

# Early Visual Sensory Deficits as Endophenotypes for Schizophrenia

## *High-Density Electrical Mapping in Clinically Unaffected First-Degree Relatives*

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**Context:** The imperative to establish so-called endophenotypes—quantifiable measures of risk for neurological dysfunction—is a growing focus of research in schizophrenia. Electrophysiological markers of sensory processing, observable in human event-related potentials, hold great promise in this regard, lying closer to underlying physiology than descriptive clinical diagnostic tests.

**Objective:** Early visual processing deficits, as measured by clear amplitude reductions in the occipital P1 component of the visual event-related potential, have been repeatedly demonstrated in patients with schizophrenia. However, before P1 amplitude may be considered as an endophenotypic marker for schizophrenia, it is necessary to establish its sensitivity to genetic liability.

**Design, Setting, and Participants:** Event-related potential responses to simple visual isolated-check stimuli were examined in 25 clinically unaffected first-degree relatives of patients with schizophrenia and 15 DSM-IV–diagnosed schizophrenia probands and compared with responses from 26 healthy, age-matched control subjects. Using high-density electrical scalp recordings, between-groups analysis assessed the integrity of the vi-

sual P1 component across the 3 groups. The study was conducted at St Vincent's Psychiatric Hospital in Fairview, Dublin, Ireland.

**Results:** Substantially reduced P1 amplitude was demonstrated in both relatives and probands compared with controls with topographical mapping and inverse source analysis localizing this deficit largely to midline regions in early visual sensory cortices and regions of the dorsal visual stream. Additional later differences between these groups, where the relatives actually show larger amplitude responses, may point toward compensatory mechanisms at play in relatives.

**Conclusions:** Our findings demonstrate a deficit in early visual processing in clinically unaffected first-degree relatives of patients with schizophrenia, providing evidence that this deficit may serve as a genetic marker for this disorder. The efficacy of using P1 amplitude as an endophenotype is underscored by the observation of a large effect size ( $d=0.9$ ) over scalp sites where the deficit was maximal.

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**A**LTHOUGH GENETIC INFLUENCES in schizophrenia have been widely reported,<sup>1</sup> the task of localizing the specific genes responsible has proven difficult.<sup>2</sup> In the hunt for the underlying risk factors for schizophrenia, establishing so-called endophenotypes has emerged as a major focus.<sup>3</sup> Endophenotypes serve as intermediate quantitative constructs, bridging the gap between genetic and environmental factors at one end and descriptive symptom-based diagnostics at the other. An effective endophenotype should index an individual's liability to develop or manifest a certain disease in much the same way that serum cholesterol predicts the risk of cardiovascular disease. Being quantifiable by definition, it should offer higher predictive power and lie closer to underlying genetic liability and gene action than

diagnostic phenotypes. One of the most promising avenues for establishing such endophenotypes in schizophrenia lies in recordings of the event-related potential (ERP) where deficits in patients have been consistently demonstrated in both visual<sup>4,5</sup> and auditory<sup>6-8</sup> processing. This promise has been borne out recently with a number of reports uncovering ERP deficits in unaffected first-degree relatives similar to those seen in patients.<sup>9-15</sup>

In a series of recent ERP studies from this group, highly robust visual sensory processing deficits have been repeatedly observed in patients with schizophrenia,<sup>16-21</sup> a finding now replicated by other groups.<sup>22</sup> In these studies, generation of one of the most robust components of the visual evoked potential (VEP), the so-called P1 component, was consistently impaired in patients. This VEP component indexes early sensory processing in extrastriate visual

areas and is recorded over both midline and lateral occipital scalp with peak latency typically varying between 75 and 110 milliseconds, dependent on stimulus features.<sup>23</sup> A number of factors point to the P1 deficit as a particularly promising candidate as an endophenotype. First, this effect is especially strong with amplitude of the P1 in patients less than half the strength seen in healthy controls. This component is also very straightforward to measure, is readily identifiable across individuals, and takes no more than a couple of minutes to obtain a sufficiently clean and stable recording. Because it is a largely automatic response, it does not require any complex task, other than fixation of the eyes, and so is not susceptible to motivational issues or the ongoing clinical state of the patient in the way that later cognitive components such as the P300 can be.<sup>24,25</sup>

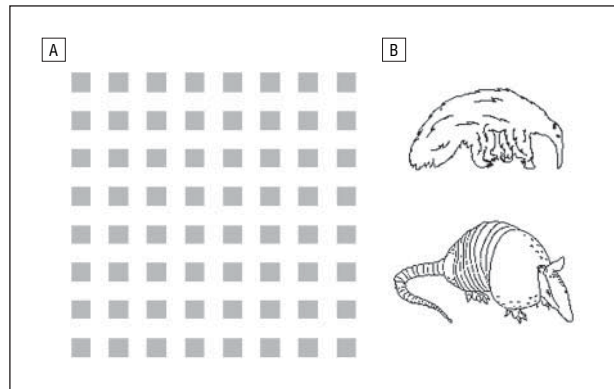
Clinically unaffected first-degree biological relatives have an elevated risk for schizophrenia in addition to showing mild impairments in neurobiological functioning (eg, executive functioning, verbal and visual memory, auditory attention, and verbal ability) similar to that found in patients.<sup>26-29</sup> These impairments are thought to reflect the genetic predisposition for schizophrenia rather than the disease process itself. Our objective here was to investigate whether the visual P1 deficit is also observed in unaffected first-degree relatives and to establish whether this component has potential use as an endophenotypic marker for schizophrenia. The study was carried out in Ireland, a country with a high degree of common ancestry and shared genetic liabilities. The traceability of Irish families is conducive to future genetic linkage studies within families.

## METHODS

### SUBJECTS

Informed consent was obtained from 25 (15 female) clinically unaffected first-degree biological relatives of known patients with schizophrenia (probands). Relatives were aged 18 to 64 years (mean  $\pm$  SD, 32.3  $\pm$  13.6 years) and were recruited from the St Vincent's Hospital catchment area in Fairview, Dublin, Ireland. They were contacted via telephone and mailings following consent from their probands, who were either being seen in the outpatient clinics or were inpatients in the hospital. First-degree relatives were recruited from 18 unique families and consisted of the parents (5), the siblings (15), or the children (5) of affected individuals meeting DSM-IV criteria for schizophrenia. For each patient with schizophrenia, a maximum of 3 first-degree relatives were recruited. The mean  $\pm$  SD score on the Scale for the Assessment of Negative Symptoms (SANS)<sup>30</sup> for the first-degree relatives was 0.64  $\pm$  1.87. Also included were 15 (4 female) original probands, aged 17 to 53 years (mean  $\pm$  SD, 32.6  $\pm$  12.7 years) with mean  $\pm$  SD scores on the Brief Psychiatric Rating Scale<sup>31</sup> and SANS of 40.80  $\pm$  11.96 and 28.87  $\pm$  22.09, respectively. Five of the 15 probands were drug-naive and experiencing their first episodes of psychosis. Nine of the patients were receiving medication with a mean chlorpromazine equivalent dose of 259.44 mg/d (range, 50-800 mg/d). The types of antipsychotics included atypicals (6), typicals (2), and a combination of both (1). One proband had ceased taking her medications 3 months prior to testing and was medication-free at the time of testing.

Control subjects were recruited from the St Vincent's Hospital staff community and through local recruitment efforts in the hospital catchment area. This group comprised 26 (13 female) paid volunteers aged 21 to 64 years (mean  $\pm$  SD, 38.7  $\pm$  12.6



**Figure 1.** The centrally presented visual stimuli used in the task. Event-related potential waveforms were derived for the isolated-check nontarget stimulus (A) while target discrimination was performed on the basis of infrequently presented animal line drawings (B).

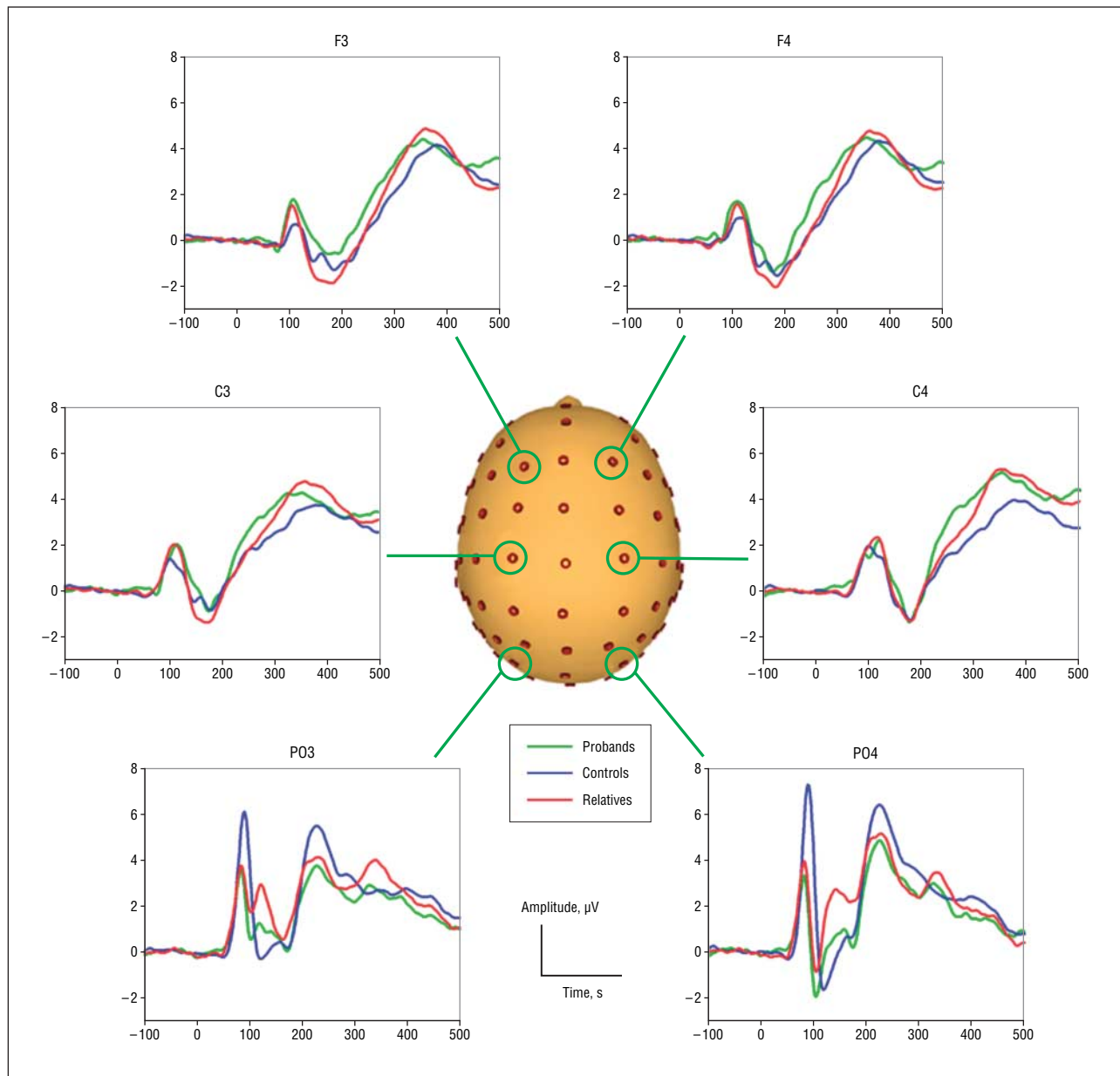
years). The mean age of relatives and controls did not differ significantly ( $t_{50} = 1.73$ ,  $P = .09$ ), and the mean age of probands did not differ significantly from either group ( $P > .10$ ). Nineteen of the 25 relatives, 21 of the 26 controls, and 12 of the 15 patients were right-handed as assessed by the Edinburgh Handedness Inventory.<sup>32</sup> All subjects reported normal or corrected-to-normal vision. None of the relatives or controls were receiving any psychotropic medication at the time of testing.<sup>33,34</sup> Relatives and controls were free of any psychiatric illness or symptoms by self-report using criteria from the Structured Clinical Interview for DSM-III-R-Non-Patient (SCID-NP),<sup>35</sup> and all reported no history of alcohol or substance abuse.

(Note that there was a marginal trend for the control subjects to be older than relatives. It is worth pointing out that to the extent that the VEP changes with age, it tends toward reduced amplitude and increased latencies, although these changes are very small and only seen over the course of many decades.<sup>36</sup> Thus, if age were playing any role here, the prediction would go in exactly the opposite direction to that proposed. That is, control subjects would be expected to show reduced P1 amplitudes relative to the first-degree group.)

### STIMULI AND TASK

In each experimental block, subjects were presented with approximately 100 isolated-check images, gray on a white background ( $4^\circ \times 4^\circ$  visual angle) at 64% contrast, and 40 line drawings of 2 kinds of animals ( $2.4^\circ$  wide  $\times$   $1.8^\circ$  high) on a white background. Each block contained a different animal pair from a possible 22. The isolated-check stimuli and 1 pair of animal stimuli are shown in **Figure 1**. The 64% contrast condition was chosen to stimulate both the magnocellular (M) and parvocellular (P) systems. On average, subjects completed 13.5 blocks (range, 10-15), each lasting 3 minutes. Stimuli were presented centrally on a cathode ray tube 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 milliseconds with a variable interstimulus interval between 740 and 1540 milliseconds (randomly in steps of 200 milliseconds) during which there was a blank white screen. The target animal was displayed at the start of the task and 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 nontarget animals were presented with equal probability, ensuring that a subject could not rely on the exogenous alerting nature of any noncheckerboard stimulus to respond. Further-



**Figure 2.** An overview of event-related potential waveforms across the scalp with 6 representative channels contrasting responses to isolated-check stimuli in the control and first-degree relative groups. Of primary interest are the visual components observable over posterior sites.

more, the task of discrimination was made difficult by pairing similar-looking animals, eg, dolphin and whale. The primary motivation for using this task rather than simply having subjects passively observe the standard stimuli was to ensure that subjects had fixated centrally on the screen. Only ERPs to the standard checkerboard stimuli were included in the analysis.

#### DATA ACQUISITION AND STATISTICAL ANALYSIS

Continuous electroencephalography was acquired through the ActiveTwo BioSemi electrode system (BioSemi, Amsterdam, the Netherlands) from 72 scalp electrodes, digitized at 512 Hz with an open pass-band from DC to 150 Hz. For analysis and display purposes, data were subsequently filtered with a 0-phase-shift 45 Hz low-pass filter (24 dB/octave) after acquisition. No high-pass filter was applied. With the BioSemi system, every electrode or combination of electrodes can be assigned as the

reference, and this is done purely in software after acquisition. BioSemi replaces the “ground” electrodes used in conventional systems with 2 separate electrodes: Common Mode Sense active electrode and Driven Right Leg passive electrode. These 2 electrodes form a feedback loop, which drives the average potential of the subject (the Common Mode voltage) as close as possible to the ADC reference voltage in the AD-box (the ADC reference can be considered as the amplifier “zero”). A detailed description of the referencing and grounding conventions used by the BioSemi active electrode system appears online (<http://www.biosemi.com/faq/cms&drl.htm>). All data were 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 criterion of  $\pm 120\mu\text{V}$  from  $-200$  to 500 milliseconds 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 calculated for a time window from 200 milliseconds prestimulus to 500 milliseconds poststimulus and baseline-corrected relative to the interval -80 to 20 milliseconds. Accepted trials were then averaged for the isolated-check stimuli only. The mean  $\pm$ SD epoch acceptance rate for the relatives was  $59.6 \pm 10.8\%$ ; for patients,  $59.5 \pm 10.7\%$ ; and for the control group,  $63.4 \pm 16.8\%$ .

Our primary analysis was motivated by a specific hypothesis, based on previous research by our group, regarding reduction in early visual sensory processing (ie, the P1 processing period) in clinically unaffected first-degree relatives. A measure of P1 amplitude was defined as the area under the curve (vs the 0- $\mu$ V baseline) in the interval 87 to 97 milliseconds, spanning the P1 component, chosen based on grand average waveforms (**Figure 2**). These area measures were then submitted to a repeated-measures multivariate analysis of variance (MANOVA) using SPSS software (SPSS Inc, Chicago, IL) with a between-subjects factor of group (relatives vs controls vs probands) and within-subjects factors of region (left, midline, or 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 2-tailed with a preset  $\alpha$  level of  $P < .05$ .

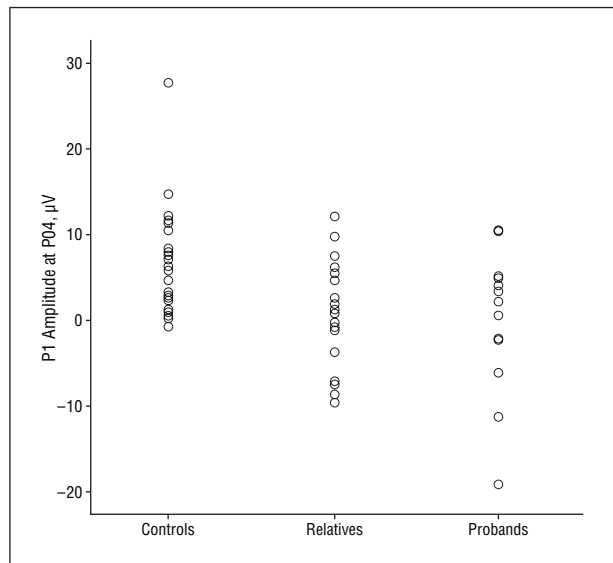
Following our primary analysis of P1 amplitude, it was of interest to further investigate spatiotemporal properties of any potential differences between groups using the statistical cluster plot method. This procedure has been used effectively in post hoc analyses as a means to fully explore complex data sets and generate pointed follow-up hypotheses.<sup>37,38</sup> Pointwise 2-tailed  $t$  tests (here between controls and relatives) are calculated at each time point for all electrodes, and a color map is subsequently generated marking time points on each electrode for which the  $t$  value exceeds that corresponding to a .05  $P$  value. Here we plot positive and negative  $t$  values in separate color scales (green and gold) to distinguish differences in opposite directions. All nonsignificant points are represented as white.

To localize the neural sources giving rise to the observed effects, we employed a source analysis technique based on a distributed linear inverse solution (LAURA).<sup>39</sup> LAURA uses a realistic head model with a solution space of 4024 nodes where voxels are restricted to the gray matter of the Montreal Neurological Institute (MNI) average brain divided into a regular grid with 6-mm spacing. It is capable of dealing with multiple simultaneously active sources of a priori unknown locations and makes no assumptions regarding the number or location of active sources. This linearly distributed inverse solution selects the source configuration that best mimics the biophysical behavior of electric vector fields and produces a unique estimator of the current source density vector inside the brain.<sup>40</sup> Source analysis was performed here on group-averaged ERP data separately for controls and relatives.

## RESULTS

The mean  $\pm$ SD target hit rate for controls was  $95.4 \pm 7.6$ ; for relatives,  $91.4 \pm 10.7$ ; and for probands,  $91.0 \pm 11.5$ . The mean rates did not differ significantly between the relatives, patients, and controls (all  $P > .10$ ). These rates indicate that subjects were actively observing the stimuli.

Figure 2 provides an overall picture of ERP morphology across the scalp for all 3 groups, showing responses from 6 representative electrodes over frontal, central, and posterior scalp regions. Group differences are evident, particularly in posterior regions. The distribution of P1 amplitudes at electrode site PO4 for each of the 3 groups is shown in the form of a scatterplot in **Figure 3**. The

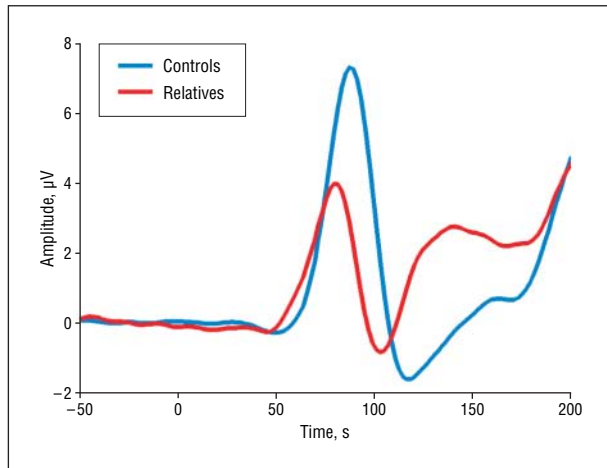


**Figure 3.** A scatterplot of the distribution of P1 amplitudes for each of the 3 groups representing measures taken from right parieto-occipital scalp-site PO4.

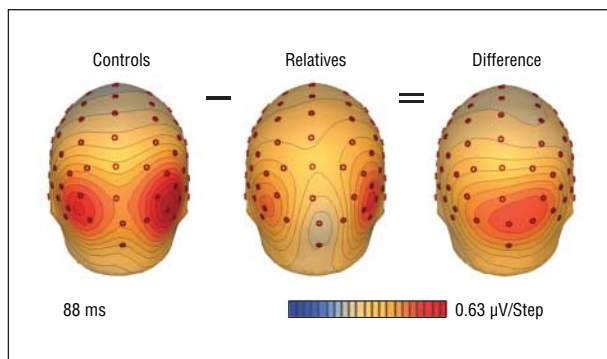
standard deviations for the controls, relatives, and probands were 6.08, 5.58, and 7.81 respectively.

A MANOVA (3 groups by 3 regions by 3 electrodes) was used to compare P1 amplitudes between all 3 groups over the left lateral occipital, midline dorsal, and right lateral occipital visual areas. This revealed a significant and highly robust main effect of group ( $F_{2,63} = 5.36$ ,  $P = .007$ ). Pairwise comparisons of group indicated substantially reduced P1 amplitude in the first-degree relative group compared with controls (mean difference, 3.72  $\mu$ V;  $P = .02$ ), confirming the main hypothesis of this study. Similarly, P1 amplitude in the proband group was also significantly reduced compared with controls (mean difference, 4.30  $\mu$ V;  $P = .02$ ), replicating our findings in a number of previous studies.<sup>5,16,17,20</sup> No difference in P1 amplitude was found between probands and relatives ( $P = 1.00$ ). As the finding of reduced P1 in probands is simply a replication of our previous work, further analysis was restricted to the comparison of first-degree relatives with controls using a protected  $2 \times 3 \times 3$  ANOVA in line with the principle aim of the study. The observed effects for these 2 groups are illustrated in **Figure 4**, which focuses on a shorter latency interval around the effect of interest at the right hemisphere parieto-occipital scalp site where P1 amplitude was maximal for both groups.

The protected  $2 \times 3 \times 3$  ANOVA revealed a significant main effect of group ( $F_{1,49} = 8.88$ ,  $P = .004$ ), again indicating substantially reduced P1 amplitude in the first-degree relative group compared with controls. There were also significant main effects of region ( $F_{2,49} = 28.42$ ,  $P < .001$ ) and electrode ( $F_{2,49} = 35.46$ ,  $P < .001$ ) and a region  $\times$  electrode interaction ( $F_{2,49} = 10.92$ ,  $P < .001$ ), reflecting the topographic specificity of the P1. Protected follow-up comparisons between regions showed a significant difference when left and right hemisphere regions 1 and 3 (both  $P < .001$ ) were compared with midline region 2. This arises from the bilateral foci in the topography of P1 amplitude (**Figure 5**). Comparison of regions 1 and 3 did not prove significant ( $P = .27$ ).



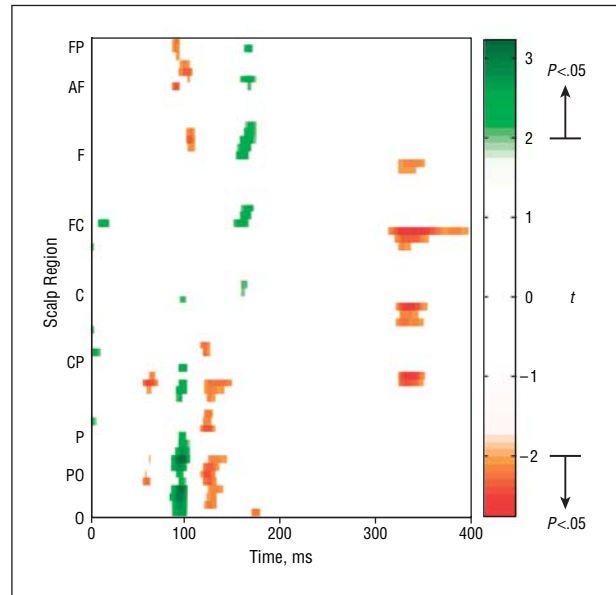
**Figure 4.** Event-related potential waveforms at a right parieto-occipital scalp electrode (PO4) are plotted over a short-latency time frame clearly showing the P1 component, which appears to strongly discriminate between groups.



**Figure 5.** Topographic maps showing the distribution of amplitude on the scalp at 88 milliseconds. A bilateral distribution of the absolute P1 amplitude is seen for both the control and first-degree relative groups. In contrast, a posterior midline focus is seen in the map of the difference (controls–first-degree relatives).

(It should be pointed out that given typical conversion rates for parents [6%], siblings [9%], and children [13%]<sup>41</sup> and given the age make-up of the first-degree relative group, one would predict that as many as 2 to 3 of our subjects could go on to develop schizophrenia. This proportion of subjects would clearly not be sufficient to drive the effects seen here.)

A significant region  $\times$  electrode  $\times$  group interaction was also found ( $F_{4,196} = 3.44$ ,  $P = .03$ ), suggesting some topographic specificity of the effect and warranting further examination. In follow-up 1-way ANOVAs, the group difference was found to be significant in all regions (all  $P < .02$ ). Looking at individual electrodes, the group difference was significant at all locations except at midparietal scalp-site Pz, where it approached significance ( $P = .07$ ). Despite this generality of significant effects, the difference topography (Figure 5) shows that the decrement in P1 amplitude is strongest over the midline dorsal parieto-occipital scalp. An effect size of  $d = 0.90$  was calculated for the difference in P1 amplitude measured over the interval 91 to 97 milliseconds at the electrode site (PO4) where the effect was maximal, which constitutes a large effect size according to the criterion of Cohen.<sup>42</sup>



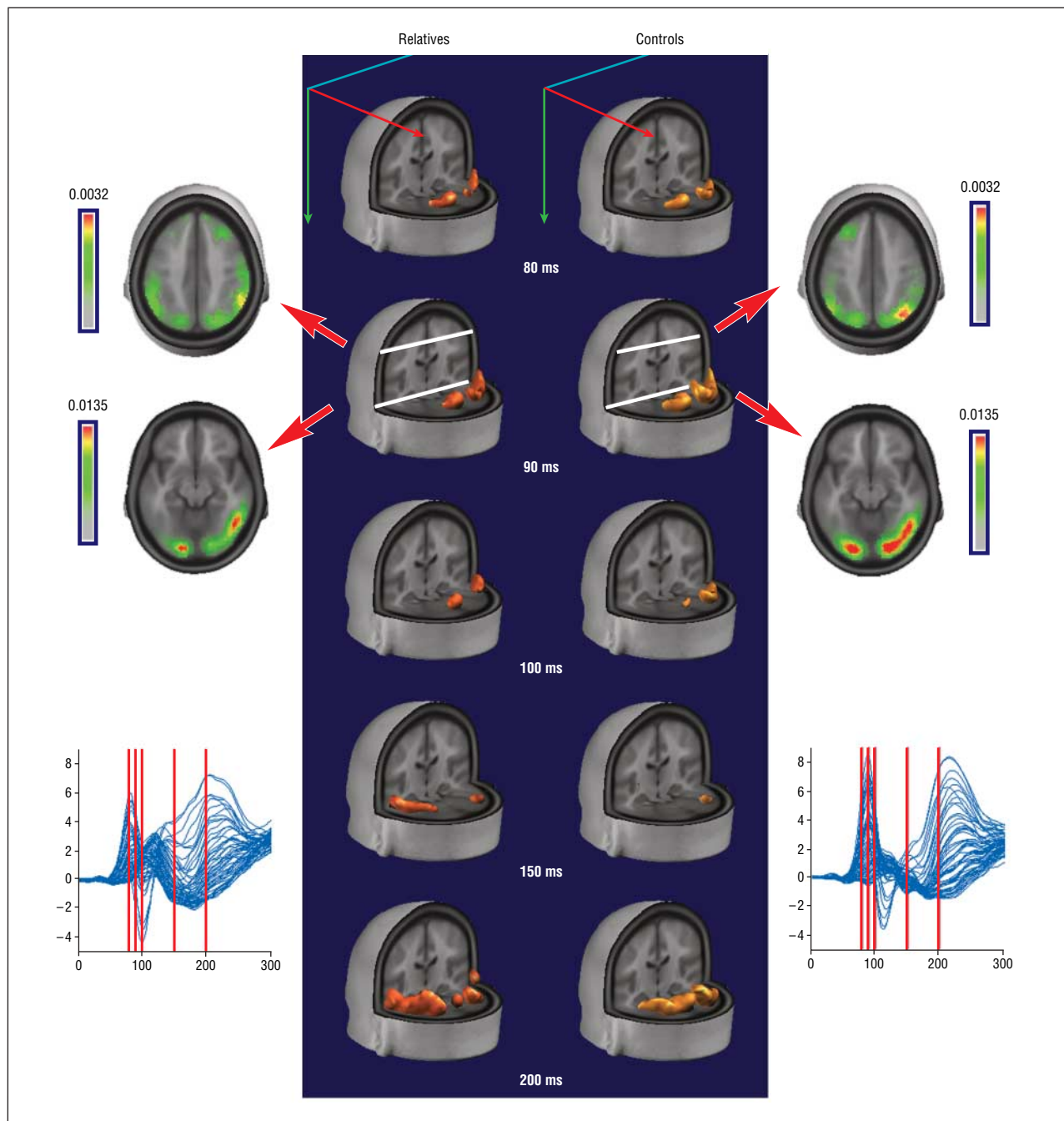
**Figure 6.** Statistical cluster plot marking for all electrodes the time points at which the event-related potential differed significantly between groups on the basis of 2-tailed  $t$  tests at an  $\alpha$  level of .05. White denotes nonsignificance while positive  $t$  values (Controls  $>$  Relatives) are marked on a green scale and negative  $t$  values (Relatives  $>$  Controls) are marked in gold. Electrodes are ordered from the bottom, occipital (O), parieto-occipital (PO), parietal (P), centro-parietal (CP), central (C), frontocentral (FC), frontal (F), and anterior-fronto (AF) proceeding in the anterior direction in rows from left to right, to frontopolar (FP) sites at the top. A cluster is seen over posterior sites in the P1 interval 87 to 97 milliseconds as expected from the results of the planned analysis of variance. In addition to this, significant differences in amplitude between groups are seen over the same region at a slightly later interval (~140 milliseconds), in the opposite direction.

As shown in **Figure 6**, the statistical cluster plot contains a posterior cluster in the time range of the P1, reflecting the group difference reported in the MANOVA. In addition to this, a cluster shortly following the P1-related cluster in the same region reflects a difference in the opposite direction, ie, greater amplitude in relatives compared with controls (gold clusters). This second phase of activity was examined more closely in the LAURA source analysis, which revealed greater activation in extrastriate regions after 125 milliseconds.

**Figure 7** displays the LAURA source analysis for 3 time points spanning the time frame of the P1 component (80, 90, and 100 milliseconds) and 2 further time points across the later sensory processing epoch (150 and 200 milliseconds). Source analysis revealed the expected generator pattern for the P1 with generators in midline visual structures, dorsal stream parietal regions, and ventral stream lateral occipital structures.<sup>17</sup> In the plots for the 90-millisecond time point, the fact that the generators are substantially more active for the control subjects is evident. Note that at 150 milliseconds, a second round of activity in these regions is greater for relatives than control subjects, suggesting an additional round of re-entrant activity that is absent from the control data.

#### COMMENT

Impaired P1 generation has been repeatedly shown in patients with schizophrenia receiving medica-



**Figure 7.** A series of 3-dimensional reconstructions of the distributed-source inverse solution obtained using the LAURA algorithm at 5 time points of interest. The outer surface of regions activated above a level of 0.013 are visible in orange. For the 90-millisecond (P1) time point, activations in key ventral and dorsal slices are further illustrated in flanking horizontal views. "Butterfly" plots show the event-related potential traces for all 64 scalp electrodes with the 5 selected time points marked.

tion,<sup>16-18,20,43,44</sup> a result that has been replicated here. However, until now, it had not been assessed in clinically unaffected first-degree relatives. To our knowledge, this study is the first to show that clinically unaffected first-degree relatives also have significant impairments in early visual processing as indexed by the P1. The observed decrement in P1 generation is found in the absence of any age, sex, or medication effects, strongly suggesting that it is associated with genetic risk for schizophrenia. In addition, the decrement in P1 amplitude for this group is not at all subtle but rather is found to have a large effect

size. As such, the P1 deficit appears to be a very promising candidate as an endophenotypic marker for the disorder.

The deficit is seen most strongly over more midline parieto-occipital scalp compared with more lateral occipito-temporal regions, a finding that is highly consistent with our previous studies in chronic patients.<sup>16,17,20</sup> The early timing of this deficit, its general scalp topography over midline and dorsal occipital scalp, and inverse source-estimation all support the possibility of an early visual processing deficit that is more prominent in

midline and dorsal regions of the visual system, as has been suggested by previous psychophysical<sup>18,43,45-48</sup> and neurophysiological research.<sup>16,17,20</sup>

These data also add weight to the thesis that early visual processing deficits in schizophrenia may be biased to the M system more than the P system,<sup>16,18,49</sup> insofar as the deficit appears mainly over midline and dorsal stream structures, which are known to receive their main cellular input from the M system.<sup>50</sup> Of course, in the present study, we used a relatively high spatial frequency and high luminance contrast (64%) stimulus that will have activated both the M and P systems. In previous work in patients, however, stimuli that specifically activated one or the other cellular system have been employed and much of this work points to greater M system dysfunction. For example, in studies of patients with chronic schizophrenia, Butler and colleagues<sup>18,19</sup> showed greater deficits in steady-state VEPs (ssVEPs) elicited by M-biased stimuli than by P-biased stimuli. Similarly, Foxe and colleagues<sup>17</sup> found that early ventral stream processing appeared largely intact as evidenced by normal illusory contour processing in the lateral occipital complex despite large-scale deficits in dorsal P1 generation, suggesting relative preservation of P-mediated processing. There is also a body of work that has looked at patient performance on visual tasks that selectively bias the M and P pathways, and again these studies point to greater M pathway dysfunction.<sup>51-53</sup> For example, patients with schizophrenia showed a larger deficit in letter discrimination compared with controls for letter stimuli composed of fast-moving dots than for stimuli composed of slow-moving dots. This deficit in high-velocity stimulus detection in patients was interpreted as indicative of a specific dysfunction in the M system, which is known to be essential for processing such stimuli. Although the issue of P vs M functioning has been well studied in patients, an obvious next step in studying first-degree relatives will be to use M and P biasing stimuli<sup>54</sup> in conjunction with VEP recordings.

A major advantage of the P1 as a potential diagnostic tool is the relative ease with which a sufficiently clean and stable recording can be obtained and the fact that it is readily identifiable across individuals. In particular, because it is a largely automatic or exogenous response that doesn't necessarily require performance of an active task to obtain, it is not nearly as susceptible to motivational issues or the ongoing clinical state of the patient as later cognitive components such as the P300 can be.<sup>4,5</sup> Nonetheless, while the P1 is largely automatic in that it is present even when subjects only passively view the stimulus, this is not to say that it is not cognitively penetrable. Most notably, modulations of P1 amplitude occur as a result of deployments of visual spatial attention and are thought to reflect facilitation of early sensory processing.<sup>55-58</sup> The notion that the P1 deficit observed in the present study is a result of impaired spatial attention is rendered extremely unlikely, however, in light of the equivalent performance across groups, each demonstrating high target detection rates. This indicates that the groups did not differ in relation to fixation on, and attention to, the centrally presented stimuli. Moreover, it has been shown that, in contrast to peripheral stimuli, the P1 elicited by centrally presented stimuli, as was the case here, is not modulated by directing atten-

tion to or away from that location; ie, the mechanisms of sensory gain invoked by spatial attention do not appear to apply to foveal space.<sup>59</sup> Similar results were observed in a recent intersensory attention study.<sup>60</sup> Subjects attended to a completely different sensory modality (auditory stimuli) on which they performed a very taxing task and were required to actively ignore concurrent visual distracter stimuli, and yet still no effect of attention was seen on the visual P1 component. Although the present results cannot be explained on the basis of differential attentional deployment across groups, the deficit in P1 in both patients and relatives may very well be related to more general deficits in attention that are found in patients.<sup>61</sup> For instance, it is plausible that dorsal P1 represents activation of the exogenous attentional orienting system, a critical function of the dorsal visual stream, and that this might explain some of the deficits in attentional orienting that have been reported in patients.<sup>62,63</sup> However, recent work has also suggested that attentional functions in schizophrenia may not be particularly more impaired than any other cognitive function.<sup>64</sup> For now, a relationship between P1 deficits and any attentional dysfunction remains to be explicitly tested in both patients and relatives.

Post hoc analyses also uncovered a second phase of differential activity (120-150 milliseconds) between groups in the time frame immediately following the initial phase of the P1 (80-100 milliseconds). In this second phase, it was the relatives who showed higher amplitude. Source analysis suggested that this second phase represented re-entrant feedback processing in striate and neighboring extrastriate regions. This re-entrant activity appears to be almost absent in probands. One possible explanation for this re-entrant activity in relatives is that it represents compensatory mechanisms to increase activation in early visual areas following an initial weak response. Clearly, this effect was not part of our original hypotheses, and although robust, it will need to be confirmed in future work.

Ultimately, a major goal in schizophrenia research is to derive measures to detect schizophrenia before the actual onset of prodromal or full-blown psychotic symptoms. To this end, there is evidence to show that the mild subclinical neuropsychological problems that are often reported in nonpsychotic first-degree relatives are reversible by low-dose antipsychotic medications.<sup>65</sup> The development of an easily measured, objective electrophysiological phenotype would be of great use in these efforts, and the findings of this study suggest that the visual P1 deficit is a very promising candidate.

## CONCLUSIONS

The finding of substantially reduced P1 amplitude in clinically unaffected first-degree relatives of patients gives considerable weight to the possibility of using the P1 deficit as an endophenotypic marker or diagnostic tool for schizophrenia. The deficit is more pronounced over the midline parieto-occipital scalp, suggesting that the impairment lies mostly in midline and dorsal visual stream structures, a contention that is supported by inverse source

analyses. Further longitudinal studies will be required to determine the integrity of the P1 across all age groups and chronicity. Ultimately, it is the early detection of schizophrenia in high-risk individuals that will enable us to treat and better manage this debilitating disorder.

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