Reduced novelty-P3 associated with increased behavioral distractibility in schizophrenia

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1. Introduction

Abnormalities in attention and information processing represent a cardinal feature in schizophrenia (see Braff, 1993 for a review). Event-related brain potentials (ERPs) have shown their utility to evaluate these cognitive deficits, as they provide a functional measure of neuroelectric brain activity that occurs time locked to a significant event, reflecting successive stages of information processing (Pfefferbaum et al., 1995). In line with this, the novelty-P3, elicited by unexpected, task-irrelevant novel events is also associated with the orienting response (see Friedman et al. (2001) for a review). It is generally accepted that similar neural sources are involved in the generation of the novelty-P3, and recent evidence supports the notion that the novelty-P3 may be the same component as the P3a (Simons et al., 2001). Studies using sophisticated analytical methods such as Principal Component Analysis (PCA; Dien et al., 2004) or Independent Component Analysis (ICA; Debener et al., 2005), have confirmed that the P300 family can be decomposed in two separated principal/independent components: an anterior one, mostly reflecting the novelty-P3, and a posterior one reflecting the target P3b. However, the novelty-P3 component structure has been demonstrated to have, based on scalp distribution differences and sensitivity to attentional manipulations, at least two subcomponents or phases, an early one peaking at circa 220 ms, and a later one peaking at around 300 ms (Escera et al., 1998). This two-phase structure has been replicated as for scalp distribution differences (Escera et al., 2001; Polo et al., 2003; Yago et al., 2003), and attentional sensitivity (Domínguez-Borràs et al., 2008; SanMiguel et al., 2008).
On the other hand, the two-phase structure of the novelty-P3 and its underlying neural generators as revealed with scalp-current density analysis (Yago et al., 2003) is compatible with the data provided by patient studies. Indeed, studies of patients with cerebral lesions, as well as intracranial recording in humans and modeling of neuromagnetic and neuroelectric responses indicate that the generation of the novelty-P3 engages a largely distributed cerebral network, including the supratemporal (Alho et al., 1998; Halgren et al., 1995a) and cingulate cortices (Baudena et al., 1995), the prefrontal (Baudena et al., 1995; Knight, 1984) and temporal–parietal association areas (Halgren et al., 1995b; Mecklinger and Ullsperger, 1995), and the hippocampus (Knight, 1996). In accordance with the functional role associated with the novelty-P3 described above, the cerebral network underlying its generation is very similar to the areas involved in the orientation to contextually novel events, including the prefrontal cortex, anterior insula, cingulate gyrus, temporoparietal junction and the hippocampal formation (Ranganath and Rainer, 2003). Remarkably, schizophrenia has been consistently associated with structural and functional abnormalities located in many of these brain regions, including prefrontal cortex (Wible et al., 1995), anterior cingulate (Carter et al., 1997), and hippocampus (see Nelson et al., 1998 for a review).

With regard to electrophysiological research in schizophrenia, whereas P3b amplitude reduction is one of the most consistently, yet non-specific reported findings (see Ford, 1999 for a review), few studies have investigated the P3a/novelty-P3 components. Evidence for abnormalities in these components is provided by studies showing amplitude reductions (Alain et al., 2002; Devrim-Uçok et al., 2006; Grillon et al., 1990; Kogoj et al., 2005; Mathalon et al., 2000; Merrin and Floyd, 1994; Pfeifferbaum et al., 1989; Sponheim et al., 2006; van der Stelt et al., 2004), suggesting a disturbed involuntary orienting response in schizophrenia. However, not all the studies confirm these amplitude abnormalities (Frodl et al., 2001; Michie et al., 2002; Schall et al., 1999). Less consistently, some studies have also shown latency prolongations of P3a/novelty-P3 responses in schizophrenic patients (Frodl et al., 2001; Grzella et al., 2001).

It is noteworthy to note that novelty-P3 has not only been associated with the orienting response but also to distraction, that is to say, to the behavioral consequences of directing the attentional resources toward task-irrelevant stimuli resulting in the impairment of the ongoing task performance (Tece et al., 1976). The disability of schizophrenic patients to process relevant information when irrelevant information is simultaneously presented has been advanced by a series of studies. These studies have usually explored performance on distraction-laden tasks by means of response time (RT) measures, reflecting prolonged RT in schizophrenic patients (Nuechterlein, 1977). Despite widespread agreement that schizophrenic patients are more vulnerable to distraction than healthy subjects, specifically in the auditory modality (Moser et al., 2001), most ERPs and imaging studies have paid little attention to providing an explanation for the patients’ poorer performance due to distractor stimuli while simultaneously displaying impaired capacity to orient attention toward these stimuli. A seminal study by Grillon et al. (1990), using a combined behavioral and ERP approach to evaluate distractibility in schizophrenia, found that the distractor stimuli yielded more impaired behavioral performance and elicited smaller novelty-P3 responses in schizophrenic patients than in their matched controls, the P3b response to task-relevant stimuli being also reduced in the patients. On the basis that the P3b of patients was very small whereas the novelty-P3 was relatively large, the authors concluded that attention was abnormally allocated to task-irrelevant versus task-relevant stimuli in schizophrenia. This conclusion was congruent with an increased distractibility in schizophrenia and compatible with an impaired orienting response toward task-irrelevant stimuli. Unfortunately, subsequent studies have not confirmed these findings, as larger amplitude reduction of novelty-P3 than P3b in schizophrenia has been observed (Merrin and Floyd, 1994; van der Stelt et al., 2004).

On the other hand, a recent functional magnetic resonance imaging study (Laurens et al., 2005) has sought to localize and distinguish the abnormalities due to orienting response dysfunction from those caused by an increased distractibility during task-irrelevant stimuli processing in schizophrenia. Consistent with the idea of a disturbed capacity to orient processing resources away from the ongoing task, the examination of novel stimuli processing relative to a non-target baseline indicated multiple regions of hypo-activity in schizophrenia. In particular, these regions comprised right amygdala–hippocampus, anterior and posterior cingulate cortices, right frontal operculum, right temporo-parietal–occipital junction, bilateral intraparietal sulcus, bilateral dorsal frontal cortex, cerebellum, thalamus and basal ganglia. However, although the authors expected some hyper-activity in the patients during novel stimulus processing in relation to target stimuli to support the well-documented increased distractibility in schizophrenia, the hemodynamic response did not show any significant differences between groups in any brain region.

The main goal of the present study was to further investigate the relationship between the involuntary orienting of attention and distractibility in schizophrenia. In order to achieve this and taking into account the functional role of the novelty-P3 as an index of attentional deficits, we used a combination of ERP measures and monitoring of behavioral performance. Distraction was induced in a well-established auditory–visual distraction paradigm (Escera et al., 2000, 2001, 2002, 2003), which has been already proved useful in other groups of patients, including chronic alcoholics (Polo et al., 2003) and closed-head injury ones (Polo et al., 2002). In this paradigm, subjects are instructed to classify visual stimuli while ignoring novel, task-irrelevant short sounds. These distracting sounds increase RT in visual task performance, revealing behavioral distraction. Unlike most ERP studies, here distracter sounds are completely irrelevant to task performance, as they are presented on a different sensory modality that is explicitly instructed to be ignored (Alho et al., 1997; Escera et al., 1998, 2001, 2002, 2003; Yago et al., 2001, 2003; see Escera et al., 2000 and Escera and Corral, 2007 for reviews). Typically, ERPs recorded during distraction in this behavioral setting reveal a neuroelectric pattern, including at least two well-characterized waveforms: an early negativity and a subsequent positivity. Each of these two waves provides an index for one of the principal stages in involuntary attention control (Escera et al., 2000; Escera and Corral, 2007): (a) a transient-detector mechanism leading to attention capture associated with N1-enhancement (Alho et al., 1998; Escera et al., 1998, 2001, 2002, 2003) and (b) the involuntary orienting of attention associated with the novelty-P3. We expected that the assessment of the behavioral results, consisting in RT and performance accuracy (e.g., hit, miss and error rates), and of the novelty-P3 elicited by this auditory–visual distraction paradigm, would provide a more integrated view of neurocognitive deficits in schizophrenic patients during the processing of task-irrelevant stimuli.

### 2. Methods

#### 2.1. Subjects

Table 1 summarizes demographic and clinical characteristics of participants. Nineteen chronic schizophrenic outpatients (mean age = 32.58, S.D. = 7.24 years) fulfilling DSM-IV criteria for schizophrenia and nine healthy controls (mean age = 33.68, S.D. = 7.77 years) participated in the experiment. Three schizophrenic
Table 1
Demographic and clinical characteristics of schizophrenic patients and healthy controls

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patients (n = 19)</th>
<th>Controls (n = 19)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean S. D.</td>
<td>Mean S. D.</td>
</tr>
<tr>
<td>Age (years)</td>
<td>32.6 7.24</td>
<td>33.7 7.77</td>
</tr>
<tr>
<td>Duration of illness (years)</td>
<td>12.7 6</td>
<td></td>
</tr>
<tr>
<td>N %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>5 26.3</td>
<td>5 26.3</td>
</tr>
<tr>
<td>Male</td>
<td>14 73.7</td>
<td>14 73.7</td>
</tr>
<tr>
<td>N %</td>
<td>10.5</td>
<td>15.8</td>
</tr>
<tr>
<td>Educational level</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Middle school</td>
<td>9 47.4</td>
<td>6 31.6</td>
</tr>
<tr>
<td>Some high school</td>
<td>3 15.8</td>
<td>2 10.5</td>
</tr>
<tr>
<td>High school</td>
<td>5 26.3</td>
<td>8 42.1</td>
</tr>
<tr>
<td>Some college</td>
<td>2 10.5</td>
<td>3 15.8</td>
</tr>
<tr>
<td>Handedness</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right-handed</td>
<td>18 94.7</td>
<td>17 89.5</td>
</tr>
<tr>
<td>Left-handed</td>
<td>1 5.3</td>
<td>2 10.5</td>
</tr>
<tr>
<td>Diagnostic subtype</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paranoid</td>
<td>17 89.5</td>
<td></td>
</tr>
<tr>
<td>Residual</td>
<td>1 5.3</td>
<td></td>
</tr>
<tr>
<td>Undifferentiated</td>
<td>1 5.3</td>
<td></td>
</tr>
<tr>
<td>Medication status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atypical antipsychotics</td>
<td>11 57.9</td>
<td></td>
</tr>
<tr>
<td>Typical antipsychotics</td>
<td>1 5.3</td>
<td></td>
</tr>
<tr>
<td>Atypical and typical antipsychotics</td>
<td>7 36.8</td>
<td></td>
</tr>
<tr>
<td>Anticholinergics</td>
<td>3 15.8</td>
<td></td>
</tr>
<tr>
<td>Antidepressants</td>
<td>4 21.1</td>
<td></td>
</tr>
<tr>
<td>Anxiolytics</td>
<td>8 42.1</td>
<td></td>
</tr>
<tr>
<td>Hypnotics</td>
<td>1 5.3</td>
<td></td>
</tr>
<tr>
<td>Lithium</td>
<td>2 10.5</td>
<td></td>
</tr>
</tbody>
</table>

patients were not included in the behavioral analysis due to their very poor performance (less than 65% hits) in the visual discrimination task, although they were all (N = 19) considered for ERP analysis.

The patients were referred from the Hospital of Terrassa and the controls were recruited by board advertisements. The two groups did not differ in age (t(36) = 0.45, P = 0.65) or gender. The educational level was indicated on a four point scale: middle school (1), high school not completed (2), high school (3) and college (4). Mann–Whitney U-test indicated that there were no group differences in educational achievement (P = 0.25). All subjects were selected by normal or corrected-to-normal vision and were tested audiometrically to exclude anyone with significant hearing loss. One of the patients and two of the healthy controls were left-handed in accordance with the Edinburg Handedness Inventory (Oldfield, 1971).

Patients received DSM-IV subtype diagnoses of residual (1), undifferentiated (1) and paranoid (17). Exclusion criteria for patients included mental disorders other than schizophrenia, neurological disorders, head injury, stroke and substance abuse (except tobacco). The mean duration of illness was 12.68 years (S.D. = 6.0). All patients were with antipsychotic medication and thirteen of them were also taking other additional medication (antidepressants, anticholinergics, anxiolytics, lithium, hypnics) at the time of the experiment. Eleven patients were on atypical antipsychotics, one patient was on typical antipsychotics and the remaining seven patients were taking both types.

Control subjects were screened by using the Structured Clinical Interview for DSM-IV and were excluded for any evidence of psychiatric and neurological disorders, head injury, stroke, substance abuse (except tobacco) or family history of schizophrenia, neurological disorders, head injury, stroke and substance abuse (except tobacco) or family history of schizophrenia.

2.2. Stimuli and procedures

Subjects sat in an armchair, in a sound-attenuated, dimly illuminated, and electrically shielded room. ERPs were recorded during performance of a well-characterized auditory–visual distraction task (Escera et al., 1998, 2000, 2001, 2002; see Escera and Corral, 2007 for a recent review). Four blocks with 190 stimulus-pairs (trials) each were presented to the subjects. Each trial consisted of an auditory stimulus followed after 300 ms (onset to onset) by a visual stimulus. The inter-pair interval (onset to onset) was 1.5 s. The auditory stimuli were standard tones (80%) and novel sounds (20%) delivered in a random order with the constraint that each novel-sound trial was preceded by at least one standard-tone trial. The standard tones were pure tones of 600 Hz and the novel sounds were 152 environmental complex sounds, such as those produced by an electric drill, hammer, telephone ringing, etc. All auditory stimuli were presented binaurally through headphones with a duration of 200 ms (including rise/fall times of 10 ms) and an intensity of 90 dB SPL. Each different novel sound occurred only once in the whole experiment. The visual stimuli were white capital letters (A, E, J, P, R, S, U, Y) or digits (2–9) displayed during 200 ms, in random order, at the centre of a black computer screen, which was located 1.5 m from the subject, with respective vertical and horizontal angles of 1.3° and 0.8°. Subjects were instructed to ignore the auditory stimulation, and to press as fast and accurately as possible, one response button for the letters and another response button for the digits, with the index and middle fingers of their dominant hand. The order of fingers was counterbalanced, with half of the subjects using the index finger to respond to the letters. In order to avoid excessive blinking and movements, subjects focused their gaze in the middle of the computer screen. Each block lasted 4.75 min and, to prevent tiredness, short breaks were given between blocks. Before the recordings, subjects underwent a training session consisting of 1–3 blocks with 48 visual stimuli in which the auditory stimulation had been omitted. All subjects received practice until they reached a criterion of 70% correct responses.

2.3. Electrophysiological recordings

The electroencephalogram (EEG) was continuously digitized at a rate of 500 Hz (bandpass 0.01–100 Hz) by a SynAmps amplifier (Compumedics NeuroScan) from 28 scalp tin electrodes positioned according to the extended 10–20 system (Fp1, Fp2, FC1, FC2, F3, F4, F7, F8, FT3, FT4, F5, C3, C4, Cz, T3, T4, T5, T6, TP3, TP4, CP1, CP2, P3, P4, Pz, Oz, IN1, IN2). These electrodes were mounted in an elastic cap (Electro-Cap International). Two additional electrodes were placed on left and right mastoid (M1 and M2 respectively). The horizontal and vertical electro-oculogram (EOG/VEOG) were recorded with electrodes attached to the right canthus and below the right eye, and the common reference electrode for all recordings was placed on the tip of the nose. All impedances were maintained below 5 kΩ during the whole experiment.

Before averaging, eye blinks were corrected using an ocular source component approach by means of the EPROBE 3.1 program (ANT software BV, Enschede, The Netherlands). After EOG correction, trials exceeding EEG amplitudes of ±75 μV at any channel, as well as the first five trials of the blocks were automatically excluded from averaging. The ERPs were averaged offline for standard and novel trials, separately for each baseline. The epoch was of 1500 ms, including a prestimulus baseline of 200 ms. Standard trial epochs occurring immediately after novel trial epochs were also excluded from the averages. Individual ERPs were digitally band-pass filtered between 0.1 and 30 Hz.

2.4. Data analyses

Pressing the correct response button within 1000 ms interval after the visual stimulus onset was considered as a hit, and the average response time (in ms) was considered. For these trials, a correct response was defined as an error, and a trial with no response was classified as a miss. Mean RTs for correct responses, and hit (HR), error (ER), and miss rates (MR) were calculated separately for the standard and novel sound trials. Calculations of the RT difference between novel and standard trials provided an index of distraction effects caused by the novel sounds on the visual performance. Statistics for this analysis were performed by means of univariate analyses of variance (ANOVA) for repeated measures with group (between-subject factor) and stimulus (standard/novel) as the within-subject factor. The post hoc analyses were performed with paired t-tests.

Visual ERP components were analyzed in the ERPs elicited to visual stimuli in both the standard and novel trials. The visual P1 peak was identified as the largest positivity in the 50–140 ms latency window from visual stimulus onset at the IN1 and IN2 electrodes, where the response was maximal. Visual N1 was identified as the largest negativity in the 200–300 ms latency window in the same two electrodes. As there were marked differences in the 100 ms preceding the visual stimulus onset in the novel compared to the standard trials, a “trial” baseline was defined (i.e., from ~100 ms to auditory stimulus onset), and for amplitude analyses the P1–N1 peak-to-peak amplitude was determined for every subject and trial type (standard, novel) at the two mentioned electrodes. Visual P3b was measured as the mean amplitude in the 340–500 ms latency window from visual stimulus onset at P3, Pz and P4 in every individual and condition. Two-way ANOVAs on the peak latency of P1 and N1, and on the P1–N1 peak-to-peak amplitude and the mean P3b amplitude were conducted with the within-subject factors stimulus (standard, novel) and electrode (IN1, IN2 for early visual responses; P3, Pz, P4 for P3b), and the group (control, schizophrenics) as between-subject factor.

Difference-waveforms were obtained by subtracting the ERPs elicited to standard trials from those elicited to novel trials, which allowed the identification of the two novelty-related brain responses in the grand-average difference waveform: the N1-enhancement and the novelty-P3. The first one was measured as the largest negative peak in the 110–170 ms latency window at Pz and Cz electrodes for each group. Initially, the novelty-P3 was measured as the largest positive peak in
the 190–400 ms latency window at Fz, Cz and Pz electrodes. Since the novelty-P3 had two consecutive phases, the mean amplitude of this waveform was measured in an early (190–280 ms) and a late (280–370 ms for controls/280–400 ms for patients) phase.

The amplitude of the N1-enhancement and the latency of this early negativity and novelty-P3 were compared by means of paired t-tests at Cz. The analysis of novelty-P3 scalp distribution was carried out by means of ANOVAs for repeated measures with group as the between-subject factor and latency (F7, T3, T5/F3, C3, P3, T5, C5, P5) and phase (early and late subcomponents) as the within-subject factors. The ERP amplitudes were normalized to prevent genuine differences in scalp distribution from being washed out by amplitude differences among electrodes. This normalization was done by dividing the amplitude at each electrode by the square root of the sum of the squared amplitudes at the selected electrodes (McCarty and Wood, 1985). The post hoc analyses were performed with paired t-tests.

In all the ANOVAs, the Greenhouse–Geisser correction was applied when appropriate, and the F-value, the uncorrected degrees of freedom, the probability value, and the uncorrected degrees of freedom are listed. Topographic maps were plotted using the EEProbe 3.1 program (ANT Software BV, Enschede, The Netherlands).

3. Results

3.1. Performance

Descriptive statistics for behavioral performance in healthy controls and schizophrenic patients are presented in Table 2. The schizophrenic patients had a lower HR to standard and novel trials than the healthy subjects [group main effect; F(1,33) = 8.65, p = 0.006]. The decrease in HR was due to the increased number of total misses [group main effect; F(1,33) = 16.50, p < 0.001], as the increase in the total number of errors was only marginally significant [group main effect; F(1,33) = 3.48, p = 0.071]. No significant main effect of stimulus type was found, nor was the stimulus type × group interaction significant.

In addition, the RT data were delayed for the two trial types in the patients [group main effect; F(1,33) = 11.27, p = 0.002, indicating a general slowed down performance. Hit RT was significantly delayed by the novel sounds [stimulus main effect; F(1,33) = 44.01, p < 0.001]. Subsequent follow-up analyses showed that this delay was of 8 ms in controls [t(18) = –2.98, p = 0.008] and 28 ms in the schizophrenic group [t(15) = –5.613, p < 0.001]. In turn, these distraction effects caused by the novel sounds were much larger in the patients than in the healthy subjects, as revealed by the significant Stimulus × Group interaction [F(1,33) = 13.46, p = 0.001]. Moreover, the novel sounds also caused a significant increase of hit rate [F(1,33) = 4.40, p = 0.044] as well as a decrease of error rate [F(1,33) = 5.44, p = 0.026] in both groups. In contrast, the stimulus factor failed to reach statistical significance for the miss rate in either group.

### Table 2

Means and standard deviations of RT to hits, and hit, error and miss rates for the schizophrenic and control groups

<table>
<thead>
<tr>
<th>Performance</th>
<th>Stimulus</th>
<th>Patients (n = 16)</th>
<th>Controls (n = 19)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>S.D.</td>
<td>Mean</td>
</tr>
<tr>
<td>RT (ms)</td>
<td>Standard</td>
<td>474.3</td>
<td>48.16</td>
</tr>
<tr>
<td></td>
<td>Novel</td>
<td>502.0</td>
<td>54.35</td>
</tr>
<tr>
<td>Hit rate (%)</td>
<td>Standard</td>
<td>87.3</td>
<td>9.32</td>
</tr>
<tr>
<td></td>
<td>Novel</td>
<td>88.4</td>
<td>9.96</td>
</tr>
<tr>
<td>Error rate</td>
<td>Standard</td>
<td>8.5</td>
<td>7.21</td>
</tr>
<tr>
<td></td>
<td>Novel</td>
<td>7.4</td>
<td>7.03</td>
</tr>
<tr>
<td>Miss rate</td>
<td>Standard</td>
<td>4.2</td>
<td>3.82</td>
</tr>
<tr>
<td></td>
<td>Novel</td>
<td>4.2</td>
<td>3.99</td>
</tr>
</tbody>
</table>

3.2. Brain responses

Fig. 1 shows the ERP elicited in standard and novel trials in the two groups. As can be seen, a complex waveform was obtained, including auditory and visual ERPs, as reported in previous studies (Escera et al., 1998, 2001; Escera and Corral, 2007). The most striking characteristics of these waveforms were the novelty-P3, observed as a large difference between the standard and novel sound ERPs, and the visual P3b seen as increasing large positivity from frontal to parietal electrodes. At more posterior sites, a clear visual N1 (peak latency of about 140 in all groups and conditions), preceded by a small visual P1 (peak latency of about 90 ms in all groups and conditions) can be seen. Statistical analyses revealed two major effects on visual ERPs. First, the visual P3b was smaller in the patients than in the control subjects, as supported by a significant group effect [F(1,36) = 4.65, p < 0.04]. The stimulus type had no effects on the visual P3b, and there were no significant interactions with the group factor. Second, the novel sounds attenuated visual stimulus processing, as supported by a significant stimulus effect on the P1-N1 peak-to-peak amplitude [F(1,36) = 6.26, P < 0.02, ε = 1.0]. However, this effect was similar in the two groups, as the interaction group × stimulus failed to reach statistical significance.

The complex morphology of the ERPs elicited during task performance almost disappeared when calculating the difference waveforms obtained by subtracting the ERPs elicited to standard trials from those elicited to novel trials, as shown in Fig. 2 for both groups. These difference waveforms reveal the neuroelectric pattern of activation underlying involuntary attention, characterized by an N1-enhancement and the novelty-P3. The N1-enhancement was obtained with similar amplitude and latency in the control and schizophrenic groups. As suggested by the previous literature, we assumed that the novelty-P3 was composed of two different subcomponents. This hypothesis was confirmed by a significant main effect of the phase factor in the ANOVA carried out on the normalized mean amplitudes for this component [F(1,36) = 15.31, P < 0.001]. The ANOVA also revealed group differences in the scalp distribution of the novelty-P3, as supported by the significant phase × frontality × laterality × group interaction [F(8,288) = 5.22, P < 0.001, ε = 0.55]. To parcel out this interaction, separate ANOVAs were carried out for the early and the late phases of the novelty-P3. Results showed that the frontality × laterality × group effect was only statistically significant for the early phase [F(8,288) = 3.23, P = 0.018, ε = 0.45]. A more detailed analysis was then performed for this phase, revealing that the early novelty-P3 was asymmetrically distributed in the controls, as supported by a significant frontality × laterality interaction [F(8,144) = 9.28, P < 0.001, ε = 0.34], and that the amplitude differences between groups emerged at the F8 electrode [t(36) = 2.29, P = 0.028]. This pattern of results suggests a significantly smaller activation of the early phase of the novelty-P3 over the right frontal region in the patients. All these effects are also illustrated in Fig. 3 as the scalp distribution of the novelty-P3. Similar to the early negativity, novelty-P3 peak latency differences between groups were not significant.

4. Discussion

The present investigation was motivated by an interest in examining the relationship between the orienting response and the vulnerability to distraction in schizophrenia. To address this issue, auditory ERPs and behavioral measures were obtained by means of an auditory–visual distraction paradigm in schizophrenic patients and their matched healthy controls. The behavioral data indicated that novel sounds caused behavioral distraction in both.
groups, i.e., increased RTs to subsequent imperative visual stimuli. However, these distracting effects of novel sounds on visual-task performance were of larger magnitude in the patients, revealing an increased vulnerability to distraction in schizophrenia.

The concomitant recording of ERPs during performance of the distraction paradigm allowed us to investigate the sequence of neural events underlying involuntary detection and orienting of attention toward task-irrelevant auditory events. In agreement with previous research, we observed a larger P3 amplitude in patients compared to controls, suggesting an enhanced reactivity to unexpected auditory events. Additionally, the visual N1 component was also augmented in patients, indicating an altered allocation of attention resources.

**Fig. 1.** ERPs to standard (thin line) and novel (thick line) trials in the control (left) and schizophrenic patients (right) at the Fz, Cz, Pz, IN1, and IN2 electrodes. Notice the complex morphology of the waveform composed by auditory and visual responses.

**Fig. 2.** ERP difference waves obtained by subtracting the ERPs elicited to standard trials from those elicited to novel trials in schizophrenic patients (thick line) and healthy subjects (thin line), at the electrodes included in the statistical analysis carried out for the novelty-P3.
with previous studies (Escera et al., 1998, 2002, 2003), a typical neuroelectric pattern, including N1-enhancement and novelty-P3 components, was obtained in both schizophrenic and healthy subjects. The novelty-P3 component, involved in the involuntary orienting response, showed similar latencies and two clearly distinct phases (Escera et al., 1998; Polo et al., 2003; Yago et al., 2003) in all subjects. Of particular interest was that the schizophrenic group showed a reduced early phase of the novelty-P3 over the right-prefrontal regions, contrasting with the bilateral scalp distribution observed in controls. Given the involvement of frontal regions in the generation of the novelty-P3 (Knight, 1984; Yago et al., 2003), this latter result may originate from an abnormal (reduced) activation of this cerebral region in the generation of the early novelty-P3 in schizophrenia. The topographic differences in novelty-P3 in the schizophrenic subjects are in line with a recent report on the P3a component in schizophrenia (Sponheim et al., 2006), and with the widely described prefrontal cortex abnormalities in schizophrenia (Goldman-Rakic and Selemon, 1997; Wible et al., 1995). Taken together, our behavioral and ERP results therefore confirm that schizophrenic individuals suffer from a disturbance in the involuntary orienting of attention toward distraction stimuli along with an increased distractibility.

Given the present results, it seems difficult to reconcile the fact that schizophrenics suffer simultaneously from a less efficient involuntary orientation to task-irrelevant stimuli and a larger distractibility caused by these very same stimuli. A plausible explanation for this behavioral-electrophysiological dissociation may be found in the analysis of the functional relationship between distraction, a behavioral phenomenon, and the novelty-P3, a neuroelectric response associated with attentional orienting. Indeed, distraction is a consequence of the direction of attentional resources toward task-irrelevant stimuli, resulting in an impoverishment of current task performance. The novelty-P3, in turn, cannot strictly be considered as an index of distraction which can be only measured a posteriori, although this electrophysiologic response is closely related to distraction as it reflects the diversion of attentional resources from central task processing toward the eliciting task-irrelevant stimulus, so that larger behavioral distraction should be associated with larger novelty-P3 amplitudes (see, however, Escera and Corral, 2007 for an extended discussion on this issue). As seen above, this was not the case of the present experiment, where a novelty-P3 attenuation was associated with an increased behavioral distraction in the patients. That is to say, despite schizophrenic subjects allocated fewer attentional resources to novel stimuli, the distracting effect of these events were larger than in the controls. In agreement with a reduced amount of available processing resources in schizophrenia (Grillon et al., 1990), we suggest that the behavioral performance would be affected drastically by the novel sounds because of the decrease of the already limited resources assigned to the task, even though there was a weak allocation of resources toward the distractor stimuli. The pattern of results obtained in the present experiment give additional support to the resource-limitations vulnerability model of schizophrenia (Nuechterlein, 1987), and is agreement with experiments showing poor performance of schizophrenic patients in tasks imposing high processing loads, such as the span of apprehension task (Granholm et al., 2000, 2007), in dual-task performance tapping working memory (Harvey et al., 2006), and tasks involving backward masking (Granholm and Verney, 2004) or repetition and semantic priming in attended and unattended conditions (Williams, 1996).

To fully support the reduced resource allocation hypothesis, however, one might have also expected a reduced hit rate caused by the novel sounds in the patients, which was not the case. Moreover, the impact of novel sounds on visual stimulus processing, as reflected in an attenuation of the P1-N1 peak-to-peak amplitude observed here and replicating previous studies (Alho et al., 1997), was of a similar magnitude for patients and controls. Therefore, considering this, one should be cautious in assuming the reduced resources interpretation. An alternative possibility is that after hearing a distracting novel sound, the patients got more engaged in its processing and simply took more time to return their attention back to visual task performance. In fact, a recent study has suggested that the behavioral costs of novel sounds on visual task performance is due to the time of moving attention from the auditory modality (i.e., processing the novel sounds) toward the visual modality at the sensory appearance of the visual imperative stimulus (Parmentier et al., 2008). This explanation, however, does not fully account for the effects observed in the present experiment, as according to the data (the reduced novelty-P3), the novel sounds engaged less

Fig. 3. (A) Gray shadows show the latency intervals used in novelty-P3 analysis for its early (dark gray) and late phase (light gray). (B) Scalp potential distribution of the two phases of the novelty-P3 in the control and schizophrenic groups.
attention in the patients. All in all, a full characterization of these deficits in schizophrenia should await further research. For instance, whether this decrease of processing resources is due to a limited pool of resources or a normal processing capacity, but mainly devoted to processing internal stimuli instead of the external stimuli provided by the experimental settings (Barrett et al., 1986; Grillon et al., 1990), remains to be clarified. The negative correlation between P3a amplitude and auditory hallucinations showed by Turetsky et al. (1998) provide support for the hypothesis of the competition between internal and external stimuli for the attentional resources. In addition, these authors proposed the anterior cingulate as the common physiologic substrate underlying the generation of P3a and the modulation of hallucinations.

Another aspect of the present study was related to the transient-detector mechanism of attention capture elicited by the novel sounds and associated with N1–enhancement. The lack of group differences indicates that the impaired orienting response associated with a reduced novelty-P3 in schizophrenia does not originate from disturbances at the preceding perceptual and cognitive processes. Moreover, this normal N1-enhancement in schizophrenia contrasts with the widely reported deficits in the stimulus-change detector system reflected in the mismatch negativity (see Michie, 2001 for a review), providing support for the involvement of some different neural areas in these two mechanisms of attention capture (Alho et al., 1998; Escera et al., 1998).

Taken together, the results obtained in the present experiment enhance confidence in the auditory novelty-P3 as an additional, useful tool for the diagnosis and monitoring of attentional disturbances in schizophrenia, and as a sensitive neurophysiologic marker of frontal cortical dysfunction in the disease. Consistent with the role of this component as trait marker of schizophrenia, there is evidence of an amplitude reduction of P3a even when patients are almost asymptomatic (Mathalon et al., 2000). Moreover, the sensitivity of P3a amplitude to fluctuations in global clinical severity (Mathalon et al., 2000) and the inverse relationship between P3a amplitude and hallucinations (Turetsky et al., 1998), leave open the possibility of this ERP component to become useful as a clinical state marker in schizophrenia. Nevertheless, more clinical and electrophysiologic assessments of patients and healthy subjects on longitudinal and cross-sectional studies are required to clarify the trait and/or state nature of novelty-P3 or P3a component.

Likewise, whether the novelty-P3 amplitude reduction is a vulnerability marker remains also to be solved. Only two studies have examined this ERP component in acute, first-episode patients, reporting contradictory results (Devrim-u ´ c u et al., 2006; Valkonen-Korhonen et al., 2003). With regard to unaffected, first-degree biological relatives of patients with schizophrenia, a first study (Turetsky et al., 2000) found an abnormal P3a in these subjects whereas two later reports suggested that these abnormalities are unique to patients (Michie et al., 2002; Sponheim et al., 2006). Although some studies suggest that novelty-P3 amplitude reduction is not dependent on medication (Merrin and Fordy, 1994; Pfefferbaum et al., 1989; van der Stelt et al., 2004), future research should explore further the potential effects of medication on novelty–P3 in order to preclude confusions between clinical state and medication status changes. In line with this, the finding that P3a might be modulated by the noradrenergic neurotransmitter system (Turetsky and Fein, 2002) raises the possibility to use this component as an index of the effectiveness of clinical treatments directed toward the noradrenergic dysfunctions in schizophrenia (Thibaut et al., 1998).

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References


