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Dissecting the cellular contributions to early visual sensory processing deficits in schizophrenia using the VESPA evoked response

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Abstract

Electrophysiological research has shown clear dysfunction of early visual processing mechanisms in patients with schizophrenia. In particular, the P1 component of the visual evoked potential (VEP) is substantially reduced in amplitude in patients. A novel visual evoked response known as the VESPA (Visual Evoked Spread Spectrum Analysis) was recently described. This response has a notably different scalp topography from that of the traditional VEP, suggesting preferential activation of a distinct subpopulation of cells. As such, this method constitutes a potentially useful candidate for investigating cellular contributions to early visual processing deficits. In this paper we compare the VEP and VESPA responses between a group of healthy control subjects and a group of schizophrenia patients. We also introduce an extension of the VESPA method to incorporate nonlinear processing in the visual system. A significantly reduced P1 component was found in patients using the VEP (with a large effect size; Cohen's $d = 1.6$), while there was no difference whatsoever in amplitude between groups for either the linear or nonlinear VESPA. This pattern of results points to a highly specific cellular substrate of early visual processing deficits in schizophrenia, suggesting that these deficits are based on dysfunction of magnocellular pathways with parvocellular processing remaining largely intact.

Keywords: EEG; Visual evoked potential; VESPA; Schizophrenia; P1 component

1. Introduction

Visual evoked potential (VEP) studies have consistently demonstrated that patients with schizophrenia exhibit relatively severe deficits in early visual sensory processing, as indexed by a robust decrement in amplitude of the occipital P1 component (e.g., Foxe et al., 2001, 2005; Butler et al., 2001, 2007; Doniger et al., 2002;

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Spencer et al., 2003; Schechter et al., 2005; Haenschel et al., in press). Concomitant structural deficits have also been shown in the visual sensory pathways (Butler et al., 2006). Scalp topographies and source analysis have suggested that these deficits may specifically reflect dysfunction of the dorsal visual stream while processing in the ventral stream remains relatively more intact (e.g. Foxe et al., 2001, 2005). It is also suggested that certain ventral stream processes are contingent on inputs from the dorsal stream and as a result failure in these 'higher-level' ventral stream processes may ultimately be a consequence of these underlying dorsal stream deficits (Doniger et al., 2002; Foxe et al., 2005).

Further to the above findings, a substantial decrement in the P1 component was recently demonstrated in clinically unaffected first-degree relatives of schizophrenia patients (Yeap et al., 2006), establishing a possible genetic basis for the observed effects (see also Donohoe et al., in press). This points to the potential use of P1 amplitude as an endophenotypic marker for schizophrenia and, as such, it may be a significant step in the quest for a diagnostic test facilitating early detection of schizophrenia in high-risk individuals.

It would be of great benefit to this line of research to have a more sensitive method for eliciting this deficit. One very promising candidate method, known as the VESPA technique (for Visual Evoked Spread Spectrum Analysis), was recently described (Lalor et al., 2006). This method uses stimuli, the luminance or contrast of which is rapidly and unobtrusively modulated by a stochastic signal, enabling the estimation of the linear impulse response of the visual system. The temporal profile of these VESPAs is highly correlated with that of transient VEPs evoked using standard, discrete stimuli. This includes a clearly defined and, hence, measurable P1 component. The rapidly estimable VESPA has been shown to be superior to the VEP in terms of the amount of time necessary to obtain a response with a specific signal-to-noise ratio. Furthermore, the method allows for a large degree of flexibility in design, not just in terms of the parameters of the stimuli, as in VEP studies, but also in the characteristics of the modulating signal.

The topography of the VESPA is notably different from that of the transient VEP. The abiding characteristic of the early VESPA maps is a persistently delimited focus over midline occipital scalp without any evidence for the characteristic early bilateral spread over lateral occipital scalp regions that is consistently seen for the standard VEP (e.g. Gomez-Gonzalez et al., 1994; Foxe and Simpson, 2002). This pattern suggests that the VESPA may well have a distinct cellular activation pattern from that of the VEP, favoring midline structures such as striate cortex and neighboring retinotopically mapped extrastriate regions, and perhaps also regions in the dorsal visual stream, activation of which are known to produce midline scalp topographies (Clark and Hillyard 1996; Foxe and Simpson 2002). This suggests the VESPA as an excellent candidate for further investigation of a dorsal stream based P1 deficit in schizophrenia.

For that reason, the aim of this paper is to compare VEPs and VESPA responses from schizophrenia patients and healthy controls. Specifically, we examine the relative magnitudes of the P1 components between groups for both types of response. A direct comparison between the VEP and VESPA is complicated by the assumption of linearity intrinsic to the VESPA estimation. In order to address this, we introduce a method for extending the VESPA analysis to higher orders and we expand our comparison between patients and controls to quadratic VESPA responses.

2. Materials and methods

2.1. Subjects

Written informed consent is obtained from 13 (1 female) patients with DSM-IV diagnosis of schizophrenia. The Ethics Committee of St. Vincent's Hospital approved the experimental procedures. Patients were aged 21 to 49 (mean±SD, 33.2±10.1 years) and had a mean illness duration of 12.3 years (SD±9.5). These patients had mean±SD scores on the Brief Psychiatric Rating Scale and SANS of 33.1±5.8 and 22.2±17.7, respectively. Twelve of the patients were receiving antipsychotic medication at the time of testing with a mean chlorpromazine equivalent dose of 406.71 mg/d (range, 50–1500 mg/d). The types of antipsychotics included atypicals, typicals or a combination of both. One patient had ceased taking medication 5 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 11 (2 female) paid volunteers aged 19 to 50 years (mean±SD, 26.5±8.7 years). The mean age of patients and controls did not differ significantly ($t_{50}=1.6$, $p=0.12$). All of the 11 controls, and 12 of the 13 patients were right-handed as assessed by the Edinburgh Handedness Inventory (Oldfield, 1971). None of the controls were receiving any psychotropic medication at the time of testing. Also, all 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), and all reported no history of alcohol or substance abuse.

2.2. Stimuli

VEPs were obtained during a study aimed at assessing schizophrenia patient deficits in visual binding processes using Kanizsa illusory figures. Accordingly, twelve different stimulus displays were presented, some containing Kanizsa illusions and others not. Specifically, the VEPs presented in the current study were obtained using a layout consisting of three centrally presented, black "pacmen" (disks with missing sectors) elements, whose arrangement was such as to *not* give any illusory effect, as in Fig. 1(a).[1] The array of elements subtended maximal visual angles of 2.28° horizontally and vertically and was presented for 400 ms. This allowed ERP analysis to be performed for the first 400 ms without contamination of any visual offset response. The mean inter-stimulus-interval (ISI) between trials was 900 ms (ranging from 600–1200 ms). Thus, each trial had a mean duration of 1300 ms. Note that this stimulus arrangement was chosen as it has previously been shown to elucidate a large VEP P1 deficit in patients with schizophrenia (Foxe et al., 2005; Spencer et al., 2003).

In the case of the VESPA, the stimulus consisted of a checkerboard pattern with equal numbers of black and white checks as in Fig. 1(b). Each check subtended a visual angle of 0.65° both horizontally and vertically, while the checkerboard as a whole subtended visual angles of 5.25° vertically and horizontally. The refresh rate of the monitor was set to 60 Hz and on every refresh the contrast of the checkerboard pattern was modulated by a stochastic signal with the mean luminance remaining constant. The stochastic signals used had their power distributed uniformly between 0 and 30 Hz. See Lalor et al. (2006) for details.

2.3. Experimental procedure

Each VEP experimental block consisted of, on average, 12.75 presentations of each of the 12 display types in a random order. Subjects underwent 20 blocks, resulting in 255 presentations of each display type. During VEP runs a small fixation point was present in the center of the screen, on which subject were instructed to maintain their gaze.

[1] Although only the non-illusion inducing arrangement was used, the reader should note that the P1 component is entirely insensitive to the presence or absence of illusory contours (Murray et al., 2002, 2004, 2006).

Fig. 1. Stimuli used to elicit (a) the VEP — non-illusory arrangement from Kanizsa study (b) the VESPA — single checkerboard the contrast of which is rapidly modulated as in Lalor et al. (2006).

Every subject underwent three VESPA runs of 200 s each. Subjects were instructed to maintain visual fixation on the center of the screen for the duration of each run. While abstaining from eye-blinks was not possible given the trial lengths, subjects were instructed to keep the number of eye-blinks to a minimum. A different modulating waveform was used for each run, although all waveforms had identical statistics.

2.4. EEG acquisition and analysis

EEG data were recorded from 72 electrode positions referenced to location Fz, filtered over the range 0–134 Hz and digitized at a rate of 512 Hz using the BioSemi Active Two system. Subsequently, the EEG was digitally filtered with a high-pass filter with passband above 2 Hz and −60 dB response at 1 Hz and a low-pass filter with 0–35 Hz passband and −50 dB response at 45 Hz.

VEPs were calculated by averaging time-locked responses to the presentations of the display type described earlier. A time window of 500 ms starting 100 ms pre-stimulus was used. Any epochs where the EEG exceeded +/−120 μV were rejected, resulting in a mean rejection rate of 11%.

The VESPA is an estimate of the linear impulse response of the visual system (Lalor et al., 2006). It is based on the assumption that the EEG response to a stimulus, whose luminance or contrast is rapidly modulated by a stochastic signal, consists of a convolution of that signal with an unknown impulse response. Given the known stimulus signal and the measured EEG, this impulse response, i.e., the VESPA, can be estimated using the method of linear least squares. In the present study VESPAs were measured using a sliding window of 500 ms of data starting 100 ms pre-stimulus.

It is possible that a VESPA founded on an assumption of linearity may not be sensitive to the deficits apparent in the VEP. The method can, however, easily be extended to higher orders. For example, in the case of a quadratic analysis, this is accomplished by including in the least squares estimation not only the

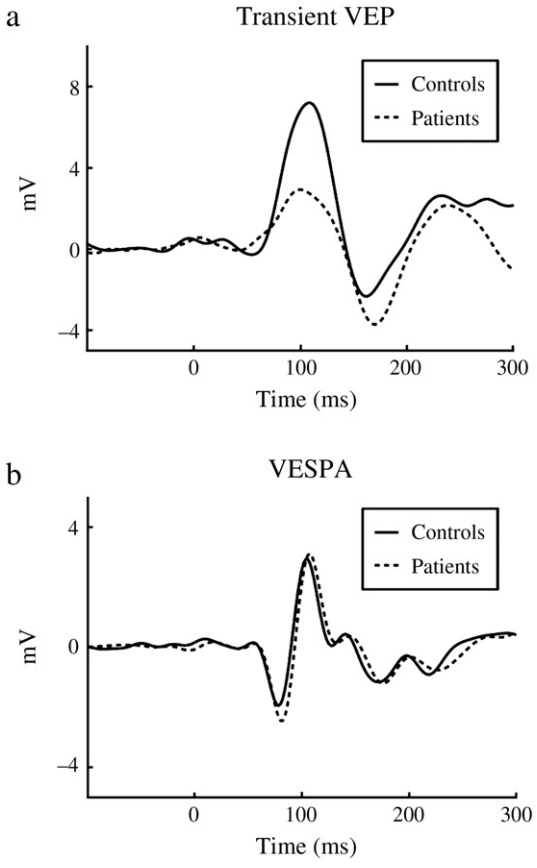

Fig. 2. Average time courses of the transient VEP and the VESPA for controls and patients for both methods at electrode location O2.

1st-order values of the modulating signal within the desired window but also all 2nd-order products of these values (see Appendix for details). This allows us to determine how the EEG depends, not only on the individual input signal values, but also on interactions between inputs at different time lags. In the present study, the quadratic VESPA response was measured using a sliding window of 120 ms of data starting 20 ms post-stimulus.

3. Results

Fig. 2(a) and (b) show the transient VEP and the average VESPA respectively for both the control group and the patients, at electrode location O2. Because the goal of this study was to examine the relative sensitivities of the VESPA and VEP methods to the P1 deficit in schizophrenia, we wished to determine the magnitudes of the P1 component for both methods and groups. We defined the P1 dependent measure as the average amplitude in the interval 90–115 ms, selected on the basis of peak latencies in group-average waveforms. First, an omnibus 2×2×9 ANOVA was carried out with factors of group (controls vs. patients), method (VEP vs. VESPA) and electrode (PO7, PO3, O1, Oz, POz, Pz, O2, PO4, PO8).

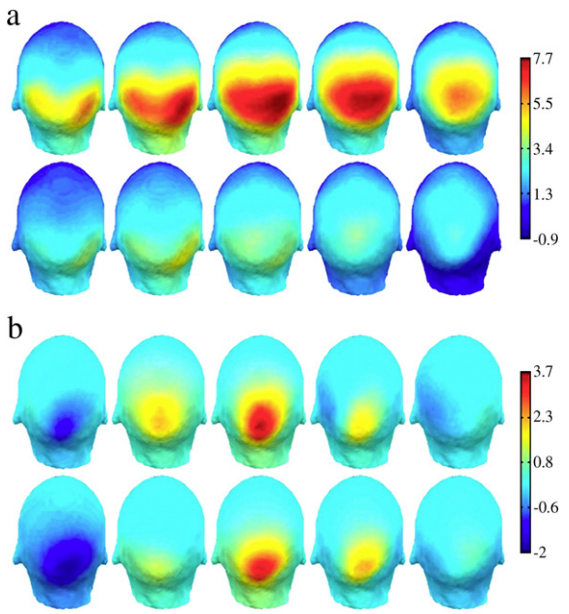

Fig. 3. (a): VEP in μV at 85, 95, 105, 115 and 125 ms. Controls (top) and patients (bottom). (b): VESPA in μV at 85, 95, 105, 115 and 125 ms. Controls (top) and patients (bottom).

A main effect of method ($F(1, 21)=32.24$, $p<0.001$) was found which simply reflects differences in response magnitudes between the two methods, either as a result of the methods themselves or of the specific stimuli used in each method. More importantly, an interaction was found between group and method ($F(1, 21)=7.89$, $p<0.05$). As can be seen in Fig. 2, this was driven by a much larger reduction in P1 amplitude for patients using the VEP method than the VESPA method. A main effect of

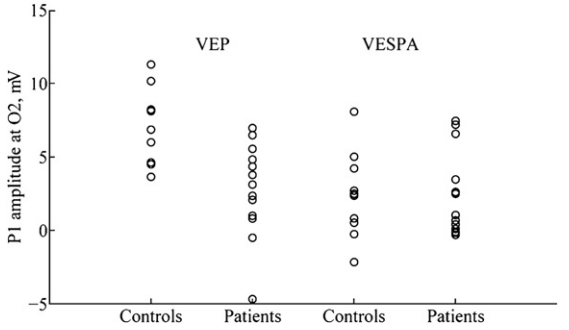

Fig. 4. Scatter plot, showing the distribution of the mean value of the P1 component in the interval 95–115 ms at electrode O2, for all control subjects and patients for both methods.

electrode ($F(8, 168)=10.29$, $p<0.001$) reflected the topographic specificity of the P1. A significant interaction between electrode and method ($F(8, 168)=3.11$, $p<0.05$) reflected the topographic differences between methods evident in Fig. 3. There was no three-way interaction between group, method and electrode ($F(8, 168)=1.57$, $p>0.1$).

To examine the interaction between group and method further, planned *t*-tests were carried out for each method separately. We used the P1, averaged across electrodes O1, Oz and O2, as the dependent measure. A significant difference was found between groups for the VEP method ($t=3.5$, $p<0.005$) whereas no difference was found between groups for the VESPA method ($t=0.08$, $p>0.9$). The Cohen's *d* effect size was calculated for the VEP P1 and found to be 1.57. Figs. 4 and 5 provide further illustration of the differing effects found using the VEP and VESPA methods. Fig. 4 is a scatter plot showing how the mean value of the P1 component in the interval 95–115 ms at electrode O2 is distributed within the control and patients groups for both methods. The standard deviations for the controls were 2.37 for the VEP and 2.76 for the VESPA and for the patients were 3.21 for the VEP and 2.83 for the VESPA respectively.

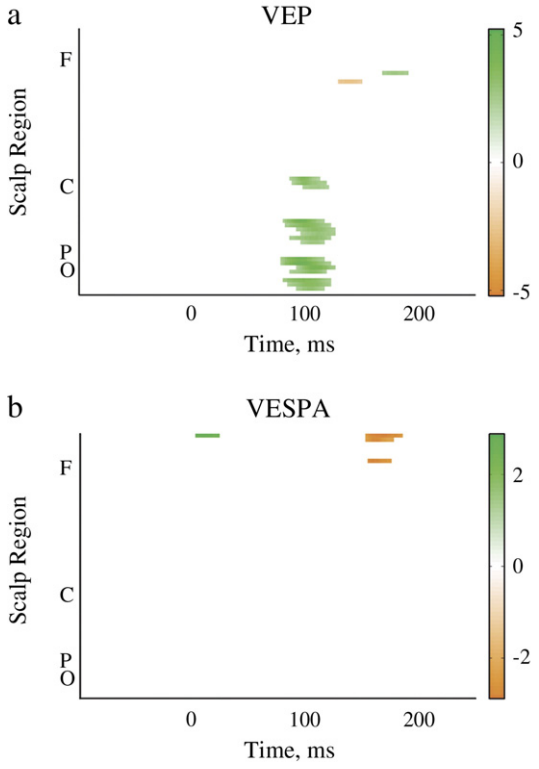

Fig. 5. Statistical cluster plot marking for all electrodes the time points at which the event-related potential differed significantly between groups on the basis of 2-tailed *t*-tests at an α level of 0.05. White denotes nonsignificance while positive *t* values (Controls>Patients) are marked on a green scale and negative *t* values (Patients>Controls) are marked in gold. Electrodes are ordered from the bottom, occipital (O), parietal (P), central (C), and frontal (F) proceeding in the anterior direction in rows from left to right. In the case of the VEP, a cluster is seen over posterior sites in the P1 interval 90 to 120 ms as expected from the results of the planned analysis of variance. No meaningful clusters are seen for the VESPA.

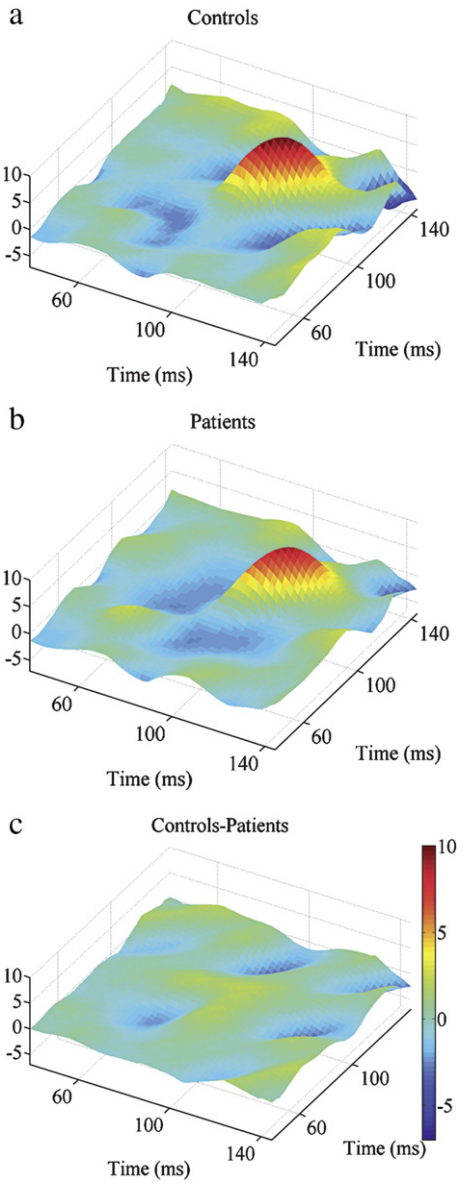

Fig. 6. Grand average quadratic VESPAs at electrode location Oz for controls, patients and the difference between controls and patients. These plots indicate how strongly the EEG at a particular time point depends on the interaction between inputs at two previous time points. Prominent "P1" activity can be see around 100×100 ms for both groups with a negligible difference between groups.

Fig. 5 illustrates a pair of statistical cluster plots marking the time points at which the VEP and VESPA respectively differ significantly between groups for all electrodes. A large cluster is evident in the VEP plot over posterior sites in the P1 interval 90–120 ms. No such cluster is evident in the VESPA plot.

Fig. 6 shows the average quadratic VESPA for both groups for electrode location Oz. Also plotted is the difference between controls and patients. Statistics confirmed the lack of a between-group difference evident from the figure. We defined the P1 dependent measure as the average amplitude in the interval 90–115 ms × 90–115 ms. A 2-way ANOVA was carried out using this P1 measure, with factors of group (controls vs. patients) and electrode (PO7, PO3, O1, Oz, POz, Pz, O2, PO4, PO8). No significant difference was found between groups ($F(1, 22) = 0.197$, $p > 0.6$).

4. Discussion

Replicating the findings of earlier studies (Foxe et al., 2001, 2005; Butler et al., 2001, 2007; Doniger et al., 2002; Spencer et al., 2003; Schechter et al., 2005; Haenschel et al., in press), a substantial reduction in the amplitude of the P1 component of the transient VEP was observed for schizophrenia patients compared with healthy controls. However, somewhat to our surprise, there was no difference whatsoever in VESPA P1 amplitude between patients and controls, in either the linear or quadratic case. This striking contrast in outcomes between two essentially similar methods points to a highly specific disparity between the early visual sensory processing systems of patients and controls. While the scalp topography of the VESPA (Fig. 3) suggests that it may preferentially activate the dorsal visual stream and given that a number of studies have proposed that the VEP P1 deficit shown by patients with schizophrenia may be due to specific dysfunction of this stream (Doniger et al., 2002; Foxe et al., 2005), we had originally expected that the midline-focused VESPA might prove to be more sensitive to this deficit. This is clearly not the case here. In what follows, we consider a number of possible reasons for the lack of a reduction in the amplitude of the VESPA P1.

One explanation concerns the subcortical source of the scalp VESPA and that of the P1 deficit in the VEP. The human visual system consists of discrete subcortical magnocellular and parvocellular pathways that project preferentially to dorsal and ventral cortical streams. In our previous studies, we have consistently posited a magnocellular basis for the observed VEP P1 deficits (e.g. Foxe et al., 2005; Butler et al., 2005, 2007; see also Kim et al., 2005a). The VESPA scalp maps of Fig. 3 suggest possible preferential stimulation of the dorsal stream and thus of magnocellular pathways. Therefore, the lack of a difference in the VESPA between controls and patients suggests that either there is no dysfunction of the magnocellular system in schizophrenia or that the VESPA does not actually reflect activity of the magnocellular system.

Magnocellular and parvocellular cells differ not only anatomically, but also functionally, in terms of preferred stimuli. Parvocellular cells with their spectrally opponent nature are know to be less sensitive to luminance contrast than magnocellular cells (Kaplan et al., 1990; Lee et al., 1990). While, the high contrast gain of cells in the magnocellular pathway might suggest that they may be more sensitive to the contrast modulations of the VESPA stimulus, their response saturates at fairly low contrasts (10–15%; e.g., Baseler and Sutter 1997). Parvocellular neurons, meanwhile, have lower contrast gain, but do not saturate (see Butler et al., 2007). Given that the stimulus described in this study spends less than 2% of its time below 15% contrast (Lalor et al., 2006), it seems reasonable to conclude that the VESPA may actually reflect mostly activity of parvocellular pathways.

The two pathways are also known to differ in their response characteristics to the temporal frequencies of stimuli. The commonly held belief is that magnocellular cells are more suited to high temporal frequency flicker (e.g., Kaplan and Benardete, 2001). As a result, it could again be concluded that the rapid modulation of the VESPA might preferentially activate that subsystem. However, both parvocellular and magnocellular cells in the lateral geniculate nucleus (LGN) of the macaque have been reported to respond best at temporal frequencies in the range of 10–20 Hz (Hicks et al., 1983). More specifically, Derrington and Lennie (1984) found that parvocellular units were most sensitive to stimuli modulated at temporal frequencies close to 10 Hz and magnocellular units to stimuli modulated at frequencies nearer 20 Hz. They also reported that the loss of sensitivity as temporal frequency fell below optimum was more marked in magnocellular than parvocellular units. These findings suggest that, while magnocellular cells are known to have a shorter latency and more transient response to stimuli (Marrocco et al., 1982; Maunsell et al., 1999), parvocellular cells should have no difficulty in following the 0–30 Hz frequency content of the VESPA stimulus.

A further property that differs between the two subsystems is the linearity of their temporal response. While the parvocellular system is approximately linear, the temporal responses of magnocellular cells are particularly nonlinear due to contrast gain control

(Kaplan and Benardete, 2001). The nonlinear nature of this system has been referred to in a recent study, which investigated early-stage visual processing deficits in patients with schizophrenia using the steady-state VEP (SSVEP; Kim et al., 2005b). This study has shown reductions in the second harmonics of the stimulus frequency. Given that second harmonics are thought to depend preferentially on magnocellular pathways, the reduced harmonics are attributed to deficits in those pathways. However, it was also pointed out that deficits in nonlinear mechanisms present in cortex, which are important in producing responses at higher harmonics or temporal frequencies, would also result in greater attenuation of higher harmonic responses in patients than controls. For these reasons, it is clear that a linear VESPA simply may not be sensitive to the nonlinear systems responsible for the generation of the P1 deficit in the transient VEP. In order to address this, we have extended the VESPA method to a quadratic analysis in this paper. The fact that no significant differences were found between patients and controls for the quadratic VESPA lends further support to the notion that, if indeed magnocellular dysfunction underlies the P1 deficit in the VEP, the stimulus used in this study was biased toward linear parvocellular cell populations.

Another potential reason for the dramatic dissociation between VEP and VESPA results stems from the debate over whether the ERP in response to a stimulus constitutes an evoked event or comes about through induced changes in ongoing brain dynamics. While most ERP studies assume the former, some studies have suggested that the ERP at least partly arises from the stimulus-induced phase-resetting of electrophysiological processes (e.g., Makeig et al., 2002; Hanslmayr et al., 2007). While the VESPA does not rule out the notion of an induced contribution to VEPs obtained using discrete stimuli, its continuous nature, which does not allow for any time-locked lower frequency phase-resetting of ongoing brain dynamics, clearly demonstrates that ERPs can be evoked. This leads to a confound in the comparison between VEP and VESPA in that it is at least possible that the reduced VEP P1 components displayed by the patients reflect dysfunction of phase-resetting processes or ongoing oscillatory activity. In support of this notion, one recent study proposed alpha band activity as the likely source of an early induced ERP contribution (Hanslmayr et al., 2007) while various characteristics of alpha oscillations have been shown to differ in patients with schizophrenia, including lower peak frequency (Javitt, 1997) and lower power (Sponheim et al., 1994). The inconclusive (and sometimes contradictory) nature of studies attempting to evaluate phase-resetting and the demonstration of the purely evoked VESPA ERP itself lend support to studies positing a predominant role for stimulus-evoked activity in sensory ERP generation (e.g., Shah et al., 2004). Therefore, attributing a divergence in results as dramatic as reported in this paper to deficiency in induced ERP generation seems, at best, speculative.

In summary, we have demonstrated a striking disparity in relative ERP responses between patients and controls using two different methods of visual stimulation. This points to the highly specific nature of early visual deficits in schizophrenia and speaks particularly to the notion that those deficits are based substantially on magnocellular stream dysfunction where activity of the parvocellular system is largely spared. While the VESPA as implemented in this study was not sensitive to the mechanisms responsible for a reduced P1 component in schizophrenia, the flexibility of the method, in terms of the characteristics of both the stimuli and the modulating signal, suggests its utility as a method for further investigation of those mechanisms.

Appendix A. Extension to quadratic VESPA estimation

As detailed in Lalor et al. (2006), we estimate the linear VESPA as an n-dimensional vector $\mathbf{w}$ consisting of the sampled points of the response function

$$(\mathbf{w}(\tau_0), \mathbf{w}(\tau_1), \ldots, \mathbf{w}(\tau_{n-1}))^T, \tag{1}$$

where n is the number of sampled points of the response function that we wish to estimate. This is done by first forming the n-dimensional vector $\mathbf{x}_t$ consisting of the sampled points of the modulating stimulus

$$(\mathbf{x}(t-t_0), \mathbf{x}(t-(t_0+1)), \ldots, \mathbf{x}(t-(t_0+n-1)))^T, \tag{2}$$

where t_0 is the estimation window offset. The values of $\mathbf{x}_t$ are simply the normalized luminance or contrast values of the displayed stimulus.

We then solve for $\mathbf{w}$ using the equation,

$$\mathbf{w} = \langle \mathbf{x}_t \mathbf{x}_t^T + \lambda M \rangle^{-1} \mathbf{x}_t \mathbf{y}_t \tag{3}$$

where λ is a regularization parameter and M is a near-diagonal matrix.

In this paper, we expand the VESPA estimation to a quadratic model of how the EEG depends on the input stimulus. This is accomplished by replacing Eq. (2) with a vector with $n+n(n+1)/2$ elements, where n is the window size, containing the n 1st-order elements as before, and the $n(n+1)/2$ 2nd-order elements (all products of the form $x(t-t_0-i)x(t-t_0-j)$ where

$0 \le i \le j \le n$). The quadratic VESPA **w**, of this same dimensionality can be solved using,

$$\mathbf{w} = \langle \mathbf{x}_t \mathbf{x}_t^T + \delta I \rangle^{-1} \mathbf{x}_t \mathbf{y}_t \quad (4)$$

where δ is a different regularization parameter and I is the identity matrix. In this study, $\delta = 5 \times 10^{-6}$ gave good reduction in estimation error.

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Contributors

Dr. Lalor designed the stimulus sequences, programmed all paradigms, analyzed all data and wrote the first draft of the manuscript. Dr. Foxe designed the experimental protocol and edited multiple drafts of the manuscript. Dr. Yeap collected all data and tabulated patient demographics, performed the clinical ratings and aided in analyses. Drs. Reilly and Pearlmutter provided critical input regarding development of the VESPA technique and its implementation and provided comments on early drafts of the manuscript. All authors contributed to and have approved the final manuscript. The principle investigator, Dr. Foxe, takes responsibility for the integrity of the data and the accuracy of the data analysis, and attests that all authors had full access to all the data in the study.

Conflict of interest

Drs. Lalor, Pearlmutter, Reilly and Foxe are listed as inventors on a patent application for the VESPA method. Dr. Yeap declares no conflict of interest.

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