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Cognitive event-related potentials differentiate schizophrenia with obsessive-compulsive disorder (schizo-OCD) from OCD and schizophrenia without OC symptoms

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ABSTRACT

Clinical and neurobiological evidence suggests that concurrent presentation of schizophrenia and obsessive-compulsive (schizo-OCD) symptoms represents a distinct clinical entity. Given that obsessive-compulsive disorder (OCD) and schizophrenia have been modeled as having different neurofunctional profiles, the overlap between them represents a heuristic challenge for cognitive and endophenotype research. Event-related potentials (ERPs) may be used to probe neurophysiological correlates of the cognitive, emotional and behavioral disturbances found in neuropsychiatric entities such as schizo-OCD. Here we measure ERPs during a discriminative response task (DRT) in patients presenting with the DSM-IV criteria for both schizophrenia and OCD. We also performed these measurements in patients with OCD without psychotic features, as well as in patients with schizophrenia without OC symptoms. Schizo-OCD patients showed a distinct ERP pattern, with abnormally increased target activation (akin to OCD patients, but unlike the pattern observed in schizophrenic patients) and reduced P300 amplitudes (akin to schizophrenic patients, but unlike OCD patients). Similar to the control subjects, schizo-OCD patients showed larger amplitudes in the non-target condition than in the target condition. These results suggest that schizo-OCD may not only be a distinct clinical entity from pure OCD and schizophrenia, but it may also be characterized by a distinguishable neurophysiologic pattern. Neurobiological underpinnings deserve further considerations and might drive to a definition of a distinctive endophenotype for schizo-OCD in the de-construction of the schizophrenia endophenotype.

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1. Introduction

Schizophrenia coupled with obsessive-compulsive disorder (schizo-OCD) is a clinical entity characterized by concurrent presentation of schizophrenia and obsessive-compulsive symptoms (OCs) (Poyurovsky et al., 2001; Kayahan et al., 2005). The clinical features of these two disorders are assumed to have opposing neurofunctional alterations (i.e., hypofrontality in schizophrenia and hyperfrontality in OCD; Seamans and Yang, 2004; Chamberlain et al., 2005), posing a challenge for both neurocognitive research and endophenotype-modeling.

Suggested diagnostic criteria for schizo-OCD include the fulfilment of DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, 4th edition) criteria for both OCD and schizophrenia (Kruger et al., 2000; Poyurovsky et al., 2003; Ohta et al., 2003), as well as an OCD symptom-severity threshold of >16 on the Yale-Brown Obsessive Compulsive Scale (Y-BOCS; Goodman et al., 1989; Lysaker et al., 2002; Ongur and Goff, 2005). At the clinical level, comorbid OCD in schizophrenia is frequent, ranging from 7 to 46% (Bermanzohn et al., 2000; Poyurovsky et al., 2001), and it is associated with lower levels of social functioning (Fenton and McGlashan, 1986; Berman et al., 1995; Hwang et al., 2000; Poyurovsky et al., 2001), longer hospitalization duration (Fenton and McGlashan, 1986; Berman et al., 1995; Hwang et al., 2000), higher re-hospitalization rates (Nechmad et al., 2003), treatment-resistance (Zohar et al., 1993; Bermanzohn et al., 1997; Poyurovsky et al., 1999) and more severe social impairment (Whitney et al., 2004) when compared with pure schizophrenia.

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Neuropsychological studies on Schizo-OCD patients have shown ambiguous results, either due to the neglect of comorbid conditions in schizophrenic patients (Buchanan et al., 2005) or because of the lack of specificity in the tests employed. Compared with schizo-OCD patients, some studies have reported decreased neuropsychological performance in frontal lobe tests in patients with pure schizophrenia (Berman et al., 1998; Hwang et al., 2000; Borkowska et al., 2003) and a better performance in OCD patients (Borkowska et al., 2003). However, others found no differences between the two groups (Hermesh et al., 2003; Ohta et al., 2003). Lysaker et al. (2002) reported that impaired performance in frontal tasks was related to comorbid OC symptoms. Finally, Sevincok et al. (2006) and Poyurovsky et al. (2007) found a higher level of “Neurological Soft Signs” in schizo-OCD and schizophrenic patients compared with OCD, but found no significant differences between them.

Event-related potentials offer an approach for eliciting neurophysiological correlates of cognitive functioning. The P300 event-related brain potential (ERP) is an index of endogenous cognitive processes typically elicited by infrequent sensory stimuli that are either novel or task relevant. It is so named because of its appearance as a large vertex-positive component with a peak latency of approximately 300 ms after stimulus presentation. The obligate evoked potential response to the stimulus reflects a variety of cognitive processes elicited by a change in the sensory environment. These include directed attention, the contextual updating of working memory, and the attribution of salience to a deviant stimulus (Turetsky et al., 2007).

A reduced amplitude of the auditory oddball P300 response is perhaps the most robust physiological abnormality observed in schizophrenia, having been replicated repeatedly with virtually uniform consistency (Bahramali et al., 1998; Frodl-Bauch et al., 1999; Karoumi et al., 2000). While a prolonged P300 latency has also been reported, this appears to be a much more equivocal and less reliable finding (McCarthy et al., 1993; Jeon and Polich, 2003; Mori et al., 2007). There is also substantial evidence that this schizophrenia trait abnormality is, at least in part, genetically mediated (Kidogami et al., 1992; Karoumi et al., 2000; Kimble et al., 2000). Studies on individuals who share a portion of the genetic diathesis for schizophrenia by virtue of being either the full siblings or offspring of schizophrenic probands show reduced P300 amplitudes (Kidogami et al., 1992; Karoumi et al., 2000; Kimble et al., 2000; Turetsky et al., 2000, 2007). Evidence from ERP data suggests that schizophrenic patients exhibit deficits in higher-level information processing and attentional regulation. The P300 amplitude, as it represents attentional deficits or uncertainty about correct target detection, has therefore been a featured candidate for genetic research in the schizophrenia endophenotype (Bramon et al., 2005). Visual P300 is not as reliably reduced in schizophrenia compared with the auditory P300 component. A few studies have investigated these ERPs with the go/no-go paradigm in schizophrenia, in general demonstrating reduced P300 amplitudes (Kiehl et al., 2000; Ford et al., 2004; Groom et al., 2008).

Many abnormalities observed in OCD patients have also been associated with abnormalities in focusing and directing attention, but in a unique way. This is evidenced by deficits in shifting attentional focus on objective neuropsychological tasks (Chamberlain et al., 2005, 2006). Data from ERPs are consistent with aberrant attentional processes in OCD. Towey et al. (1990) showed reduced P300 amplitudes for target stimuli, but enlarged amplitudes for non-target stimuli in OCD patients versus control patients.

These data were supported in a different study by our group, in which OCD patients failed to show differential P300 amplitudes for target versus non-target stimuli, and showed abnormally large P300 amplitudes compared with values in controls for specifically non-target stimuli (Di Russo et al., 2000). In addition, N200 amplitude has been reported to be larger in OCD patients than in control patients (De Groot et al., 1997). A number of studies have also reported shorter latencies in OCD than in normal control subjects (Towey et al., 1990; Miyata et al., 1998; Morault et al., 1998; Mavrogiorgou et al., 2002).

Collectively, these ERP abnormalities in OCD have been interpreted in terms of over-focused attention to random details (both relevant and irrelevant stimuli) with cerebral hyperactivation of the frontal lobe (Beech et al., 1983; Towey et al., 1990; Morault et al., 1998).

Considering the comparison between schizophrenic and OCD patients, a recent study reported smaller P300 amplitudes in both patient populations compared with controls, but found no significant difference between them. A correlation between P300 abnormalities and the Luria Nebraska Test was also observed in the schizophrenic patients sample, while P300 alterations in OCD patients correlated with the Trail Making Test (part B; Kim et al., 2003).

Given that neurophysiological measures relating to cognition may be useful in the search for endophenotypes (Turetsky et al., 2007), the aim of the present study was to investigate ERPs in schizo-OCD patients, and compare them to patients with OCD without psychotic features and patients with schizophrenia but without OCD. To our knowledge, this population has never been studied using neurophysiological testing. These patient populations were compared with healthy controls.

Considering the inconclusive results of the scientific literature on cognitive deficits in schizo-OCD, we also wanted to test whether this group had greater impairment compared with schizophrenic and OCD patients. In this case, considering schizo-OCD as a comorbid entity might show both the quantitative schizophrenic and specific OCD deficits. Alternatively, it may be possible that schizo-OCD is not simply a more severe comorbid form but a distinct entity, with a unique pattern of neurophysiological deficits.

Using P300 oddball and go/no-go paradigms to register frontal functionality/dysfunctionality has been criticized due to the limited efficacy in measuring frontal functionality (Towey et al., 1990; Morault et al., 1998). In the classical oddball paradigm, the high probability of non-target stimuli most likely only permits a small involvement of the frontal inhibition system (Ritter et al., 1983). No difference has been reported between schizophrenic and OCD patients in terms of ERP abnormalities; both these conditions were associated with significantly smaller amplitudes in patients than those observed in control patients.

In the go/no-go paradigm, one could argue that the greater wave amplitude that occurs when the subject has to stop (no-go signal) is affected by the warning stimulus and not only by inhibitory activity. It is not clear if inhibitory activity itself (without a warning stimulus) is sufficient to produce greater wave amplitudes (Ritter et al., 1983).

To emphasize the aspects of activation and inhibition, a task similar to a go/no-go paradigm was chosen, but the task lacked a warning signal. This paradigm could also be considered as an equal-frequency variant of the oddball paradigm. In the present study, visual ERPs were examined in schizo-OCD, OCD, schizophrenic and normal control subjects during a discrimination response task (DRT) employing simple visual stimuli. In this paradigm (a variation of the auditory version devised by Ritter), the non-target stimulus requires a high degree of inhibition with considerable frontal involvement (Ritter et al., 1983).

To our knowledge, this is the first ERP study to be conducted in schizo-OCD patients. It is also the first to make comparisons between patients with schizo-OCD, OCD, schizophrenic patients without comorbid OCD and normal control subjects.

2. Materials and methods

The study was carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans. All subjects gave written informed consent prior to participating. The Institutional Review Board of the University of Florence approved this study.

2.1. Subjects

Patients were recruited from the Day Hospital at the Institute of Neurosciences, and controls came from the background population in Florence.

Some participants took part in a prior study and their ERP data have been reported previously (all controls and eight of the OCD patients; Di Russo et al., 2000). Eleven schizo-

OCD patients (mean age \pm S.D.: 38.3 ± 7.4 ; five female), 16 OCD patients (mean age \pm S.D.: 29.7 ± 6.3 ; seven female), 14 schizophrenic patients (mean age \pm S.D.: 30 ± 2.2 ; six female) and 12 controls (mean age \pm S.D.: 30.4 ± 5.3 years; six female) participated in this study. All subjects were aged between 18 and 65 years; they were right-handed and had normal or corrected vision.

The mean \pm S.D. duration of illness was 82 ± 62 months for OCD, 84 ± 54 months for schizo-OCD, and 75 ± 53 months for schizophrenic patients.

Diagnostic assessment included a structured clinical interview for DMS-IV (SCID-CV; First et al., 1997). Diagnoses were confirmed via clinical interview conducted by SP and LQ. Symptom severity of OCD was recorded using the Y-BOCS (Goodman et al., 1989), with scores for obsessions and compulsions defined as “persistent unwanted ideas not related to their delusions” for the schizo-OCD group (Eisen et al., 1997). Schizophrenia severity was quantified according to the Scale for Assessment of Positive Symptoms (SAPS, Andreasen, 1984) and the Scale for Assessment of Negative Symptoms (SANS, Andreasen, 1983).

For inclusion, patients required a DSM-IV (SCID-CV; First et al., 1997) diagnosis of schizophrenia and/or OCD. In the cases of schizo-OCD, psychiatrists ensured OC symptoms were separate from schizophrenic delusions. For patients with OCD, a severity threshold of ≥ 16 points on the Y-BOCS was chosen (Lysaker et al., 2002; Ongur and Goff, 2005) and absence of psychotic symptoms was required. To avoid state-dependent biases, participants were screened twice, 2 months apart, to confirm the consistency of the diagnosis. Patients with comorbid panic disorder, unipolar depression, or bipolar disorder were excluded from the study. Other exclusion criteria included: (1) a clinically notable neurological disease; (2) a history of head injury; (3) speech or hearing impairment; and (4) substance abuse. All patients were drug-free for at least 2 weeks before ERP-recording; confirmation of this requirement was achieved via monitoring during Day Hospital attendance.

An estimate of premorbid IQ was obtained using the TIB (Test Intelligenza Breve – Sartori et al., 1995), which is an Italian examination analogous to the NART (National Adult Reading Test; Nelson, 1982).

Patients with significant clinical depression (Hamilton Rating Scale for Depression ≥ 17) were excluded from the study. None of the patients presented panic, high levels of generalized anxiety or psychomotor agitation at the time of the study.

2.2. Procedure

Details for the Discriminative Response Task (DRT) have been described previously (Di Russo et al., 2000).

Subjects were comfortably seated in a dimly lit soundproofed room. During the task, volunteers made simple motor responses to the Go (target) stimuli, but avoided responses to the No-Go (non-target) stimuli. Stimuli were presented using a VGA computer monitor approximately 100 cm from the participants. The screen provided a $24^\circ \times 18^\circ$ visual angle. A small circular red spot ($0.3^\circ \times 0.3^\circ$) in the center of the display was employed as the fixation point. Stimuli were generated by the STIM[™] system (NeuroScan Inc.) and were composed of vertical yellow bars or horizontal yellow bars ($5^\circ \times 0.5^\circ$). Stimuli were presented at the center of the screen for 100 ms on a dark gray background, the vertical and horizontal line sequence was random, and a Stimulus Onset Asynchrony (SOA) of 2.5 s was used. Subjects were required to press a button using their right hand when target stimuli appeared. For half of the exercise (101 trials), target stimuli were horizontal bars and vertical bars were distracters and contrariwise for the other half of the exercise (101 trials). The order of these two task segments was randomized, and there was a 2-min break between segments. Total testing time was approximately 15 min. The first trial from each segment was discarded for the purposes of the analysis.

2.3. Data recordings

Reaction times (RTs) and ERPs were recorded on-line as the subjects performed the task. Wideband EEG and EOG were sampled continuously at 2 ms/channel using NeuroScan Inc. software (SCAN ver. 3.1) on a Pentium PC. The EEG was recorded from 20 scalp electrodes (FP1, Fp2, F7, F3, Fz, F4, F8, T3, C3, Cz, C4, T4, T5, P3, Pz, P4, T6, O1, Oz, O2) according to the 10–20 system using an electrode cap (Electro-Cap International). Vertical and horizontal EOG was recorded with disk electrodes situated above and below the right eye and on the outer canthi of each eye, respectively (both bipolar). The

EOG was amplified $25,000\times$ (dynamic range 11 mV, sensitivity 0.168 μ V/bit) and the EEG was amplified $50,000\times$ (dynamic range 5.5 mV, sensitivity 0.084 μ V/bit) using a SYNAMPS DC coupled amplifier, band-pass filtered at DC–70 Hz (-12 dB down). Linked mastoids were used as the signal reference for all EEG electrodes and FPz was used for the signal earth.

2.4. Data analysis

The reaction-time window was from 100 to 800 ms after stimuli. Epochs of 1200 ms in duration including a 200-ms pre-stimulus baseline were extracted from the continually digitized EEG. All epochs in which EOG amplitudes were greater than ± 80 μ V and EEG amplitudes were greater than ± 60 μ V were excluded from further analysis. Epochs were also excluded if a missed or false alarm was associated with the eliciting stimulus. Event-related potentials from the two DRT runs were combined and sorted into two categories for each subject: ERPs for non-target stimuli (non-target condition) and ERPs for target stimuli (target condition).

Peak amplitudes (relative to the pre-stimulus baseline) and peak latencies of major ERP components were calculated for each subject in the following time window: P100 (70–150 ms), N100 (130–230 ms), P200 (200–300 ms), N200 (250–350 ms) and P300 (300–500 ms). The time window for the components was selected in an attempt to distinguish between the early components, apparently modulated only when the task was in high demand of perceptual processing (70–150), attentional (130–230), or (N2 and P300) components more related to time orientation, attentional preparation of decision and/or motor processes (Correa et al., 2006). The data for each time window were evaluated using separate analyses of variance (ANOVA). To avoid excessive multiple comparisons, data were analyzed only from electrode sites chosen *a priori* to be of interest, on the basis of prior studies (Di Russo et al., 2000).

Data for the early components (P100, N100, P200) were entered into a repeated measures ANOVA using group as the between-subjects factor (normal, schizo-OCD, OCD, and schizophrenia) and task condition (go/no-go) and electrode position (T5, P3, Pz, P4, T6, O1, Oz and O2) for within-subjects factors. For late components (N200 and P300), the between subjects factor was group, with the within-subjects factors of task condition and electrode position (F3, Fz, F4, C3, Cz, C4, P3, Pz and P4). Behavioral data for reaction times were subjected to one-way ANOVAs, with group as the between-subjects factor and task condition as the within-subjects factor. To investigate significant effects or interactions, post-hoc comparisons were conducted using Tukey's Honest Significant Difference (HSD) tests. The threshold of significance was set at $P < 0.05$.

3. Results

3.1. General characteristics

Demographic and clinical features are shown in Table 1. Overall, the groups did not differ significantly in terms of gender ratio, IQ or mean duration of illness.

With regard to age, no significance differences were found among OCD, schizophrenic patients and controls using a one-way ANOVA. A significant difference was found between these groups and schizo-OCD patients ($F_{(3,49)} = 6.38$; $P < 0.05$ – Tukey's HSD test).

3.2. Behavioral data

Motor reaction times showed a significant effect of group ($F_{(3,49)} = 14.52$; $P < 0.01$). Latencies observed in OCD patients (mean \pm S.D.: 301 ± 28 ms) did not differ from normal latencies (mean \pm S.D.: 286 ± 16 ms), while schizophrenic (mean \pm S.D.: 331 ± 18 ms) and schizo-OCD (mean \pm S.D.: 328 ± 15 ms) latencies differed from these two groups. The error

Table 1
Demographic and clinical features in the three groups of patients and healthy controls

Groups	Healthy controls (n: 12)	Schizo-OCD (n:11)	OCD (n:16)	Schizophrenic patients (n:14)
Age	30.4 ± 5.3	38.3 ± 7.4	29.7 ± 6.3	30 ± 2.2
IQ	112 ± 6	110 ± 5	113 ± 6	110 ± 4
Y-BOCS average obsession		14.6 ± 2.9	15.6 ± 1.4	5.2 ± 1.9
Y-BOCS average compulsion		13.9 ± 2.3	14.1 ± 2.6	7.15 ± 1.5
Y-BOCS total		28.5 ± 4.1	29.7 ± 2.8	12.35 ± 3.0
Average SANS		12.3 ± 2.4	3.8 ± 1.2	21.0 ± 5.7
Average SAPS		13.8 ± 2.5	1.3 ± 0.4	18.6 ± 5.5

Y-BOCS: Yale–Brown Obsessive Compulsive Scale.

SAPS: Scale for Assessment of Positive Symptoms.

SANS: Scale for Assessment of Negative Symptoms.

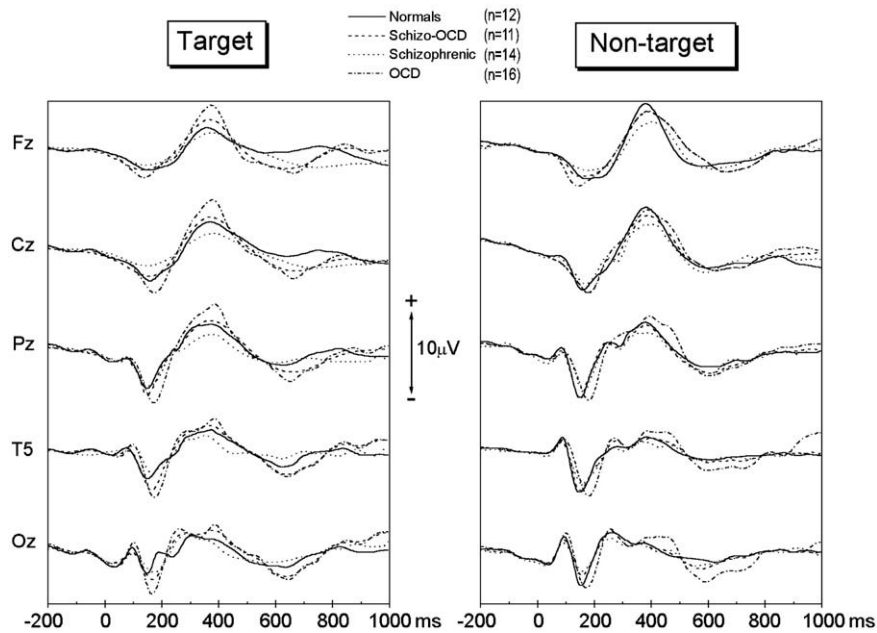


Fig. 1. Grand average ERP in normal subjects and schizo-OCD, schizophrenic and OCD patients for target (right panel) and non-target (left panel) conditions recorder in 5 selected electrodes.

rates for the controls were 2.1% and 3.3% for omission and false alarms, respectively. For OCD patients, omission was 2.8% and the false alarm rate was 3.8%. For schizophrenic patients, omission was 2.5% and the false alarm rate was 3.6%. Finally, for schizo-OCD patients, omission was 2.3% and the false alarm rate was 3.4%. Groups did not differ significantly from each other for any of these measures.

3.3. ERPs data

The grand average ERP waveforms of control, schizo-OCD, OCD, and schizophrenic subjects are presented in Fig. 1. As expected, five major peaks were always identified across the three conditions, a small positive peak (P100) at around 100 ms, a large negative peak

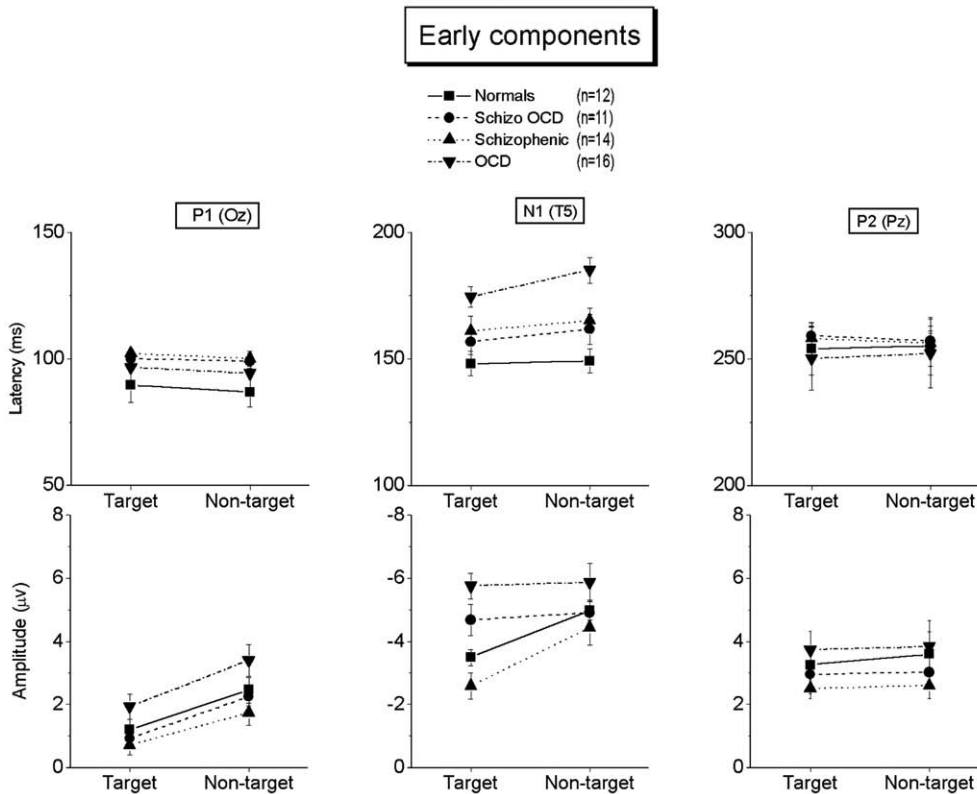


Fig. 2. Mean latency (upper panels) and amplitudes (lower panels) of early components.

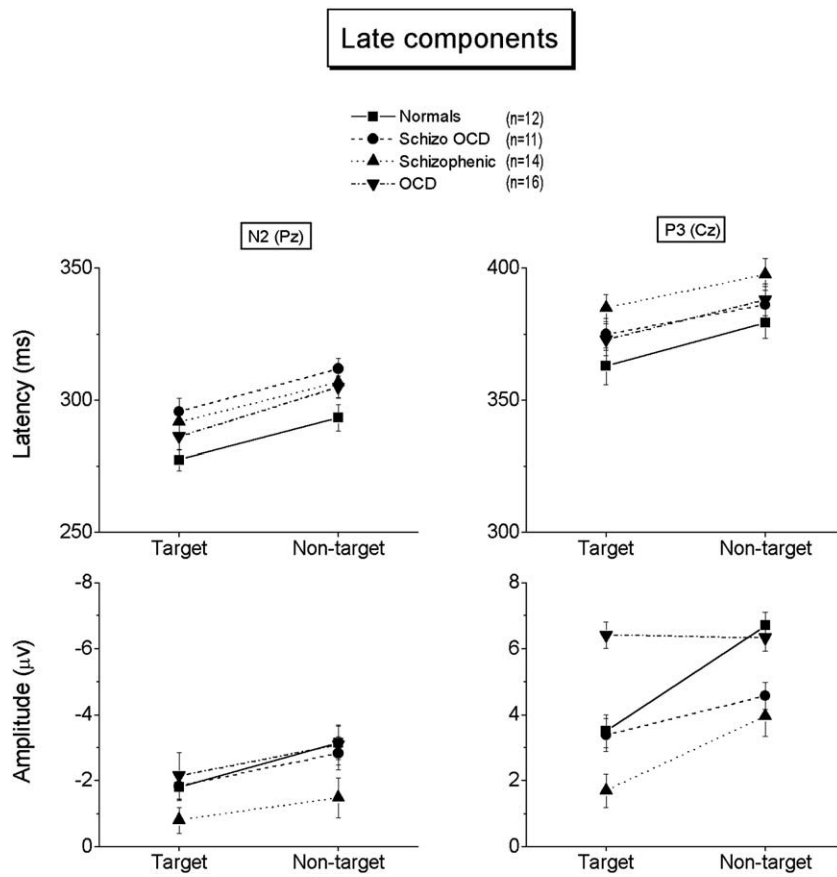


Fig. 3. Mean latency (upper panels) and amplitudes (lower panels) of late components.

(N100) at around 150 ms, a positive peak (P200) around 240 ms, a negative peak (N200) at around 320 ms and a large positive peak (P300) at around 370 ms.

The mean latency and amplitude of the early component in the four groups are shown in Fig. 2. As expected for P100 amplitudes, we found a significant effect of trial type (go vs. no-go) ($F_{(1,51)} = 6.05$,

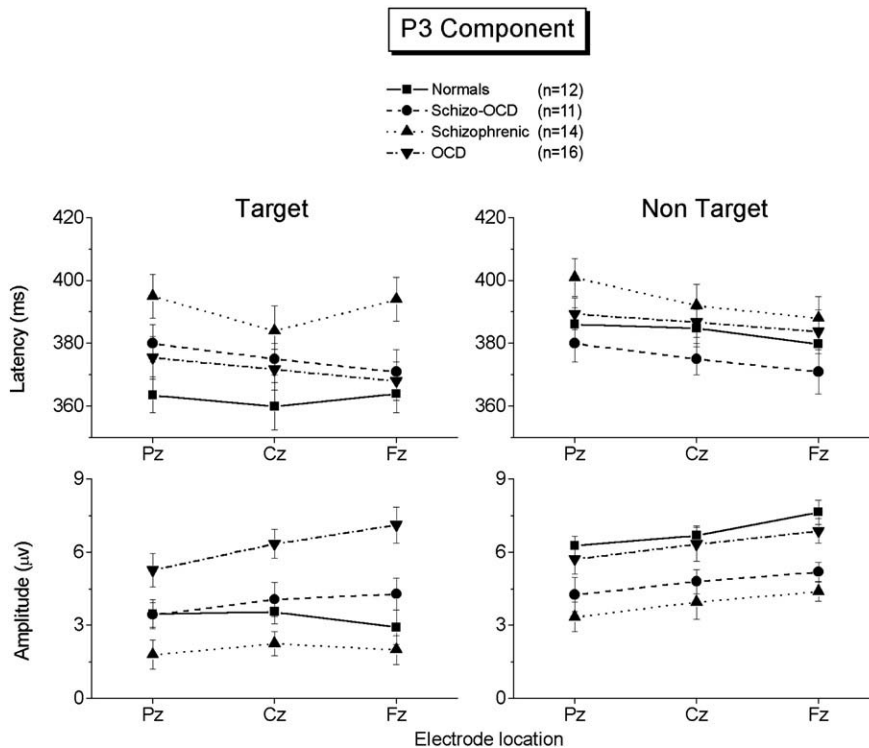


Fig. 4. Mean latency (upper panels) and amplitudes (lower panels) of P 3 components recorded in three selected electrodes.

$P < 0.05$). No effects of group or interactions approached significance for P100 amplitudes.

For N100 amplitudes, there was a significant effect of group ($F_{(3,49)} = 3.84, P < 0.05$) and of trial type ($F_{(1,51)} = 7.69, P < 0.01$). Furthermore, there was a significant group by trial type interaction ($F_{(4,45)} = 6.85, P < 0.01$). Post-hoc analysis showed that the N100 target amplitude in schizo-OCD was higher than in schizophrenic patients ($P < 0.01$). For N100 amplitudes, other comparisons were not significant. No effects or interactions were significant for P200 amplitudes.

Mean latency and amplitude of the late component of the four groups are shown in Fig. 3. For N200 amplitudes, there was a significant effect of group ($F_{(3,49)} = 3.01, P < 0.05$). Post-hoc analysis showed that this was due to the schizophrenic patients differing from other groups. For the N200 amplitude, all other comparisons were not significant.

P300 amplitudes showed a significant effect of group ($F_{(3,49)} = 4.01, P < 0.05$) and of trial type ($F_{(1,51)} = 6.43, P < 0.01$), and group by trial type by electrode location ($F_{(8,304)} = 7.85, P < 0.01$). P300 target amplitude in schizo-OCD patients was lower than that of OCD patients ($P < 0.01$). In controls, P300 amplitude for the non-target was larger ($P < 0.01$) than the target for the Cz, Pz and Fz electrodes (Cz non-target = $6.7 \pm 0.5 \mu\text{V}$, Pz non-target = $6.30 \pm 0.4 \mu\text{V}$, Fz non-target = $7.6 \pm 0.6 \mu\text{V}$, Cz target = $3.5 \pm 0.4 \mu\text{V}$, Pz target = $3.2 \pm 0.4 \mu\text{V}$, Fz target = $2.7 \pm 0.6 \mu\text{V}$). In schizo-OCD patients, non-target ($4.3 \pm 0.5 \mu\text{V}$) and target ($3.9 \pm 0.5 \mu\text{V}$) did not differ. Moreover, the target P300 amplitude in schizo-OCD patients was higher ($P < 0.05$) than in controls in Fz ($P < 0.05$), while in the non-target condition, amplitude P300 in schizo-OCD was lower than in controls in Fz ($P < 0.01$), Cz ($P < 0.01$), and Pz ($P < 0.01$) (Fig. 4). In OCD patients, the non-target ($6.5 \pm 0.5 \mu\text{V}$) and target ($6.2 \pm 0.5 \mu\text{V}$) did not differ; however, the Fz amplitude in the target condition ($7.3 \pm 0.7 \mu\text{V}$) was higher ($P < 0.01$) than the amplitude at Pz ($5.1 \pm 0.7 \mu\text{V}$). Moreover, target P300 amplitude in patients was higher ($P < 0.01$) than in controls, while in the non-target condition, control and patient P300 amplitudes did not differ (Fig. 4). Non-target P300 amplitude in OCD patients was higher than in schizophrenic patients ($P < 0.01$). In schizophrenic patients, the target P300 amplitude differed from the non-target amplitude ($P < 0.01$). The P300 target amplitude was lower than in controls in Pz ($P < 0.01$), while in the non-target condition, the P300 amplitude in patients was lower than in controls in Fz ($P < 0.01$), Cz ($P < 0.01$) and Pz ($P < 0.01$) (Fig. 4). Other comparisons were not significant.

The P3 latency ($F_{(3,49)} = 3.74, P < 0.05$) showed a significant effect of group. According to the post-hoc analysis, schizophrenic patients showed a higher latency compared with other groups in target and non-target conditions.

The P300 latency showed a significant effect of group by task and by electrode location ($F_{(8,304)} = 4.00, P < 0.05$) (Fig. 4). Post-hoc analysis revealed that schizophrenic patients showed higher P300 target latency in Cz and Fz compared with the other three groups.

For P100, P200, N200, and P300 latency, no other effects or interactions were significant (Fig. 2).

4. Discussion

We attempted to characterize cognitive evoked potentials and response inhibition in patients with schizo-OCD compared with OCD, schizophrenic and control subjects.

The main finding in this study was that schizo-OCD patients showed a distinct ERP patterns compared with both OCD patient and schizophrenic patient groups.

With regard to behavioral data reported by Sevincok et al. (2006) and Poyurovsky et al. (2007), we found that schizophrenic and schizo-OCD patients showed a decreased performance for reaction times compared with OCD patients and healthy controls.

4.1. Schizo-OCD patients compared to normal controls

Schizo-OCD patients showed no differences between non-target and target conditions (akin to OCD patients), with target P300 amplitudes higher than in controls in Fz (similar to OCD patients) and with non-target P300 amplitudes being lower than in controls in Fz, Cz and Pz (similar to schizophrenic patients). Patients with schizophrenia (without OCD) had longer latencies and smaller amplitudes compared not only to controls and OCD as expected, but also compared to schizo-OCD patients. This may be interpreted as patients with schizophrenia but without OCD possibly being more dysfunctional than patients with schizophrenia and OCD.

In controls, the non-target stimuli (no-go task) produced a larger activation than the target stimuli (go task). Interestingly, OCD patients showed a larger amplitude than controls for the target with the stimulus (particularly evident in the N100 and P300 amplitudes), but not in the non-target stimuli. These data are consistent with previous reports (Towey et al., 1990; Di Russo et al., 2000). Schizo-OCD patients also have larger amplitudes compared to controls and schizophrenic patients for the target stimuli. This, however, is less evident than for OCD patients compared to schizophrenic patients and controls.

4.2. Comparison within patients – early components

Our finding that the N100 target amplitude in schizo-OCD patients was higher than that in schizophrenic patients may be interpreted as schizo-OCD patients having a better performance in terms of the initial orientation response (selective attention) compared to schizophrenic patients without comorbid OCD.

4.3. Comparison within patients – late components

Schizo-OCD patients showed a target stimulus response similar to OCD patients, with no differences between the P300 target and the P300 non-target, while schizophrenic patients showed a spared difference between target and non-target. This may be interpreted as an expression of the same abnormal attentional shift observed in OCD patients.

Patients with OCD showed larger amplitudes both in the target and in the non-target condition than the other two groups (schizophrenic and schizo-OCD), and showed no differences from the mean amplitude of controls in the non-target condition.

These results demonstrate a larger non-target P300 with the maximum activation located in the frontal areas of the brain of OCD patients. According to the hypothesis that no-go P300 reflects the activity of a response inhibition system in the frontal areas of the brain (Jodo and Kayama, 1992; Roberts et al., 1994), the evidence of increased target amplitude compared to controls in Fz has been interpreted in terms of increased arousal to minimal stimulation (Beech et al., 1983), over-focused attention with cerebral hyperactivation of the frontal lobe region and a prevalence of task-directed processes that induces a subsequent loss of information (Towey et al., 1990). Patients with OCD are overfocused on the physical features defining the relevant stimuli (Morault et al., 1998). Higher frontal amplitude in target stimuli, however, may be explained in terms of high switching cost, previously found in OCD patients on neurocognitive go or no-go tasks (Watkins et al., 2005).

Tasks that examine switching performance may be useful not only in examining response inhibition failures but also set-shifting (Chamberlain et al., 2005). Set-shifting represents the ability to switch attention from one aspect of a stimulus to another in an ongoing task, in accordance with changing reinforcement contingencies. Our data seem to confirm a set-shifting deficit in OCD patients (Hymas et al., 1991; Okasha et al., 2000), and this deficit may be present in schizo-OCD patients as well.

No-go N200 and no-go P300 are known to be electrophysiological indices of response inhibition (Fallgatter and Strik, 1999; Bokura et al.,

2001). According to previous studies, schizophrenic patients showed a higher P300 latency (McCarley et al., 1993; Jeon and Polich, 2003; Mori et al., 2007), and lower P300 amplitudes (Kiehl et al., 2000; Ford et al., 2004; Groom et al., 2008) compared to other groups in the target and the non-target condition. Amplitude of schizo-OCD patients were larger compared with schizophrenic patients in target and non-target conditions, where they have larger amplitudes even when compared with controls. P300 reduction has been interpreted as a reflection of the deficits in complex cognitive processes, such as expectancy and context updating (Braff, 1993; Squires-Wheeler et al., 1993). As reported in other studies (Strandburg et al., 1994), small P300 amplitude may indicate a subject's uncertainty of correct target detection. Because of their object-working memory impairment, schizophrenic patients may feel less confident about target identification. Kamio et al. (2001) demonstrated that schizophrenic patients had lower amplitudes of inhibitory ERP activities related to the suppression of task-irrelevant auditory information. The disturbed no-go potentials have also indicated stimulus inhibition and/or monitoring deficits in schizophrenic patients (Kiehl et al., 2000).

4.4. Conclusive remarks

In terms of ERP abnormalities, schizo-OCD patients showed a distinct pattern compared to both OCD and schizophrenic patients: a lower non-target P300 similar to schizophrenic patients as an expression of a response inhibition deficit, but a higher amplitude compared to comorbid schizophrenic patients without OCD.

In this study, the P300 elicited through a go/no-go paradigm emphasizes the aspects of activation and inhibition, and without a warning signal (a paradigm that could be considered as an equal-frequency variant of the oddball paradigm; but the non-target stimulus requires a high degree of inhibition), highlights the differences between schizophrenic and OCD patients. Our results confirm previous findings, which demonstrate that schizophrenic patients have more generalized cognitive impairments. These impairments result in a wide range of cortical dysfunctions, documented by ERPs, neuropsychological abnormalities (Kim et al., 2003), and morphometric studies, which compared schizophrenic and OCD patients (Kwon et al., 2003; Ha et al., 2005).

Patients with OCD showed P300 abnormalities, which in previous studies have been related to attention-shifting abilities measured by neuropsychological tests such as the Trail Making Test part B, which is mediated by the fronto-striatal system (Lezak, 1995; Kim et al., 2003).

Although schizo-OCD is not yet considered a nosological entity, comparative assessment of cognitive function with specific tests has shown a specific pattern of alteration that is distinguishable from schizophrenia and OCD.

Considering the conflicting positions in the literature regarding the neuropsychological and clinical features of schizo-OCD, our data confirmed findings by Borkowska et al. (2003), who showed that schizophrenic patients were the most neuropsychologically impaired group and that the OCD group was the least impaired, whereas the schizo-OCD patients scored between these two groups.

Moreover, several neuropsychological studies have suggested that OCD with schizotypal personality traits may have distinct patterns of neurocognitive deficits (Harris and Dinn, 2003) and morphometric abnormalities (Lee et al., 2006) that differ from those of OCD without schizotypal personality traits.

These data may support the suggestion of a specific pattern of neurobiological deficits in the subgroup of patients that accounts for symptom co-expression, and that "schizo-OCD" can be considered a specific disorder instead of a severe form of OCD or a complicated form of comorbidity with schizophrenia.

Of interest in our sample, the presence of OCD clinical symptoms was scarcely relevant in schizophrenic patients, as documented by the YBOCS mean values (mean \pm S.D.: 12.35 \pm 3.0).

The main limitation of our study was the number of patients; this was due to our strict inclusion criteria. The small sample size made it more difficult to identify specific differences according to the psychophysiological hypothesis in relation to the different time windows. Further studies with larger samples may better demonstrate these differences. Other limitations may include the difference in age between the schizo-OCD group and the other groups, and the fact that the DRT is a non-standard go/no-go procedure with less normative data. The typical P300 is not elicited with this task, and it has a more difficult interpretation. Nevertheless, we chose this procedure to emphasize the aspects of activation and inhibition. In fact, it does not have a warning signal, making it a certainty that the greater wave amplitude that occurs when the subject does not have to respond to the stimulus (no-go) is caused by inhibitory activity. In this paradigm, the non-target stimulus requires a high degree of inhibition with considerable frontal involvement.

Differences in treatment responses (normalization/or exacerbation of symptoms of OCD already reported with second generation antipsychotic medication) may be better detected by ERPs, considering the long-term effects on P300 and N200. A change in cortical activity under medication might reflect different genetic polymorphisms (Yu et al., 2001).

There is some evidence that typical and second generation antipsychotic drugs may affect the P300 wave (Pallanti et al., 1999). The present data were collected during a period when patients were drug-free.

In schizophrenia, there appears to be excessive transmission of the allele that produces more catechol-O-methyl transferase (COMT) activity and less prefrontal cortex dopamine (Egan et al., 2001; Weinberger et al., 2001; Goldberg et al., 2003). Given its role in dopamine degradation, the COMT gene (the Val158Met polymorphism) is thought to influence prefrontal cognition. Recent studies have reported an association between the COMT genotype and P300 phenotypes (Gallinat et al., 2003; Tsai et al., 2003) and constitute the first descriptions of a precise genetic influence on the P300 wave. In addition, family and twin studies indicate that these P300 traits are heritable, and that deviances are also observed amongst the unaffected relatives of the patients. This makes the P300 wave a promising intermediate endophenotype for genetic research into psychotic disorders (Frangou et al., 1997; Bramon et al., 2004, 2005). As such, the understanding of its genetic basis may help in the identification of susceptibility genes for the disease as well as in the understanding of their function.

Very recently, some significant hypotheses regarding the correlation between the schizophrenic spectrum phenotype and ERP measurements across three different schizophrenia models have been P50 suppression, P300 amplitude and latency in a study on twins (Hall et al., 2007).

The genetic relationship between biological ERP measures of neural activity and behavioral non-ERP measures of working memory function, processing speed, and general cognitive ability is yet to be fully explored in the spectrum of schizophrenic disorders.

According to the endophenotype strategy, this aim could be pursued by involving unaffected relatives of the population studied in this investigation. The adoption of ERPs for understanding the relationship between neurofunctional vulnerabilities and their underlying genetics is still in its infancy, but it holds great promise for future research.

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