Specificity and sensitivity of visual evoked potentials in the diagnosis of schizophrenia: Rethinking VEPs

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ABSTRACT

Alterations of the visual evoked potential (VEP) component P1 at the occipital region represent the most extended functional references of early visual dysfunctions in schizophrenia (SZ). However, P1 deficits are not reliable enough to be accepted as standard susceptibility markers for use in clinical psychiatry. We have previously reported a novel approach combining a standard checkerboard pattern-reversal stimulus, spectral resolution VEP, source detection techniques and statistical procedures which allowed the correct classification of all patients as SZ compared to controls. Here, we applied the same statistical approach but to a single surface VEP — in contrast to the complex EEG source analyses in our previous report. P1 and N1 amplitude differences among spectral resolution VEPs from a POz-F3 bipolar montage were computed for each component. The resulting F-values were then Z-transformed. Individual comparisons of each component of P1 and N1 showed that in 72% of patients, their individual Z-score deviated from the normal distribution of controls for at least one of the two components. Crossvalidation against the distribution in the SZ-group improved the detection rate to 93%. In all, six patients were misclassified. Clinical validation yielded striking positive (78.13%) and negative (92.69%) predictive values. The here presented procedure offers a potential clinical screening method for increased susceptibility to SZ which should then be followed by high density electrode array and source detection analyses. The most important aspect of this work is represented by the fact that this diagnostic technique is low-cost and involves equipment that is feasible to use in typical community clinics.

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1. Introduction

Despite the promising results from studies investigating the neurobiological underpinnings of schizophrenia (SZ), its clinical diagnosis is still based on the assessment of psychopathological and behavioral symptoms. Clear biomarkers that indicate an increased susceptibility to schizophrenia are still not available. One of the shortcomings of these neurobiological studies is that group results do not allow for diagnostic specificity and sensitivity on an individual level. Deficits of visual information processing represent one of the most often reported neurophysiological disturbances in SZ (Yeap et al., 2006, 2008a, 2008b; Butler et al., 2005, 2008; Doniger et al., 2002; Foxe et al., 2005; Lalor et al., 2012). However, assessing visual information processing by standard visual evoked potentials (VEP) has not yet been established as a routine for the diagnosis of SZ (Walsh et al., 2005). We have recently published (González-Hernández et al., 2014) a novel approach for analyzing VEPs on an individual patient level that correctly classified all patients with SZ (n = 78) and 79% of controls (n = 55) to their referring groups. This approach is based on source localization (LORETA) of VEPs with spectral resolution assessed by a full-field checkerboard pattern reversal stimulus. The disadvantage of this approach for clinical use is represented by the high density electrode array required for recording and the expertise in electrophysiological neuroimage needed for analyses. Here, we applied our novel statistical approach to single surface VEP-recordings using a standard two electrode bipolar montage. Individual differences of EEG band-effects on P1 and N1 amplitudes were computed and Z-transformed for use in clinical validation. We hypothesized that specificity and sensitivity of this simple approach are comparable to those based on complex VEP source localization using a high density EEG electrode array. This would make this approach highly attractive for

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the extended use in "real-world" clinical settings in order to help identify patients with increased vulnerability to schizophrenia when there is diagnostic uncertainty.

2. Subjects

We reanalyzed data from forty-three medicated patients with schizophrenia (DSM-IV R) and forty-eight medication free volunteers without any history of psychiatric or neurological disease including drug/alcohol abuse who were included in our recent study (González-Hernández et al., 2014). The study was approved by the Ethical Committee of the Hermanos-Ameijeiras Hospital.

2.1. Visual task

A full-field black–white checkerboard stimulus (60 arc/min; 1.15 cpd) was presented (distance from nasion: 0.9 m) with a reversal rate of 1 Hz (240 trials). Luminance was constant and the contrast was 100%. Viewing was monocular, and data were collected from both eyes separately (for details see González-Hernández et al., 2014).

2.2. Electrophysiology

From the original 58 electrode monopolar recordings (Neuronic, SA, Havana, Cuba), we selected the two electrodes (one occipital, one frontal) that showed the highest rate of correctly classified participants as either SZ or healthy controls (>70%) based on both P1 and N1 amplitudes (supplementary data). By this criterion POz and F3 electrode sites with the references at the earlobes were selected for bipolar analysis. Marks corresponding to the stimuli were co-registered with the EEG. The continuous two-channel EEG was epoched from −100 to 260 ms, linearly detrended and DC corrected. Each EEG was visually inspected and trials with EEG signals greater than 100 µV and/or other artifacts were eliminated. Averages were determined for the original patterned image (120 trials) and its reversal (120 trials), respectively.

2.3. Spectral resolution VEP (srVEP)

Before averaging, each EEG was filtered with different pass bands to discriminate between the classical bands. Thus, individual averages were calculated for all subjects for F3 and POz electrodes for both conditions and both eyes, separately for theta, alpha, beta, beta-1 and gamma bands. For the VEPs analysis we re-referenced the monopolar averaged EEGs to the bipolar standard montage: occipital electrode – POz – with the frontal electrode – F3 – as voltage reference. Then, peak amplitudes of the spectral resolution VEPs were defined for the intervals 90–130 ms (P1) and 135–200 ms (N1), respectively in each individual subject.

2.3.1. Band effect (F) and Z-transformation

For both components P1 and N1, individual VEPs from both eyes and both conditions were assigned to five groups corresponding to the five bands. The intraindividual amplitude differences were explored using repeated-measures analysis of variance (rm-ANOVA). The obtained F-values were assessed in terms of their Gaussian distributions. F-values were then Z-transformed according to Crawford (Crawford et al., 2003; Crawford and Garthwaite, 2004). Significant positive Z-values indicate more differences among bands compared to normal distribution while significant negative Z-values represent fewer differences among bands.

2.4. Validation

For clinical validation, we used crossvalidation and leave-one-out procedures for both groups and components. To classify subjects as either SZ or control, we defined a cutoff Z-value for each distribution then used as positivity criterion. Subsequently, we constructed a 2 × 2

table unifying the VEP components to consider the test results (positive or negative) and true status (disease positive or disease negative) and calculated ROC-curves (CI 95%). A subject was considered as false positive or false negative if classified incorrectly during both the validation and crossvalidation for at least one of the components P1 or N1.

3. Results

P1 and N1 components were identified in the srVEPs of all individuals. The band amplitude-effect was evidenced in all evoked responses (Fig. 1A).

3.1. Statistical analysis and validation

For P1, the cutoff defined on the basis of the normal distribution in controls was $Z = \pm 2.55$. In 33 of 43 patients, Z-scores of F-values from srVEPs were outside the range of the control group classifying these patients as SZ while P1 Z-scores from 10 patients were within the range of the control group. For N1, the cutoff was $Z = \pm 2.30$. 29 of 43 patients were outside the range of the normal distribution of controls while 14 patients were within the range of the control group. There were five patients for whom both components P1 and N1 were within the range of the normal control group (Fig. 1B).

Crossvalidation against the SZ-sample showed that for P1 four of the 10 patients who were inside the range of controls were lying outside the range of the normal distribution of patients (cutoff: $Z = \pm 2.18$) indicating that these patients were not classified as patients in either validation. For N1, three of the 14 patients who were inside the normal range of controls were also outside the range of the normal distribution of patients (cutoff: $Z = \pm 1.96$). From these seven patients, for one patient both components P1 and N1 were lying outside the SZ normal range and inside the normal range of controls. In all six patients must be regarded as misclassified after crossvalidation resulting in a total detection rate of 37/43 (Fig. 1C).

Clinical validation following the same criterion yielded an AUC of 0.85, a sensitivity value of 93.03% and a specificity value of 78.13%, with 21.80% of controls classified as false positive. While the positive predictive value was 79.21% and the negative predictive value was 92.60%.

4. Discussion

To the best of our knowledge, this is the first report about the combination of a standard VEP stimulus, simple two electrode bipolar recordings, and spectral resolution VEPs with a novel statistical approach using Gaussian distributions to quantify the effect of different EEG frequency bands on the surface evoked response amplitude. By this procedure we revealed a striking level of accuracy for correctly classifying patients with SZ. The introduced procedure detected a specific sensory-perceptual deficit reflected by abnormal P1–N1 components in 93% of patients with SZ and also showed high predictive values that support its potential utility. In the majority of cases, the Z-score was negative reflecting a reduced band-effect or band differences in SZ (González-Hernández et al., 2014). Crossvalidation revealed that from the group of patients whose VEPs were within the normal range of controls (10 patients for P1 and 14 patients for N1) VEPs of six patients were also outside the normal range of SZ leaving these patients as misclassified.

Early visual processing deficits mostly related to P1 have been repeatedly demonstrated in SZ (Yeap et al., 2006; Foxe et al., 2001; Doniger et al., 2002; Martinez et al., 2012). Evidences exist that vision capability, i.e. visual information processing per se, represents a susceptibility factor (necessary condition) for SZ, not by itself, but rather by the visual processing impairment in lower visual regions involving bottom-up mechanisms, which prevent from normal functioning of higher order multisensory integration processes (González-Hernández et al., 2003;
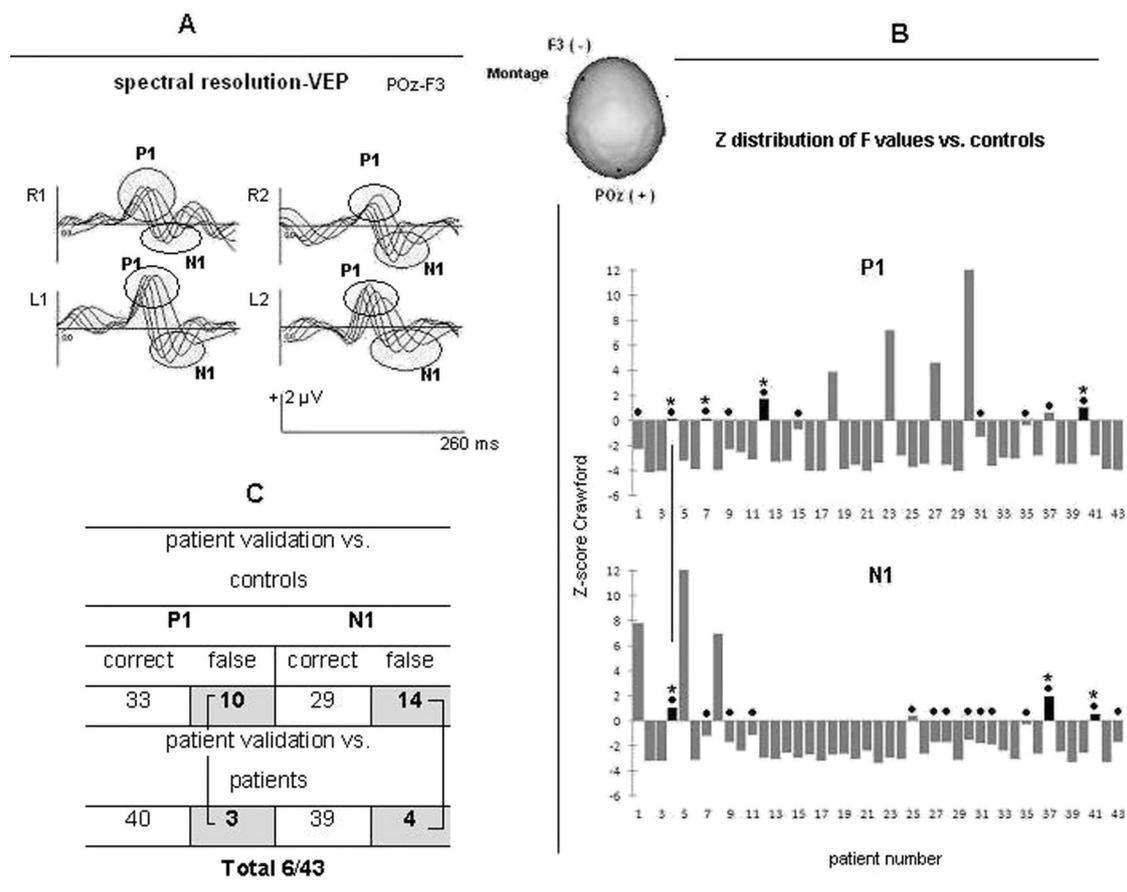
Fig. 1. (A) Appearances of the individual spectral resolution VEPs (chosen randomly) with the bipolar montage using POz and F3 as voltage reference; (B) Z-scores of the band differences of the VEPs from 43 patients with schizophrenia compared to controls; (C) individual patient comparisons against normal distribution of control group and normal distribution of patient group at both components: P1 and N1. Legend: [•] patients misclassified – within normal range – by the first comparison (10 + 14), but within the patient range when compared with the patient group; [•*] patients from the previous misclassified group that were also wrongly classified after comparison with the patient group (3 + 4). Note that patient number 4 (vertical line) is repeated in P1 and N1, thus the final account of misclassification was 6/43.

Butler et al., 2008; Javitt, 2009; González-Hernández et al., 2006; Silverstein et al., 2013; Landgraf and Osterheider, 2013). These facts support the concept that basic deficits of visual information processing are always present in patients with SZ requiring an adequate test to 'easily' uncover them in clinical testing.

Future studies including also patients from other diagnostic groups, such as bipolar disorder, unipolar depression, and anxiety disorder are needed to clarify diagnostic specificity of the here presented results. Cases with positive findings of impaired surface VEPs should be followed by complex source detection techniques applied to high density electrode array recording as previously described (González-Hernández et al., 2014). The method proposed here adheres to international procedures for VEP recording used in clinical neurophysiology, simplifying the process to develop standards just for the novel VEP analysis, its interpretation and clinical report. However, individual laboratory reference values are still recommended. Future studies should define disease-specific VEP alteration patterns recorded under the same conditions.

To remark, the most important aspect of this work is represented by the fact that this very simple diagnostic technique is low-cost and involves equipment that is feasible to use in typical community clinics.

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Contributors

Authors González-Hernández, Pita-Alcorta and Marot designed the study and wrote the protocol, and González-Hernández wrote the draft of the manuscript. Authors Padrón and Finalé managed the literature searches while Galán-García undertook the neurostatistical analysis. Lencer and Wolters revised and discussed the final version. All authors contributed to and have approved the final manuscript.

Conflict of interest

None of the authors report any biomedical financial interests or potential conflicts of interest.

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