Agència de Gestió d'Ajuts Universitaris i de Recerca

Memòria justificativa de recerca de les convocatòries BE, PIV, BCC, NANOS i BP

La memòria justificativa consta de les dues parts que venen a continuació:
1.- Dades bàsiques i resums
2.- Memòria del treball (informe científic)

Tots els camps són obligatoris

1.- Dades bàsiques i resums

Nom de la convocatòria

BE

Llegenda per a les convocatòries:

BCC	Convocatòria de beques per a joves membres de comunitats catalanes a l'exterior (BCC)
BE	Beques per a estades per a la recerca fora de Catalunya (BE)
BP	Convocatòria d'ajuts postdoctorals dins del programa Beatriu de Pinós (BP)
NANOS	Beques de recerca per a la formació en el camp de les nanotecnologies (NANOS)
PIV	Beques de recerca per a professors i investigadors visitants a Catalunya (PIV)

Títol del projecte: ha de sintetitzar la temàtica científica del vostre document.
Estudi neurofisiològic del control executiu de l'atenció en l'esquizofrènia.

Dades de l'investigador

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Paraules clau: cal que esmenteu cinc conceptes que defineixin el contingut de la vostra memòria.
Atenció, funcions executives, potencials evocats, esquizofrènia, paradigmes de canvi de tasca

Data de presentació de la justificació

05/07/2007

Resum del projecte: cal adjuntar dos resums del document, l'un en anglès i l'altre en la llengua del document, on s'esmenti la durada de l'acció

Resum en la llengua del projecte (màxim 300 paraules)

Les alteracions en les funcions executives, inclosa l'habilitat de canviar de tasca, representen una característica fonamental de l'esquizofrènia. Aquesta habilitat per adaptar el comportament a les contingències o als events ambientals canviants requereix d'un mecanisme per canviar el focus de l'atenció entre les associacions estímul - resposta apreses. Aquest projecte pretenia aprofundir en el coneixement dels mecanismes cerebrals relacionats amb el control executiu de l'atenció en l'esquizofrènia durant l'execució d'un paradigma de canvi de tasca. A més, com a objectiu secundari es van examinar les interrelacions entre els processos de control endògens i exògens que participen en l'habilitat de canviar de tasca. Per aconseguir aquests objectius, es va emprar un paradigma de canvi de tasca inspirat en el test de classificació de cartes del Wisconsin. Els subjectes havien de canviar les regles de la tasca d'acord a les indicacions contextuals (tons binaurals de 500 Hz o 1000 Hz) prèviament especificades. Les dades comportamentals es van combinar amb l'excel•lent resolució temporal dels potencials evocats (N1, P1, N2, novelty P3) per tal d'estudiar la cronologia de les operacions mentals realitzades. Els resultats conductuals coincidiren amb la idea de que els factors exògens i endògens interactuen multiplicativament per a produir els costos comportamentals observats en els paradigmes de canvi de tasca. Sorprenentment, aquest efecte multiplicatiu va ser exactament igual pels dos grups. El resultat electrofisiològic més important va ser l'amplitud augmentada de la novelty P3 dels pacients davant dels canvis de les indicacions contextuals en comparació amb les repeticions de les mateixes. La present evidència electrofisiològica suggereix una alteració en els mecanismes cerebrals responsables del control executiu de l'atenció en l'esquizofrènia durant l'execució d'un paradigma de canvi de tasca.

Resum en anglès(màxim 300 paraules)
Abnormalities in executive functions, including set shifting ability, represent a cardinal feature in schizophrenia. This ability to adapt behavior to changing environmental events or contingencies requires a mechanism for switching attention between learned stimulus-response associations, or task-sets. This project aimed at gaining further knowledge on the brain mechanisms related to the executive control of attention in schizophrenia during the performace of a task switching paradigm. Furthermore, a secondary goal was to further examine the interrelationships between endogenous and exogenous control processes in task set switching. In achieving these two aims, we used a task switching paradigm inspired by the Wisconsin card sorting test. Subjects were required to switch the task rules according with previously specified and task relevant contextual cues (500 Hz and 1000 Hz binaural tones). The behavioral performance was combined with the excellent temporal resolution of event-related potentials (N1, P1, N2, novelty P3) in order to examine the chronology of mental operations. The behavioral results concurred with the idea that exogenous and endogenous factors interact multiplicatively to produce the behavioral costs observed in task switching paradigms. Surprisingly, this multiplicative effect was equivalent in the control and schizophrenic groups. The most important electrophysiological result was the larger novelty P3 amplitude to changes compared to repetitions in the cueing event in patients. The present electrophysiological evidence suggests a disruption in the brain mechanisms responsible for the executive control of attention in schizophrenia during the performance of a task-switching paradigm.

2.- Memòria del treball (informe científic sense limitació de paraules). Pot incloure altres fitxers de qualsevol mena, no més grans de 10 MB cadascun d'ells.

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Barcelona, 5 de juliol de 2007

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1. INTRODUCTION

Schizophrenia is a severe mental disorder associated with abnormalities in attention and information processing (see Braff (1993) for a review). A major impairment is in executive functions (Shallice et al., 1991), including set shifting ability. Human adaptive behavior relies on this ability to flexibly move the focus of mind among changing environmental events or contingencies (Miller, 2000). This ability to adapt behavior to changing contextual contingencies requires a mechanism for switching attention between learned stimulus-response associations, or task-sets (Rubinstein, 2001). The brain mechanisms responsible for this flexible control of behavior can be explored using task switching paradigms (Monsell, 2003). In these paradigms, subjects are required to switch the task rules (task set) according with previously specified and task relevant contextual cues. Extensive neuroimaging and lesion studies have begun to unveil the brain mechanisms responsible for the control of task switching, as an important case in the executive control of human attention (Rubinstein et al., 2001; Braver et al., 2003; Monsell, 2003; Meiran et al., 2000). These studies in humans suggest a role of prefrontal cortex in set shifting (Konishi et al., 1998), an area associated with structural and functional abnormalities in schizophrenia (Wible et al., 1995).

Flexible behavior can be adaptive, but not without a cost. Adapting our minds to a new context, makes us clumsier and slower for a moment, until the new plan of action has been definitely established and rehearsed. What is relevant now may be a distractor later. In line with this, there are two classes of competing theories for explaining switch costs, each varying in the relative importance assigned to endogenous and exogenous mechanisms of control. The “Task-Set Reconfiguration” (TSR) hypothesis proposes that switch costs reflect the time taken for an executive process to switch the cognitive system from a readiness to perform one task, to a readiness to perform the other (Meiran et al., 2000; Monsell, 2003; Rubinstein et al., 2001). A group of alternative proposals emphasize the role of exogenous factors in the origin of residual switch costs, such as stimulus-primed associative retrieval of previous task-sets (Allport et al., 1994; Waszak et al., 2003; Wyllie & Allport, 2000), or perceptual priming from prior stimulation (Logan, 2002; Logan & Bundesen, 2003). In sum, TSR proponents emphasize the role of endogenous factors as the main explanation for behavioral switch costs and proponents of the second hypothesis, The “Stimulus Priming” hypothesis, emphasize the importance of exogenous factors in the control of task switching. In any case, this should not be seen as a sharp dichotomy since few authors in either side would deny some type of interaction between the endogenous and exogenous mechanisms of control (Monsell, 2003).

The main goal of the present study was explore the dynamics of brain activation in schizophrenia during the executive control stage in a task switching paradigm. Furthermore, we also wished to further examine the interrelationships between endogenous and exogenous control processes in task set switching. In achieving these two aims, we used a task cueing paradigm, a kind of task switching paradigm inspired by a classic test of prefrontal impairment, the Wisconsin card sorting test (Milner, 1963; Rubinstein, Meyer, & Evans, 2001). The use of a task cueing paradigm allowed us to separate the brain responses to task cues (executive control) from those to targets (task execution) demanding an imperative motor response. As we were interested in the executive control of attention, we only analyzed the responses to task cues. The behavioral performance was combined with the excellent temporal resolution of event-related potentials (ERPs) in order to examine the chronology of mental and brain operations. Up to date, only a minority of ERP studies have offered a fine spatio-temporal analysis of brain activation related to task switching (Rushworth et al., 2002; Wylie et al, 2003a; 2003b).

2. METHODS

2.1. Subjects

Sixteen healthy university students (19-48 years, mean age: 31.94; 3 females) and sixteen chronic schizophrenic outpatients (18-48 years, mean age: 30.75; 3 females) fulfilling DSM-IV criteria for schizophrenia took part in the study. The controls were recruited by board advertisements and the patients were referred from the Hospital of Terrassa. 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 subjects were left-handed in accordance with the Edinburg Handedness Inventory (Oldfield, 1971).

Patients received DSM-IV subtype diagnoses of residual (1), undifferentiated (2) and paranoid (13). Exclusion criteria for patients included mental disorders other than schizophrenia, neurological disorders, head injury, stroke and substance abuse (except tobacco). All patients were with antipsychotic medication and nine of them were also taking other additional medication (antidepressants, anticholinergics, anxiolytics, hypnotics) at the time of the experiment. Twelve patients were on atypical antipsychotics, one patient was on typical antipsychotics and the remaining three 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 psychiatric diseases (first degree relatives). The experiment was performed in accordance with the Declaration of Helsinki and with the approval of the Ethical Committee of University of Barcelona. Informed consent was obtained from all subjects.

2.2. Stimuli and Procedures

We used a version of a task-cueing protocol inspired in the Wisconsin card sorting test (Milner, 1963; Rubinstein, Meyer, & Evans, 2001), and adapted for measuring event-related potentials (Barcelo, 2003). Each trial consisted of a tonal cue followed by a target display with four key cards on top of one choice card, all centered on a computer screen 2 meters away from the observer (Fig. 1). The target stimulus subtended a visual angle of 3.5º x 3.5º, and remained on display until a response was given. Subjects were instructed to match the choice-card with one of the four key-cards following two rules of action (color or shape of items on the cards). Subjects were told that the correct rule would change unpredictably after a variable number of card sorts, and hence, they would have to shift their sorting rule accordingly. Before target onset, a tonal cue informed the subject whether to switch or to repeat the previous task (200 ms duration, 10 ms rise/fall times; 75 dB SPL; 500 Hz and 1000 Hz binaural tones for 'switch' and 'repeat' cues, respectively). Tonal cues occurred semi-randomly with an overall probability of 0.50 for both switch and repeat trials, and with the only constraint of a maximum number of five consecutive switch or repeat trials in a row. Tonal cues indicated whether to switch or repeat the previous task rule, but did not inform about the accuracy of the response to the previous trial. Subjects used their thumbs for responding while holding a 4-button response panel in their palms. The far left button designated the key-card on the far left of the display, the far right button designated the key-card on the far right, and so on. The task sets declared in the instructions consisted of 4-feature-stimulus to 4-forced-response mappings (Si – Ri, with i= 1, 2, 3 or 4 units). For instance, when sorting by color, a 'blue' target card was to be matched with the 'blue' key-card by pressing the right-most response button (S4 – R4, Fig. 1). Response-to-cue intervals varied randomly between 800 and 1500 ms, with a constant cue-to-target onset asynchrony of 2250 ms.

Subjects sat in an armchair, in a sound-attenuated, dimly illuminated, and electrically shielded room. Before the experimental run, each subject practiced for 5-10 min, until they could sort cards efficiently. Each subject completed two blocks of 140 trials, with a 5 min rest period between blocks. Overall accuracy was better than 65% correct trials for all schizophrenic patients and control subjects.

2.3. Electrophysiologic recordings

The electroencephalogram (EEG) was continuously digitized at a rate of 500 Hz (bandpass 0.01 to 100 Hz) by a SynAmps amplifier (Compumedics NeuroScan) from 28 scalp Ag/AgCl electrodes positioned according to the extended 10-20 system (Fp1, Fp2, FC1, FC2, F3, F4, F7, F8, FT3, FT4, Fz, 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-occulogram (HEOG/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 EEprobe 3.1 program (ANT software BV, Enschede, The Netherlands). After EOG correction, trials exceeding EEG amplitudes of ± 75 μV at any channel were automatically excluded from averaging.

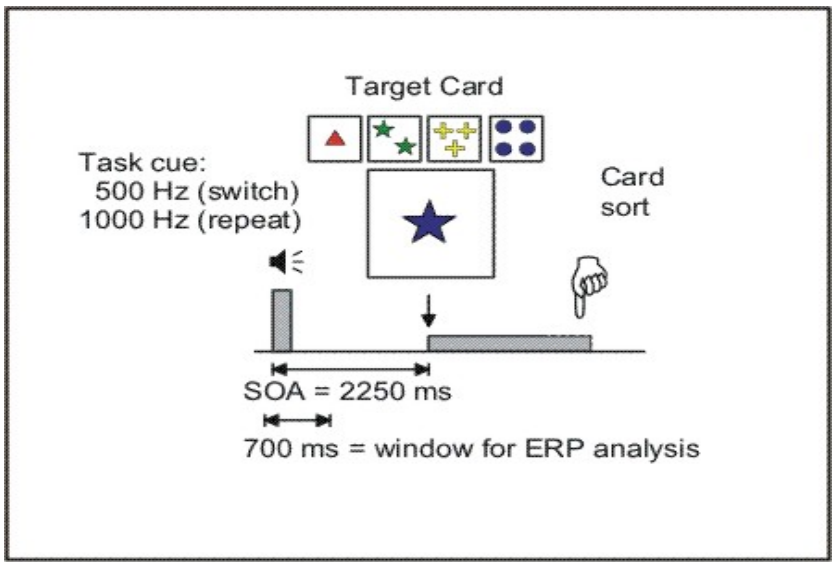

Figure 1. Task design and window for ERP analysis.

2.4. Statistical design and analyses

Event-related potentials were obtained from correct trials only. The averaging window was 700 ms for the auditory cues (Fig. 1), including a 100-ms pre-stimulus baseline. Individual ERP waveforms were digitally band-pass filtered between 0.1 and 30 Hz and contained a minimum of 25 clean EEG epochs (range 25-63). Mean ERP amplitude values were measured relative to the 100-ms pre-stimulus baseline for the novelty P3 (360-400 ms post-stimulus onset), the N1 (80-100 ms), the P2 (190-230 ms),and the N2 (260-300 ms) components.

The 'Stimulus Priming' hypothesis was tested by comparing ERPs from trials starting with the same or different cueing event as in previous trial in an ANOVA design with Group (schizophrenics, controls) as the between-subject factor, Stimulus Priming (same, different), and Electrode (FC1, FC2, F3, Fz, F4, FT3, C3, Cz, C4, FT4) as the repeated measures factors. The

"Task-Set Reconfiguration" hypothesis was tested by comparing ERPs from switch and repetition trials in an ANOVA design with Group (schizophrenics, controls) as the between-subject factor, Task-Set Reconfiguration (repeat, switch), and Electrode (FC1, FC2, F3, Fz, F4, FT3, C3, Cz, C4, FT4) as the repeated measures factors.

Behavioral measures (reaction times and errors) were subjected to an overall ANOVA design with Group (schizophrenics, controls), Stimulus Priming (same, different) and Task-Set Reconfiguration (repeat, switch) as repeated measures factors.

3. RESULTS

3.1. Performance

Error rates. Healthy subjects correctly responded to 77% trials compared with an overall 69% hit rate in schizophrenic patients, but this overall difference did not reach significance [$F(1,30) = 2.635$, $p = 0.14$] [(1)]. Both schizophrenic patients and controls made more errors during switch as compared to repeat trials [$F(1,30) = 8.22$, $p = 0.007$, for the main TSR factor], but there were no differences in the number of errors between the two conditions of the Stimulus Priming factor [$F(1,29) < 1$, for the main Stimulus Priming factor]. Finally, a significant interaction between Task-Set Reconfiguration and Stimulus Priming [$F(1,30) = 13.46$, $p = 0.001$], revealed that larger number of errors during switch as compared to repetition trials were observed only when the sensory cues were the same as in the previous trial. In turn, no task switch costs are observed when the sensory cues are different as in the previous trial (Fig.2). The absence of a main effect of the Group factor, or indeed, of any interaction between the Group factor and Task-Set Reconfiguration or Stimulus Priming indicated that error rates were similarly influenced by the present experimental manipulations in both schizophrenic patients and controls.

Reaction times. RT were slower in schizophrenic patients than in controls [$F(1,30) = 16.66$, $p < 0.001$; patients: 1.62 ± 0.06 s; controls: 1.28 ± 0.06 s]. Both schizophrenic patients and controls responded faster to task repetition as compared to task switch trials [$F(1,30) = 11.24$, $p = 0.002$, for the main TSR factor], and also faster after a cue repetition as compared to a cue change [$F(1,30) = 15.88$, $p < 0.001$, for the main Stimulus Priming factor]. Finally, a marginally significant interaction between Task-Set Reconfiguration and Stimulus Priming [$F(1,30) = 3.44$, $p = 0.07$], suggested that the differences in RTs between switch and repetition trials appeared only when the cueing events

[1] The absence of group differences in error rates was motivated by our screening of the sample of schizophrenic patients in order to make the two samples comparable in the number of accepted correct trials in the ERP averages. The original sample of N=25 patients showed significant differences in the overall number of correct trials. However, the overall pattern of errors and reaction times and the absence of interactions between Stimulus Priming and Task-Set Reconfiguration with the Group factor remained unaltered in the original (N=25) and the screened (N=16) sample of patients.

were the same as in the previous trial (Fig. 3). In turn, no task switch costs were observed when the sensory cues differed with the previous trial. The absence of a main effect of the Group factor, or indeed, of any interaction between the Group factor and Task-Set Reconfiguration or Stimulus Priming indicated that RTs were equally influenced by the present experimental manipulations in both schizophrenic patients and controls.

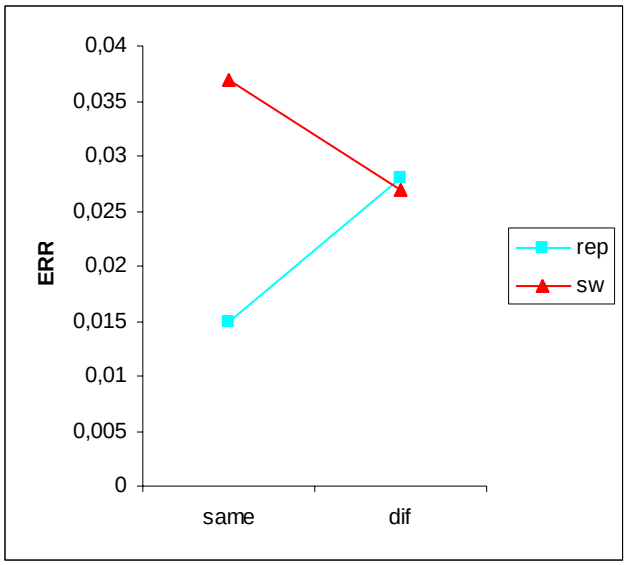

Figure 2. Errors in the Task-Set Reconfiguration and Stimulus Priming conditions.

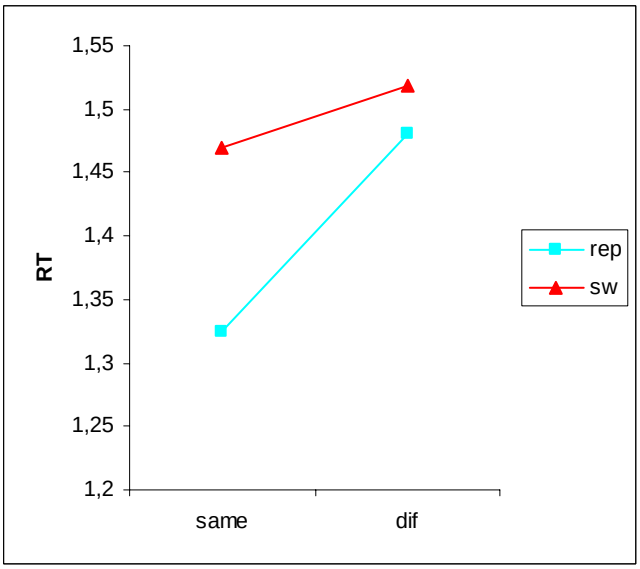

Figure 3. Reaction times in the Task-Set Reconfiguration and Stimulus Priming conditions.

3.2. Electrophysiology

Auditory cueing events elicited well-known sensory ERPs recorded as positive (i.e., P2, novelty P3) and negative (i.e., N1, N2) voltage deflections. The present results focused on the significant

group differences in early and late latency brain potentials to auditory stimulation recorded from ten electrodes (FC1, FC2, F3, Fz, F4, FT3, C3, Cz, C4, FT4).

The main group differences in the brain responses to auditory cueing events were observed during the early N1 and the novelty P3 (see Figures 4 and 5).

Schizophrenic patients showed reduced frontally distributed N1 amplitudes, as revealed by a main Group effect in both the Stimulus Priming [$F(1,30) = 5.74$, $p = 0.023$] and Task-Set Reconfiguration conditions [$F(1,30) = 6.92$, $p = 0.013$], although there were no higher interactions between these manipulations and the group factor.

Unlike healthy subjects, schizophrenic patients showed larger frontally distributed novelty P3 amplitudes to changes compared to repetitions in the cueing event [$F(1,30) = 4.78$, $p = 0.037$, for the Group x Stimulus Priming interaction]. In contrast, schizophrenic patients showed normal novelty P3 amplitudes in Task-Set Reconfiguration condition. As in previous studies, larger novelty P3 were elicited by a change compared to a repetition in task-set [$F(1,30) = 7.01$, $p = 0.013$, for the TSR main effect].

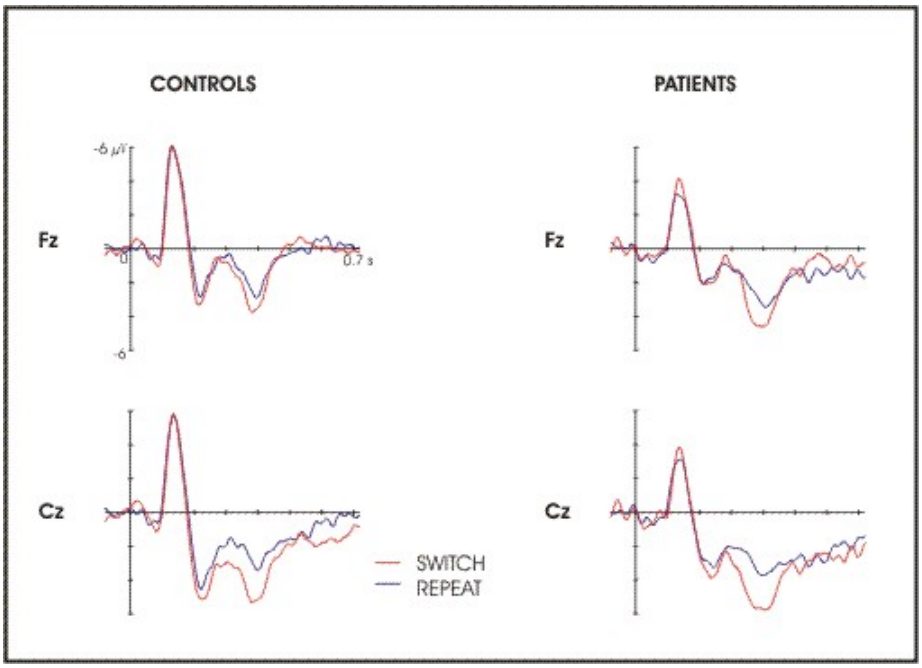

Figure 4. Grand ERP averages to auditory cueing events in the Task-Set Reconfiguration condition.

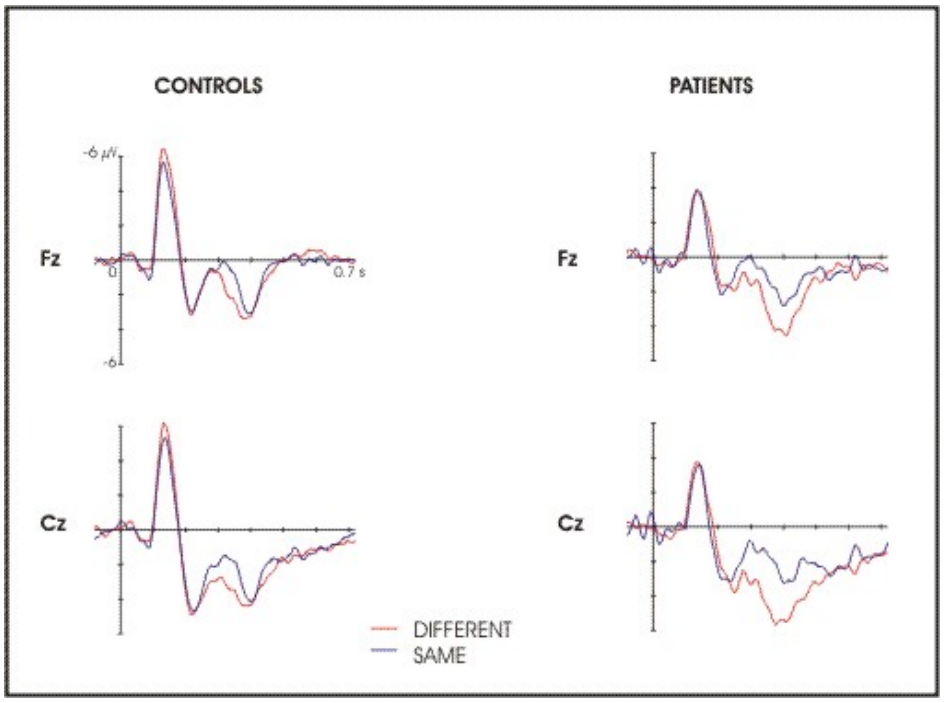

Figure 5. Grand ERP averages to auditory cueing events in the Stimulus Priming condition.

4. DISCUSSION

The behavioral results suggest that “Stimulus Priming” and “Task-Set Reconfiguration” had a multiplicative –rather than additive– influence on card sorting performance (Ruthruff et al., 2001). Moreover, this multiplicative effect was equivalent in the control and schizophrenic groups. This outcome is consistent with, and allows us to reconcile, apparently contradictory views that task-switch costs are due to a benefit in repetition trials (Logan & Bundesen, 2003), but also with evidence that task-set switching partly reflect a mechanism of endogenous reconfiguration that results in a larger probability of making errors (Monsell, 2003; Meiran et al., 2000). These behavioral results concur with the idea that exogenous (Stimulus Priming) and endogenous (cognitive set) factors interact multiplicatively to produce the behavioral costs observed in task-switching paradigms.

The most important electrophysiological result is the larger frontally distributed novelty P3 amplitude to changes compared to repetitions in the cueing event in patients. Taking into account that novelty-P3 reflects transient activation in a neural network involved in updating task set information for goal-directed action selection (Barcelo et al., 2006), the present electrophysiological evidence suggests a disturbance in the brain mechanisms necessary for updating to a novel

stimulus in working memory but not for updating to novel task-set representations during the performance of a task-switching paradigm.

In line with previous literature (Alain et al., 2002; Kogoj et al., 2005), schizophrenic patients also showed deficits at early processing of sensorial stimuli as indexed by a reduced frontally distributed N1 amplitude in both Stimulus Priming and Task-Set Reconfiguration conditions.

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