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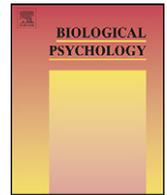
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## Impaired preparatory re-mapping of stimulus–response associations and rule-implementation in schizophrenic patients—The role for differences in early processing

Mareike Finke<sup>a,b</sup>, Francisco Barceló<sup>b,c</sup>, Maite Garolera<sup>d</sup>, Miriam Cortiñas<sup>b</sup>, Gemma Garrido<sup>d</sup>, Marta Pajares<sup>d</sup>, Carles Escera<sup>a,b,\*</sup>

<sup>a</sup> Institute for Brain, Cognition and Behavior (IR3C), University of Barcelona, Catalonia, Spain

<sup>b</sup> Department of Psychiatry and Clinical Psychobiology, University of Barcelona, Catalonia, Spain

<sup>c</sup> Laboratory of Clinical Neuropsychology, Department of Psychology, University of the Balearic Islands, Spain

<sup>d</sup> Mental Health Department, Hospital of Terrassa. Consorci Sanitari de Terrassa, Ctra Torrebónica s/n, E-08227 Terrassa, Barcelona, Catalonia, Spain

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## ABSTRACT

An accurate representation of *task-set* information is needed for successful goal directed behavior. Recent studies point to disturbances in the early processing stages as plausible causes for task-switching deficits in schizophrenia. A task-cueing protocol was administered to a group of schizophrenic patients and compared with a sample of age-matched healthy controls. Patients responded slower and less accurate compared with controls in all conditions. The concurrent recording of event-related brain potentials to contextual cues and target events revealed abnormalities in the early processing of both cue-locked and target-locked N1 potentials. Abnormally enhanced target-locked P2 amplitudes were observed in schizophrenic patients for task-switch trials only, suggesting disrupted stimulus evaluation and memory retrieval processes. The endogenous P3 potentials discriminated between task conditions but without further differences between groups. These results suggest that the observed impairments in task-switching behavior were not *specifically* related to anticipatory set-shifting, but derived from a deficit in the implementation of task-set representations at target onset in the presence of irrelevant and conflicting information.

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### 1. Introduction

Cognitive impairment in schizophrenia has been conceptualized as a failure of executive control and contextual processing (Barch et al., 2001; Braver et al., 1999). The cognitive impairment of schizophrenic patients has been suggested to be generalized while intact sensory processing is often assumed (Bleuler, 1950; Javitt, 2009a,b). The ability to adapt behavior to changing contextual contingencies requires cognitive flexibility to switch between learned stimulus–response (S–R) associations. This requires a reliable representation of the task context, namely, the contextual *task-set* information that has to be held, maintained and updated in working memory (Barch et al., 2001; Braver et al., 1999). This aspect of the executive control of attention is known to vary between indi-

viduals, with underlying brain mechanisms mediated by different neurotransmitter systems that have been shown to be disturbed in schizophrenia (Braver et al., 1999; Garcia-Garcia et al., 2010a). Recent studies argue for delimited deficits, especially in lower-level stages of contextual processing but against general cognitive dysfunction of higher-order processes. The observed abnormal sensory and perceptual processes in turn might affect cognition which results in modulated low- as well as high-order processing stages (Gold et al., 2009; Haenschel et al., 2007; Javitt, 2009a). To summarize, early processing stages do not involve only sensory processing, but might too reflect interacting sensory and cognitive mechanisms. Therefore, it is necessary to explore this possibility by manipulating sensory updating and task-set updating orthogonally in order to examine whether early (sensory) processes are specifically disturbed in schizophrenia.

Adapting our minds to a new context makes us maladroit and slower for a moment, until the new plan of action has been definitely established and rehearsed. Task-set switching paradigms have been used to examine the type of high-level control processes required for such context-updating situations, where schizophrenic patients are typically impaired (Gold et al., 2009;

\* Corresponding author at: Cognitive Neuroscience Research Group, Institute for Brain, Cognition and Behavior (IR3C), Department of Psychiatry and Clinical Psychobiology, University of Barcelona, Passeig Vall d'Hebron 171, 08035 Barcelona, Spain. Tel.: +34 933 125 048; fax: +34 934 021 584.

E-mail address: [cescara@ub.edu](mailto:cescara@ub.edu) (C. Escera).

Kieffaber et al., 2006). Because there seems to be a constant interplay between bottom-up and top-down processes which lead to efficient task-set switching, it is important to segregate sensory (i.e., priming) from higher order control (i.e., preparation) factors. In particular, a task-cueing paradigm could help us to orthogonally manipulate both sensory processing and executive control (Nicholson et al., 2006), in order to address the main question behind this study: how and related to which processing stage do schizophrenic patients differ from healthy controls in task-set representation, maintenance and updating?

Most task-switching studies on schizophrenia have focused on behavioral performance (Hartman et al., 2003; Li, 2004; Pantelis et al., 1999). Typically, schizophrenic patients perform worse compared with healthy controls, but results differ probably due to different experimental procedures. Overall slower responses are reported as well as higher switching costs (Jamadar et al., 2010; Meiran et al., 2000). Conversely, there are studies that report normal response times in task-switching for schizophrenics (Manoach et al., 2002; Merrin et al., 2006). Similar conflicting results are observed with respect to error rates made by schizophrenics compared with healthy controls (Gold et al., 2009; Hartman et al., 2003; Jamadar et al., 2010; Karayanidis et al., 2006; Li, 2004; Prentice et al., 2008). Common results for task-switching studies are longer response times and higher error rates for switch compared with repeat trials.

The fast pace of cognitive control operations in task-switching has been studied by using event-related brain potentials (ERPs). Modulations in ERP components, namely the N1, N2, P2 and P3 depending on task condition have been observed (Adrover-Roig & Barceló, 2010; Barcelo et al., 2006; Garcia-Garcia et al., 2010b; Nicholson et al., 2006). Contrariwise to the behavioral evidence, there is a scarcity of ERP studies on task-switching in schizophrenia, and the available evidence has revealed differences mainly in the endogenous P3 component and later time windows (González-Hernández et al., 2003; Jamadar et al., 2010; Kieffaber et al., 2007). More generally, patients seem to have difficulties to form or maintain an internal representation of the current task-set (Galletly et al., 2007; O'Donnell et al., 1994; Schechter et al., 2005). Modulations in various aspects of this P3 component have been found in several studies (Adrover-Roig & Barceló, 2010; Barcelo et al., 2006; Nicholson et al., 2006). In particular, the hypothesized disruption in context (task-set) updating and representation in schizophrenia could be mirrored in P3 which has been proposed to index the updating of task-set information in working memory (WM) (Adrover-Roig & Barceló, 2010; Barcelo et al., 2006). Our hypothesis about the different mechanisms underlying cue-locked P3 and target-locked P3 activity is compatible with Verleger's (2008) proposal that P3 reflects the decision about what to do with the ensuing stimulus. From his viewpoint, very different P3 components result from stimuli requiring responses from those which do not (Verleger, 2008). Similar ideas recently led us to reformulate the old context-updating hypothesis to interpret cue-locked P3 amplitudes (Adrover-Roig & Barceló, 2010; Barcelo et al., 2006). The rationale behind this new perspective is that some task-set switching (i.e., context-updating) operations involve preparatory control and can take place mostly at the onset of the warning cue – rather than the target-stimulus (Brass et al., 2005; Garcia-Garcia et al., 2010a,b; Jamadar et al., 2010; Kieffaber & Hetrick, 2005; Perriñez & Barceló, 2009).

In turn, ERP studies on schizophrenia have examined mainly sensory gating which shows early disruptions in the P50 as well as the N1 components, pointing to disturbances in early (sensory) processing (Boutros et al., 1999; Brenner et al., 2009; Brockhaus-Dumke et al., 2008; Patterson et al., 2008). However, it remains unclear whether disturbances in early processing stages contribute to deviations in more complex paradigms (e.g. stimulus-processing

in task-cueing protocols). WM research in schizophrenia has also uncovered differences in early ERP components (P1, N1) as well as in the P3 (Galletly et al., 2007; Haenschel et al., 2007). This evidence suggests that early-stage differences between schizophrenic patients and healthy controls during both cue and target processing should be mirrored in the N1 component. Alternatively P3-like effects have been attributed to impairments in task-set control (both encoding and WM updating). Conceivably, these P3-like effects could be related to disrupted early sensory processes leading to inefficient WM performance (Galletly et al., 2007; Haenschel et al., 2007). Moreover, cognitive control of task-switching has also been shown to modulate the earlier P2 component (Adrover-Roig & Barceló, 2010). A number of recent studies show evidence for a plausible implication of the fronto-centrally distributed P2 waveform in preparatory control of attention, detection of stimulus salience and stimulus evaluation (Adrover-Roig & Barceló, 2010; Kieffaber & Hetrick, 2005; Potts, 2004).

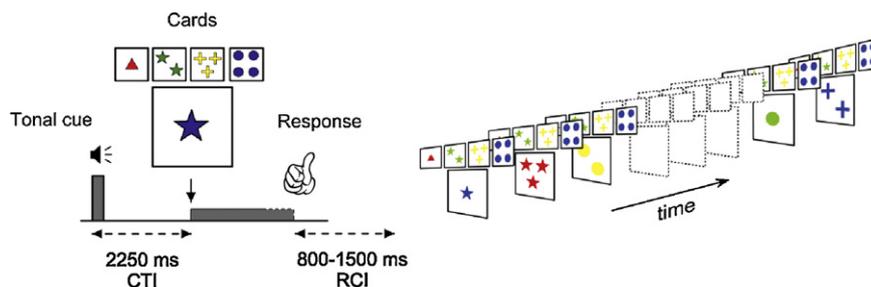
In summary, recent studies have reported abnormalities in both early and late ERP components in schizophrenic patients in low-level (sensory) processing and high-level encoding, updating and maintenance of task-set information for efficient task-set switching performance (Barch et al., 2001; Braver et al., 1999). The present study addresses the contribution from sensory and task-set representations during anticipation (cue-locked) and task preparation (target-locked) independently in schizophrenic patients. The main purpose was to examine the nature of contextual representations that are compromised in schizophrenic patients through the orthogonal manipulation of cue- and task-related information. In doing so, we investigated the deficits of schizophrenic patients in a task-switching paradigm, namely the Madrid Card Sorting Task, a task-cueing protocol inspired by the Wisconsin Card Sorting Task (Barceló, 2003). This paradigm allows for a separate measurement of updating and maintenance processes in memory during anticipation and preparation stages of task performance. A separate appraisal of these different stages is important because task-set switching may be prompted exogenously by contextual events, but it can also be generated endogenously through a change in the plans of action. Through the separate analysis of cue- and target-locked ERPs we segregate cue encoding and task-set reconfiguration from target encoding and task-set maintenance.

According to the reviewed literature, we predicted group differences in mean P3 amplitudes for the sensory priming and task switching factors, as well as an interaction between these factors for both cue- and target-locked P3 amplitudes. These P3-like effects would reflect the difficulty in context (task-set) updating in schizophrenic patients compared with healthy controls. The deficits in sensory processing and WM performance in schizophrenic patients were expected to result in diminished N1 amplitudes for both cue- and target-locked ERPs. At the behavioral level, we hypothesized comparatively slower and less accurate responses in schizophrenic patients due to impaired encoding, maintenance and updating of task-set information. According to former studies, we expect slower responses and lower hit rates in task-switch and cue-switch trials in all participants.

## 2. Material & methods

### 2.1. Participants

Sixteen schizophrenic patients fulfilling the DSM-IV criteria (American Psychiatric and Association, 2000) for schizophrenia (mean age  $\pm$  SD = 30.75  $\pm$  1.94) and 16 healthy controls (mean age  $\pm$  SD = 31.94  $\pm$  1.96) participated in the present study. The patients were referred from the Hospital of Terrassa and the controls were recruited with advertisements at the campus of the University of Barcelona. The two groups had similar ( $t(30) = .431, p = .669$ ) age, and all their participants had normal or corrected to normal vision and were tested audiometrically to exclude anyone with significant hearing loss. All patients received subtype diagnoses of residual ( $n = 1$ ), undifferentiated ( $n = 2$ ) and paranoid ( $n = 13$ ) schizophrenic disorder accord-



**Fig. 1.** Experimental design. Each trial consisted of a tonal cue followed by a visual target display with four key cards on top of one choice card. Participants were instructed whether to repeat or switch the sorting rule they applied to the previous target depending on the tonal cue (500 or 1000 Hz). The meaning of the two tones was counterbalanced across participants.

ing to the DSM-IV. Exclusion criteria for patients were any mental disorder other than schizophrenia, neurological disorder, head injury, stroke or substance abuse (except tobacco). The mean duration of illness was 9.88 years (SEM = 1.7), with a mean onset time of 20.88 years (SEM = 1.49). All patients were on anti-psychotic medication at the time of the experiment and seven patients were also taking at least one additional medication: antidepressants (1), anticholinergics (4), anxiolytics (6) and hypnotics (2). Control participants 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 psychiatric diseases in first degree relatives.

The whole procedure was approved by the Ethical Committee of the University of Barcelona, and performed in accordance with the declaration of Helsinki. All participants gave a written consent for participating in the study.

## 2.2. Task and procedure

A computerized task-cueing paradigm inspired in the original Wisconsin Card Sorting Task and adapted for measuring ERPs was used (Barceló, 2003). Each trial consisted of a tonal cue followed by a target display with four key cards on the top of one choice card which had to be matched with one of the key cards either by color or shape (Fig. 1). Stimuli were presented centrally on a computer screen with display subtending a visual angle of  $4^\circ \times 3.5^\circ$ . Stimuli remained on the screen until a response was given. Response times (RT) and hit rates were recorded by using the Presentation® software (Neurobehavioral Systems, Inc.).

Participants were informed that the correct rule would change unpredictably after a variable number of card sorts, and hence, that they would have to shift their sorting rule. Before each target onset a valid cue informed the participant whether to repeat or to switch the previous sorting rule (500 Hz or 1000 Hz binaural tones, respectively with a common duration of 200 ms, 10 ms rise/fall times, 75 dB sound pressure level). The cue-to-target interval (CTI) had a constant onset asynchrony of 2250 ms after button press, a randomly jittered (800–1500 ms) response-to-cue interval (RCI) was used to prevent systematical noise in the target-locked ERP.

The tone-to-cue mapping was counterbalanced across participants, and tonal switch cues occurred semi-randomly with an overall probability of 50% for both switch and repeat trials. The only constraint was a maximum number of five consecutive switch or repeat trials in a row. There was no feedback to inform the participant about the accuracy of the response to the previous trial. Participants used their thumbs to respond while holding a four-button response panel in their hands to match the choice card with one of the four key cards.

The far left button designated the key card on the far left of the display and the far right button designated the card on the far right and so on. Thus, the task sets as described above consisted of a 4-stimulus to 4-response mappings and the participants respectively used their left/right thumb for the two left/right buttons. For instance, when sorting by the color rule, a blue choice card had to be matched with the blue key card by using the right-most response button (Fig. 1). This task-cueing paradigm allowed us to isolate cue-locked (task anticipation) from target-locked (task preparation) brain processes (Brass et al., 2005; Rubinstein et al., 2001).

Prior to the experimental run participants completed a short training session for about 10–15 min until they reached a criterion of 100% correct sorts within 1 min. Each participant completed 140 trials in two experimental blocks. Correct task performance implicated that (1) the participant complied with the tonal cue to switch or repeat the previous rule, and (2) there were neither preservative nor distraction errors.

## 2.3. EEG recording

The EEG was recorded from 28 scalp electrodes (FP1, FP2, F7, F3, Fz, F4, F8, FC5, FC1, FC2, FC6, T7, C3, Cz, C4, T8, CP5, CP1, CP2, CP6, P7, P3, Pz, P4, P8, IN1, Oz and IN2) positioned according to the extended 10–20 system. Two additional electrodes were placed at M1 and M2. The reference electrode was placed on the tip of the nose. Horizontal and vertical electrooculography (EOG) was recorded bipolarly from four electrodes placed at the outer canthi of both eyes as well as above and below the

left eye. The EEG was amplified and digitized at 500 Hz and impedances were kept below 5 k $\Omega$  during the whole recording session.

EEG data was processed offline with a band pass filter from 0.1 to 30 Hz (24 dB/octave roll/off) and averaged over an 800 ms epoch for both the auditory cues and visual targets including a 100 ms pre-stimulus baseline. The first three trials from each block were excluded from analysis. EOG correction was performed using a regression algorithm (EEprobe 3.1 program, ANT software BV, Enschede, The Netherlands). Trials exceeding  $\pm 75 \mu\text{V}$  after EOG correction at any of the active electrodes were not included in the averages. Individual ERP waveforms consisted of at least 25 artifact-free EEG epochs from correct trials.

Mean amplitudes of the following auditory cue-locked ERP components were computed, relative to the 100 ms pre-stimulus baseline, in the specified time windows: frontal N1 (110–130 ms), P2 (190–230 ms) and P3 (360–400 ms). Likewise, visual target-locked ERP components were computed in the same latency windows except the occipital N1 (140–160 ms). All ERP components were analyzed from the three midline electrodes Fz, Cz and Pz as their most prominent sites for these components. Accordingly, target-locked N1 was measured at Oz.

## 2.4. Data analysis

For behavioral analysis, a correct trial was defined as a correct button press that occurred between 100 and 3000 ms from target onset. Mean response time (RT) relative to target-onset was computed for correct trials only. RT as well as hit rate (HR) were analyzed using a repeated measures  $2 \times 2$  ANOVA with the factors Sensory priming (cue repeat, cue switch) or task switching (task repeat, task switch), and the between factor group (controls, patients).

The ERP components to (a) the auditory cueing events and (b) the visual targets were analyzed in separate repeated measures  $2 \times 2 \times 3$  ANOVAs with the within factors sensory priming (repeat, switch) or task switching (repeat, switch) and electrode (Fz, Cz and Pz), and the between factor group (controls, patients). Noteworthy, the effects related to the cue were tested in two different manners. First, we tested whether ERPs differed between cues indicating either repetitions or switches in the sorting rule used in the previous task. Then, the sensory priming factor was also addressed considering whether the cue was the equal or different from the previous trial but regardless of the task-switching condition. Therefore, the factor sensory priming could be interpreted in two different ways. Either, signaling a repetition or a switch in task or being equal or different in physical features of the tonal cue.

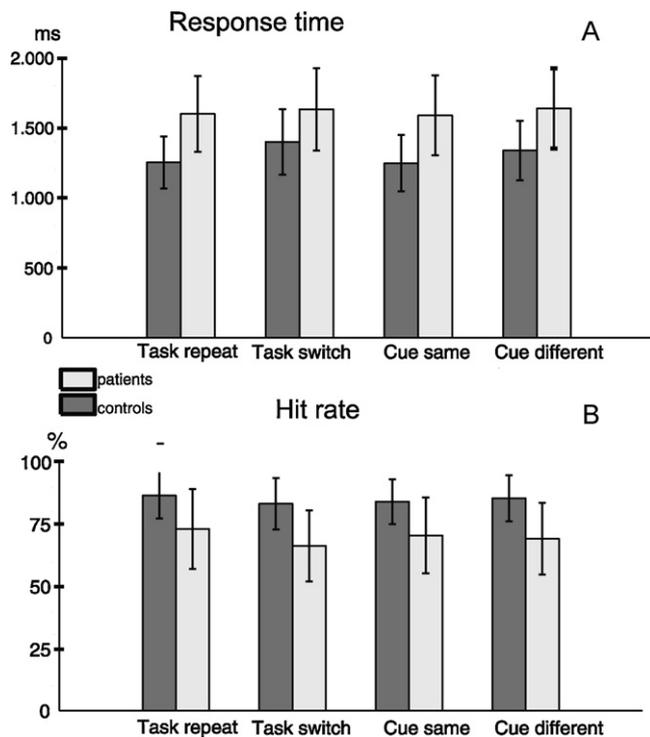
The visual N1 was analyzed only at the Oz electrode, and therefore the ANOVA did not include the factor electrode. All planned post-hoc comparisons for behavioral and ERP analyses were performed by using the Newman-Keuls correction for multiple comparisons.

To investigate whether target-locked P2 amplitudes are associated to mean RT -suggesting increased processing demands-, bi-variate Pearson correlations were used. We correlated mean RTs with mean P2 amplitudes (averaged over the electrode locations Fz, Cz and Pz).

## 3. Results

### 3.1. Performance

As compared with controls, schizophrenic patients responded significantly slower (mean RT  $\pm$  SEM for patients and controls  $1615 \pm 60$  and  $1296 \pm 60$  ms, respectively;  $F(1,30) = 13.853$ ,  $p = 0.001$ ) and less accurately (mean HR  $\pm$  SEM for patients and controls  $70 \pm 3\%$  and  $85 \pm 3\%$ , respectively;  $F(1,30) = 13.166$ ,  $p = 0.001$ ). Both groups showed increased RT and decreased hit rates after a switch in task compared with a task repetition (mean RT  $\pm$  SEM for switch and repeat  $1486 \pm 47$  ms and  $1426 \pm 41$  ms, respectively;  $F(1,30) = 7.262$ ,  $p = 0.011$ ; and mean HR  $\pm$  SEM for switch and repeat



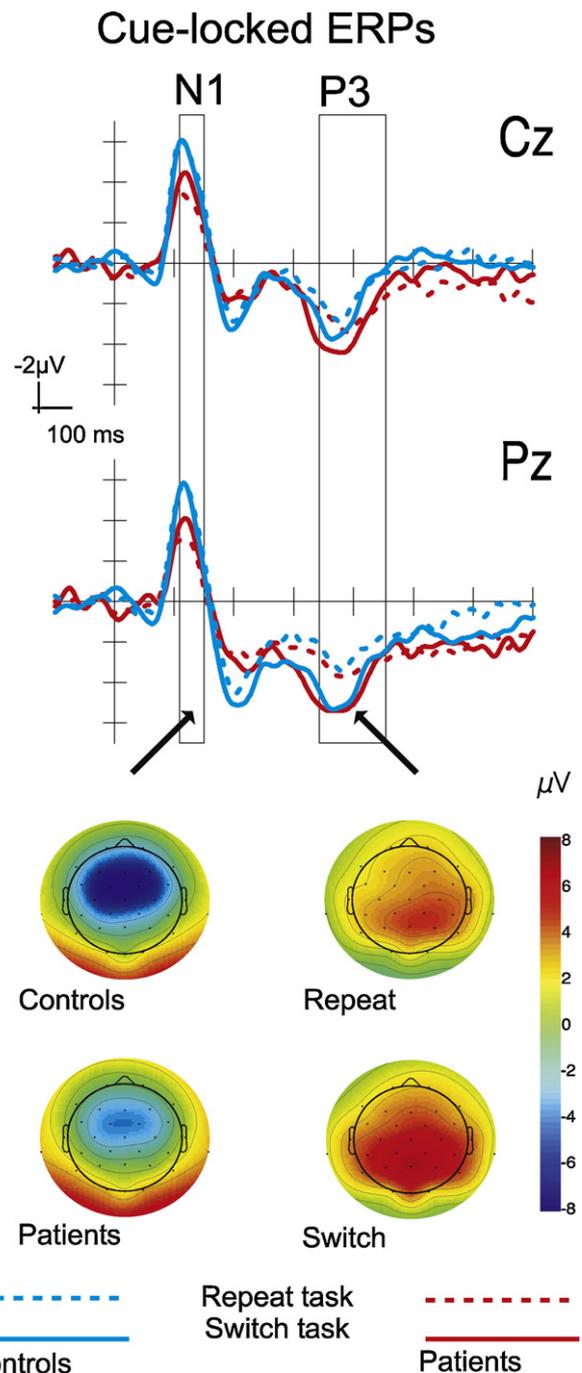
**Fig. 2.** Performance of schizophrenic patients (dark gray) and healthy controls (light gray). Reaction times (A) and hit rates (B) are shown for trials including a repeat or switch in task (task-switching factor) and a repeat or switch in cue (sensory priming factor), respectively. Error bars denote the standard error of the mean (SEM).

75 ± 2% and 80 ± 2%, respectively;  $F(1,30)=8.936$ ,  $p=0.006$ ). No interaction between the two factors was found (Fig. 2).

A similar RT pattern was found concerning sensory priming. Schizophrenic patients responded significantly slower than controls independently of cue repetition or change (mean RT ± SEM for patients and controls 1612 ± 60 ms and 1292 ± 60 ms, respectively;  $F(1,30)=14.119$ ,  $p=0.001$ ) and a decreased HR (mean HR ± SEM for patients and controls 70 ± 3% and 85 ± 3%, respectively;  $F(1,30)=13.166$ ,  $p=0.001$ ). Both groups showed increased RT after a cue switch compared with a cue repetition (mean RT ± SEM for switch and repeat 1487 ± 45 ms and 1417 ± 44 ms, respectively;  $F(1,30)=9.966$ ,  $p=0.03$ ) but there were no differences in HR related to the type of cue (HR ± SEM for switch and repeat 77 ± 2% and 77 ± 2%, respectively;  $F(1,30)=1.557$ ,  $p=0.989$ ). Again, no interaction between the factors was observed (Fig. 2).

### 3.2. Brain potentials

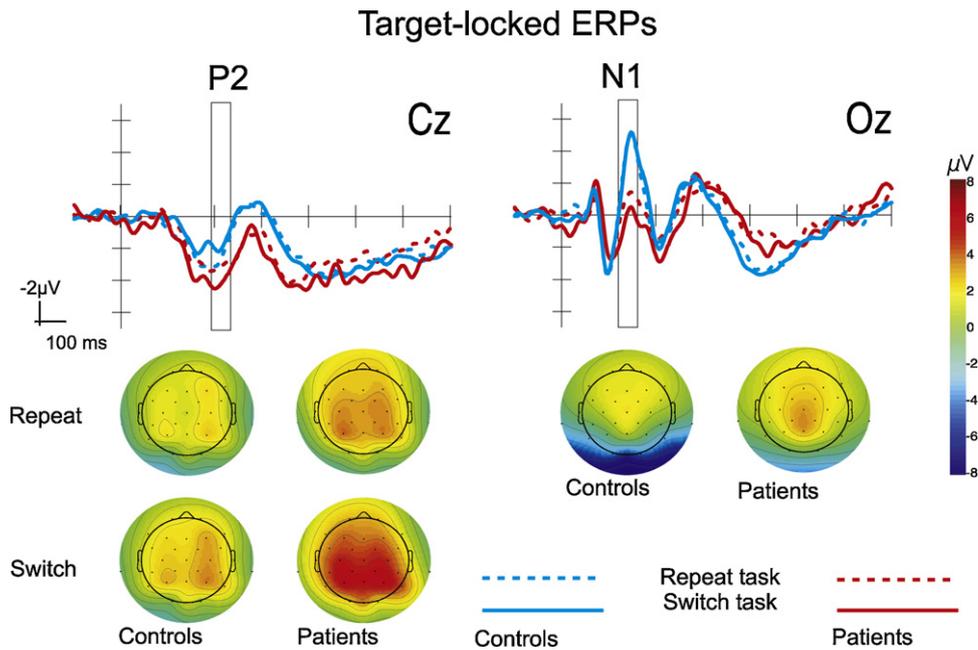
**Cue-related responses.** There was an overall reduction in the frontal N1 amplitude (110–130 ms) in patients compared with controls irrespective of the task switching condition ( $F(1,30)=6.916$ ;  $p=0.013$ ). The absence of any interaction with the group factor indicated diminished N1 amplitudes for patients compared with controls across all task conditions (mean amplitudes ± SEM for patients and controls  $-2.5 \pm 0.5$  and  $-4.4 \pm 0.5$ , respectively). The scalp distribution of cue-locked N1 amplitudes revealed a maximum over frontal and central electrodes. Task-switch trials elicited significantly larger cue-locked parietal P3 amplitudes (360–400 ms) whenever there was a change in cue or task as compared with either a cue or task repetition, respectively. This resulted in a significant main effect for sensory priming for the P3 ( $F(1,30)=8.137$ ;  $p=0.008$ ), as well as a significant main effect for task switching for the P3 ( $F(1,30)=13.376$ ;  $p<0.001$ ). In all cases, a



**Fig. 3.** Grand averages of cue-locked ERPs (N1 and P3) are shown for schizophrenic patients (red) and healthy controls (blue) for task switch trials (solid line) and task repeat trials (dashed line). Time point 0 ms refers to target onset. Topographies are shown for the mean amplitudes according to the analyzed time windows. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

change in either sensory or task representation resulted in larger mean P3 amplitudes compared with a sensory or task repetition (Fig. 3). No group differences were found between the mean amplitudes of the cue-locked P3. No other cue-locked ERP component revealed differences between groups.

**Target-related responses.** There was a main group effect ( $F(1,30)=10.583$ ;  $p=0.003$ ) on the target-locked N1 which was caused by diminished amplitudes (140–160 ms) for patients (mean amplitudes ± SEM for patients and controls  $-0.04 \pm 1.0$  and  $-4.85 \pm 1.0$ , respectively). Similar to the auditory N1 in the cue-



**Fig. 4.** Grand averages of target-locked ERPs (N1 and P2) are shown for schizophrenic patients (red) and healthy controls (blue) for task switch trials (solid line) and task repeat trials (dashed line). Time point 0 ms refers to target onset. Topographies are shown for the mean amplitudes according to the analyzed time windows. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

locked ERPs, this group effect was not modulated by interactions with any other factor (Fig. 4).

For mean target-locked P2 amplitudes (190–230 ms) a significant group  $\times$  task-switching interaction was obtained ( $F(1,30)=8.085$ ;  $p=0.008$ ). In patients, we observed larger P2 amplitudes in task-switch compared with task-repeat trials ( $p=0.023$ ; mean  $\pm$  SEM for switch and repeat =  $4.41 \pm 0.99$  and  $2.94 \pm 0.70$ , respectively). In controls, mean P2 amplitudes did not differ between task conditions ( $p=0.116$ ; mean  $\pm$  SEM for switch and repeat =  $1.38 \pm 0.99$  and  $2.38 \pm 0.77$ , respectively; Fig. 4). The analysis of the target-locked P3 did not uncover differences in the mean amplitudes concerning the factors groups, task condition or sensory priming.

Finally, there was a significant positive correlation for all subjects between the mean amplitude of target-locked P2 and mean reaction times ( $p=0.014$ ).

In sum, schizophrenic patients showed ERP abnormalities during both the cue and target periods in the present task-switching paradigm. At both, cue and target periods, mean N1 amplitude was significantly diminished for patients compared with controls. The target-locked P2 was increased for patients in task-switch trials only. Both patients and controls showed the typical pattern of enhanced P3 amplitudes to switch cues as compared with repeat cues. Moreover, increased P3 amplitudes were also found in response to cues that were different than in the previous trial compared with cue repetition, but again this modulation of cue-locked P3 amplitude was true both for controls and the patients.

#### 4. Discussion

The present study served the main purpose to examine the nature of task-set representations that are compromised in schizophrenic patients through the orthogonal manipulation of task preparation (cue-locked) and task execution (target-locked) information. The distinct measurement of task-set updating and maintenance processes during the preparation and execution stages of task performance allowed us to investigate cognitive flexibility, namely, the ability to represent, maintain and update

task-set information in schizophrenic patients. Our task-cueing protocol allowed us to perform separate analyses of cue- and target-locked brain responses reflecting both early sensory and late cognitive control processes involved in updating task-set information (i.e., encoding, updating and maintenance in task anticipation and preparation processes). The main outcomes of the present study were the evidence for disturbances in early processing in schizophrenia in a complex task-switching paradigm. This deficit became evident in the reduced N1 amplitudes observed in both cue-locked and target-locked ERP waveforms. This outcome suggests that early disturbances in stimulus processing might affect higher-order functions such as those involved in the cognitive control of task-set switching. Even though we did not find significant differences in cue-locked or target-locked P3 amplitude between schizophrenic patients and healthy controls, such group differences were found for the relatively less well known target-locked P2 component. Behaviorally, schizophrenic patients responded slower and with less accuracy than controls. The lack of an interaction between group and task condition (switch or repeat) in neither sensory priming nor task-switching at a behavioral level suggests that patients were not *specifically* impaired in the neural control of sensory priming and task switching, but instead that patients' impairments affected some basic processes common to both switch and repeat trials (i.e., memory maintenance). Next we discuss these results in the light of current models of dysexecutive symptoms in schizophrenic patients.

##### 4.1. Task preparation

In contrast to former research and our original hypothesis, we did not find any significant cue-locked P3 abnormalities in schizophrenic patients in the present study (cf., Cortiñas et al., 2008; Jamadar et al., 2010; Kieffaber et al., 2007). Indeed, and according to our original hypothesis, we found larger cue-locked P3 amplitudes for switch compared with repeat trials, thus revealing larger context-updating operations at task transitions, as has been described in many recent task-cueing ERP studies in healthy participants (Barcelo et al., 2006; Garcia-Garcia et al., 2010a;

Periáñez & Barceló, 2009). Moreover, context-updating operations also elicited larger cue-locked P3 amplitudes in trial sequences involving cue switches compared with cue repetitions. Nevertheless, these cue-locked P3 modulations were similar for both groups, which suggests that the neural mechanisms underlying cue encoding and task-set updating were not particularly affected in the patients. Importantly, the enhanced P3 amplitudes for trials containing a task-switch as well as those containing a cue-switch indicate that the present paradigm was sensitive to investigate task-switching processes, as has been shown in many previous studies (Adrover-Roig & Barceló, 2010; Barceló et al., 2006; Garcia-Garcia et al., 2010a).

Taken together these results support the view that context-updating operations can be elicited both exogenously and endogenously by changes in sensory and task representations well in advance to target onset, but these anticipatory processes did not reveal any group differences in the present study (Barceló et al., 2006; Periáñez & Barceló, 2009). This outcome is also consistent with the findings by Kieffaber et al. (2006, 2007) who also found preserved set-shifting abilities in schizophrenic patients.

In sharp contrast to the absence of group effects for cue-locked P3 amplitudes, we found significant group differences for the frontally distributed N1 component. This component does not represent a unitary process, but involves several endogenous and exogenous components (Näätänen & Picton, 1987), and has been related to attentional control and sensory and perceptual encoding as well as integration (Clark & Hillyard, 1996; Hillyard & Anllo-Vento, 1998). The present N1 results go in line with former studies that found disturbances in early processing in schizophrenia (Galletly et al., 2007; Haenschel et al., 2007; Neuhaus et al., 2011). Importantly, Neuhaus et al. (2011) found evidence that diminished N1 amplitudes in schizophrenia are due to disturbances in both bottom-up and top-down processes. This points in the same direction as studies which could uncover that early sensory processing in cognitive tasks is modulated by the dopamine system, indexed by N1 amplitude modulations associated to the task relevance of the cue (Garcia-Garcia et al., 2010b; Näätänen & Picton, 1987). Taken together, these and our recent findings suggest that the disturbances in early processing stages in schizophrenia are not only due to disrupted sensory processing per se, but also to disrupt top-down processing. Neuhaus and colleagues could link this early disturbances mirrored in the N1 with sources in occipital cortex areas as well as the ACC which in turn allows a possible link between early (sensory) processing and higher-order processes. Taken together these and our recent findings it can be suggested that the disturbances in early processing stages in schizophrenia are not only due to disrupted sensory processing as such but also to disrupted top-down processing. Neuhaus and colleagues could link this early disturbances mirrored in the N1 with source in occipital cortex areas as well as the ACC which in turn allows a possible link between the early (sensory) processing and higher-order processes.

#### 4.2. Task execution

The present study did not find, in contrast to former studies, any significant target-locked P3 differences between switch and repeat trials that are usually found in task-switching paradigms. Paradigm differences seem to be a source of different outcomes. While Jamadar et al. (2010) could show strong P3 differences between schizophrenic patients and healthy controls, Kieffaber et al. (2006, 2007) did not find modulated P3 amplitudes in patients (Jamadar et al., 2010; Kieffaber et al., 2006, 2007). The enhanced P3 amplitudes found in previous studies comparing schizophrenic patients with healthy controls were mainly obtained in oddball paradigms (Jeon & Polich, 2003). Noteworthy, these paradigms cannot distinguish preparation from execution processes (i.e., the selection of

a target-response) but typically confound these two distinct processes (Adrover-Roig & Barceló, 2010; Barceló et al., 2006; Barceló, 2003). Kieffaber et al. (2007) suggest that the ability of a successful set-shifting and the representation of task-set information could be two different concepts which would assume that they can be disturbed separately as indicated by our present results. Schizophrenic patients seem to be able to represent the task-set and do not suffer by preparing their response (as indicated by the cue-locked P3 amplitudes). In turn, they cannot implement and execute the task-set as well as controls caused by conflicting and irrelevant information which is reflected in the enhanced target-locked P2 in switch.

Schizophrenic patients had diminished target-locked N1 amplitudes compared with controls in the present study. However, this group differences did not interact with any other factor. Previous studies also reported smaller N1 amplitudes in schizophrenics and could link the N1 amplitudes which were modulated by mental effort to the BOLD signal of the anterior cingulate cortex, a brain structure known to monitor conflict detection processing and task difficulty (Botvinick et al., 2004; Carter & van Veen, 2007; Mulert et al., 2001, 2008). Noteworthy, the view of the early sensory brain regions changed within the last years from a “simply passing along” of environmental representations to higher order systems to a more complex view which admit filtering of information and modulation depending on contextual information (Javitt, 2009b; Ross et al., 2010). This goes in line with a recent study of Haenschel et al. (2007) who found a diminished P1 during the encoding phase of a WM task in schizophrenics. This is pointing to the direction that impairments of cognitive control in schizophrenic patients could be caused (at least partially) by disturbances in the early processing stages. Importantly, these effects do also occur when controlling for medication (Haenschel et al., 2007; Mulert et al., 2001). The finding of a main effect for group without a corresponding interaction with task-switching in the present study could suggest that the disrupted mechanism is common to several processes. The observed early modulations in both cue- and target-locked N1 amplitudes might reflect early stimulus processing modulated by the dopamine system (Garcia-Garcia et al., 2010b). As early stimulus processing is not the same as sensory processing, because the stimulus can receive a top-down modulation, these early N1 effects are not meant to be restricted to sensory processing but should be linked to several simultaneous activities which can be partly related to higher-order processes like task-switching (Barceló et al., 2006; Garcia-Garcia et al., 2010a; Näätänen & Picton, 1987; Wylie et al., 2003). Neuhaus et al. (2011) dissociated the bottom-up and top-down modulations in schizophrenia during the early visual processing stages. Their results go in line with former work and it could be proved that disruption in the N1 amplitude is caused by both bottom-up and top-down modulation. Moreover, there is evidence that this might contribute to higher-order processing. Hence, the observed disturbances might reflect a very basic and general disruption in early stimulus processing. The next question to answer is whether and how these early differences in stimulus processing could lead to differences in later processing stages, mirrored by other ERP components different from the P3 component in a task-cueing protocol.

We found an interaction effect for the target-locked P2 between Group and Task condition. While participants in the control group showed similar amplitudes for switch and repeat trials, increased P2 amplitudes in the patients group were found for task-switch trials compared with repeat trials which means that patients brain activity in the P2 time window differ depending on condition while it does not in controls. In the field of task-switching and cognitive control paradigms increased P2 amplitudes have been found depending on task condition as well as cognitive control in task-switch trials (Adrover-Roig & Barceló, 2010; Barceló & Rubia, 1998).

For schizophrenic patients decreased P2 amplitudes are reported as well as a smaller enhancement of the P2 amplitude when stimuli were attended (Davenport et al., 2006; O'Donnell et al., 1994; Salisbury et al., 2009). However, Du et al. (2007) found P2 modulations depending on interference solution and concluded that an increased P2 amplitude probably mirrors a higher mental effort to solve the task which goes in line with the idea of Kieffaber & Hetrick (2005) that the target-locked P2 could be seen as an index of the retrieval of S-R associations as a part of the stimulus processing. This result goes in line with a study by Freunberger et al. (2007) who linked the time window of P2 with the inhibition of irrelevant and distracting information. Likewise, Graupner et al. (in press) showed that increases in mean P2 amplitude reflect increased processing demands. This seems to be particularly true, whenever the target and the irrelevant stimuli appear simultaneously. This in turn is compatible with a deficit in task-set implementation since difficulties in fending out distraction have to be resolved before the task-rules can be executed.

In the present study, schizophrenic patients did not show higher switch costs but performed slower and less accurate than controls in all conditions. However, the P2 amplitude was increased in switch trials only. This could be interpreted as extra effort to solve the (more difficult) task which in turn demands high cognitive control. In the current literature the P2 component has been related to target detection, stimulus encoding, interference solution, the evaluation of salience and relevance (Gajewski et al., 2008; Potts, 2004; Potts et al., 2006), processes which are especially involved in switch trials. Following the idea of García-Larrea et al. (1992) that this component (or the P250 as they called it) "indexes some aspects of the stimulus-classification process whereby a stimulus will be considered or not as *the target*". Increased P2 amplitudes could mirror the effort to engage in attentive target processing in order to protect it from conflicting (and irrelevant) stimuli through suppression of distracter-related information in cortical areas (Graupner et al., in press). In our study this conflict would involve making decisions about which target dimension (color or shape) has to be processed. The significant positive correlation we found supports the view that larger P2 amplitudes and prolonged mean RTs both reflect larger processing demands. From this view, the larger P2 amplitudes in schizophrenic patients could suggest that conflict-related effortful processing is particularly enhanced in schizophrenic patients when they have to update (switch) task-set information. Recent studies linked the P2 amplitude with the PFC and an association with the dopamine system (Gajewski et al., 2008; Potts, 2004; Potts et al., 2006). Higher disturbances in these systems are well known for schizophrenic patients. As all patients who participated in the present study were medicated and had a mean duration of illness of nearly ten years, we are not able to answer the question whether the present findings could be found in un-medicated patients or in early stage of illness. However, the present data suggests that, due to disturbances in early-stage processes as well as in the encoding and evaluation of the stimuli, schizophrenic patients cannot implement the task-set as efficient as healthy controls which leads to reduced performance in task-switching paradigms.

## 5. Conclusions

In summary, the results of the present study led us to conclude that the activation of a widespread network for attentional control is disturbed in schizophrenia. Early processing was modulated differently for the two groups but not affected by trial. As the P3 revealed no group differences the poor performance in schizophrenic patients seems to be not caused by impaired rule-implementation and task-set reconfiguration. The target-locked P2 was significantly increased in the patients group in task-switch

trials only indicating disrupted processing of stimulus categorization and an enhancement of cognitive control processes in schizophrenia in task-switch trials. This enhanced P2 might indicate a more effortful stimulus classification process for task-switch trials in patients during task-set implementation. Controls seem to solve task-switching conflicts on a more automatic (i.e., sub-cortical) bases, whereas schizophrenic patients do so in repeat trials only. The purpose of the present study was to examine the putative differences between schizophrenic patients and healthy controls in the temporal ERP dynamics (processing stages) in a task-cueing protocol. The present results do not reveal any specific impairment in the preparatory stage of task-set shifting (updating) in schizophrenic patients, as indexed by cue-locked P3 activity. Instead, patients' impaired task-switching performance seemed caused by a disruption in early stages of sensory processing (as indicated by the frontal and occipital N1 components).

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