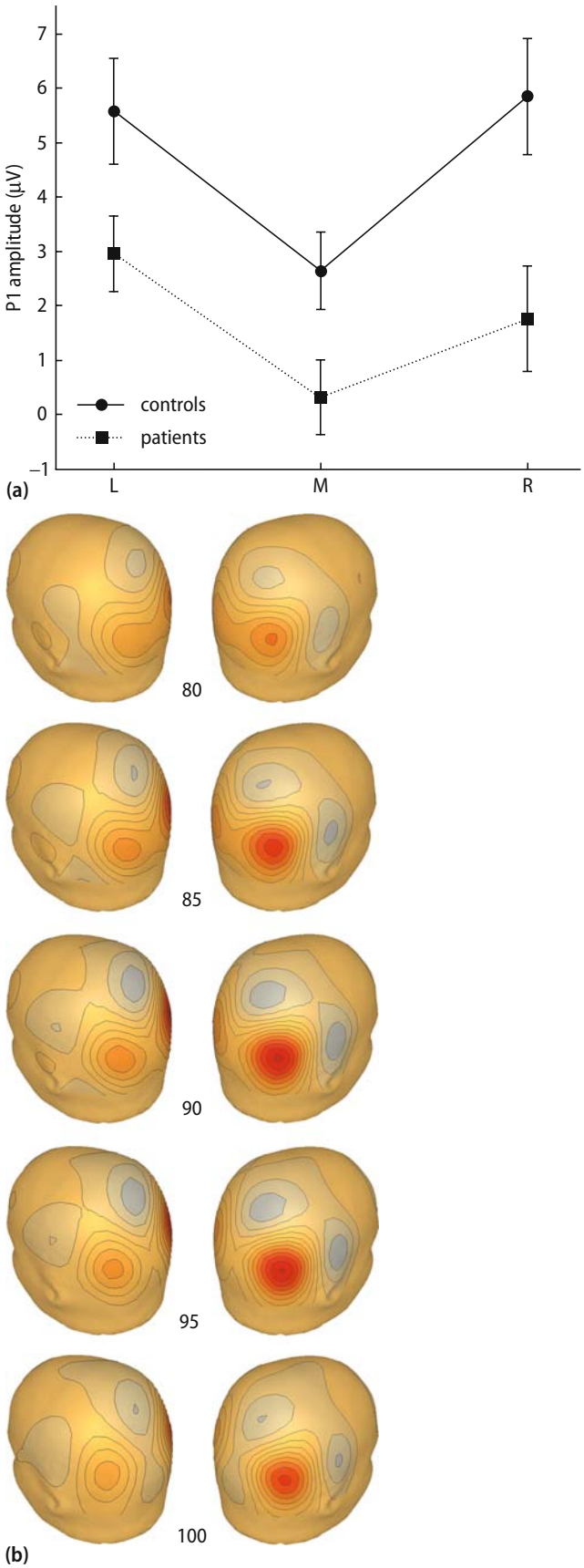


Fig. 1 Grand-average ERP traces at six selected electrodes across the scalp for the control and patient groups



◀ **Fig. 2** **a** P1 amplitude as a function of region (left hemisphere, midline and right hemisphere respectively), illustrating group × region interactions. **b** Current Source Density (CSD) difference topographies (controls minus patients) over the time frame of the P1 (80–100 ms). The deficit is clearly greater over the right hemisphere, with both dorsal and ventral projections. CSD mapping, as implemented in BESA [53], calculates the second spatial derivative of the scalp field potential, thus eliminating tangential current flow. This provides improved visualization of approximate locations of intracranial generators

Protected 2 × 2 ANOVAs were carried out to further explore the topography of this group effect, comparing each pairing of scalp regions in their turn, with data collapsed across electrodes. A marginal group × region interaction was found comparing the left and right hemisphere regions ($F(1,76) = 3.22$, $P = 0.08$). A significant interaction was found comparing the right and midline regions ($F(1,76) = 4.38$, $P = 0.04$), and no interaction comparing left to midline ($F(1,76) = 0.27$, $P = 0.61$). The underlying pattern is illustrated in Fig. 2. Somewhat in contrast to previous studies where a midline focus for the relative reduction in P1 in patients was found [22, 24, 27], here the group effect appears greatest over right hemisphere sites. The current source density (CSD) difference topographies of Fig. 2b demonstrate the stability of the right-hemisphere laterality of the deficit over time.

Figure 3 shows the distribution of P1 amplitude for all patients (each marked with an 'x') and controls (each marked with a '+') at the right hemisphere parieto-occipital scalp site PO4, where the P1 amplitude difference was maximal. The mean values are

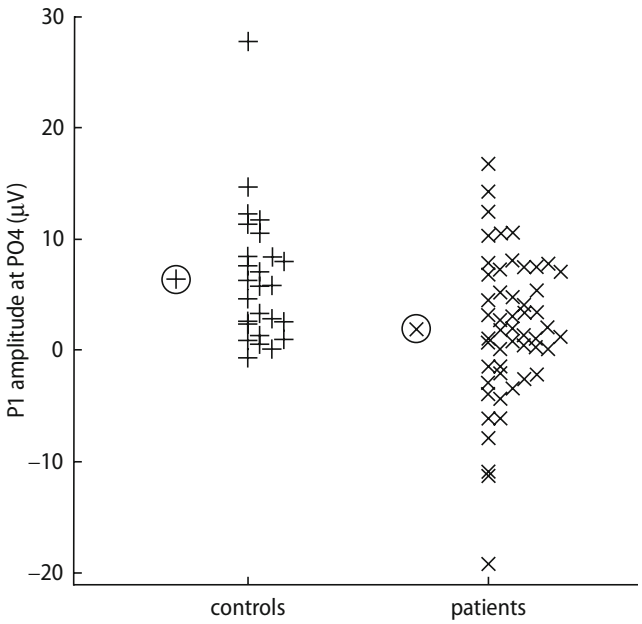


Fig. 3 Scatter Plot showing the distribution of P1 amplitudes in the controls (+) and the patients (x) with the mean values circled to the left of each distribution

shown to the left of the individual values. There is considerable overlap between the patient and control group distributions, with standard deviations for the controls and the patients at 6.07 and 6.61, respectively. The effect size was found to be 0.70 at this electrode, which is large according to Cohen's criterion [18].

There was no significant correlation between age and the P1 in patients ($r = 0.21$, $P = 0.14$) (see Fig. 4a). There was a significant positive correlation between the P1 amplitude and negative symptoms (SANS) ($r = 0.34$, $P = 0.03$) (see Fig. 4e) as well as the BPRS ($r = 0.34$, $P = 0.03$) (see Fig. 4d). Further, P1 amplitude was not correlated with either length of illness ($r = -0.03$, $P = 0.86$) or medication status ($r = 0.05$, $P = 0.75$) (Fig. 4b, c).

Figure 5 is the *statistical cluster plot* illustrating a posterior cluster in the time range of the P1, reflecting the group differences as reported in the ANOVA. Immediately following the P1 component, an increased positive activation was observed over frontal scalp in patients (see Fig. 1)[1]. This may reflect increased recruitment of frontal brain regions similar to that found in recent studies [22, 27], albeit in an earlier time interval. "Hyperfrontality" in patients has been postulated to represent additional processing carried out in compensation for sensory deficits [27]. If this is indeed the case, then one might expect to find greater frontal activity in those patients exhibiting more deficient P1 amplitudes. To test whether the amplitude of the frontal positivity (here named 'P1f') in patients depends on the amplitude of the preceding posterior P1, a post-hoc correlation analysis was carried out. P1f was measured as the average amplitude in the interval 105–120 ms at fronto-central electrode site FCz where the increased activity relative to controls was maximal. As the full extent of these components may overlap both temporally and spatially, we controlled for biases arising from the choice of reference electrode by transforming the data to average-reference for this analysis. A significant negative correlation was found for the patient group ($r = -0.42$; $P = 0.002$) (Fig. 6a). As the frontal positivity is temporally coincident with the posterior N1 component, it might be argued that it reflects the same process, manifesting more faintly and with opposite polarity over frontal scalp. However, group differences are only observed for this frontal component, and not for the posterior N1, which is much larger and more robust and would therefore be expected to produce stronger effects. Moreover, if the correlation could simply be explained by physical factors relating to dipolar sources and referencing, then a similar correlation should be observed in the control group. When tested in the same way, no such correlation was found in control subjects ($r = 0.06$; $P = 0.78$) (Fig. 6b).

Following the suggestion of one reviewer, a series of post-hoc regression analyses were conducted to test whether the P1f, which was found here to differentiate between groups and to negatively correlate with the P1, might correlate with symptom scores, age, length of illness and medication status, and whether when combined in a multiple regression with the P1 measure, there might be an increase in explained variance for any of these factors. We found that P1f did not correlate with SANS, BPRS or with medication ($P > 0.1$). However, we found that age was significantly correlated with P1f amplitude ($r = 0.28$, $P < 0.05$), and that when both the P1 and P1f measures were factored together, explained variance increased to 16.3% (compared to 7.9% for P1f alone). P1f also correlated with length of illness ($r = 0.29$, $P < 0.02$).

Discussion

In patients with schizophrenia, significant impairments in early-stage visual processing, as indexed by reductions in the amplitude of the P1 component of the VEP, have now been repeatedly described (See Table 1A). In this context, it has been of particular importance to establish the general robustness of these impairments and whether they are pathognomonic of the disease. In the present study, we again found a substantial reduction in the P1 amplitude in 52 patients compared to healthy age-matched controls ($P = 0.016$) with a large effect size of $d = 0.70$ (Cohen's Criteria). Together with our recent finding of a similar P1 deficit in unaffected first-degree relatives [69], the present finding of no effects of age, length of illness or medication dose, reinforces the view that these marked deficits in P1 are linked to the underlying genetic liability for schizophrenia rather than a function of the disease state itself [23]. As such, the P1 deficit appears to be a very promising candidate as an endophenotype for schizophrenia [28].

Of the 26 studies that have reported on the visual P1 component in patients with schizophrenia, fully 18 have recorded significant deficits. It is worth pointing out that in the bulk of the remaining eight studies where a P1 deficit was not observed, later cognitive potentials were typically the dependent measures of interest (e.g. P300) and the P1 findings were incidental to the main focus of these studies [1, 5, 33, 34, 64]. In some of these studies, there are very obvious reasons why a P1 deficit was not observed. For example, [34] used a very limited electrode montage,

[1]The reader may note that an earlier difference at ~50 ms over fronto-central sites also reaches significance in the statistical cluster plot. As this effect was unpredicted and not observed in any previous studies, we are inclined not to conjecture on its significance until such time as it is replicated

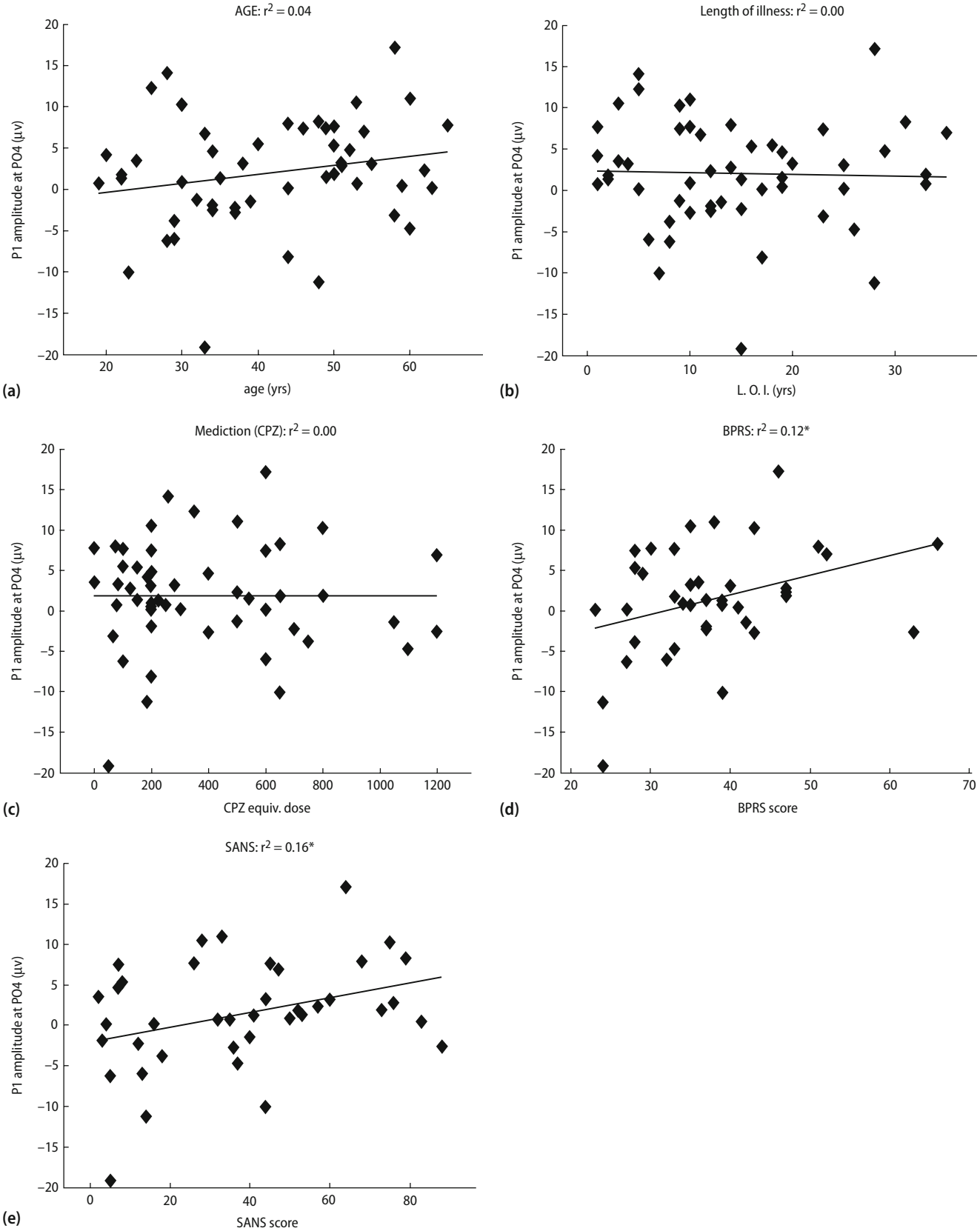


Fig. 4 Scatter plots showing **a** no correlation between P1 amplitude (μV) and age (years), **b** no correlation between P1 and length of illness (years), **c** no correlation between P1 and medication as indexed by the chlorpromazine dose (mg/day), **d** a positive correlation between P1 and the Brief Psychiatric Rating Scale (BPRS) and **e** a positive correlation between P1 and Negative Symptoms (SANS). *Asterisk* denotes significance at the 0.05 level

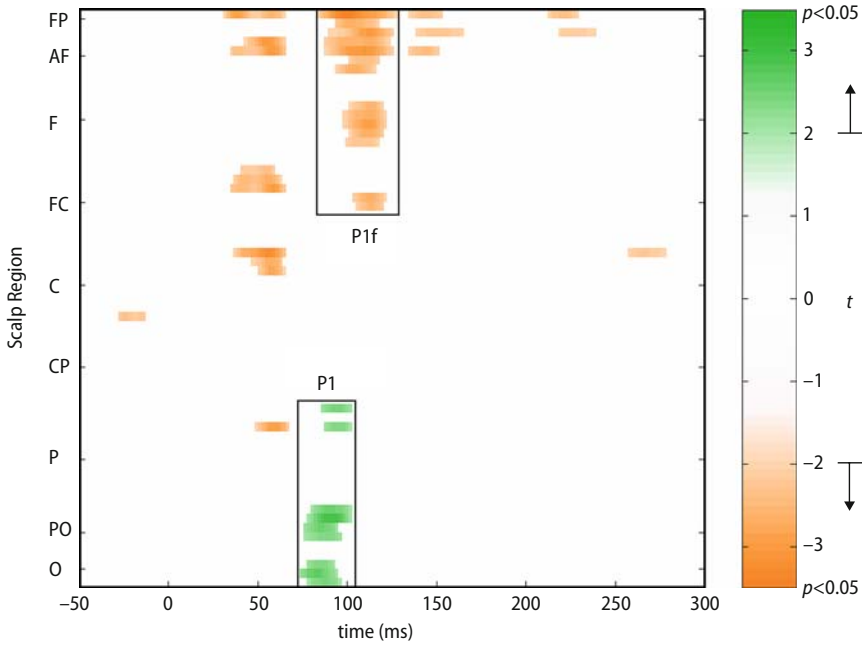


Fig. 5 Statistical cluster plot marking for all electrodes the time points at which the event-related potential differed significantly between groups on the basis of 2-tailed *t* tests at an α level of 0.05. Electrodes are ordered from occipital (O) at the bottom, proceeding anteriorly in rows from left to right though parieto-occipital (PO), parietal (P), centro-parietal (CP), central (C), fronto-central (FC), frontal (F), anterior-frontal (AF) to frontopolar (FP) at the top

investigating only three central scalp electrode sites (C3, CZ, C4), sites where the P1 signal is highly attenuated if present at all. Another reason for not finding the P1 deficit in this minority of studies includes not focusing on scalp regions where the P1 is prominent (e.g. electrode site Oz in [65] and [33]), since the P1 is best observed over more lateral-occipital scalp sites. Nonetheless, Strandburg et al. [64] did not find a significant P1 reduction in patients with schizophrenia in a visual detection task, nor did Bruder et al. [5] using a dot enumeration task. It is also possible that different methods of analysis may play a part in explaining the differences between the various studies [1]. Sponheim et al. [62] investigated P1 amplitude in the context of modulation of attention and perceptual load. Their study showed that schizophrenia patients failed to augment the P1 component during vigilance demands and concluded that this finding suggests a deficit in early processing of stimuli in patients. Although these eight studies did not find P1 deficits, as above, the large majority of studies where P1 was measured have. In many of these studies [29] the effect size was very large. All in all, the weight of evidence appears to overwhelmingly favour a robust P1 deficit in patients with schizophrenia.

Age, length of illness, medication and symptomatology

Only a handful of studies to date have directly looked at the relationship between early VEP and neuropsychological functioning and outcome. Schechter et al. [57] in an investigation aimed at parsing the Magnocellular and Parvocellular contributions to visual system functioning in schizophrenia also found the P1 deficit in patients. They then found significant correlation of the P1 deficit with global outcome and community functioning measures using the Independent Living Scale (ILS) [41]. However, no significant correlations between BPRS or SANS scores and any components of the VEP were found. Butler et al. [9] used the steady-state visual evoked potential (SSVEP) technique to investigate early stage visual processing deficits in schizophrenia. These investigators found deficits primarily in the magnocellular system as indexed by a reduction in contrast sensitivity and this deficit significantly correlated with poorer performance on the Digit Symbol task and with decreased IQ scores. No significant correlations were found with the Wisconsin Card Sorting task (WCS), a measure of cognitive control, or with the so-called and self-explanatory Logical Memory Tasks. Again, no correlation between SSVEP amplitude measures and clinical symptom scales (BPRS and SANS) was seen. The authors concluded that early-stage visual deficits contributed in turn to higher-level cognitive deficits. Spencer et al. [60] investigated gamma oscillatory and event related potential responses to Kaniza figures (figures that produce illusory contours) and also found deficits in patients with schizophrenia in the P1 component. This study did not attempt to correlate the VEP measures with clinical symptom scales but did find significant correlations between gamma responses over the occipital region and several positive symptoms (i.e. conceptual disorganization, visual hallucinations, thought withdrawal) and at parietal regions with negative symptoms. They did not find significant correlations with age, with age of onset or with medication dosage. Strandburg et al. [64] found no correlation between ERP measures and behavioural

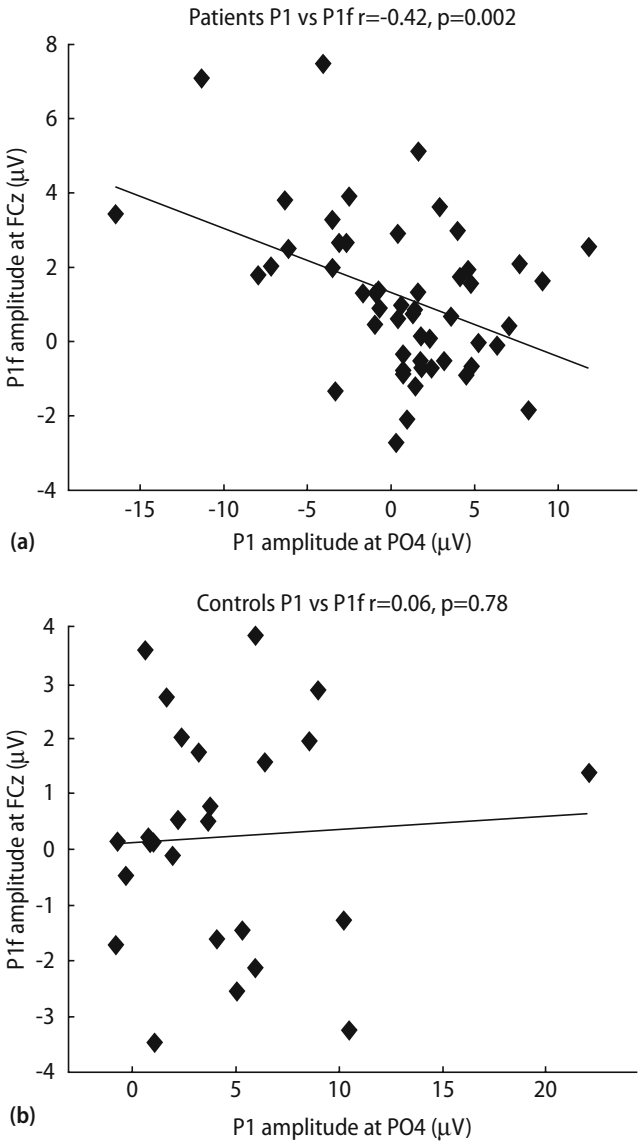


Fig. 6 Scatter plots of frontal positivity "P1f" against P1 for **a** patients and **b** controls

results during performance of a difficult visual discrimination task. They used the amplitude of the so-called 'Span Negativity' component as their dependent measure, which is manifest as a relative negativity over parietal scalp during the timeframe of N1-P2 components. This 'Span Negativity' was not significantly correlated with IQ or clinical scales (BPRS or SANS scores). Bruder et al. [5] also found no correlation between ERP amplitudes and the total positive, negative and general psychopathology scores. They also reported no correlation with education level or age. Overall, one would have to conclude that measures of early visual processing in schizophrenia have not been found to correlate consistently with symptom scales.

In our study, there was a weak but significant positive correlation between the P1 amplitude and both BPRS and SANS scores. This finding is somewhat counter-intuitive. That is, one might predict that since P1 amplitude reduction appears to be a robust marker for schizophrenia, that greater deficits in this component would be associated with more severe forms of the disorder (i.e. higher scores on clinical scales). However, the correlation found here was an inverse one with patients who showed more preserved P1 amplitudes also recording the highest clinical scores. This finding will bear replicating before any firm conclusions can be reached. It is worth noting that the P1 amplitude accounted for only 11% of the variance in clinical measures, therefore over-interpretation is best avoided at this stage, especially in light of the fact that a number of previous studies have failed to find consistent correlations with symptomatology, albeit in smaller samples. Nonetheless, if the result holds, the implication is that although the P1 deficit may be related to risk for schizophrenia, it does not relate to the severity of the disorder once a person has succumbed. If anything, once sick with the disease, smaller P1 amplitudes appear to confer some protection against the severity of symptoms.

If P1 is a true trait marker, the prediction would be that the P1 impairment should remain largely constant across the lifespan, and this is what was found here. There was no correlation between the P1 amplitude and age of the patients. In addition, we wanted to determine whether P1 was associated with duration of the illness i.e. whether the deficit worsened over time. The results showed no correlation between length of illness and P1 amplitude.

Medication status has not been previously shown to correlate with VEP amplitudes [7, 60]. Again, if P1 is a trait marker for schizophrenia, then medication status should play little or no role in its expression. Studies looking at unmedicated patient groups have also seen reductions in P1 amplitude [49] and we have seen P1 deficits in unmedicated healthy biological relatives [69], suggesting that medication does not in fact play a significant role. The results of this study are fully consistent with this notion, as we found no correlation whatsoever between P1 amplitude and antipsychotic dosage levels.

The role of attention

The difference in behavioural performance found here, with the control group scoring higher than the patient group, gives rise to the question, whether differences in the ability to maintain focused attention could have played a role in the present findings. However, even though previous studies have determined that attention effects can influence the amplitude of the P1 [31, 32, 42, 45, 55], the use of central presentations here helps to minimise the possible influence of attention [4]. The fact that patients detected the centrally presented targets with over 80% accuracy shows that they actively participated in the task and that they must have been centrally fixating as

instructed. Handy and Khoe [30] have shown that spatial attentional modulation of the P1 does not occur for transiently presented central stimuli. That is, they contended that stimuli presented to the foveal region appear to automatically engage attention. In a recent intersensory attention study, when subjects were concurrently asked to attend to a completely different sensory modality (e.g. auditory stimuli) the visual P1 remained unchanged [27].

Further, recent data from our laboratory [39] also make it unlikely that attentional factors play a significant role in the observed P1 deficit in schizophrenia. In that study, we used a novel visual evoked potential technique (which we have termed the VESPA—for visual evoked spread spectrum analysis) to preferentially evoke activity in the parvocellular system, one of the two major visual cellular divisions. A striking pattern of results was obtained. First, using the standard VEP technique, a significantly reduced P1 component was found once again in patients (with a very large effect size; Cohen's $d = 1.6$). However, an assessment of parvocellular functioning using the VESPA showed identical P1 responses for both patients and controls. It seems very unlikely that attention or arousal mechanisms would so completely affect one cellular system and not the other. Nor can this finding be ascribed to a lack of attentional modulability of the VESPA P1 since Lalor et al. [37] showed clear modulation thereof during a spatial attention task. As such, the present results do not easily lend themselves to a differential attentional account.

Hyperfrontality

A clear positive going ERP component (which we termed P1f here) was observed over midline frontal sites in patients over the time period immediately following the occipital P1 (~105–120 ms), an effect barely observable in healthy control subjects. That this component was significantly enhanced in patients raises the possibility that some recruitment of frontal regions may occur in schizophrenia to compensate for basic deficiencies in early visual sensory processing. This notion receives some measure of support from the finding that the amplitude of this P1f was inversely correlated with the amplitude of the occipital P1. That is, the weaker the posterior P1, the larger the frontal component was in schizophrenia patients, and this was not the case for healthy control subjects. This finding is decidedly reminiscent of observations in the aging literature, where a similar "compensation hypothesis" has been invoked to explain consistent findings of increased frontal activation in high-functioning older adults performing a variety of cognitive tasks [6, 11–14, 21, 40). Increased frontal activation has also been seen in healthy aging adults during basic sensory stimulation [20], so the finding of frontal hyper-activation does not require active participation in a demanding cognitive task. It should also be pointed out that we have found similar frontal hyper-activation in a number of our previous studies in patients with schizophrenia [22, 27].

An alternate account for this hyper-activation may lie in the neurochemical underpinnings of the P1 component. While surprisingly little is known about the underlying neurophysiology of the major human VEP components, electrophysiological work by Zemon et al. [70] in anaesthetized cats suggested that the P1 component of the VEP might represent an intracortical inhibitory process—that is, that it is largely GABAergic (gamma-aminobutyric acidergic) in origin. Using topical application of bicuculline, a GABAergic antagonist, the authors showed a substantial decrease in the amplitude of the first major positive component of the cat VEP (a putative homologue of the human visual P1). One implication of these results, insofar as they can be reasonably applied to recordings in humans, is that a failure of normal posterior inhibition might in turn allow for increased transmission of signals into higher-order frontal regions, resulting in hyper-activation of structures that under normal circumstances should not be activated in response to simple non-target stimuli. That is, one might hypothesize that a function of the processing represented by the P1 is to arrest anteriorization of signals when incoming stimuli are irrelevant to task performance and need not be processed further. An upshot of failure of this inhibitory function would be the unnecessary activation of frontal control regions that should be otherwise engaged in higher-order processing, potentially leading to cognitive disorganization. Clearly this is speculative and it should be pointed out that the P1 deficit has also been linked to excitatory (n-methyl-d-aspartate (NMDA)) functioning (see [10]). It will take pharmacological manipulations to disentangle the contributions of the various receptor systems to P1 processing.

Conclusions

The finding of a substantially reduced P1 in this large unique cohort adds to a growing body of evidence for early visual sensory processing dysfunction in patients with schizophrenia. This P1 deficit is independent of age, length of illness and medication status, reinforcing the notion that the P1 is a trait marker for the disease and may serve as a useful index of genetic liability for schizophrenia.

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