Brain mechanisms of executive control: Event-related potentials and oscillations in schizophrenic patients and healthy controls during task-switching

Mareike Finke

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PhD Thesis

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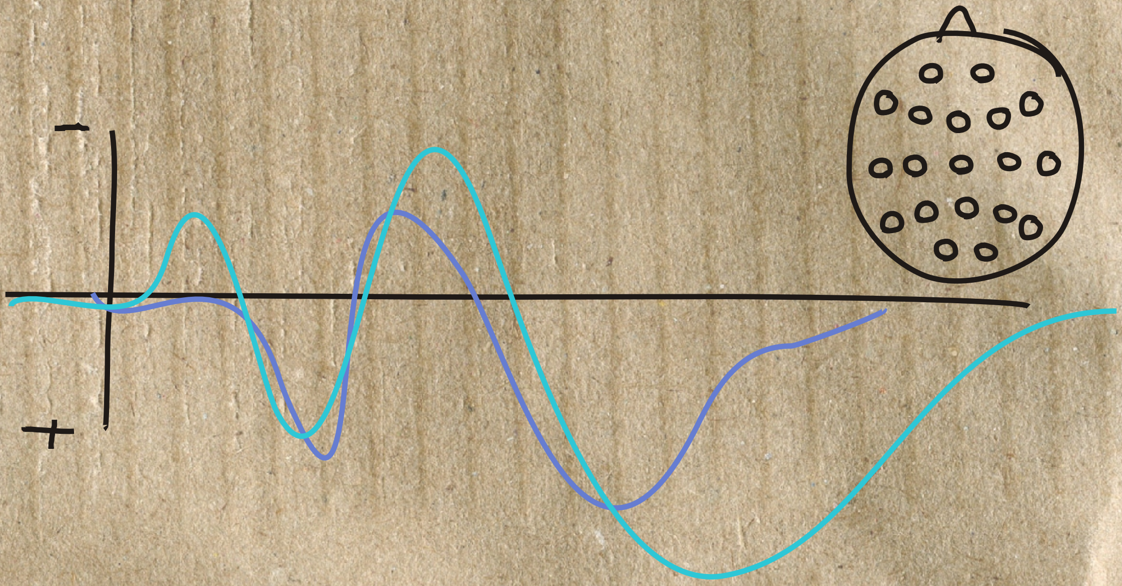

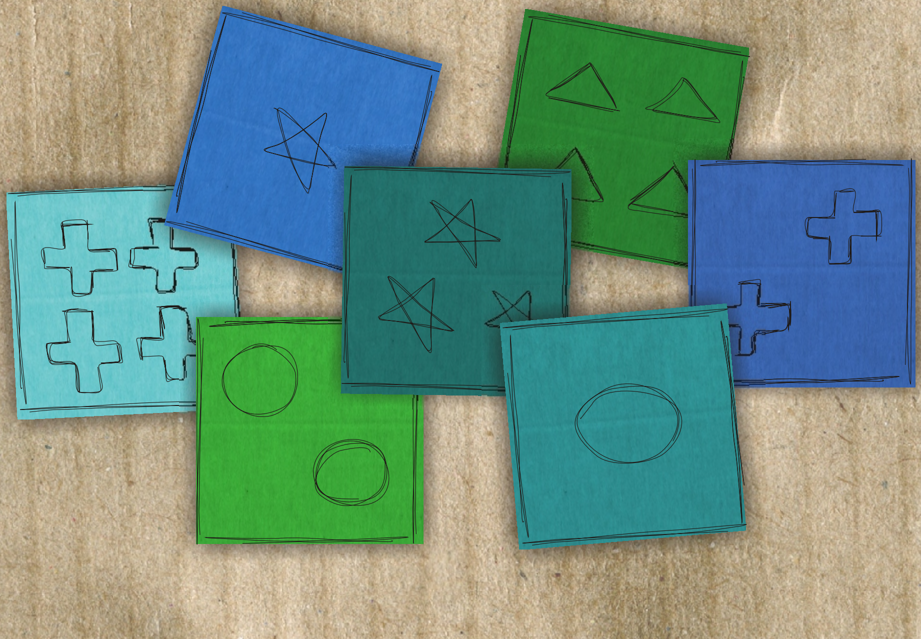

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BRAIN MECHANISMS OF EXECUTIVE CONTROL: EVENT-RELATED POTENTIALS AND OSCILLATIONS IN SCHIZOPHRENIC PATIENTS AND HEALTHY CONTROLS DURING TASK-SWITCHING

Thesis submitted by
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to obtain the
Grau de Doctor per la Universitat de Barcelona
in accordance with the requirements for the
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Programa de Doctorat en Biomedicina

Supervised by
Dr. Carles Escera (University of Barcelona)

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Barcelona, November 2012

To curiosity, the incitement of all (science)

Knowing is not enough,
we must apply.
Willing is not enough,
we must do.

Johann Wolfgang von Goethe

Acknowledgments

This work was made possible thanks to many persons who accompanied me during the last years. As a thesis project is far more than a scientific project, the support and contribution of colleagues, friends and family has been both, professional and personal in many ways.

My first gratitude goes to my supervisors, the fathers of this work, Carles Escera and Francisco Barceló. Thank you for guiding me through the jungle, for your wisdom and patience, for fruitful discussions, for intensive scientific training and extensive traveling.

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I owe many thanks and my gratitude to my parents. I thank you for being there, for all your support in so many ways. You never left me, but always let me go.

Martin, my dear, I thank you for your patience and support but foremost I thank you for being *you*. With you my life is not as before and I wish we will keep standing shoulder to shoulder with a feeling so wonderful – where ever the journey of our life goes to.

Summary

The brain's ability to represent, maintain and update contextual (task-set) information enables us to alternate successfully between tasks. A reconfiguration of this task-set is required when the task demands change, as goal directed behavior has to be adjusted to the new task. Task-cueing paradigms are widely used to investigate the underlying processes which include attentional shifting from one task to the other (task-shifting), the retrieval of goals and rules as well as the inhibition of the previous (irrelevant) task-set.

Three studies have been conducted in this thesis in order to shed light on the different contributions of bottom-up and top-down influences on task-switching.

In the first study, different aspects regarding the extraction of cue information and its importance for task-switching processes were investigated. The electrophysiological modulations regarding sensory changes in cues which (1) are or are not related to a switch in task or (2) may not even carry any task-relevant information in some trials were the focus of interest. The process of early (task-relevant) change detection is important in order to prepare the upcoming task. However, it is not clear yet whether the process of cue and task processing occur serial or in parallel.
The data suggest that sensory cue changes do not affect cue-locked event-related potentials (ERPs) due to mere sensory changes but rather reflect a task-related process. We found a detection of fast task-relevant change (as early as 180 ms) followed by the process of cue-response mapping and the reload/updating of stimulus-response mapping. Target-locked analysis revealed that non-informative cue switches do not affect task preparation in a particular way.

The second study consisted of the analysis of the data from study I in the time-frequency domain in order to elucidate power changes in the alpha and theta band. We independently manipulated (1) the anticipatory task preparation by manipulating the informativeness of cues about the upcoming task, and (2) the exogenous contribution to endogenous task-set switching. This design enables us to examine the relative

contribution from exogenous cue changes upon endogenous task-set reconfiguration effects, and whether those effects depend on the presence of foreknowledge.

The data confirmed strong generic preparation benefits as visible in behavioral performance and both frequency bands. Task switching effects in the alpha band could be related to both shifting and rule activation while task switch effects in the theta band seems to be related to initial task-set reconfiguration rather than task-se implementation. Strong oscillatory modulations for cue switch trials suggest an "incongruent cue-task transition" effect. When the cue-to-target interval was taken as a baseline, stronger alpha desynchronization was found for non-informatively cued trials suggesting that the lack of preparation leads to high cognitive control while the strong theta synchronization in informative trials for this analysis probably reflects the retrieval of cue information. Importantly, no special bias for "task-neutral cue switches" was found.

The third study aimed to investigate cognitive impairment in schizophrenia. Previously, this has been conceptualized as a failure of executive control and contextual processing. However, disturbances in high-order cognitive functions might be due to delimited deficits, especially in lower-level stages of contextual processing. In turn they might affect cognition which could result in modulated low- *and* high-order processing. Moreover, early processing stages do not involve only mere sensory processing, but rather reflect interacting sensory and cognitive mechanisms. Therefore, it is necessary to explore the patients' task-switching abilities by manipulating sensory updating and task-set updating orthogonally in order to examine the interplay between bottom-up and top-down processes.

We could show that the observed impairments in task-switching behavior were not specifically related to anticipatory set-shifting, but derived from a disruption in early stages of sensory processing during cue- and target-locked processing as well as from a deficit in the implementation of task-set representations at target onset in the presence of irrelevant and conflicting information.

Original studies

Study I:

Finke, M., Escera, C., & Barceló, F. (in press). The effects of foreknowledge and task-set shifting as mirrored in cue- and target-locked event-related potentials. *PLoS ONE*. doi: 10.1371/journal.pone.0049486.

Study II:

Finke, M., Escera, C., Prada, L., & Barceló, F. Alpha and theta oscillations are modulated by both, foreknowledge and task-switching. *In preparation*.

Study III:

Finke, M., Barceló, F., Garolera, M., Cortiñas, M., Garrido, G., Pajares, M., & Escera, C. (2011). Impaired preparatory re-mapping of stimulus-response associations and rule-implementation in schizophrenic patients--the role for differences in early processing. *Biological Psychology*, 87(3), 358–365.

This work has been carried out in the Cognitive Neuroscience Research Group (Centre of Excellence established by the Generalitat de Catalunya) at the Department of Psychiatry and Clinical Psychobiology, Faculty of Psychology, University of Barcelona, led by Carles Escera and partially at the Research Group of Neuropsychology in the Department of Psychology, Karl-Franzens University of Graz, led by Christa Neuper. It was supported by grants from the Spanish Ministry of Science and Innovation (PSI2010-17419, Consolider-Ingenio 2010 CSD2007-00012, PSI2008-05803-C02-02), as well as by the 2009SGR-11 and the FI MF052362 grant from the Catalan Government. Additionally, the first study was funded by the Fundació La Marató de TV3 (012810) and the second/third by the Institució Catalana de Recerca i Estudis Avançats (ICREA) Academia Distinguished Professorship awarded to C.E.

Abbreviations

ACC	Anterior cingulate cortex
ANOVA	Analysis of variance
CTI	Cue-to-target interval
EEG	Electroencephalogram
EOG	Electro-oculogram
ERD	Event-related desynchronization
ERP	Event-related potential
ERS	Event-related synchronization
ERSP	Event-related spectral perturbation
HR	Hit rates
MCST	Madrid card sorting test
RCI	Response-to-cue interval
ROI	Region of interest
RT	Response times
SEM	Standard error of the mean
S-R associations	Stimulus-response associations
WCST	Wisconsin card sorting test
WM	Working memory

Content

Introduction

The representation, maintenance and updating of contextual (task-set) information allows us to alternate successfully between two or more tasks. When task demands change, a reconfiguration of the task-set is required and goal directed behavior needs to be adjusted to the new task. This adjusting process to the new task-set makes us maladroit and slower for a moment, until the new plan of action has been definitely established and rehearsed. The use of (pre-) cues allows us to prepare the upcoming task as a certain goal can be activated anticipatorily. Consequently, it is necessary that the task-relevant information which is carried by a particular cue can be processed in an optimal manner. However, (abnormal) sensory and perceptual processes seem to modulate cognitive control processes finally resulting in both, modulated low- as well as high-order processes. As recent studies suggest a constant interplay between bottom-up and top-down processes, it is important to segregate the sensory (i.e., priming) processes from those related to higher order control (i.e., preparation) when researching task-switching effects.

In the following sections an overview of the task-switching literature, including the discussion of the endogenous part of task-set reconfiguration, will be given and important electrophysiological correlates will be introduced. Moreover, results of the time-frequency research are summarized. Finally, principle information of the psychiatric disorder schizophrenia and the recent state of its research will be described.

Task switching and cognitive control

The adaptive shifting of attention and action has been researched in psychological laboratories for many decades and several paradigms have been used since Jersild came up with his "task alternating paradigm" (Jersild, 1927). In the typical task-switching paradigm participants are facing two or more tasks and are asked to perform either of them whenever a certain circumstance is fulfilled (Kiesel et al., 2010; Wylie, Javitt, & Foxe, 2003). While one option is to supply a cue or feedback which informs the participants what to do in the upcoming trial, another option is to let them perform the tasks in a fixed sequence. When using sequences, one can compare those trials where the same rule has to be applied as in the previous trial with those where the task-set has to be shifted. Or so-called single blocks in which just one rule has to be applied are compared to mixed-blocks in which participants alternate between tasks according to a certain pattern (Barceló, 2003; Kieffaber & Hetrick, 2005; Meiran, Levine, Meiran, & Henik, 2000; Rogers & Monsell, 1995; Wylie et al., 2003). Figure 1 shows an overview over the basic task-switching paradigms (Kiesel et al., 2010). As a common result performance is better in repeat trials compared to switch trials. Response times are shorter and accuracy – depending on the particular task design – is higher (Barceló, 2003; Barceló, Escera, Corral, & Periáñez, 2006; Logan & Bundesen, 2003; Meiran et al., 2000; Nicholson, Karayanidis, Bumak, Poboka, & Michie, 2006; Wylie et al., 2003). This effect has been named the "switch cost" and it is thought to reflect the extra amount of cognitive control which is needed in switch trials due to mental shifting, information updating and monitoring as well as the inhibition of the previous response (Barceló et al., 2006; Gladwin & de Jong, 2005; Mayr & Kliegl, 2003; Meiran et al., 2000; Miyake et al., 2000; Monsell, 2003; Wylie et al., 2003). During the last decades task-switching has been researched with increasing interest and much effort has been made to find models which explain the empirical data. A recent review by Kiesel and colleagues summarizes the different models nicely and takes into account both, two-stage models and "all-or-none" process models (de Jong, 2000; Kiesel et al., 2010; Logan & Bundesen, 2003; Rogers & Monsell, 1995; Rubinstein, Meyer, & Evans, 2001). Importantly, two-stage models assume that the task-switching process consists of an endogenous preparation of *goal-shifting* and an exogenous reconfiguration process of *rule-activation* which can occur only after stimulus presentation (Kiesel et al., 2010). On the other hand, the "all-or-none models" suggest (1) a switch specific preparation and assume (2) that it is not gradual but that switch costs arise due to wrong/incomplete task preparation (de Jong, 2000; Kiesel et al., 2010).

The discussion about the endogenous and exogenous parts of task-switching will be described further in a later section, where the cue switch effects will be introduced and discussed. Noteworthy, task-cueing paradigms, such as Card Sorting Tests which have been used in this work, have the advantage that the processes of goal shifting and rule activation can be disentangled (Barceló, 2003; Karayanidis et al., 2009; Kieffaber & Hetrick, 2005; Periáñez & Barceló, 2009; Rubinstein et al., 2001).

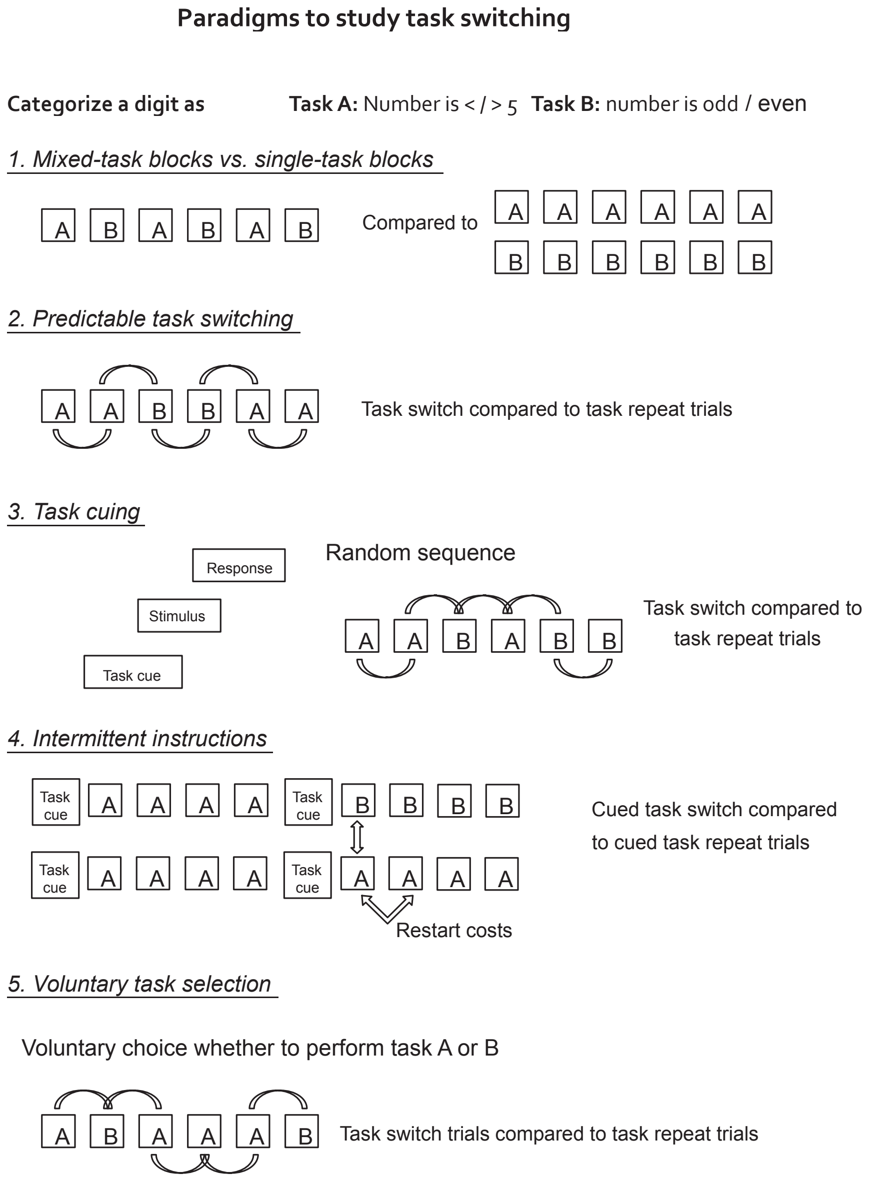

Figure 1: (1) Performance in mixed ABABAB task blocks is compared with performance in single-task blocks AAAA/BBBB. (2) In predictable task-switching paradigms, such as the alternating-runs paradigm, tasks switch after a predictable run length. Performance in task-switch trials is compared with performance in task-repetition trials. (3) In the task-cuing paradigm, a cue is presented in each trial to indicate the currently required task. Performance in task-switch trials is compared with performance in task-repetition trials. (4) In the intermittent-instruction paradigm, the same task is required until a new task cue is presented. Performance in cued task-switch trials is compared with performance in cued task-repetition trials. (5) In the voluntary task-selection procedure, participants voluntarily decide whether they perform Task A or B. (Modified from Kiesel et al., 2010).

Electrophysiological correlates

The fast pace of cognitive control operations in task-switching has been studied by using event-related brain potentials (ERPs) and modulations in several components, namely the N1, N2, P2 and P3, have been observed (Adrover-Roig & Barceló, 2010; Barceló et al., 2006; Garcia-Garcia, Barceló, Clemente, & Escera, 2010; Kieffaber & Hetrick, 2005; West, Langley, & Bailey, 2011; Wylie et al., 2003). Moreover, the late positivity has been found to be modulated as well as a negative component which has been named the switch negativity (Garcia-Garcia et al., 2010; Jamadar, Hughes, Fulham, Michie, & Karayanidis, 2010; Karayanidis et al., 2009; Nicholson et al., 2006). In the following paragraphs, those components which were modulated by task switching processes in the studies of this thesis are introduced more in depth.

Modulations in various aspects of the P3 component have been found in several studies and they have been proposed to index the updating of task-set information in working memory (WM) (Barceló, 2003). The modulations in the cue-locked P3 in these studies are compatible with the idea that the P3 reflects the decision about what to do with the ensuing stimulus, as proposed by Verleger (2008). From his viewpoint, very different P3 components result from stimuli requiring responses from those which do not (Verleger, 2008). Importantly, this endogenous P3 has been associated with task-relevant updating processes such as the anticipatory reconfiguration of stimulus- and response-sets, as well as with a task-set updating process which is especially needed when task demands change (Adrover-Roig & Barceló, 2010; Barceló, 2003; Gajewski & Falkenstein, 2011; Kiesel et al., 2010). The target-locked P3, usually smaller in switch compared to repeat trials, is suggested to reflect response selection (Adrover-Roig & Barceló, 2010; Barceló, 2003; Gajewski & Falkenstein, 2011).

There is evidence that cognitive control processes involved in task-switching modulate the P2 component. Recent studies showed a relation between the cue-locked P2 waveform and the complexity of the (anticipated) task (Kieffaber & Hetrick, 2005; Tieges, Snel, Kok, Plat, & Ridderinkhof, 2007). Moreover, this component has shown modulations with respect to preparatory attentional control and attentional processes due to a switch in task (Adrover-Roig & Barceló, 2010; C. D. Martin, Barceló, Hernandez, & Costa, 2011; Tieges et al., 2007). In particular, the endogenous and fronto-centrally distributed P2 component has been shown to be sensitive to change detection (Brown, Reynolds, & Braver, 2007; West et al., 2011). The target-locked P2 is thought to reflect stimulus depending processes such as the retrieval and implementation of stimulus-response (S-R) associations, interference resolution and mental effort, as well as the detection of stimulus salience and stimulus evaluation (Du, Zhang, Xiao, & R. Wu, 2007; Gajewski, Stoerig, & Falkenstein, 2008; Hsieh & M. Wu, 2011; Kieffaber & Hetrick, 2005; Potts, 2004).

Another important ERP component has been classically related to cognitive control mechanisms: the N2. It indicates action monitoring as well as target-selection and response preparation which in turn has been related to the function of the anterior cingulate cortex (ACC) (Botvinick, Cohen, & Carter, 2004; Carter & van Veen, 2007; Gajewski, Kleinsorge, & Falkenstein, 2010; Hsieh & M. Wu, 2011; Jamadar, Hughes, et al., 2010; Leleu et al., 2012). Regarding the task-switching literature, there have been inconsistent results for N2 effects. While some studies found enhanced N2 amplitudes for switch trials compared to repeat trials, others found the reversed pattern or no effects at all [for an overview see (Leleu et al., 2012)]. Gajewski and colleagues (2010) interpreted N2 modulations as being related to stimulus classification during target-selection and decision processes. This goes in line with the idea that N2 amplitudes could reflect anticipatory task preparation (Folstein & Van Petten, 2008; Hsieh & M. Wu, 2011). There is also evidence that the N2 itself is mirroring a general process of selection (modulated by interference) and cognitive control over selective attention (Gajewski et al., 2010; Leleu et al., 2012). Both task-preparation and task implementation modulated the target N2 in a recent study (Hsieh & M. Wu, 2011).

Task switching in the time-frequency domain

Although the importance of oscillatory phenomena has been noted increasingly, there are only few studies which analyzed brain oscillations modulated by task-switching (Gladwin & de Jong, 2005; Sauseng et al., 2005). In the last decade event-related synchronization (ERS) or desynchronization (ERD) which refers to a relative power change in a frequency band, have been associated with several cognitive functions

(Başar, Başar-Eroglu, Karakaş, & Schürmann, 2001; Donner & Siegel, 2011; Gladwin & de Jong, 2005; Nigbur, Ivanova, & Stürmer, 2011; Pfurtscheller & Lopes da Silva, 1999; Race, Badre, & Wagner, 2010; Sauseng et al., 2005; Schnitzler & Gross, 2005; Wang, 2010; Ward, 2003). The few studies which analyzed brain oscillations in task-switching focused on the alpha (8-13 Hz) and theta (4-6 Hz) bands. Stronger alpha desynchronization has been found for switch compared to repeat trials (Gladwin & de Jong, 2005; Sauseng et al., 2005; Verstraeten & Cluydts, 2002). A decrease in frontal and occipital alpha has also been found for conflict trials in a Stroop task (Compton et al., 2012). This goes in line with the general idea that decreased alpha power is related to attention and visual stimulation as well as memory processes (Başar et al., 2001; Donner & Siegel, 2011; Ward, 2003). Additionally, (pre-stimulus) alpha desynchronization could be linked to anticipatory attention in former studies (Bastiaansen et al., 1998; Bastiaansen, Böcker, Brunia, de Munck, & Spekreijse, 2001; Bastiaansen & Brunia, 2001; Bastiaansen, Posthuma, Groot, & de Geus, 2002; MacLean & Arnell, 2011). Moreover, there is evidence that alpha ERD at central electrodes is generated by a desynchronization of pyramidal neurons of the motor cortex which in turn has been related to motor preparation and execution (Gladwin, 't Hart, & de Jong, 2008; Neuper & Pfurtscheller, 2001; Pfurtscheller & Lopes da Silva, 1999).

The picture of the theta band during task-switching is less consistent across studies. A significant increase in theta synchronization at central sites was found by Gladwin and de Jong, while only a slight modulation in this frequency band was found by Sauseng and colleagues (Gladwin & de Jong, 2005; Sauseng et al., 2005). The relative increase in theta power for task switch trials goes in line with a study of Nigbur and colleagues who found increased theta power in interference situations using Go/No-Go, Flanker and Simon tasks (Nigbur et al., 2011). Moreover, Gladwin and colleagues found evidence that theta power during task preparation reflects processes which are necessary for task performance (Gladwin, Lindsen, & de Jong, 2006). More generally, theta has been related to (working) memory processes and selective attention as well as information encoding and retrieval (Başar et al., 2001; Gladwin & de Jong, 2005; Mitchell, McNaughton, Flanagan, & Kirk, 2008).

The cue switch effect

There is an important and ongoing debate in the task-switching literature; the discussion of whether, and to which extent, task switch costs can be attributed to a sensory change in the task-indicating cue. In other words, it is still under discussion whether and to which extent, there is an "endogenous task-set reconfiguration" process (Logan & Bundesen, 2003; Monsell & Mizon, 2006). As in usual task-switching experiments a task change is confounded with a cue change; it is not possible to disentangle whether the initial goal shifting process after cue-onset indeed mirrors an endogenous task-set reconfiguration or not (Kiesel et al., 2010; Monsell & Mizon, 2006). Consequently, several studies attempt to dissociate the effect of cue processing from the task-switching process (Barceló et al., 2006; Jost, Mayr, & Rösler, 2008; Logan & Bundesen, 2003; Mayr & Kliegl, 2003; Monsell & Mizon, 2006; Nicholson et al., 2006). Some behavioral studies found clear cue switch effects while others did not find any (Logan & Bundesen, 2003; Mayr & Kliegl, 2003; Monsell & Mizon, 2006; Nicholson et al., 2006). Importantly, recent ERP studies could find clear effects for cue changes, particularly in the P3 component (Barceló et al., 2006; Finke et al., 2011; Garcia-Garcia et al., 2010; Jost et al., 2008; Nicholson et al., 2006). These ERP results also led to a reformulation of the old context-updating hypothesis in order to interpret cue-locked P3 amplitudes (Barceló et al., 2006). The rationale behind the 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 after the target stimulus (Brass, Ullsperger, Knoesche, Cramon, & Phillips, 2005; Garcia-Garcia et al., 2010; Kieffaber & Hetrick, 2005; Periáñez & Barceló, 2009). Taken together, the results of recent (ERP) studies support the view that context-updating operations can be elicited both, exogenously and endogenously (Barceló et al., 2006; Garcia-Garcia et al., 2010; Jost et al., 2008; Periáñez & Barceló, 2009). Closely linked to this discussion is the discussion about cue-task transition congruency effect (Forstmann, Brass, & Koch, 2007; Van Loy, Liefooghe, & Vandierendonck, 2010; Schneider & Logan, 2007). Importantly, these studies showed that the task-switching process is not only composed of cue-related and task-related operations but also of conflicts between cue and task transitions present in cue repeat/task switch and task switch/cue repeat trials. This incongruency between cue and task changes also occurs in cue switch trials when using explicit cues. Hence, direct comparisons between cue-repeat/task-repeat and cue-switch/task-switch trials should be interpreted with caution (Nicholson et al., 2006). As a consequence, an orthogonal manipulation of cue and task should be implemented in order to independently measure the effects due to their respective changes. The question regarding the so-called repetition benefit in task repeat trials compared to changing sensory stimulation in task switch trials, or in other words, how much of the task-switch cost can be attributed to a sensory cue change, is not yet fully answered. Moreover, since cues usually contain task-relevant information, there is (to our knowledge) no study which has addressed the question of whether the repetition benefit in task repeat trials may be strictly related to task-relevant information. Since informative cues do carry task-relevant information, and cue repetition effects are normally related to better task preparation, it is not clear to which extent task-irrelevant sensory repetition may also result in a cue repetition benefit. Therefore, the second task design aimed to examine the use of foreknowledge in a task-cueing protocol while manipulating sensory updating and executive control in both informatively and non-informatively pre-cued trials. Sensory updating (cue switch effects) and task-switching were orthogonally manipulated using a 2:1 mapping between cues and task rules (Figure 2), in order to address the question of whether, and to which extent, the sensory processing of cue changes can partly or totally explain the final task switch costs.

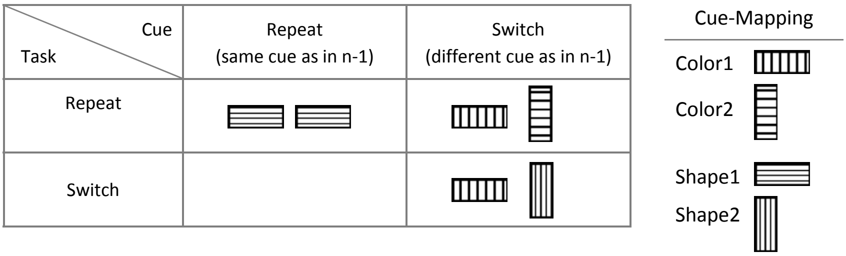

Figure 2: Independent manipulation of Cue and Task using two explicit cues per rule.

In contrast to the first two studies, transitional cues (Figure 3) have been used in the third study. It is yet unclear whether working memory dysfunction in schizophrenic affects their impairments during task-switching. Hence, it was decided to use transitional cues as they can tax working memory more than explicit cues. We investigated the deficits of schizophrenic patients in a task-cueing paradigm, namely the Madrid Card Sorting Test (MCST), a protocol inspired by the Wisconsin Card Sorting Test (Barceló, 2003). This paradigm also allows for a separate measurement of updating and maintenance processes in memory during anticipation and preparation stages of task performance (cue-locked potentials) as well as during task-set implementation (target-locked potentials).

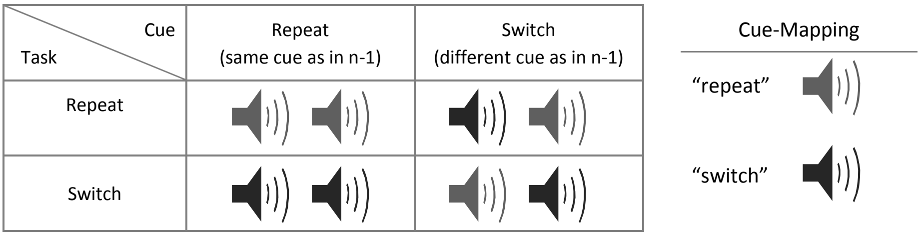

Figure 3: Independent manipulation of Cue and Task using transitional cues.

Schizophrenia

Schizophrenia is a major psychiatric disorder with a prevalence of 1% worldwide (Jamadar, Michie, & Karayanidis, 2010; Javitt, 2009a). Alterations in the brain structure are accompanied by changes in neurotransmitter systems such as, among others, Dopamine (van Os & Kapur, 2009). Although the disorder is known since many decades, the understanding of its mechanisms is still at its beginning. Current evidence suggests a genetic susceptibility overlapping with altered brain development (van Os & Kapur, 2009). Prominent clinical symptoms include cognitive and emotional aspects as well as disturbances in social behavior (Braver, Barch, & Cohen, 1999; Jamadar, Michie, et al., 2010; Javitt, 2009a). Noteworthy, the picture of the impairments schizophrenic patients suffer has changed quite a bit during the last years. Formerly, the cognitive impairment in schizophrenia has been mainly conceptualized as a failure of executive control and contextual processing (Barch et al., 2001; Braver et al., 1999). Hence, the assumption was that schizophrenic patients show a rather generalized cognitive impairment while intact early (sensory) processing was often assumed (Bleuler, 1950; Javitt, 2009a, 2009b). In the last years, the research interest has been broaden and top-down as well as bottom-up processes and their particular impairment in schizophrenic patients have come into the focus of scientific research. This is particularly important as recent studies found (1) both, auditory and visual processing deficits in early/primary processes and (2) that these disturbed sensory processing lead to impairments in higher-order processes (Javitt, 2009b; Leitman et al., 2010; Neuhaus et al., 2011). Noteworthy, there is also work focusing on the areas of preserved cognitive functions in schizophrenic patients (Gold, B. Hahn, Strauss, & Waltz, 2009). In their review the authors point out that not every aspect of cognition is impaired equally and that some functional aspects are preserved as in healthy controls (Gold et al., 2009). In summary, cognitive and affective processes seem not to be impaired in a generalized or undifferentiated way in schizophrenia (Gold et al., 2009; Javitt, 2009b). Therefore, it is highly important to find out the particular impairments from which these patients suffer in order to better understand the disorder and to improve its treatment.

Impairments in early (sensory) processing stages

ERP studies on schizophrenia regarding early (sensory) processing stages mainly used gating paradigms and uncovered early disruptions in the P50 as well as the N1 components confirming disturbances in these processes (Boutros, Belger, Campbell, D'Souza, & Krystal, 1999; Brenner et al., 2009; Brockhaus-Dumke et al., 2008; Patterson et al., 2008). However, disturbed early processing has been found also in WM tasks. Additionally to the P3, early ERP components (P1, N1) differed between schizophrenic patients and healthy controls (Galletly, MacFarlane, & Clark, 2007; Haenschel et al., 2007). A study from Neuhaus and colleagues (2011) revealed that diminished N1 amplitudes in schizophrenia are due to disturbances in both, bottom-up and top-town processes. Taken together, there is evidence from several studies that early-stage processes differ between schizophrenic patients and healthy controls across modalities and tasks. Importantly, these studies underline the importance of early processes in cognitive tasks (Galletly et al., 2007; Haenschel et al., 2007; Neuhaus et al., 2011).

(General) higher-order impairments

The ability to adapt behavior to changing contextual contingencies requires cognitive flexibility to switch between learned 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). Different task-set switching paradigms have been used to examine the type of high-level control processes required for such context-updating situations. The majority of task-switching studies on schizophrenia relied on behavioral data and reported slower response times as well as larger switching costs (Hartman, Steketee, Silva, Lanning, & Andersson, 2003; Li, 2004; Pantelis et al., 1999). Conversely, there are studies that report normal response times in task-switching for schizophrenic patients (Manoach et al., 2002; Merrin, Floyd, Deicken, & Lane, 2006). Similar conflicting results are observed with respect to the error rates made by patients compared to healthy controls (Gold et al., 2009; Hartman et al., 2003; Jamadar, Michie, et al., 2010; Karayanidis et al., 2006; Li, 2004; Prentice, Gold, & Buchanan, 2008). Contrariwise to the behavioral evidence, there is a scarcity of ERP studies on task-switching in schizophrenia. The available data has revealed differences mainly in the endogenous P3 component and late cognitive potentials (Jamadar, Michie, et al., 2010; Kieffaber, O'Donnell, Shekhar, & Hetrick, 2007). However, as ERP modulations in schizophrenic patients have been found in cue-locked as well as target- and response-locked components, it is not yet clear whether patients have difficulties to form and maintain an internal representation of the current task-set, or whether they suffer more from difficulties during task- and response-implementation stages (Galletly et al., 2007; Jamadar, Michie, et al., 2010; Kieffaber et al., 2007; O'Donnell et al., 1994; Schechter et al., 2005). As mentioned earlier, the picture becomes even more complex when taking into account the fact that those disturbances in early sensory processing in schizophrenic patients might contribute to their impairment in task-switching. Consequently, we further wanted to light up the disturbances in schizophrenia during task-switching by taking into account both, the sensory (i.e., priming) processes and higher order processes during task preparation (goal shifting) and task implementation (rule activation).

Research objectives

Study I

The first study investigated different aspects regarding the extraction of cue information and its importance for task-switching processes. Foreknowledge (informative and non-informative pre-cues), sensory updating and task-switching were orthogonally manipulated in order to test three different research questions: (1) Does a sensory change in cue that is unrelated to the upcoming task modulate performance and brain activity even if this sensory change does not carry information about the upcoming task? This is important as no study to date has addressed the question of whether the repetition benefit in task repeat trials may be strictly related to task-relevant information. (2) Can we find evidence to support a serial or parallel processing of cue and task information? (3) The current design enables us to investigate how non-informative cue switches compared to normal cue changes modulate target-locked ERPs. So far, cue switch effects have been investigated using informative cues only. However, it remains to be known whether and how a sensory switch in a non-informative cue might bias the ensuing target-locked ERPs.

Study II

For the second study, the data from the first study was analyzed in the time-frequency domain. The aim of this study was to broaden the knowledge regarding the (de-) synchronization of alpha and theta rhythms during task-switching. In sharp contrast to ERP studies investigating the effects of task-switching, only a few studies have analyzed brain oscillations modulated by task-switching. Importantly, none used a task-cuing paradigm in order to separately investigate the task-switching effects in both, cue- and target-locked brain oscillations. Hence, the second study examined the modulations of neural oscillations in the alpha and theta bands of anticipatory updating (goal shifting) and task-set implementation (rule activation) during task-switching. Anticipatory task preparation was manipulated by varying the informativeness of cues about the upcoming task. The contribution from exogenous sensory control to endogenous task-set switching mechanisms was examined by way of a 2:1 mapping between cues and tasks. This design can examine the relative contribution from exogenous cue changes upon endogenous task-set reconfiguration effects, and whether those effects depend on the presence of foreknowledge about the upcoming task.

Study III

The third study served the main purpose to examine the nature of task-set representations (namely, the flexible ability to represent, maintain and update task-set information) in schizophrenic patients. Task-set updating and maintenance processes during the preparation (goal shifting) and execution (rule activation) stages of task performance were analyzed in cue- and target-locked ERPs. Importantly, sensory updating (cue changes) and task-set updating (task switching) have been manipulated orthogonally in order to independently examine early (sensory) processes and higher-order processing. With the third study we want to shed light on the questions whether we (1) find evidence for disturbances in sensory processing stages during task-switching, (2) whether we find differences between schizophrenic patients and healthy controls regarding task-switching performance on behavioral and electrophysiological level (3) whether we find evidence that the hypothesized modulated higher order processes are due to disturbances in the early (sensory) processing stages.

Study I

The effects of foreknowledge and task-set shifting as mirrored in cue- and target-locked event-related potentials

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Abstract

The present study examined the use of foreknowledge in a task-cueing protocol while manipulating sensory updating and executive control in both, informatively and non-informatively pre-cued trials. Foreknowledge, sensory updating (cue switch effects) and task-switching were orthogonally manipulated in order to address the question of whether, and to which extent, the sensory processing of cue changes can partly or totally explain the final task switch costs. Participants responded faster when they could prepare for the upcoming task and if no task-set updating was necessary. Sensory cue switches influenced cue-locked ERPs only when they contained conceptual information about the upcoming task: frontal P2 amplitudes were modulated by task-relevant cue changes, mid-parietal P3 amplitudes by the anticipatory updating of stimulus-response mappings, and P3 peak latencies were modulated by task switching. Task preparation was advantageous for efficient stimulus-response re-mapping at target-onset as mirrored in target N2 amplitudes. However, N2 peak latencies indicate that this process is faster for all repeat trials. The results provide evidence to support a very fast detection of task-relevance in sensory (cue) changes and argue against the view of task repetition benefits as secondary to purely perceptual repetition priming. Advanced preparation may have a stronger influence on behavioral performance and target-locked brain activity than the local effect of repeating or switching the task-set in the current trial.

Introduction

The brain's ability to represent, maintain and update contextual (*task-set*) information enables us to alternate successfully between tasks [1,2]. Task-set reconfiguration is required when task demands change, as goal directed behavior needs to be adjusted to the new task. Task-cueing paradigms are used to investigate the underlying processes such as attentional shifting from one task to the other (task-switching), retrieval of goals and rules, and the activation of the current task-set, or the inhibition of the previous irrelevant one [3,4].

Task-switching effects are inversely proportional to the length of the preparation interval. The so-called task-switch cost is the additional time needed to switch a task compared to a task repetition. However, a residual switch cost always remains, suggesting that anticipatory preparation cannot fully overcome the cost of switching tasks [5–7]. Anticipatory effects and goal activation have been explored by manipulating the preparation time and the information content conveyed at cue onset [4,8–11]. In spite of a wide consensus that task preparation is advantageous, the underlying cerebral processes are still a matter of debate. There is evidence about the relative independence of a mechanism of general task preparation (independent from the upcoming task), and specific task activation (i.e., either repeat the former task or switch to another task). This has been tested in different studies that manipulated the informational content of the cue. In informatively cued trials the cue contained specific task-relevant information, i.e., the stimulus-response (S-R) rule for the upcoming task, while this was not the case in non-informatively cued trials. The two processes of task preparation and specific goal activation engage common and distinct areas of prefrontal cortex, as activating Brodmann areas (BA) 45, 46 and 40 varies depending on foreknowledge, while activation in BA 8, 39 and 40 is modulated by task switching [9]. Moreover, there is evidence that an early event-related potential (ERP) positivity reflects the differences between informative and non-informative cues while differences between task repeat and task switch occur later in time [4]. This is consistent with the idea of various independent processes in task-switching [4,5,9,12]. A related and important ongoing debate in the task-switching literature is whether, and to which extent, task switch costs can be attributed to a sensory change in the task-indicating cue [13–18]. Most previous studies that researched the effects of a cue change on the final switch cost employed informative cues with a 2:1 cue-task mapping, and hence, cue switches and cue repetitions both conveyed relevant information about the upcoming task. These studies suggested that cue repetition benefits could partly explain the switch costs (cf., [13,14]). However, these studies did not clarify whether such cue repetition benefits (or cue switch costs) would also be found for non-informative cues that do not convey any information about the upcoming task. By using two sensory different non-informative cues, we investigated whether task-irrelevant sensory changes, which are unrelated to any task rule, can also modulate behavior and target-locked ERPs in a similar way as informative cue changes do [13,18].

Additionally to the question of whether the cue repetition effect is (partially) related to sensory mechanisms, the current design enables us to investigate how non-informative cue switches also modulate target-locked ERPs. Up to date cue switch effects have been investigated using informative cues only [18,19]. However, it remains to be known whether and how a sensory switch in a non-informative cue can bias the ensuing target-locked ERPs. The manipulation of a Cue type factor (informative versus non-informative) and a Task condition factor (including cue repeat, cue switch and task switch) allowed us to examine to which extent sensory updating and task-switching differentially contribute to the behavioral and brain responses with and without foreknowledge about the upcoming task. Thus, for instance, a cue switch in a non-informatively cued trial might increase alertness and speed up the response to the upcoming target in a task non-specific manner [20]. In such a case, we would hypothesize an interaction between the Cue type and Task condition factors on target-locked brain activity. On the contrary, if non-informatively cued switches influenced processing at a strictly sensory level, then target-locked brain activity should not be modulated by the interaction of the Cue type and Task condition factors. Several previous studies have shown that the mean amplitude of the cue-locked P3 component in the ERPs are modulated by both sensory updating and task switching, at least in the auditory modality [15,19,21]. Even though less well studied than the P3, the endogenous and fronto-centrally distributed P2 component has also been shown to be sensitive to change detection [22,23]. Some authors have proposed that this fronto-central P2 component reflects the detection of stimulus salience and stimulus evaluation processes [24], and recent studies showed that this component is modulated by preparatory attentional control [11,25–27]. According to the existing evidence, we hypothesized that mean cue-locked P2 amplitudes at fronto-central scalp regions will be modulated by task switching, but might also by the type of cue-information content (foreknowledge). With the present task design we want to answer the question whether the P2 is a general "change detector" or rather a more specific "task-related change detector" which would not be affected by task-irrelevant changes. Consequently, we want to light up further the interpretation of previous P2 effects found in response to task-switching cues, and whether these P2 effects could be related either to the early (sensory) processing of the cue, or to the complexity of the upcoming task [22,23,27]. Under the first hypothesis, cue-locked P2 should be enhanced both in cue and task switch trials, whereas from the latter interpretation the cue-locked P2 should be significantly enhanced in task switch trials only. Regarding the P3 we expect different modulations depending on the task and the foreknowledge as former work could link this component to working memory and cognitive control processes [15,19]. Enhanced P3 amplitudes should appear for informatively cued trials compared to non-informatively cued trials mirroring the general processes of cue-response mapping and anticipatory task preparation. Moreover, P3 amplitudes are expected to differ depending on task condition as we assume that the process of reloading the previous task-set into working memory should lead to smaller P3 amplitudes compared to an updating of cue-response mapping, as only the latter includes a task-set reconfiguration process [28–30]. In the present study we expect similar effects for the visual modality, although smaller P3 amplitudes are often observed in response to visual stimuli as compared to auditory stimuli. Apart from our interest in the distinct processes related to cue encoding in task-switching, the study aimed to elucidate how general or specific anticipatory task preparation influence target-locked brain activity. Former studies found a clear task switch effect in target-locked brain activity, but only for informative trials [4]. Moreover, there is evidence that task preparation diminishes task switch effects but cannot override it entirely as visible in ERP modulations such as P3, late positive potentials and the switch negativity [4,6,15,17,19,21]. The target-locked N2 is thought to indicate action monitoring as well as target-selection and response preparation [4,28,31–34]. Regarding task-switching, the target N2 has been related to post-perceptual and executive processes such as intentional task-set reconfiguration and other aspects of task switching [32]. Thus, task-preparation and task implementation both modulated the target N2 in a recent study [28]. In the present study we manipulated task-preparation and task implementation by using informative and non-informative cues, and three different task conditions, respectively. The N2 component seems to be a promising component to look at both processes in order to find out how each of them leads to modulations in the target-locked ERPs or whether cue and task condition might interact. We expect target-locked N2 to be modulated by both cue and task. Moreover, the possibility to explore the interaction between these factors will allow us to shed new light on how non-informative cue switches also affect the target-locked N2. Finally, we predicted prolonged response times for all non-informatively cued trials, as well as for cue switch and task switch trials compared to task repeat trials in the informatively cued condition [4,9,21].

Material & Methods

Participants

Seventeen healthy individuals (3 male, mean age 23.5 years ± 0.92 [SEM], range 19-33 years) recruited from the University of Barcelona participated in the study. All participants were right-handed and had normal or corrected-to-normal vision. None of the subjects reported a neurological or psychiatric history.

Ethics Statement

Participants gave informed written consent before the experiment. The experimental protocol was approved by the Ethical Committee of the University of Barcelona and was in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Task and procedure

A computerized task-cueing protocol inspired by the original Wisconsin Card Sorting Test and adapted for measuring ERPs was used [35]. Each trial consisted of a visual cue followed by a target display with four key cards on the top of one choice card that had to be matched with one of the key cards either by color or shape (Figure 1). Stimuli were presented centrally on a computer screen with display subtending a visual angle of 6° horizontally and 5° vertically. Stimuli remained on the screen until a response was given. Response times (RT) and hit rates were recorded using Presentation® (Neurobehavioral Systems, Inc). Each trial began with the presentation of a visual explicit cue that could be either informative (Ic) or non-informative (NIc). In total, six differently striped rectangles were used (white frame and white stripes on a black background). The two sorting rules, color and shape, were indicated by two different rectangles per rule to disentangle the effects of cue and task switching. The actual rule could be read out via the combination of rectangle orientation (vertical/horizontal) and line orientation (vertical/horizontal) as shown in Figure 1. For instance, the color rule was indicated by a horizontal rectangle with vertical stripes, and also by a vertically oriented rectangle with horizontal stripes. The shape rule was indicated by a horizontal rectangle with horizontal stripes, and also by a vertical rectangle with vertical stripes. Two diagonally striped rectangles, one horizontal, one vertical, did not supply any information about the ongoing sorting rule. Instead, in non-informatively cued trials, the contextual information about the ongoing sorting rule was presented simultaneously with target onset. In order to keep the physical similarity between the two cueing conditions, a non-informative cue was presented in the target period of informatively cued trials. Consequently, the participants were required to use informative cues in order to prepare for the upcoming task, as no rule information was present at the target period. In turn, no preparation was possible in the non-informatively cued trials. Noteworthy, participants always received information about the ongoing sorting rule in every trial, either at cue onset or at target onset, and hence, every trial contained information about how to sort the cards. Before starting with the task, the cue mapping was explained to the participants and they were informed that the correct rule would change unpredictably after a variable number of card sorts, and that they would have to shift the sorting rule consequently. Each participant completed a practice block before starting the experimental session, to make sure that they understood the task instructions.

Three task conditions were defined to dissociate the effects of cue- and task-switching in both informatively and non-informatively cued trials. Firstly, there were repeat trials where both cue and task were repeated relative to the previous trial (cue repeat). Secondly, there were cue-switch trials, where only the cue changed but the task repeated compared to the previous trial (cue switch). Finally, in task-switch trials both cue and task changed (task switch). This design allowed us an orthogonal manipulation of cue switches involving either a sensory change only, or a change in both sensory and higher-order task-set information. Ideally, a combination of cue-repeat and task-switch conditions would be possible in non-informative trials. This condition has been used in former studies that explored the influence of independent changes in cue and task on task performance [13,16,17]. However, such a combination cannot be implemented for informative trials, and hence, it will not be considered in this study. The present 2:1 mapping between cues and task rules was meant as a control for cue switch costs as opposed to task switch costs [13], as it has been recently shown to modulate ERPs differently [17,21]. Informative and non-informative cues occurred with the same overall probability each over the course of the experiment. Additionally, all three task conditions appeared equiprobably (33.33 % each), and so were all possible cue-task combinations (16.67 % each). After a practice block, each participant performed 312 trials grouped into six blocks within which changes in cue and task occurred in a semi-randomized order. The cue-target interval (CTI) varied randomly between 700 and 900 ms to minimize the effects of a constant preparation interval. The target remained on the screen until a response was given. The response-to-cue interval (RCI) also varied randomly between 2500 and 2750 ms to prevent systematical noise in the cue-locked ERPs. The jitter in both CTIs and RCIs was meant to minimize the effects of time estimation processes -as distinct from anticipatory task-set preparation- in the pre-stimulus interval.

Participants used their index and middle fingers of both 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. The task sets as described above consisted of a 4-stimulus to 4-response mapping, and participants used their left/right hand for the two left/right buttons, respectively.

For instance, when sorting by the “shape” rule, a triangle choice card was to be matched with the triangle key card by using the left-most button on the response panel (Figure 1).

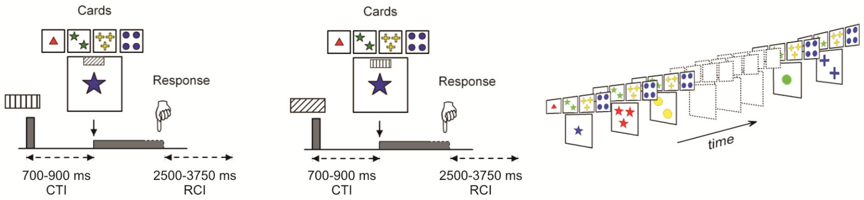

Figure 1: Stimulus material and experimental design. Each trial consisted on a visual cue, either informative (Ic) or non-informative (NIc), followed by the target cards to be sorted. Target cards also contained a similar cue (this was a non-informative cue in informatively cued trials, and vice versa). Participants had to match the choice card with one of the four key cards according to either the color or shape of their elements. Examples of an Ic trial (left panel), and a NIc trial (middle panel) are shown on the figure.

EEG recording

The EEG was recorded from 61 scalp electrodes positioned according to the extended 10-20 system. The reference electrode was placed on the tip of the nose. Horizontal and vertical electro-oculographic recordings (EOG) were recorded with electrodes placed below and at the outer canthi of the right eye. The EEG was amplified and digitized at 512 Hz and impedances were kept below 10 kΩ during the whole recording session. EEG data was processed offline with a band pass filter from 0.5-40 Hz. EOG correction was performed by applying the blind source separation technique with ASA 4.7.3 of ANT® Software (Enschede, The Netherlands), as described in Belouchrani and colleagues [36]. After EOG correction, any epochs containing EEG activity exceeding ±75 μV were rejected from further analysis. This procedure resulted in a final rejection of 4.71% of all correct trials. Mean amplitudes of selected cue- and target-locked visual ERP components were computed over a time window of 800 ms including a 100 ms pre-stimulus baseline.

Data analysis

For behavioral analysis, a correct trial was defined as a correct button press occurring between 100 and 3000 ms from target onset. Mean RT relative to target-onset was computed for correct trials only. RT and hit rate were analyzed using repeated measures 2x3 ANOVAs with two within-subject factors: Cue type (informative, non-informative) and Task condition (cue repeat, cue switch, task switch).

Our choice of analysis windows and channels was done according to former task-switching studies (cf., [4,19,21,25,37]), and in agreement with a visual inspection of mean ERP data. Mean amplitudes were extracted for the cue-locked P2 in the window of 180-220 ms at F1, Fz, F2, FC1, FCz, FC2 as in West et al., 2011 [23]. A similar analysis windows for mean P2 amplitudes were used in previous studies [19,25,37]. Mean cue-locked P3 amplitudes (450-550 ms; CP1, CPz, CP2, P1, Pz, P2) were measured within the same time window as Jamadar and colleagues (2010; also cf., [19,25]). Target-locked N2 peak amplitude and latency were measured at C1, Cz and C2 sites in the time window 200-500 ms, following former literature which researched modulations in the N2 regarding cognitive control [29,37–39]. Target-locked N2 analyses were performed at mid-central sites, consistent with previous studies which described the central N2 peaking at Cz [40], and with the scalp topographies of target-locked peak N2 amplitudes for both informatively cued trials and non-informatively cued trials. One study that guided our choice of this rather wide window for peak N2 latency is by Leleu and colleagues (2010) [31]. These authors analyzed the N2 component within a 400 ms time window (200-600 ms) and found task related effects from 200-450 ms post-target.

For the analysis of target-locked ERPs, a full factorial design was used including Cue type (informative, non-informative) and Task condition (cue-repeat, cue-switch, and task-switch) and Laterality (left, central, right).

In order to examine whether a pure sensory change in cue modulates performance and brain activity, we compared cue repeat trials with cue switch trials for both, informative and non-informative trials using repeated ANOVAs with a 2 (Cue type) x 2 (Task condition) x 2 (Frontality) x 3 (Laterality) design. Due to the null result of this analysis, a random selection of trials assured similar numbers of switch and repeat trials across both non-informatively and informatively cued trials. Moreover, data was subsequently subjected to a second repeated measures ANOVA with factors: 3 (Trial type: non-informative cued trials, informative task repeat, informative task switch) x 2 (Frontality) x 3 (Laterality). Channel lines F and CP served as Frontality level 1 and lines FC and P as factor level 2, respectively for the analysis of the P2 and P3. The three levels for Laterality are associated with the left, central and right channels. All post-hoc tests for behavioral and ERP analyses were performed with t-tests and a Bonferroni correction was used to adjust p-values for all multiple pairwise contrasts. Greenhouse-Geisser corrections were used to adjust degrees of freedom whenever the assumption of sphericity was violated.

Results

Performance

Mean RTs and hit rates were analyzed using 2x3 repeated-measures ANOVAs with factors: Cue type (informative, non-informative) and Task condition (cue repeat, cue switch, task switch). Participants responded faster to informatively cued trials compared to non-informatively cued trials (main effect for Cue: $F(1,16) = 224.77$, $p < 0.001$; partial $\eta^2 = 0.9$) caused by increased RT for NIc trials (1293 ms) compared with Ic trials (1012 ms). The main effect for Task condition ($F(2,32) = 8.41$, $p = 0.001$; partial $\eta^2 = 0.3$) was due to significantly increased RT in trials containing a switch in task ($p < 0.001$, 1185 ms) compared to repeat trials (1116 ms) while the difference between repeat trials and cue switch trials (1157 ms) did not reach statistical significance ($p = .067$), and no differences were apparent between cue switch and task switch trials (Figure 2). There was no difference in mean RT between cue-switch and task-switch trials, and there was no interaction between the Cue and Task factors ($F(2,32) = 2.02$; $p = 0.15$). No significant differences concerning cue or trial type were found on the participants' hit rates. Noteworthy, hit rates were very high (over 90% across conditions) which confirms that participants managed to correctly implement the corresponding cue-to-response mapping most of the time on task (Figure 2).

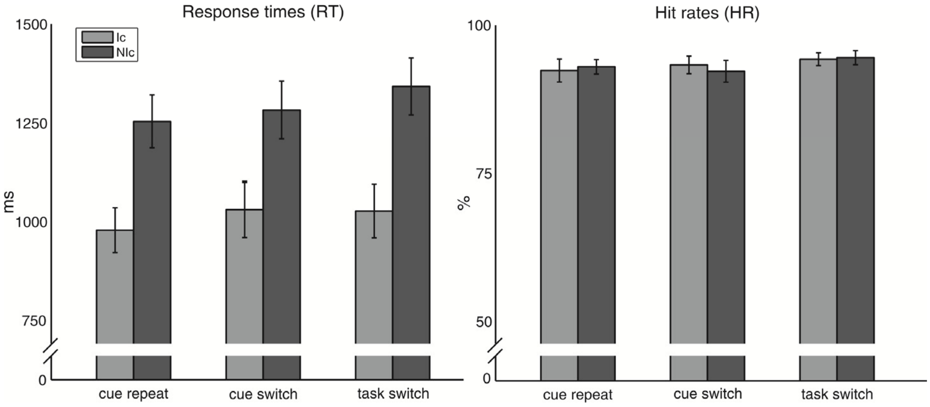

Figure 2: Response times (RT) in milliseconds (ms) and percent hit rates (HR) across the three task conditions for both, Ic trials (light gray) and NIc trials (dark gray). Mean RTs were faster in Ic trials compared to NIc trials, and faster in cue repeat trials compared to task switch trials. No effect on HR was found.

Cue-locked event-related potentials

The hypothesis of whether pure sensory changes, unrelated to any task rule, can modulate behavioral and brain responses to a subsequent target, was addressed through a 2x2x2x3 repeated-measures ANOVA with factors Cue type (informative vs non-informative), Task condition (cue repeat *vs* cue switch), Frontality (either F/FC or CP/P, respectively) and Laterality (left, central, right) on the mean amplitudes of the cue-locked P2 (180-220 ms) and P3 (450-550 ms) components. Figure 3 depicts the results of these analyses. With regard to mean P2 amplitudes, there were no significant main effects or interactions between Cue type and Task condition, and hence, cue switch and cue repeat trials elicited similar P2 amplitudes in informatively and non-informatively cued trials. A main effect for Cue type was found for mean P3 amplitudes (F(1,16) = 22.477; $p < 0.014$; $\eta 2 = 0.6$), but the interaction between Cue type and Task showed no tendency to significance for this component.

Following up from this first analysis, cue switch and repeat trials were collapsed to focus on the effects of task-relevance on the cue-locked ERPs using a 3x2x3 repeated-measures ANOVA with factors: Trial type (non-informative trials, informative task repeat, informative task switch), Frontality and Laterality as previously described in the Method section.

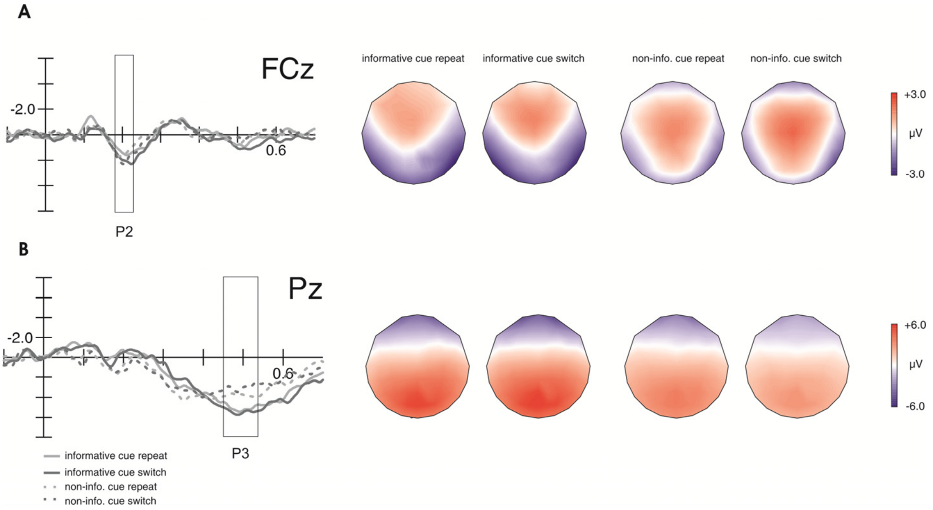

Figure 3: Cue-locked ERPs for the P2 (A) and P3 (B) components for informative and non-informative cue repeat and cue switch trials and their respective topographical distribution.

Regarding the P2, this analysis enables us to shed light on the question of whether the P2 is a general change detector or detects task-specific changes. Moreover, modulations in the P3 due to preparatory updating and task anticipation can be investigated.

There was a main effect for Trial type ($F(2,32) = 6.453$, $p = 0.004$; partial $\eta^2 = 0.3$) for the cue-locked P2 (Figure 4). Post-hoc tests uncovered significantly increased P2 amplitudes in informative task switch trials (2.0 µV) compared to informative task repeat trials (1.1 µV; $p = 0.005$), and to non-informative cued trials (NIc) trials (1.1 µV; $p = 0.007$). A main effect for Laterality ($F(2,32) = 8.880$, $p = 0.005$, corrected; partial $\eta^2 = 0.4$) uncovered larger mean P2 amplitudes in the left and central electrodes ($p= 0.006$). The Trial type x Laterality interaction ($F(4,64) = 3.589$, $p = 0.038$, corrected; partial $\eta^2 = 0.2$) confirmed the main effect of Trial type (all $p < 0.02$) except for the comparison task switch versus non-informative trials at right electrodes ($p = 0.08$). For mean P3 amplitudes (Figure 4), there was a main effect for Trial type $F(2, 32) = 9.818$, $p = 0.00$, corrected; partial $\eta^2 = 0.4$). Post-hoc tests revealed that this was caused by significant differences between non-informatively cued trials and informatively cued switch trials ($p = 0.005$) and compared to informative task repeat trials ($p = 0.029$).

To further investigate the possible reasons for this absence of differences in mean P3 amplitudes between informatively cued trial conditions, additional ERP analyses were performed.

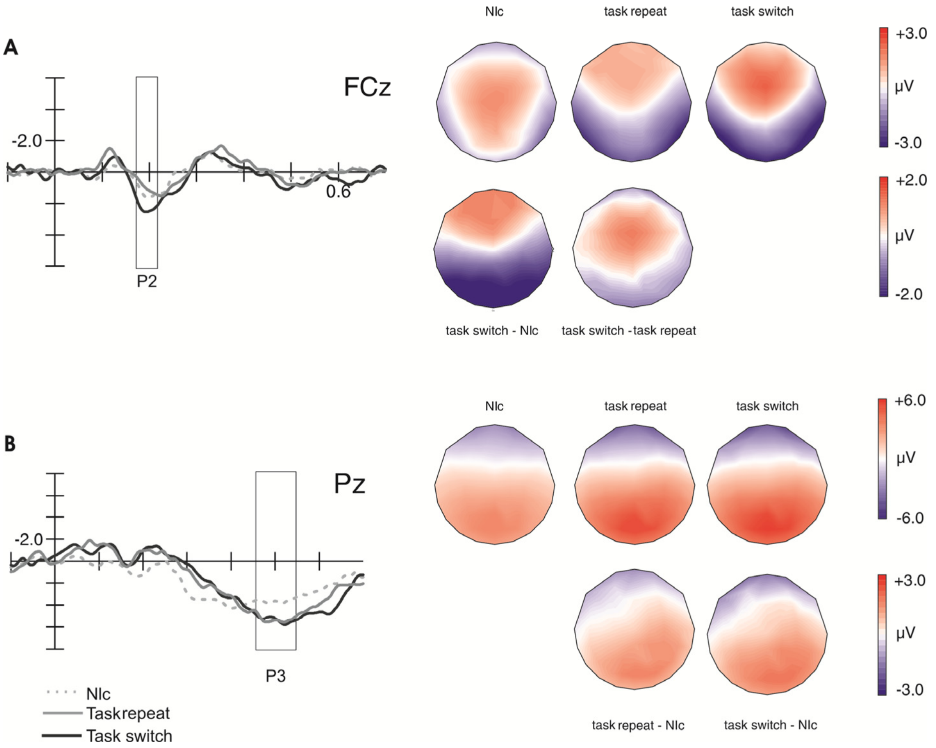

Figure 4: Cue-locked ERPs and topographical distributions for the respective waveforms of the P2 and P3 components. Additionally, topographical maps of difference waveforms are presented. (A) Frontal P2 mean amplitudes were larger for task switch trials compared to task repeat trials and NIc trials. (B) The amplitude of the midparietal P3 component was enhanced for both, informative task repeat and task switch trials compared with NIc trials.

One plausible hypothesis was that a delayed speed of processing of the relatively complex 2-dimensional visual cues might have blurred the expected differences in mean P3 amplitudes (see the Discussion section).

The individual peak P3 latency, as the local positive maximum of the signal within the time window from 400 to 700 ms was obtained automatically for every subject at the same electrode we used for the amplitude analysis, in order to examine whether this measure was affected by Task condition in informatively cued trials. Statistical analysis revealed a main effect for Task ($F(2,32) = 5.52$, $p = 0.009$; partial $\eta^2 = 0.3$). Post-hoc comparisons uncovered significantly delayed peak P3 latencies for switch (539 ms) compared to repeat trials (503 ms; $p = 0.008$). No significant differences were found for cue switch trials (514 ms) compared to any other task condition.

Target-locked event-related potentials

The same repeated-measures ANOVA design used in the behavioral analyses was also used with target-locked ERP data, including the factors Cue type (informative, non-informative), Task condition (cue-repeat, cue-switch, and task-switch) and Laterality (left, central, right). Repeated measures ANOVAs were performed on the target-locked N2. ERP results for the target-locked components are displayed in Figure 5.

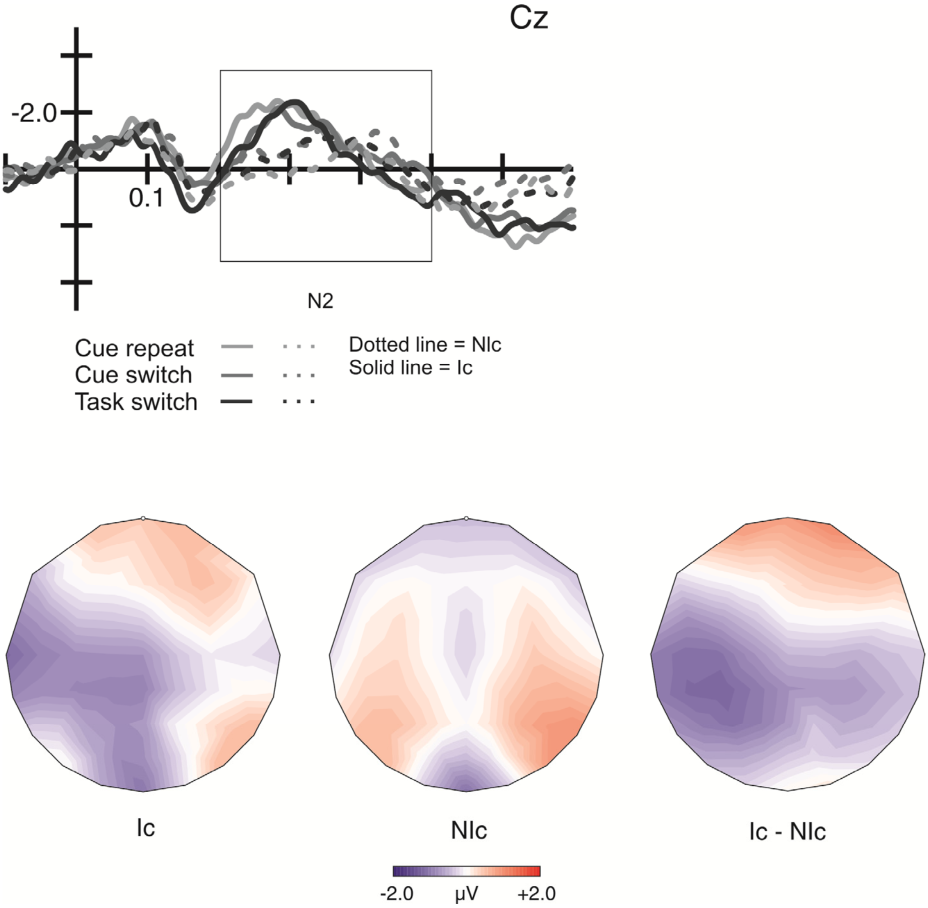

Figure 5: Target-locked ERPs and topographical distributions for the informatively and non-informatively cued waveforms in the N2 time window. Moreover, the topographical map of their difference waveform is shown. Amplitudes were enhanced for Ic trials compared to NIc trials for both ERP components. Shortest N2 peak latencies occurred in repeat trials.

The analysis of N2 peak amplitude revealed a main effect for Cue type with amplitudes being more negative for informative trials ($F(1.16) = 8.11$, $p = 0.012$; partial $\eta^2 = 0.3$). As for the latency we also found a main effect for Laterality ($F(2,32) = 7.8$, $p = 0.002$) due to highest amplitudes at Cz. For the N2 peak latency, a main effect for Task condition was found ($F(2,32) = 3.5$, $p = 0.042$; partial $\eta^2 = 0.18$), which was caused by longer N2 latencies for cue switch compared to cue repeat trials (328 ms versus 307 ms; $p = 0.042$). Task switch trials did not yield different N2 latencies (321 ms) compared to the other two task conditions. A main effect for Laterality was due to shorter peak N2 latencies at Cz compared to C2 compared to C1.

Discussion

The current study aimed to elucidate processes related to anticipatory task-set updating during the foreperiod of a task-cueing paradigm considering the combined influence of changes in sensory cues and abstract task rules, as well as the extraction of informational content (foreknowledge) in anticipation of target onset. RT was modulated by the cue type and task condition without an interaction between these factors. The amplitude of an endogenous P2 component was enhanced for informatively cued task switch trials suggesting a considerably fast process of contextual task-relevant “change detection”. The cue-locked P3 amplitude was enhanced for all informatively cued trials, probably reflecting preparatory updating for informative trials. This process was prolonged in informative switch trials compared to repeat trials as indicated by prolonged P3 latencies. Sharper target-locked N2 amplitudes for informatively cued trials suggested better task-implementation and prepared responses. Shorter N2 latencies for all repeat compared to task switch trials were related to faster response mapping.

Performance data

In line with former work the present study revealed faster RTs in informatively cued trials compared to non-informatively cued trials [4,9]. As expected, the slowest RTs were found in switch trials, while participants responded faster in repeat trials in the present study replicating the typical switch costs [3–5,10,11,15,23]. As in previous studies, no interaction was found between the two factors [4,9]. Trials containing a cue switch prolonged response times, thus confirming that sensory updating in the visual modality can affect response times in a similar way as auditory changes do, though this effect was weak and the difference marginally failed significance [15,17,21]. Importantly, former work showed different sensibility to this "distraction" depending on individual variability in the DAT1 gene for the dopamine transporter and subject variability was indeed high in cue-shift informative trials in the present study [21]. In contrast to former studies, hit rates were not affected by foreknowledge or trial type [4,19,21]. A possible reason for these null hit rate effects could be the very high overall accuracy of participants in our study (with a mean hit rate of over 90% correct responses).

The relevance of pure sensory cue changes

There was a difference between mean P3 amplitudes for informatively and non-informatively cued trials. However, no differences in the cue-locked P2 and P3 components could be found between task conditions. Mean P2 amplitudes were larger for cue switch compared to cue repeat trials but this difference failed significance. This null result fails to replicate the cue switch effect found in previous studies [13,15,18,19,21,29]. Importantly, it should be noted that most previous studies did not isolate cue switching effects from the anticipatory task-relevant information about the upcoming task [13, 14]. Consequently, a direct analysis of both, Cue type and cue switch effects has never been done before. The present P3 data suggest that task information is most relevant in order to prepare a response mapping. Contrariwise, the influence of bottom-up processes seems to be very little. The information of the cue, the top-down processing, is important. This is also supported by a more frontal and more focused P2 distribution for informative compared to non-informative trials as visible in Figure 3. Hence the present results can help clarify the ongoing discussion on how much of the task switch cost is related to a pure sensory change, and suggest that simple perceptual cue repetition might not be sufficient to explain the benefits found for informative repeat trials, as other task preparation processes seem to be involved. Admittedly, this null effect could also be due to the weaker cue switch effects obtained with our visual displays, as compared with the auditory cues used by previous studies

[15,19,21]. Future research should be done to further explore the relative impact of pure sensory cue changes on behavioral switch costs independent from task relevance in informative versus non-informative cues.

The present study further explored whether cue repetitions, that are often held responsible for the cost benefit in task repeat trials, could also depend on task-relevant information. In addressing this question, a 2:1 cue:task mapping was used in order to control for cue switch costs as opposed to task switch costs in both informative and non-informative trial conditions [13,18]. Though transitional cues have been used in previous studies [17,19], our paradigm offers the advantage of a randomized order of both cue and task manipulations. However, this would not be the case if using transitional cues as non-informatively cued switch trials could only occur after an informatively cued trial but never following a non-informatively cued trial (as this order allows a cue repeat only). Moreover, previous contradictory results regarding the effect of cue switches might be due to their different probability of occurrence [13,14]. Like recent ERP studies we used the 2:1 cue:task mapping since ERP components such as the P3 are sensible to stimulus probability [18,21,41].

Parallel versus serial cue and task processing

The fast detection of task-relevant cue changes was indexed by the P2 component. Increased frontal P2 amplitudes were elicited by informatively cued task switch trials compared to informatively cued task repeat trials, or non-informatively cued trials. The sensitivity of the frontal cue-locked P2 component to anticipatory task-set updating (in repeat versus switch trials) replicates previous work [23,29]. Moreover, these results allow us to complement the common interpretation of the frontally distributed P2 component in terms of a general "change detector", since this component does not only reflect task-set updating in switch trials, but is also modulated in anticipation of task-relevant information [22,23]. This is supported by the fact that task switch trials differ significantly from task repeat trials and from non-informative trials. Taken together, these results lead us to the interpretation that the cue-locked P2 component conveys task-relevance, and hence, it could be regarded as a task-specific "change detector". This result is important as it indicates that even as early as during initial cue processing, bottom-up sensory aspects are not necessarily processed before top-down task relevant aspects [27]. Possible influences for cue changes on the P2 could be addressed in a future study using auditory cues as they seem to elicit stronger effects. Probably, the frontal P2 is related to task-set activation and cue-retrieval processes as suggested previously [25]. Likewise, increased P2 amplitudes have been reported for trials or tasks including preparatory control and stimulus evaluation [11,23,29].

With the present study we show that the frontal P2 component is sensitive to these two distinct but related processes of anticipatory task-set retrieval or activation on the one hand, and with the interruption, inhibition, and deactivation of a previously active task set on the other hand. In a second step the processes of cue-response mapping and the reloading/updating of stimulus-response mappings take place as mirrored in the cue-locked P3 component. Increased mean P3 amplitudes for informatively cued cue-switch and a task-switch trials compared to non-informatively cued trials, replicates former studies and goes in line with the sensitivity of the cue-locked P3 component regarding preparatory control of task-set switching [4,15,18,25,42]. The delayed P3 peak latencies for switch compared to repeat cues mirrored a prolonged stimulus evaluation process, and thus, may have been putatively associated with delayed task-set shifting given our complex task switch cues [43–45]. On the other hand, a cue switch did not prolong P3 latencies in the present study.

However, the present results did not show the typical enhancement of cue-locked P3 amplitudes in response to task switch cues compared to task repeat cues, as shown in most previous studies, although our results are consistent with the strong effects of foreknowledge in behavioral performance [15,19,21]. The null result regarding task-switching effects in the P3 amplitudes might be due to the complex cue design as it has been argued in previous studies that the encoding of complex cues might be a “task” itself [3]. The observed P3 latency differences lend support to such a hypothesis. The readout of our complex 2-dimensional visual cues may have induced a significant delay compared to simpler visual and auditory cues. In order to examine this idea more directly, we analyzed peak P3 latencies for informative trials and also conducted a new behavioral follow-up study. In this new study, we re-defined the meaning of informative cues so that a horizontal rectangle now instructed the color rule, and a vertical rectangle now instructed the shape rule, independently from the orientation of the stripes within those rectangles. This “easy version” of our task-cueing protocol was then run on four participants from the original sample, plus another five new subjects who performed both the new and old versions of our task-switching protocol. The order of both versions was counterbalanced between subjects. Taken together, nine healthy individuals (2 male, mean age= 27 years ± 1.23 SEM, range= 21-33 years) participated in this follow-up study. As predicted by our cue complexity hypothesis, mean RTs in the easy version were significantly faster for cue-repeat ($p = 0.004$) and cue-switch trials ($p = 0.009$) compared to the same conditions in the original task-cueing protocol (960 ms compared to 1038 ms, and 989 ms compared to 1059 ms, respectively), as indicated by a significant interaction between Cue complexity x Task condition ($F(2,16) = 4.639$; $p = 0.026$). Taken together, the re-analysis of cue-locked peak P3 amplitude and latency as well as the behavioral results of the new follow-up study suggest that the information read-out of complex visual cues in the original task-cueing protocol became a task in itself as suggested by Monsell [3].

Preparation for the upcoming task

Mean N2 amplitudes were enhanced for informatively cued trials but were clearly diminished –or even abolished– in non-informatively cued trials. The N2 has been related to the monitoring of action which in turn has been related to the function of the anterior cingulate cortex (ACC) [33,34]. Regarding the task-switching literature, there have been inconsistent results for N2 effects; some studies found enhanced N2 amplitudes for switch trials compared to repeat trials while others found the reversed pattern or no effects at all (for an over view see [32]). Gajewski and colleagues interpreted N2 modulations as being related to stimulus classification during target-selection and decision processes. Consequently, the sharper N2 peak amplitudes in informatively cued trials could reflect anticipatory task preparation [28,38]. There is also evidence that the N2 itself is mirroring a general process of selection (modulated by interference) and cognitive control over selective attention [31,32]. For the current study, the observed enhancement of target-locked N2 amplitudes for informatively cued trials might mirror top down control in terms of implementation the current task rule, and the selection of the appropriate correct response button for a particular target stimulus [31,32]. However, the present data cannot confirm any task-switch effect in the N2 amplitude.

In contrast to peak amplitudes, N2 peak latencies were modulated by task condition. Statistical analyses revealed that cued repeat trials lead to shorter latencies compared to switch trials. A former study linked N2 latency differences with the time participants need to achieve a certain level of categorization of stimuli [46]. For our data this means that the monitoring processes occur earlier in time for repeat trials, and consequently, the stimulus-response remapping may be addressed faster than for switch trials. This goes in line with results by Swainson and colleagues, and with the shorter RT for repeat trials in both cue conditions [47]. Likewise, it agrees with the idea that anticipatory preparation cannot fully overcome task switching costs [4,7]. We expected to find differences between cue repeat and task switch trials. Instead, N2 latencies for task switch trials were delayed compared to cue repeat trials and faster than for cue switch trials. This suggests that stimulus-response re-mapping maybe prolonged in trials where a cue-switch is not associated with a switch in task. One explanation for this result might be that participants seem to generate expectancies regarding the probabilities of the upcoming choice if the inter-trial interval is not particularly short, and thereby tend to overestimate the probability of a switch [48]. A conflict occurs as the sensory switch is strengthening this expectation of a switch by bottom-up processes but no task-switch is required later. There is an "incongruent cue-task transition" whenever a cue switch is not accompanied by a switch in task [29].

Regarding our third research question, how the benefit for task preparation will affect target-locked brain responses, we can show that due to informative cues and task-preparation in the CTI response mapping can be accomplished more efficiently after target-onset but is faster in all repeat trials. Importantly, the current study could not find an interaction between the Cue and Task factors. Consequently, we did not find any bias of a non-informative cue switch for the task preparation. As in the cue-locked ERPs, a non-informative cue switch seems to elicit a mere sensory effect but do not affect task related processing stages. Apparently, there seems to be an undue switch preparation in all cue switch trials that can be inferred from the prolonged N2 latencies for these trials.

Conclusion

With the present study we investigated three different questions regarding the extraction of cue information and its importance for task-switching processes: (1) Does a sensory change in a cue that is unrelated to the upcoming task modulate performance and brain activity even if this sensory change does not carry information about the upcoming task? (2) Can we find indisputable evidence to support a serial or parallel processing of cue and task information? (3) How does the purported benefit of anticipatory task preparation affect target processing and the target-locked ERPs? The present data suggest that sensory cue changes do affect cue-locked ERPs only when they convey contextual information about upcoming task performance. This is an important result for the interpretation of cue switch costs. Our data shows that differences in ERP components between cue repeat and cue switch trials are not related to a mere sensory effect but rather reflect a task related process. We found no evidence to support a serial or parallel processing of cue and task information but rather fast task-relevant change detection (P2). The following process of cue-response mapping and the reloading/updating of stimulus-response mappings occur later (P3). Importantly, our data revealed that task-relevant change detection occurs quite early (starting from 180 ms). Moreover, it highlights the importance of the P2 for the processing of cognitive processes. Finally, task preparation is generally advantageous for response re-mapping after target-onset (N2 amplitude) though task monitoring is fastest in repeat trials (N2 latency). Noteworthy, a non-informative cue switch seems not to affect task preparation in any particular way.

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Study II

Study III

Summary & Discussion

In general, this PhD thesis aimed to further explore the nature of cognitive control processes during task-switching in schizophrenic patients and healthy controls. By using a card sorting task and the high temporal resolution of the EEG, the processes of goal-shifting and rule-activation could be investigated. Importantly, sensory processing and task-set reconfiguration were manipulated independently in all studies. A separate appraisal of these different processes is important as task-set switching seems to be prompted exogenously by contextual events, but it can also be generated endogenously through a change in the plans of action (Barceló et al., 2006; Forstmann et al., 2007; Kiesel et al., 2010; Nicholson et al., 2006).

The first study focused on different aspects regarding the extraction of cue information and its importance for task-switching processes. The goal was to shed light on two main questions regarding cue-locked ERP components. Namely, how task-irrelevant cue changes modulate performance and brain activity depending on whether they contain task-relevant information or not, and whether the information read-out of cue and task information occur in parallel or serially. Previous studies that researched the effects of a cue change on the final switch cost with a 2:1 cue:task mapping employed informative cues. Hence, cue switches and cue repetitions both conveyed relevant information about the upcoming task (Garcia-Garcia et al., 2010; Jost et al., 2008; Logan & Bundesen, 2003; Mayr & Kliegl, 2003; Monsell & Mizon, 2006). However, these studies cannot clarify whether such a cue repetition benefit (or cue switch costs) would also be found for non-informative cues that do not convey any information about the upcoming task. Consequently, a direct analysis of both, cue information and cue switch effects has never been done before. Our analysis revealed cue switch effects neither in the P2 nor in the P3 components, but enhanced P3 amplitudes were found for informatively cued compared to non-informatively cued trials. The present P3 data suggest that task information is most relevant for the preparation of response mappings. Contrariwise, the influence of bottom-up processes seems to be limited. This is also supported by a more frontal and focused scalp distribution of P2 amplitudes for informative compared to non-informative trials. Hence, the present results could help to clarify the ongoing discussion on how much of the task switch cost is related to a pure sensory change. Furthermore, they suggest that simple perceptual cue repetition might not be sufficient to explain the benefits found for informative repeat trials, as other task preparation processes seem to be involved. The data did not reveal any evidence to support a serial or parallel processing of cue and task information but rather fast task-relevant change detection as mirrored in the cue-locked P2 (Brown et al., 2007; C. D. Martin et al., 2011; Tieges et al., 2007; West et al., 2011). The following process of cue-response mappings and the reload/updating of stimulus-response mappings seem to be mirrored in the P3 (Barceló et al., 2006; Finke et al., 2011; Garcia-Garcia et al., 2010). Furthermore, we wanted to light up the question of how informative and non-informative cue changes affect task implementation processes. The data revealed that preparing the upcoming task is generally advantageous for the response mapping after target-onset, as visible in the N2 amplitude and that rule activation is faster in all repeat trials as mirrored in shorter N2 latencies. This replicates the findings of a recent study that also found that task-preparation and task implementation both modulated the target N2 (Hsieh & M. Wu, 2011). Noteworthy, a non-informative cue switch seems not to affect the rule activation in a particular way as no interaction between foreknowledge and task condition was found. In sum, the data of Study I revealed that early sensory processes are crucial for effective task-switching, and that task-relevant change detection occurs quite early (up from 180 ms).

The subsequent time-frequency analysis of the data of the first study (study II) aimed to examine power changes in the alpha and theta frequencies. Former studies found both frequency bands associated with task-switching as mirrored in stronger alpha ERD and theta ERS in switch compared to repeat trials (Gladwin & de Jong, 2005; Sauseng et al., 2005; Verstraeten & Cluydts, 2002). However, in contrast to former studies, we used a task-cueing paradigm in order to disentangle the processes of goal shifting and rule activation could (Barceló, 2003; Kiesel et al., 2010). The used 2:1 cue:task mapping allowed the examine the exogenous contribution to endogenous task-set switching (Barceló, 2003; Finke et al., 2011; Garcia-Garcia et al., 2010; Jamadar, Hughes, et al., 2010; Jost et al., 2008; Logan & Bundesen, 2003; Mayr & Kliegl, 2003). As we independently modulated the aspects of task-switching and the informativeness of the cue (which resulted in a "task neutral cue switch"), we could investigate whether cue switch costs can be observed depending on the presence of foreknowledge about the upcoming task.

The data confirmed that participants respond faster to informative trials replicating benefits related to generic task preparation. The stronger cue-locked alpha ERD and theta ERS in these trials go in line with their purported rule in anticipatory attention, stimulus encoding and working memory (Başar et al., 2001; Bastiaansen et al., 1998, 2001; Bastiaansen & Brunia, 2001; Bastiaansen et al., 2002; Gladwin & de Jong, 2005; MacLean & Arnell, 2011; Mitchell et al., 2008). In line with former studies we found task-switching effects in both frequency bands (Gladwin & de Jong, 2005; Sauseng et al., 2005; Verstraeten & Cluydts, 2002). Stronger alpha ERD was found in switch trials compared to cue repeat trials during both, goal shifting and rule activation. Interestingly, the results uncovered that early frontal alpha ERD is stronger in task switch trials but that this effect reverses later during the CTI at central regions. This interaction might mirror the initial cognitive processes related to initial goal shifting, the task-set reconfiguration followed by a generic pre-activation of the motor cortex in order to optimize the upcoming response for repeat trials (Gladwin et al., 2008; Neuper & Pfurtscheller, 2001; Pfurtscheller & Lopes da Silva, 1999). Enhanced theta ERS was enhanced for task-switch cues suggesting that it is related to initial goal shifting rather than to rule activation at the subsequent stage of task-set implementation. Interestingly, the cue switch condition showed the strongest power changes in both frequencies. In the light of the rather scare evidence, the hypothesis that this effect is it is caused by "incongruent cue-task transition" due to incongruent bottom-up and top-down processing seems to be a plausible explanation (Forstmann et al., 2007; Van Loy et al., 2010; Schneider & Logan, 2007). Interestingly, when the power changes were computed using the CTI as the baseline, stronger alpha ERD was found for non-informative trials suggesting additional demands of cognitive control in these trials relative to informative trials in which preparatory attentional ontrol can be partially implemented during the foreperiod (Başar et al., 2001; Donner & Siegel, 2011; Ward, 2003). Finally, this analysis revealed stronger theta ERS for informative trials probably reflecting the retrieval of cue information after target-onset (Başar et al., 2001; Gladwin & de Jong, 2005; Mitchell et al., 2008). The lack of an interaction between the factors Cue information and Task condition argue against a specific bias for cue switch trials in non-informative trials.

The third study focused on the research question of how task-set representations are compromised in schizophrenic patients, and which role their (potential) early sensory and/or their cognitive impairments play during the task-switching process. The data indeed revealed disturbances in the early sensory processing stages in schizophrenic patients as indicated by diminished N1 amplitudes compared to healthy controls in both, cue- and target-locked ERPs. These effects go well in line with former studies which also found disruptions in early processing stages during complex tasks such as WM and Flanker tasks (Haenschel et al., 2007; Neuhaus et al., 2011). Noteworthy, Neuhaus and colleagues could link the diminished N1 amplitudes to disruptions in both, bottom-up and top-down processes. We could not reveal evidence for impairments in anticipatory set-shifting but schizophrenic patients showed a deficit in the implementation of task-set representations at target onset in switch trials. Noteworthy, conflicting results are found regarding the question whether schizophrenic patients have problems in task anticipation or implementation during task-switching, which might be due to different task procedures (Jamadar, Michie, et al., 2010; Kieffaber et al., 2007; Wylie et al., 2003). Our data showed similar P3 amplitudes for both groups but the typical enhancement of P3 amplitudes for trials containing a task-switch as well as those containing a cue-switch. The present study uncovered that schizophrenic patients showed enhanced target-locked P2 amplitude for switch compared to repeat trials, hence in the presence of irrelevant and conflicting information. Contrariwise, no difference between task conditions was observed for controls. This suggests that schizophrenic patients need more effort to solve the more difficult switch task which in turn demands high cognitive control. The P2 component has been related to target detection, stimulus encoding, resolution of interference, evaluation of salience and relevance (Gajewski et al., 2010; Potts, 2004; Potts, L. E. Martin, Burton, & Montague, 2006). All these concepts are especially involved in switch trials. In line with previous results, the first study argues for disruption in the early stages of sensory processing in schizophrenia but against Bleuler's point of view which assumed these processes to be preserved (Bleuler, 1950; Haenschel et al., 2007; Javitt, 2009a; Neuhaus et al., 2011). Moreover, the results go well in line with the idea that modulated sensory processing leads to problems during task-set implementation during switch trials as well as to an overall diminished performance speed. Importantly, early sensory processing mirrors not only bottom-up but also top-down processes and both seem to be -maybe independently- impaired in schizophrenia as it has been shown previously, and has been supported by our data (Haenschel et al., 2007; Neuhaus et al., 2011). In sum, the present results suggest 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 efficiently as healthy controls, which in turn leads to reduced performance in task-switching paradigms.

The early aspects of (sensory) processing have been classically associated with ERP components such as the P50, P1 or N1 (Boutros et al., 1999; Brockhaus-Dumke et al., 2008; Luck, Heinze, Mangun, & Hillyard, 1990; Näätänen & Picton, 1987). Moreover, the perceptual analysis of stimuli has been associated with the P2 component (Luck & Hillyard, 1994). Recently, these early ERP components moved in the focus of cognitive research as the question arose how early (sensory) processing might also affect higher-order processes (Barceló et al., 2006; Finke et al., 2011; Gold et al., 2009; Haenschel et al., 2007; Javitt, 2009a, 2009b; Leitman et al., 2010; Neuhaus et al., 2011; Periáñez & Barceló, 2009). The underlying neuronal correlates of the P2 are still poorly understood and its relation to sensory and/or cognitive processes is still under discussion (Crowley & Colrain, 2004; Du et al., 2007; Tieges et al., 2007). However, there is evidence that the P2 mirrors processes which go beyond feature detection and include post-perceptual processes [for an overview see (Crowley & Colrain, 2004; Tieges et al., 2007)]. Concurrently, also the P1 and the N1 have been found to be modulated by top-down processes such as attention or working memory load (Haenschel et al., 2007; Neuhaus et al., 2011). The increasing amount of studies reporting P2 modulation related to cognitive and attentional control as well as task-switching in particular are building a growing body of evidence that the P2 plays a significant role in complex tasks and might be related to task complexity and change detection (Adrover-Roig & Barceló, 2010; Brown et al., 2007; Du et al., 2007; Hsieh & M. Wu, 2011; Kieffaber & Hetrick, 2005; Tieges et al., 2007; West et al., 2011). The impaired sensory processing in schizophrenic patients, as mirrored in diminished cue- and target-locked N1 amplitudes, indeed seems to lead to slower performance. Moreover, it took them more effort to implement a task-switch as the target-locked P2 was enhanced in these trials for schizophrenic patients only. This suggested a deficit in rule activation at target onset due to the presence of irrelevant and conflicting information. This matches well the idea that increased P2 amplitude mirrors a higher mental effort to perform a switch in task (Du et al., 2007; Kieffaber & Hetrick, 2005). Moreover, we found the cue-locked P2 being modulated in the first study only by task-relevant changes which leads to the assumption that the cue-locked P2 is an endogenous component being sensible to *task-relevant* changes. In turn, higher cognitive control is needed in those trials compared to task repeat trials (Brown et al., 2007; Tieges et al., 2007; West et al., 2011). On the other hand, the target-locked P2 component has been associated with stimulus depending processes such as the evaluation of the stimulus, the retrieval of S-R associations and the following implementation of the response mapping as well as interference resolution or mental effort (Gajewski et al., 2010; Hsieh & M. Wu, 2011; Kieffaber & Hetrick, 2005).

In sum, the results of the N1 and P2 components in both ERP studies (study I and III) suggest that an intact early (sensory) processing and a fast detection of task-relevant changes are crucial for successful task switching. Moreover, the data give evidence that early sensory processing is related to high-order processes such as task-switching. Particularly, our results point out the importance of the P2 component and its putative association with the cognitive control of goal shifting and rule activation.

The endogenous P3 component has been associated with several cognitive functions such as attention, memory as well as task-switching and many studies have proofed its significance regarding brain mechanisms of executive control in healthy and clinical samples (Adrover-Roig & Barceló, 2010; Barceló et al., 2006; Cortiñas et al., 2008; Finke et al., 2011; Galletly et al., 2007; Garcia-Garcia et al., 2010; Haenschel et al., 2007; Kieffaber et al., 2007; Polich, 2007; Wylie et al., 2003). In contrast to former studies, the P3 amplitude was not modulated by cue switches in the first study. The present P3 data rather suggest that task information is most relevant in order to prepare a response mapping. Contrariwise, the influence of bottom-up processes seems to be less important. The task-relevant content of the cue, the top-down processing, seems to be most important and the analysis is prolonged in task-switch trials. However, this direct comparison of both, cue information (informative versus non-informative cues) and cue switch effects (cue repeat versus cue switch trials) has never been done before. Therefore, they could help to clarify the ongoing discussion on how much of the task switch cost is related to a pure sensory change. They suggest that simple perceptual cue repetition might not be sufficient to explain the benefits found for informative repeat trials, as other task preparation processes seem to be involved. Admittedly, this null effect could also be due to the weaker cue switch effects obtained with our visual displays, as compared with the auditory cues used in previous studies (Finke et al., 2011; Garcia-Garcia et al., 2010; Jost et al., 2008). Future research should be conducted to further explore the relative impact of pure sensory cue changes on behavioral switch costs independent from task relevance in informative versus non-informative cues. In contrast to the first study, we could replicate the enhanced cue-locked P3 amplitudes for task switch compared to task repeat trials in the third study, thus revealing larger context-updating operations at task transitions, as it has been described in many recent task-cueing ERP studies in healthy participants (Barceló et al., 2006; Garcia-Garcia et al., 2010; Periáñez & Barceló, 2009). Moreover, context-updating operations also elicited larger cue-locked P3 amplitudes in trial sequences involving cue switches which confirms the cue switch effect found previously (Barceló et al., 2006; Jost et al., 2008; Nicholson et al., 2006). Importantly, and in contrast to former studies (Jamadar, Michie, et al., 2010; Kieffaber et al., 2007), P3 amplitudes in schizophrenic patients did not differ from those of healthy controls. This suggests that the patients' impaired task-switching performance is not caused by disruptions during the preparatory stages of task-switching.

In a nutshell, we replicated the typical P3 modulations regarding task switching and cue switching using auditory transitional cues. The first study revealed that cue encoding is prolonged in task switch trials as reflected by longer cue-locked P3 latencies. Moreover, our data suggest that task-relevant information plays a major role compared to task-irrelevant changes. However, future studies might research the importance of task relevant changes as well as the differences in informative and pure sensory cue changes in the auditory modality to gain more evidence for this hypothesis.

Though the importance of oscillatory phenomena has been noted increasingly, there are only few studies which analyzed the modulation of brain oscillations during task-switching (Başar et al., 2001; Donner & Siegel, 2011; Gladwin & de Jong, 2005; Holz, Glennon, Prendergast, & Sauseng, 2010; Nigbur et al., 2011; Race et al., 2010; Sauseng et al., 2005; Schnitzler & Gross, 2005; Wang, 2010; Ward, 2003). Frequency specific oscillatory changes play a major role in the functional communication in the brain as most general dynamics are reflected in the brain's natural oscillations (Başar, Başar-Eroğlu, Karakaş, & Schürmann, 1999). Particular task procedures can light up the functional mechanisms of neural oscillations by investigating particular frequencies and topographical distributions which in turn reflect certain cognitive processes (Delorme & Makeig, 2004; Nigbur et al., 2011; Uhlhaas, Haenschel, Nikolic, & Singer, 2008). Importantly, the time-frequency domain can reveal aspects of event-related brain dynamics which are not visible in the ERP of the same epoch. First, the ERP does not capture the whole frequency spectrum of relevant electro-cortical activity and second, the averaging procedures cancel out potentially important brain activity with a trial-to-trial latency jitter (Makeig, 1993; Race et al., 2010). The present results revealed that the process of a generic task preparation which leads to faster target classifications also results in stronger cue-locked theta ERS and alpha ERD. Moreover, stronger target-locked alpha ERD for non-informatively cued trials revealed when taking the CTI as the baseline suggesting that the lack of preparation in non-informative trials leads to a high level of cognitive control in order to solve the task within the given time. As non-informative cues could not be used to prepare for the upcoming task, cue encoding and target evaluation have to be implemented simultaneously after target-onset. Theta ERS was enhanced for informative trials in this analysis probably mirroring the retrieval of cue information. These results go well in line with the general finding of alpha and theta modulations as being related to anticipatory attention, stimulus encoding and retrieval as well as memory processes (Başar et al., 2001; Gladwin & de Jong, 2005; Mitchell et al., 2008). Moreover, these results concur with findings from former studies as well as with the results of study I (Finke, Escera, & Barceló, in press; Jamadar, Hughes, et al., 2010; Sohn, Ursu, Anderson, Stenger, & Carter, 2000). Stronger alpha in task switch trials revealed for cue- and target-locked analysis suggesting that the task switch effects as mirrored in the alpha ERD found in previous studies can be related to both, goal shifting as well as the rule activation. However, we found enhanced theta ERS only for task-switch cues which suggests that the theta frequency is more related to initial task-set reconfiguration rather than to the subsequent stage of task-set implementation. Interestingly, we found strong alpha ERD and diminished theta ERS for cue switch trials. This effect confirms our hypothesis that cue repeat and cue switch trials are processed differently and suggest an endogenous effect of cognitive control as mirrored in alpha ERD and theta ERS (Logan & Bundesen, 2003). Likewise in study I, we did not find an interaction between foreknowledge and task switching in the performance data, neither in the oscillatory activity. Again, this argues against a cue switch specific bias in non-informative trials. Taken together studies I and II, this suggests that cue repetition benefits do not occur due to mere sensory repetition.

The work presented in this PhD thesis could shed light on various aspects regarding the task-switching processes in schizophrenic patients and healthy controls. Different implications could be drawn from the present data. Nonetheless, several questions remain and might be solved in future work:

The cue-switch effects in study I revealed to be rather small compared to former studies (Barceló et al., 2006; Garcia-Garcia et al., 2010; Jost et al., 2008; Nicholson et al., 2006). In the present paradigm, differences between cues were subtle and the cue information was coded in a quite complex way which might be a reason for this null effect. Task designs in former studies could not clear up to which extent task-irrelevant sensory repetition may also result in a cue repetition benefit. However, future studies should be conducted in order to revise our results. It would be interesting to further investigate the effect by using different task procedures. Moreover, the possible influences of modality should be tested as change detection is thought to be more prominent in the auditory modality.

Our results from study II should be replicated in future studies in order to test whether to strong cue switch effects indeed arouse from an "incongruent cue-task transition".

In contrast to former studies, we used transitional cues in the third study in order to control independently for sensory updating and task-switching processes. Noteworthy, some studies could show differences in performance and ERPs between transition cues and explicit cues in healthy controls (Forstmann et al., 2007; Van Loy et al., 2010; Saeki & Saito, 2009; West et al., 2011). Therefore, it would be interesting to further explore the disturbances schizophrenic patients suffer during task-switching by using different cue mappings within the same sample in order to compare the results for transitional and explicit cues. Importantly, the schizophrenic participants in the present study were all medicated. Although Haenschel and colleagues (2007) found disruptions in early sensory processing stages in early-stage schizophrenia and Barch and colleagues (2001) found disturbances in the PFC in first episode patients who had not yet received any medication, it remains a big challenge to disentangle real task effects from possible effects due to medication. Especially, as longitudinal studies are rare and their results not always consistent more research is necessary in order to shed light on the influences of medication and illness duration on the patient's impairments [for an overview see (Bozikas & Andreou, 2011; Napal et al., 2012)].

Conclusions

The conclusions of this thesis can be formulated as follows:

First, and foremost, the results from all studies point out that an intact early sensory processing and a fast detection of task-relevant changes is crucial for successful task-switching.

The results of the first study suggest that the cue switch effect does not arise due to a mere sensory updating. The cue-locked ERPs showed that task-relevant change detection is the most prominent process for solving the upcoming task. Noteworthy, the brain seems to be able to detect as early as up from 180 ms whether a cue signals a task change or not. This highlights the importance of early processing stages and the P2 component as a relevant component in the task-switching process. Subsequently, the cue-response mapping and the reloading/updating of stimulus-response mappings are processed which takes more time in switch trials. The target-locked analysis of the second study revealed no bias of a non-informative cue switch for the task preparation. This strengthens the hypothesis that cue change effects are not elicited by a mere sensory change but rather by task effects related to goal shifting.

The subsequent time-frequency analysis (study II) could show that both, alpha and theta oscillations, play an important role in generic task preparation and goal shifting. This was indicated by cue-locked ERSP effects due to foreknowledge as well as due to task-switching. However, while alpha ERD was also modulated depending on task condition during rule activation processes after target-onset, this was not the case for theta ERS. Noteworthy, our results uncovered an endogenous act of cognitive control during task-switching as indicated by enhanced alpha ERD and diminished theta ERS for cue switch trials. In line with the ERP results of study I we did not find an interaction between foreknowledge and task switching in the oscillatory activity which argues against a cue switch specific bias in non-informative trials. Finally, the time-frequency analysis corroborates our conclusion of the ERP analysis that a read-out of cue information is crucial for optimal task-switching performance and that task-preparation, though generic, can optimize it.

With the third study we could show that, if the early sensory processing is disturbed, like in schizophrenia, task performance is overall diminished. Cue-locked and target-locked N1 amplitudes were diminished in schizophrenic patients compared to healthy controls independently of condition. Similarly, response times were overall slower and response less accurate in patients. Interestingly, the task anticipation processes seem to be normal in schizophrenia, as cue-locked P3 amplitudes did not differ between groups. Both, healthy controls as well as schizophrenic patients showed enhanced P3 amplitudes for task switch and cue switch trials confirming a higher level of cognitive control when task-set reconfiguration is needed. Importantly, schizophrenic patients need more effort during the stimulus evaluation and following rule-activation in switch trials as mirrored in the enhanced target-locked P2.

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Annex: Spanish summary

Introducción

La capacidad del cerebro para representar, mantener y actualizar información contextual de una tarea *(task-set)*, nos permite alternar dos o más tareas. Cuando las reglas de una tarea cambian, se requiere una reconfiguración del contexto de la tarea, y el comportamiento dirigido a la meta ha de reajustarse (Barch et al., 2001; Braver, Barch, & Cohen, 1999; Kiesel et al., 2010). Como resultado común, los tiempos de respuesta en estos casos son más lentos, lo cual se ha denominado "coste del cambio” *(switch cost)* (Barceló, 2003; Kiesel et al., 2010; Logan & Bundesen, 2003; Meiran, Chorev, & Sapir, 2000; Monsell, 2003). Además, la activación cerebral en los ensayos de cambio *(switch trials)* difiere de los ensayos de repetición *(repeat trials)*, tal como se puede observar por ejemplo en varios componentes del potencial evocado (PE), tales como P2 o P3, o también en la (de-) sincronización (ERD/ERS por sus siglas en inglés) de ciertos ritmos cerebrales, por ejemplo el ritmo alfa (~ 8-13 Hz) y el ritmo theta (~ 4-6 Hz) (Adrover-Roig & Barceló, 2010; Barceló, Escera, Corral, & Periáñez, 2006; Finke et al., 2011; Finke, Escera, & Barceló, in press; Garcia-Garcia, Barceló, Clemente, & Escera, 2010; Gladwin & de Jong, 2005; Nicholson, Karayanidis, Bumak, Poboka, & Michie, 2006; Sauseng et al., 2005). El uso de señales indicadoras *(cues)* posibilita la preparación de una tarea inminente mediante la activación de un objetivo de tarea concreto. Por otra parte, paradigmas de señalización de la tarea *(task-cueing)* inspirados en el Wisconsin Card Sorting Test, permiten investigar las distintas fases del cambio de tarea, tanto la preparación, reflejada en PEs en respuesta a la señal *(cue-locked)*, como también procesos de implementación de la tarea, reflejados en PEs en respuesta al estímulo diana *(target-locked)* (Barceló, 2003; Finke et al., 2011; Kiesel et al., 2010; Nicholson et al., 2006). Es importante destacar que procesos sensoriales anómalos podrían afectar a la cognición, a saber, modular tanto las etapas de procesamiento de niveles inferiores, como de niveles superiores. Estudios recientes de cambio de tarea han podido demostrar la importancia de segregar los procesos sensoriales (como por ejemplo *priming*) de los procesos relacionados con control de orden superior (por ejemplo preparación). Esto sugiere que actos de control endógeno en los procesos de señalización de la tarea como un cambio en la señal no relacionado con un cambio en la tarea (cambio de indicador, *cue switch*) tienen un impacto tanto sobre el rendimiento como en la actividad cerebral (Barceló et al., 2006; Finke et al., 2011; Logan &

Bundesen, 2003; Monsell & Mizon, 2006; Nicholson et al., 2006). Por lo tanto, parece que hay una interacción continua entre los procesos de abajo-arriba *(bottom-up)* y de arriba-abajo *(top-down)*. La mayoría de los estudios, al investigar los efectos de un cambio sensorial en la señal sobre el coste final del cambio, utilizan señales informativas (Garcia-Garcia et al., 2010; Jost, Mayr, & Rösler, 2008; Nicholson et al., 2006). Esto significa que tanto los cambios como las repeticiones de las señales de tarea proporcionan información relevante acerca de la siguiente tarea a realizar. A partir de estos estudios se ha sugerido que los beneficios de la repetición del indicador podrían explicar parcialmente los costes del cambio (Logan & Bundesen, 2003; Mayr & Kliegl, 2003; Monsell & Mizon, 2006). Sin embargo, estos estudios no aclararon si tales ventajas de repetición del indicador (o costes de cambio del indicador) también se podrían encontrar para indicadores no informativos que no proporcionaran ninguna información sobre la tarea a realizar.

En consecuencia, uno de los objetivos del primer estudio fue investigar la actualización sensorial y el control ejecutivo tanto en ensayos con indicador informativo como en ensayos con indicadores no-informativos. Conocimientos previos, actualización sensorial (efectos de cambio del indicador) y cambio de tarea fueron manipulados ortogonalmente con el fin de abordar la cuestión de sí, y en qué medida, el procesamiento sensorial de los cambios de indicador puede explicar en parte o totalmente los costes finales del cambio de tarea. Un candidato prometedor para investigar esta cuestión, en línea con la cuestión de si la información relacionada al indicador y a la tarea se procesan en serie o en paralelo, es el componente P2 frontal. Se ha demostrado que es sensible a la detección de cambios, y estudios previos sugieren que este componente P2 fronto-central refleja la detección de la eminencia del estímulo, procesos de evaluación del estímulo y que es modulado por el control atencional preparatorio (Adrover-Roig & Barceló, 2010; Gajewski, Stoerig, & Falkenstein, 2008; Hsieh & Wu, 2011; Kieffaber & Hetrick, 2005; Martin, Barceló, Hernandez, & Costa, 2011; Potts, 2004; Tieges, Snel, Kok, Plat, & Ridderinkhof, 2007). Sin embargo, hasta ahora la literatura carecía de un estudio que pudiera responder si el P2 es un "detector de cambio" general, o más bien "detector de cambio de la tarea" más específico (Brown, Reynolds, & Braver, 2007; Kiesel et al., 2010; West, Langley, & Bailey, 2011). Además, este diseño puede arrojar luz sobre la cuestión de si el procesamiento del indicador y de la información relacionada con la tarea se produce en serie o en paralelo, y si un cambio en un indicador no-informativo puede afectar la preparación de la tarea de una manera determinada.

En segundo lugar, otro aspecto abordado en esta tesis doctoral es cómo las oscilaciones alfa y theta del electroencefalograma (EEG), que resultan moduladas diferencialmente en los ensayos de cambio de tarea y en los ensayos de repetición, se pueden estudiar mejor mediante un paradigma de indicación de la tarea (Gladwin & de Jong, 2005; Sauseng et al., 2005). En otras palabras, las modulaciones de alpha y theta observadas en estudios previos, ¿reflejan la preparación de tareas y/o procesos de implementación de la tarea? Por otra parte, ningún estudio ha investigado la actividad oscilatoria en relación con un cambio del indicador. Con el fin de arrojar luz sobre los aspectos mencionados, los datos EEG del estudio I se analizaron en el dominio de tiempo-frecuencia.

En tercer lugar, se sabe que los pacientes esquizofrénicos muestran un menor rendimiento en paradigmas de cambio de tarea, así como una modulación anormal de sus respuestas cerebrales (Gold, B. Hahn, Strauss, & Waltz, 2009; Hartman, Steketee, Silva, Lanning, & Andersson, 2003; Jamadar, Michie, & Karayanidis, 2010; Kieffaber, O'Donnell, Shekhar, & Hetrick, 2007). Es importante señalar que también el procesamiento sensorial temprano, tal como el filtrado sensorial *(gating)*, se encuentra alterado en estos pacientes (Boutros, Belger, Campbell, D'Souza, & Krystal, 1999; Brockhaus-Dumke et al., 2008). Sin embargo, según nuestros conocimientos, hasta la fecha ningún estudio ha investigado en un mismo paradigma estos dos aspectos de forma independiente, a saber, tanto el procesamiento sensorial temprano como los procesos de orden superior. El tercer estudio de esta tesis pretende llenar este vacío. Por lo tanto, la actualización sensorial y de la tarea fueron manipuladas ortogonalmente, con el fin de examinar la interacción entre los procesos de abajo-arriba y de arriba-abajo en pacientes esquizofrénicos y controles sanos. En la sección siguiente, los objetivos particulares de cada uno de los tres estudios serán presentados seguidos de un resumen de cada estudio consistente en una traducción de los resúmenes *(abstracts)* originales.

Objetivos

Estudio I

Con el primer estudio investigamos tres aspectos distintos de la extracción de información sobre el estímulo señal y su importancia para los procesos de cambio de tarea: (1) Un cambio sensorial, no relacionado con la tarea inminente, ¿puede influenciar la ejecución de la tarea y la actividad cerebral, a pesar de que el cambio no contenga información sobre la tarea a realizar? Esto es importante, ya que hasta la fecha, ningún estudio ha abordado la cuestión de si el beneficio por repetición en ensayos de repetición de la tarea es debido a información estrictamente relevante para la tarea. Dado que las señales informativas *(informative cue)* proveen información relevante sobre la tarea a realizar, y los efectos de la repetición de estímulos indicativos normalmente se relacionan con una mejor preparación para la tarea, no queda claro en qué medida la información sensorial irrelevante podría, a su vez, resultar en un beneficio de repetición del estímulos indicativo. (2) ¿Podemos encontrar pruebas que apoyan un procesamiento serial o paralelo de la información de los estímulos indicadores y de la tarea? El componente P2 frontal endógeno ha sido conceptualizado como un "detector de cambio". El presente diseño experimental pretende responder a la pregunta de si la modulación de P2 es de tipo general, o refleja un "detector de cambio" específico para la tarea que no se vería afectado por cambios sensoriales irrelevantes para la tarea. (3) ¿Cómo afecta la preparación anticipada a los potenciales evocados por estímulos relevantes a la tarea? Los efectos de cambio sensorial en la señal indicadora han sido investigados exclusivamente utilizando señales informativas. Sin embargo, se desconoce sí y cómo un cambio sensorial en una señal no informativa *(non-informative cue)* también puede modular a los potenciales evocados por estímulos diana relevantes para la tarea.

Estudio II

Para el segundo estudio, los datos del estudio I fueron analizados en el dominio de tiempo-frecuencia. El objetivo de este estudio fue ampliar nuestro conocimiento acerca de la (de-) sincronización de los ritmos cerebrales alfa y theta durante el cambio de tarea. En marcado contraste con los numerosos estudios de PEs sobre los efectos del cambio de tarea, existen muy pocos estudios centrados en la modulación de las oscilaciones cerebrales durante el cambio de tarea. Además, hasta donde alcanza nuestro conocimiento, ningún estudio previo ha utilizado un paradigma de señalización de tarea para investigar las modulaciones del cambio de tarea sobre las oscilaciones cerebrales inducidas por los estímulos señal y diana, por separado. Por lo tanto, este segundo estudio pretendía arrojar luz sobre la cuestión de si los dos ritmos cerebrales son modulados durante la preparación de la tarea (cambio de meta) en el intervalo entre la señal y la diana, y/o por la ejecución de la tarea (activación de la regla) tras la aparición del estímulo diana. Así mismo, desenmarañamos los efectos endógenos y exógenos del cambio mediante la inclusión de una condición de cambio del indicador no relacionado a un cambio de tarea. Esto nos permitió estudiar en qué medida los efectos de cambio de tarea encontrados en estudios anteriores, reflejados en la actividad oscilatoria, se deben a cambios de referencia.

Estudio III

El propósito del tercer estudio fue examinar la integridad de la representación mental de la configuración de una tarea *(task-set)*, supuestamente alterada en pacientes esquizofrénicos, mediante la manipulación ortogonal de la información sobre la preparación de la tarea (ligada al indicador) y la ejecución de la tarea (ligada al estímulo diana). Es importante destacar que tanto la actualización sensorial como la actualización contextual fueron manipuladas ortogonalmente con el fin de examinar si los procesos tempranos (sensoriales) se ven especialmente alterados en la esquizofrenia y cómo/ si interactúan el procesamiento sensorial y el procesamiento cognitivo. Las medidas de la actualización contextual y de procesos de retención durante las etapas de preparación y ejecución de la tarea permiten investigar la flexibilidad cognitiva, es decir, la capacidad de representar, retener y actualizar el contexto de la tarea en pacientes esquizofrénicos. Con el tercer estudio quisimos arrojar luz sobre la cuestión de si y cómo alteraciones de las etapas de procesamiento sensorial podrían afectar la cognición. Por consiguiente, ¿encontramos modulaciones en los procesos de orden superior debidas a alteraciones de etapas tempranas (sensoriales) en pacientes esquizofrénicos?

Resumen

Estudio I (Traducción del abstract del artículo original)

El estudio presente examinó el uso de conocimiento previo en un protocolo de indicación de tarea, manipulando actualización sensorial y control ejecutivo tanto en ensayos con indicador informativo como con un indicador no-informativo. Conocimientos previos, actualización sensorial y cambios de tarea fueron manipulados ortogonalmente con el fin de abordar la cuestión de sí, y en qué medida, el procesamiento sensorial de cambio del estímulo indicador puede dar cuenta parcial o totalmente del coste final del cambio de tarea. Los participantes respondieron más rápidamente cuando se pudieron preparar para la tarea consiguiente y una actualización configuracional de la tarea no era necesaria. Cambios sensoriales en el estímulo indicador influyeron los PEs ligados al indicador sólo cuando contuvieron información conceptual sobre la tarea: amplitudes de P2 frontal fueron moduladas por cambios del indicador relevantes para la tarea, amplitudes parietales mediales de P3 por la actualización anticipatoria de asignaciones estímulo-respuesta y las latencias del pico de P3 fueron moduladas por cambios en la tarea. La preparación para la tarea fue ventajosa para una re-asignación estímulo-respuesta con la aparición del estímulo blanco tal y como lo reflejan las amplitudes de N2 ligadas al blanco. Sin embargo, las latencias de N2 indican que este proceso es más rápido para todos los ensayos repetitivos. Los resultados proporcionan evidencia a favor de una detección muy rápida de cambios sensoriales (del indicador) relevantes para la tarea y argumentan en contra del punto de vista de beneficios por repetición de tarea debidos a una acuñación perceptiva por repetición. Una preparación avanzada podría tener mayor influencia sobre la conducta y la actividad cerebral ligada al blanco que efectos locales de repetición o cambios configuracionales de la tarea en el ensayo actual.

Estudio II (Traducción del abstract del artículo original)

Este estudio examinó las modulaciones de oscilaciones neuronales en las bandas alfa y theta de la actualización anticipatoria (cambio de meta) y la implementación del

contexto *(task-set)* de la tarea (activación de la regla) durante el cambio de tarea. Dos aspectos fueron manipulados de forma independiente mediante un paradigma de señalización de la tarea: (1) preparación anticipada de la tarea mediante la manipulación de la informatividad de señales sobre la tarea inminente, y (2) la aportación exógena al cambio de tarea endógeno por medio de una cartografía 2:1 entre señales y tareas. Este diseño examinó la contribución relativa de los cambios de señal exógenos a los efectos endógenos de reconfiguración del contexto de la tarea, y si estos efectos dependen de la presencia de conocimientos previos acerca de la tarea inminente. Los resultados revelaron fuertes beneficios en el rendimiento, así como modulaciones de la energía de alfa y beta ligada a la señal, en consonancia con la función reportada de ritmos alfa y theta en atención anticipatoria, la codificación sensorial y la memoria de trabajo. En los ensayos de cambio de tarea durante la actualización y la implementación de la tarea, se obtuvo una desincronización de alfa ligada al evento (ERD) más fuerte. A su vez, una sincronización ligada al evento (ERS) más fuerte de theta, se obtuvo sólo para las señales de cambio de tarea, sugiriendo que está más relacionado con las etapas iniciales de preparación de tarea en lugar de la etapa subsiguiente de implementación de la tarea. Curiosamente, los ensayos de cambio de la señal suscitaron un incremento de ERD de alfa y una disminución de ERS de theta, lo que podría reflejar " transiciones tarea-señal incongruentes" que implican procesos de control conflictivos abajo-arriba y arriba-abajo. Por último, los blancos no señalizados informativamente, evocaron una ERD de alfa fuerte en comparación a la señal neutra respecto a la tarea precedente, lo que sugiere que una presión temporal incrementada al inicio de blancos señalizados sin valor informativo requiere mayor control cognitivo. Por el contrario, una fuerte ERS de theta para señales informativas probablemente refleja la recuperación de la información de la señal.

Estudio III (Traducción del abstract del artículo original)

Para un comportamiento dirigido a lograr una meta, una representación precisa de la información contextual de la tarea es imprescindible. Estudios recientes apuntan a alteraciones en etapas de procesamiento temprano como posibles causas de deficiencias relacionadas con el cambio de tarea en la esquizofrenia. Un protocolo de indicación de tarea fue administrado a un grupo de pacientes esquizofrénicos y comparado con una muestra control sana, emparejada por edad. Comparados con los controles, los pacientes respondieron más lento y con menos precisión en todas las condiciones. El registro simultaneo de potenciales evocados reveló anormalidades en el procesamiento temprano tanto de potenciales N1 ligados al estímulo indicador como ligados al estímulo blanco. En esquizofrénicos se observaron amplitudes de P2 anómalamente incrementadas sólo en ensayos de cambio de tarea, sugiriendo una evaluación interrumpida de la evaluación del estímulo y procesos de recuperación de la memoria. El potencial endógeno P3 discriminó entre condiciones de la tarea, pero sin diferencias entre grupos. Estos resultados sugieren que las alteraciones observadas en la conducta de cambio de tarea no fueron relacionadas *específicamente* con el cambio configuracional (*set-shifting*), sino derivadas de un déficit en la implementación de la representación configuracional de la tarea a partir de la aparición del estímulo blanco en presencia de información irrelevante y conflictiva.

Resultados y Discusión

En términos generales, esta tesis tuvo como objetivo investigar los procesos de cambio de tarea en pacientes esquizofrénicos y controles sanos mediante un paradigma de indicación de tarea explícita. Un punto importante que se ha tenido en cuenta para ambos diseños de tarea fue la manipulación independiente de la actualización sensorial y el cambio de tarea.

Los datos del primer estudio no relevaron ningún efecto de cambio del indicador en P2 y P3 amplitudes ligadas al indicador en ensayos con un indicador informativo ni en ensayos con un indicador no-informativo. Sin embargo, P3 difirió entre ensayos con indicadores informativos y no-informativos aunque no había ningún efecto por el cambio del indicador. Es importante destacar que todos los estudios anteriores encontraron efectos para los ensayos con un indicador informativo, es decir, empleando indicadores que siempre proporcionaban información relevante para la tarea (Finke et al., 2011; Garcia-Garcia et al., 2010; Jost et al., 2008; Nicholson et al., 2006). Este resultado en la P3 sugiere que la información sobre la tarea es lo más importante a la hora de preparar un mapeo de respuesta. Mientras que la influencia de los procesos de abajo-arriba parece ser mínima. Por lo tanto, el estudio presente sugiere que la simple repetición del indicador sensorial parece ser insuficiente para explicar los beneficios encontrados en los ensayos de repetición con indicador informativo, ya que otros procesos de preparación de tarea parecen estar involucrados. Curiosamente, encontramos modulaciones de P2 por el cambio de tarea pero no por un cambio del indicador. Esto sugiere que la P2 detecta cambios relevantes para la tarea (Brown et al., 2007; West et al., 2011). Por otra parte, las amplitudes de P3 se vieron incrementadas para todos los ensayos informativos en comparación con los no-informativos aunque no mostraron el efecto típico de cambio de tarea (Barceló et al., 2006; Finke et al., 2011; West et al., 2011). Sin embargo, cambiar de tarea llevó a latencias de P3 prolongadas comparadas con la repetición de tarea. Los datos no apoyan un procesamiento de la información del indicador y de la tarea en serie o en paralelo, sino que reflejan más bien una detección rápida de cambios relevantes para la tarea (P2). El siguiente proceso de asignación de indicador (cue) -respuesta y la recarga/ actualización de las asignaciones de estímulo-respuesta se produjeron más tarde y se prolongaron en los ensayos de cambio de tarea (P3). La amplitud de N2 ligada al blanco resultó aumentada en los ensayos con un indicador informativo en comparación con no-informativos, probablemente reflejando el control arriba-abajo en términos de aplicación de las reglas a la tarea (Hsieh & Wu, 2011). Por otra parte, la latencia de N2 fue menor en la condición de repetición del indicador. Esto sugiere que el re-mapeo estímulo-respuesta podría ser prolongado en ensayos donde una cambio del indicador no se asocia con un cambio de tarea. Es importante destacar que el presente estudio no encontró ninguna interacción entre los factores indicador y tarea. En consecuencia, para la preparación de la tarea no encontramos ningún sesgo por un cambio en el indicador no-informativo.

El posterior análisis tiempo-frecuencia de estos datos reveló un fuerte efecto genérico de preparación, manifiesto en una desincronización de alfa ligada al indicador y sincronización theta, probablemente reflejando procesos atencionales y anticipatorios y codificación de información, respectivamente (Gladwin & de Jong, 2005; Sauseng et al., 2005; Verstraeten & Cluydts, 2002). Asimismo, durante la preparación de la tarea, encontramos efectos de cambio de tarea en ambas bandas de frecuencia. Curiosamente, la condición de cambio del indicador mostró los cambios de potencia más fuertes en ambas frecuencias. Como ningún estudio anterior incluyó esta condición, la explicación más plausible de la evidencia actual es que esto se debe a una "transición incongruente de indicador-tarea” debido al procesamiento incongruente de abajo-arriba y de arriba-abajo (Forstmann, Brass, & Koch, 2007; Van Loy, Liefooghe, & Vandierendonck, 2010; Schneider & Logan, 2007). La ERD de alfa y ERS de theta más fuerte en ensayos de cambio de tarea en comparación con los ensayos de repetición del indicador replica los resultados de estudios anteriores (Gladwin & de Jong, 2005; Sauseng et al., 2005; Verstraeten & Cluydts, 2002). Además, una interacción interesante entre Tarea y Tiempo reveló que la ERD frontal de alfa a niveles tempranos fue más fuerte en los ensayos de cambio de tarea, mientras que la ERD central de alfa a niveles más tardíos (o mu) fue más fuerte para los ensayos de repetición del indicador, lo cual refleja probablemente una pre-activación general de la corteza motora con el fin de optimizar la respuesta inminente en los ensayos de repetición (Gladwin, ’t Hart, & de Jong, 2008; Neuper & Pfurtscheller, 2001; Pfurtscheller & Lopes da Silva, 1999). Los efectos ligados al indicador o a la tarea estuvieron presentes en la banda theta, sugiriendo una relación con el cambio de meta más que con la activación de la regla. La actividad Alfa ligada al estímulo blanco mostró, sin embargo, modulaciones similares tanto para la activación de la regla como durante el cambio de meta, indicando que la ERD de alfa tiene un papel en las dos etapas de procesamiento del cambio de tarea. Por otra parte, cuando se compararon los cambios de potencia con el intervalo de indicador-a-blanco (CTI, por sus siglas en inglés), se encontró una ERD de alfa más fuerte para ensayos no-informativos, sugiriendo que la falta de preparación en ensayos no-informativos conduce a un apremio de tiempo mayor y a un alto nivel de control cognitivo comparado con el CTI, necesario para resolver la tarea dentro del marco temporal dado (Başar, Schürmann, Demiralp, Basar-Eroglu, & Ademoglu, 2001; Donner & Siegel, 2011; Ward, 2003). En contraste, este análisis reveló fuertes ERS de theta para los ensayos informativos, sugiriendo una recuperación de la información sobre el indicador (Başar et al., 2001; Gladwin & de Jong, 2005; Mitchell, McNaughton, Flanagan, & Kirk, 2008).

El tercer estudio reveló que los pacientes esquizofrénicos, en efecto, mostraron un procesamiento anómalo tanto en PEs ligados al estímulo indicador, como en los PEs ligados al estímulo blanco. Por una parte se manifiesto en la disminución de amplitud de N1 ligado a indicador y al blanco. Este resultado confirma estudios anteriores que encontraron amplitudes disminuidas de P1 durante la codificación de memoria, así como la disminución de amplitudes de N1 durante los procesos de atención visual en esquizofrénicos (Haenschel et al., 2007; Neuhaus et al., 2011). Es digno de mención que Neuhaus y sus colegas (2007) encontraron las amplitudes de N1 disminuidas tanto para procesos de abajo-arriba como para procesos de arriba-abajo. Por otra parte, las amplitudes de P2 ligadas al blanco se vieron incrementadas en pacientes esquizofrénicos comparando ensayos de cambio de tarea con ensayos de repetición, este no fue el caso en los controles sanos. Dado que este componente se ha asociado con procesos dependientes tales como la recuperación y la implementación de las asociaciones de S-R, así como con la detección de eminencia y la evaluación del estímulo, es plausible que los pacientes esquizofrénicos requieran un mayor esfuerzo mental para resolver la interferencia en ensayos de cambio de tarea (Gajewski et al., 2008; Potts, 2004). Al contrario que en estudios anteriores, no se hallaron diferencias entre los grupos respecto a la P3 ligada al indicador, sino un efecto de cambio de tarea para ambos grupos (Kieffaber et al., 2007). Esto sugiere que los pacientes esquizofrénicos en este estudio no sufrieron problemas al cambiar de tarea por tener dificultades con el cambio anticipatorio en la configuración de la tarea, sino derivados de alteraciones en el procesamiento sensorial temprano y un déficit en la implementación de la representación configuracional de la tarea en el momento de la aparición del blanco en presencia de información irrelevante y conflictiva (Jamadar et al., 2010).

Conclusiones

Las conclusiones de esta tesis pueden formularse de la siguiente manera:

En primer lugar, los resultados de todos los estudios de PEs señalan que un procesamiento sensorial temprano intacto y una rápida detección de los cambios relevantes para la tarea son cruciales para cambiar de tarea exitosamente.

A través de los PEs por las señales indicadoras del primer estudio, se pudo demostrar que la detección de cambios relevantes para la tarea constituye un proceso importante para resolver la tarea inminente. Estos resultados indican que el cerebro puede detectar si una señal indica un cambio de tarea o no, tan pronto como a partir de los 180 ms tras la presentación de la señal. Esto subraya la importancia de las etapas tempranas de procesamiento reflejadas en el componente P2 como un elemento importante del proceso de cambio de tarea. En una etapa posterior, se producen la asignación indicador- respuesta y la recarga/ actualización de las asignaciones de estímulo-respuesta, manifiestas en modulaciones de la P3. El análisis ligado al blanco del segundo estudio no reveló ningún sesgo del cambio de un indicador no-informativo para la preparación de la tarea. Esto refuerza la hipótesis de que los efectos del cambio del indicador no son provocados por un cambio sensorial simple, sino más bien por los efectos de tarea relacionadas con el cambio de meta. Esperamos que estos resultados ayuden a esclarecer existente controversia sobre cómo gran parte del coste de cambio de tarea se relaciona con un cambio puro del indicador.

En el segundo estudio demostró que mientras que la ERD de alfa fue modulada por procesos de activación de la regla después de la aparición del blanco, este no fue el caso para la ERS de theta, sugiriendo que theta está más relacionado con la reconfiguración del contexto de la tarea (cambio de meta) inicial y la codificación de la información específica sobre la tarea, más que con la etapa de implementación final del contexto de la tarea (activación de la meta). El "aplazamiento" del cambio de meta en ensayos no-informativos dio lugar a una ERD de alfa más fuerte para los cambios de potencia ligados al blanco, mientras que los ensayos informativos provocaron una mayor ERS de theta. En conjunto, los resultados de ambas bandas de frecuencia sugieren que en los ensayos no-informativos un alto nivel de control cognitivo (en comparación con el CTI) es necesario para resolver la tarea en el tiempo dado, mientras que la ERS de theta incrementada después de los indicadores informativos parece reflejar la recuperación de la información del indicador.

Finalmente, el último estudio reveló que si el procesamiento sensorial temprano se altera, como en la esquizofrenia, el rendimiento general resulta disminuido. Al contrario que en estudios anteriores, no se hallaron diferencias entre los grupos respecto a la P3 ligada al indicador, sino un efecto de cambio de tarea para ambos grupos que sugiere que los pacientes esquizofrénicos en este estudio no sufrieron problemas al cambiar de tarea por tener dificultades con el cambio anticipatorio en la configuración de la tarea. Por otra parte, aunque los procesos de anticipación de la tarea parecen ser normales en la esquizofrenia, la evaluación temprana del estímulo en los ensayos de cambio de la tarea (que exigen una reinterpretación de las cartas) requiere más esfuerzo, tal como queda reflejado en el P2 ligado al blanco incrementado.

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