THE ROLE OF ATTENTION AND COGNITIVE CONTROL IN DEPRESSION:

AN EXPERIMENTAL INVESTIGATION OF UNDERLYING NEUROBIOLOGICAL WORKING MECHANISMS

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GENERAL INTRODUCTION

Worldwide depression is one of the most common psychological problems (Judd, Akiskal, & Paulus, 1997; Segal, Williams, & Teasdale, 2000), affecting nearly everyone either through personal experience or through depression in a family member.

The lifetime prevalence of depression is very high, approximately 18-23% for women and 8-11% for men (Chen et al.,2006) and researchers predict that depression will be one of the most frequent diseases by 2020 (Hermans & Van de Putte, 2004).

A growing consensus is emerging regarding neuronal, cognitive distortions and possible treatment strategies in depression. Nevertheless, over 50% of all treated patients drop with the same complaints (Ramana et al., 1995; Mueller et al., 1999; Van Londen, Molenaar, Goekoop, Zwinderman, & Rooijmans, 1998). Johnson and co-workers (2000) demonstrated that 76% of the formerly depressed patients relapse within 10 years. This high relapse rate is indicative for the presence of vulnerability factors.

To create interventions that are successful on a long term basis, it is important to investigate the underlying working mechanisms of depression. These underlying working mechanisms and possible vulnerability factors for depression can be explored by integrating cognitive and neurobiological models.

VULNERABILITY FOR DEPRESSION: ATTENTIONAL PROCESSES

Major depression is frequently characterized by recurrent episodes over the life course. First lifetime episodes of depression, however, are typically more strongly associated with major life stress than are successive recurrences (e.g. Brugha et al., 1994). After multiple episodes of depression, clinical and research observations report a decrease in the stress threshold leading to general increased stress sensitivity (Teasdale, 1988). This implies that after each episode in the depressed state, depression becomes more severe or persistent since negative thinking patterns become more accessible. Clarke et al. (1999) propose that after multiple depressive episodes, patients are characterized by a tendency to become more vulnerable to activate latent negative self-schemas upon stressors. This stronger link between stressors and the elaboration of negative schemata can be labelled as a cognitive vulnerability (Teasdale, 1988).

At a neurobiological level, a stressor leads to the activation of the Hypothalamic-Pituitary-Adrenal (HPA) axis, causing an increase of cortisol secretion (e.g. Van Praag, 2004). An important finding in depression is a dysregulation of the HPA axis. More specific, the HPA system becomes hyperactive, because the normal negative feedback suppressing cortisol release after sustained activation does not occur anymore. Cortisol secretion leads to an initial increase of serotonergic activity (e.g. Davis et al., 1995), followed by a decrease after sustained hyper activation (Karten et al., 1999). This provokes a linear cascade effect with decreased frontal functioning (e.g. Evers et al., 2005, Audenaert, 2003) and impaired cognitive control processes (Ridderinkhof et al., 2004). These latter changes after multiple depressive episodes can be labelled as a biological vulnerability factor that prevents inhibition and disengagement from the elaboration from negative schemata (cognitive vulnerability).

These reduced cognitive control processes leading to increased schema-activation and negative mood states can thus be explained by the interplay between increasing cognitive and biological vulnerability. Overall, this mechanism might be a result of increased sensitivity in depression (Beck, Rush, Shaw, & Emery, 1979; Teasdale & Barnard, 1993).

Support for an attentional bias as a possible cognitive vulnerability factor for depression, has been demonstrated in recent behavioural studies. These

experimental studies demonstrated that depressed patients demonstrate a difficulty to disengage from negative stimuli (e.g. Koster et al., 2005), present a maintained attention for negative information (e.g. Leyman et al., 2007) and show a decreased inhibition for negative stimulus material (e.g. Joormann et al., 2004; Goeleven et al., 2006).

The aim of this dissertation is to explore the role of these dysfunctional attentional mechanisms and cognitive control processes in depression by an experimental investigation of underlying neurobiological working mechanisms in healthy volunteers and depressed patients. In this way, we will provide more insight in the pathophysiology of cortico-subcortical prefrontal functioning as a part of the biological vulnerability factor of mood disorders. We will use repetitive Transcranial Magnetic Stimulation (rTMS) as a causal interference technique and Event Related Potentials (ERP) as a correlational technique to investigate the neuro-circuitry of cognitive control in healthy volunteers and depressed patients. In order to investigate cognitive control, we chose two well-established cognitive tasks a Stroop paradigm and a Task Switching paradigm which are associated with cortico-subcortical prefrontal functioning.

COGNITIVE CONTROL

The term cognitive control describes a collection of brain processes with the function of guiding actions in accordance with internally generated goals or plans (Botvinick et al., 1999). These functions are invoked when it is necessary to override responses that may otherwise be automatically elicited by stimuli in the external environment.

Many of the tasks performed in daily life require an information processing system in an attentive state (i.e. regulative control) which monitors the presence of conflict (i.e. evaluative control) when competing sources of information are present in the environment (MacDonald et al., 2000). Experimental evidence has underpinned these two processes as main components of cognitive control (Carter et al., 1999).

Different neuro-cognitive studies revealed that cognitive control is related to a specific cortico-subcortical circuit (Bush, Luu, & Posner, 2000; MacDonald, Cohen, Stenger, & Carter, 2000; Barber & Carter, 2005).

Specifically, the Conflict Monitoring Hypothesis proposes that the dorsolateral prefrontal cortex (DLPFC) and the anterior cingulate cortex (ACC) play a dynamic and interactive role (Botvinick et al., 1999). More recently, Taylor & Fragopanagos (2005) proposed that two important frontal attentional circuits are involved in cognitive control: a dorsal and a ventral attentional circuit structurally represented by the DLPFC and the ACC.

Consistent within these theories, the DLPFC (Brodmann 9/46) takes a central role in activation and implementation of cognitive control (regulative component) (Bush et al., 2000). For an illustration of the Brodmann area, see Figure 1. This brain region seems to be involved in the representation and active maintenance of attentional demands during cognitive tasks (MacDonald et al., 2000). The DLPFC activates or inhibits the activity in brain regions which are involved in this conflict (Davidson, Pizzagalli, Nitschke, & Putnam, 2002). The representations maintained by the DLPFC can be emotional or unemotional as their selection depends on their importance in the attainment of behavioural goals.

The ACC establishes a bridge between attention and emotion (Mayberg, 1997) and can be divided into a cognitive and an affective region (Devinsky et al., 1995).

The cognitive region comprises the dorsal area (BA 24/32) of the ACC. This region plays an important role in the evaluation of cognitive information (Bush et al., 2000), perception of a cognitive conflict and the signalisation of needed top-down attentional processes and executive functioning (Devinsky et al., 1995).

The regulative DLPFC and evaluative dorsal ACC are interconnected through a negative feedback loop. The evaluative component of the ACC signals that more attentional control is needed for a task, resulting in an increased DLPFC activity. Subsequently, a negative feedback signal will decrease the ACC activity when DLPFC has augmented the attentional control. This conflict control mechanism regulates cognitive control necessary for selective attention and mental flexibility (MacDonald et al., 2000).

The affective region of the ACC consist a rostral (BA 24'/32') and a ventral (BA 25, 33) region (Dreher & Grafman, 2003). Their function comprises the evaluation of responses to emotional events and stimuli, such as human expressions (Bush et al, 2000).

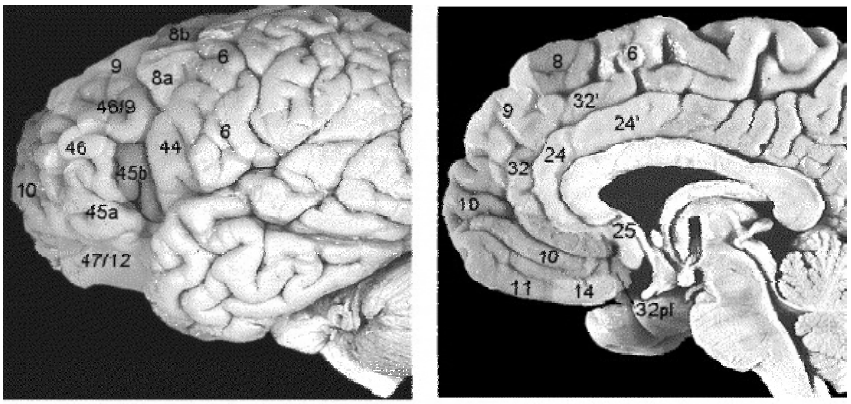


Figure 1. An overview of the frontal Brodmann areas (BA).

The interactions between affective and cognitive brain regions remain relatively unknown. Taylor & Fragopanagos (2005) present a computational model involving the interplay between the cognitive and emotion-sensitive frontal cortical areas. These reciprocal interactions between the ventral network for emotion and the dorsal network for cognition have also been reported by other researchers (Corbetta & Shulman, 2002; De Raedt, 2006).

As presented in these models, emotional information registered in the ventral ACC can influence the executive priorities coded in the DLPFC and ultimately alter the direction of attention or more generally modify the distribution of processing resources in a given context (Taylor & Fragopanagos, 2005). This ventral ACC region plays a crucial role in directing the attention to affective stimuli (Taylor & Fragopanagos, 2005). Within this context, we refer to the abovementioned negative feedback loop between the ACC and the DLPFC.

The ventral cingulate trajectories and amygdala trajectories for affective processes are converging in BA 24 (Davidson et al., 2002; Mega, Cummings, Salloway, & Malloy, 1997; Davidson et al., 2002).

Activity in the amygdala is associated with rapid registry and assimilation of the emotional value of incoming stimuli as it receives input from low-level sensory cortices (Adolphs, 2002). More over, the ventral ACC and the amygdala are closely interacting. The ventral cingulate trajectories receive emotional information about stimuli being processed from the amygdala. On the other hand, the ventral ACC gives feedback to the amygdala to suppress or enhance emotional processing according to prefrontally determined priorities (Siegle et al., 2007).

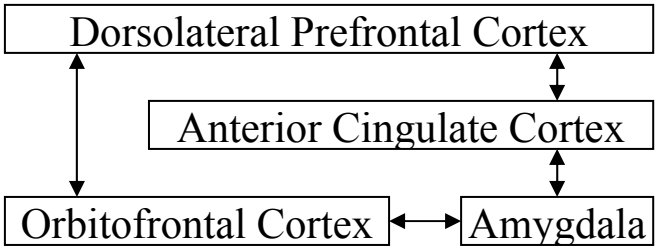
The amygdala is not essential for cognitive control processes but is closely interconnected with the above described dorsal circuit.

Another component of the ventro-medial prefrontal circuit is the orbitofrontal cortex (OFC). This region can be characterized through an inhibitory interaction with the DLPFC (Mayberg et al., 1997). On the other hand, the orbitofrontal cortex is excitatorily coupled to the ventral ACC of the attention circuit (Yamasaki, LaBar, & McCarthy, 2002).These brain region also seems to be important in generating responses to emotionally-valenced stimuli (Leppänen, 2006).

Overall, the ventromedial regions of the prefrontal cortex can be seen as a bridge that conveys emotional information from subcortical limbic regions such as the amygdala to the higher cortical executive centres of the PFC.

In sum, the DLPFC, whether it is related to non-emotional or emotional information, occupies a central role in cognitive control processes. In the following we will focus on basic non-emotional stimuli to investigate attentional processes related to this dorsal circuit.

The abovementioned interaction between attention and emotion can be represented through the sensory-motor attentional control model of Taylor & Fragopanagos (2005), presented in figure 2.



Sensory-motor attentional control model of Taylor & Fragopanagos (2005)

DEPRESSION AND THE CORTICO-SUBCORTICAL CIRCUIT

Depression seems to be related to a hypoactivity of the left relative to the right prefrontal cortex associated to the frontocortical-subcortical circuit (Sackeim, Greenberg, Weiman et al., 1982).

When exploring the working mechanisms of the biological vulnerability factor in depression, the concept of "simple" hypofrontality does not offer a satisfactory explanation. Rather, a more dynamic model will be discussed in order to achieve a more realistic concept of executive deficits in depression.

Neuroimaging data reveal a hypometabolism and hypoperfusion of the left DLPFC and extended connections of this area with other cortical and subcortical regions, e.g. dorsal and ventral ACC, in mood disorders (Drevets, 2000). On the other hand, hyperactivity of the amygdala when processing emotionally evocative information and in resting state is consistently found in major depression (e.g. Drevets et al., 1992; Mayberg et al., 1999; Fu et al., 2004).

Effects of the hypoactivity in the DLPFC can be seen in problems with controlling of goal directed behaviour and dominant automatic responses.

The hypoactivity in the dorsal region of the ACC could be associated with a decreased modulation of executive functioning in attentional control and a decreased evaluation of conflict between different response options. Hypoactivity in the ventral regions of the ACC could be related to anhedonia and reduced coping possibilities in situations which are characterised by conflict. However, hypoactivity within the dorsal regions of ACC has also been linked to failure to increase cognitive control after committing errors (Fales et al., 2007).

In the rostral region of the ACC, research has demonstrated that hyperactivity is possibly associated to an increased emotional arousal (Drevets et al., 2000).

In dorsal ACC and DLPFC areas, activity increases while attentionally demanding cognitive tasks are performed, while the opposite effect arises during emotional states (Drevets et al., 2000). These reciprocal patterns of neural activity hold implications for the interactions between emotion and cognition.

However, a crucial role in the interaction between attentional and emotional information processing also seems to be played by the amygdala. Abnormal cortico-limbic connectivity has been reported a lot in brain imaging literature.

Within the pathophysiology of depression, the amygdala is related to an increased activity (Davidson et al., 2002). During a depressive episode, the prefrontal cortex receives abnormal excitatory signals of the hyperactive amygdala (Drevets, 2000). The increased activity of the amygdala can bias the attention (Taylor & Fragopanagos, 2005). This hyperactivity can lead to a bias in the evaluation and response to incoming information due to a failure to recruit the DLPFC (Fales et al., 2007). Decreased DLPFC signals to the amygdala have been advanced for increased emotional biases and failure in emotion regulation during depression.

Importantly, there seem to be no direct connections between the DLPFC and the amygdala. The ventromedial prefrontal regions (ventral regions of the ACC and OFC can be seen as a bridge that conveys the DLPFC and amygdala activation (Taylor & Fragopanagos et al., 2005). More specific, Siegle et al. (2007) reported Brodmann's area 24 (ventral ACC) implications for the variance in the observed relationships between sustained amygdala and decreased DLPFC activity. Functional connectivity between BA 24 and both the amygdala and DLPFC were reduced in depression. Inefficient communication between these structures potentially leads to a decreased regulatory and inhibitory influence on the amygdala (Irwin et al., 2004).

In contrast, the dorsal ACC showed error processing abnormalities independent of the emotional valence of the stimuli or the level of amygdala activity. Abnormalities might occur in dorsal ACC signalisation to the DLPFC to reallocate attentional resources as needed (Braver et al., 2003).

This pathological amygdala-ACC-DLPFC-projection is typically found in a major depressive episode and seems to account for a depressive mood and for deficits in attentional processes.

Researchers proposed that a problematic inhibition and regulation of negative information in a major depression is based on a changed activity of brain circuits and reciprocal neuro-pathological cortico-limbic projections (e.g. for a review, see Leppänen, 2006). Therefore, persons with a major depressive disorder have problems with inhibition for negative material (e.g., Goeleven et al., 2006) resulting in a tendency for rumination (Drevets, 2001).

Overall, this negativity bias in depression is reflected by a dysfunction in both emotional processing and cognitive control (Fales et al., 2007).

CORTICO-SUBCORTICAL CIRCUIT: INTERPLAY BETWEEN ATTENTIONAL AND EMOTIONAL INFORMATION PROCESSING

In sum, researchers have postulated that the dorsal circuit would play an important role in the interplay between emotional and attentional information processing (Taylor & Fragopanagos, 2005) and that dysfunctional activation in this area of the brain can be a potential factor that may contribute to the development of affective disorders (e.g. Leppänen, 2006).

Since the interplay between cognitive and biological processes can account for an underlying working mechanism of depression, research should investigate the cortico-subcortical circuit and related cognitive functioning during an anti-depressant treatment. However, evidence for cognitive impairments, associated to dysfunctions in the DLPFC and dorsal ACC brain networks, as underlying working mechanisms of depression have been inconclusive to date (Martin et al., 2003).

It is difficult to interpret the functional role of these separated cortical brain activations given the impossibility to infer straightforward causality based on functional magnetic resonance imaging (fMRI) studies (Rushworth et al., 2003). Because of the possibly crucial interaction between attentional and emotional information processing, a technique should be used to establish a causal interference in the DLPFC that can specifically influence mood and cognition.

This might offer new ways to study the relationship between basic cognitive processes and emotional information processing.

In addition, a neurobiological technique should be used to investigate the temporal interactions between specific brain regions in the central cortical-subcortical network.

For these reasons, we will use repetitive Transcranial Magnetic Stimulation (rTMS) as a causal interference technique and Event Related Potentials (ERP) for its high temporal resolution to investigate these functional cognitive processes in the human brain.

REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION

Repetitive Transcranial Magnetic Stimulation (rTMS) is a relatively new technology with significant potential to offer therapeutic advances and research insights into a variety of common, disabling and poorly understood psychiatric disorders. rTMS is a non-invasive means of stimulating nerve cells in superficial areas of the brain. During the TMS procedure, an electrical current passes through a small coil placed close to the participants head. This current induces a magnetic field that stimulates electrical activity in nerve tissue below the coil (George et al., 1994). This stimulation may be repeated many times per second and with variation in intensity and orientation (rTMS) (Pascual-Leone et al., 1999).

Depending on the parameters used in the stimulation such as intensity, frequency, site of stimulation (Chen et al., 1997; Pascual-Leone et al., 1999), potential modulatory effects of rTMS on the excitability of cortical neurons have been measured (Maeda et al., 2000; Pascual-Leone et al., 1999). Results from electrophysiological research suggest that high frequency (HF, > 1 Hz) rTMS has an excitatory effect on neurons; in contrast, low frequency (LF, < 1 Hz) rTMS has an inhibitory effect on neurons (Pascual-Leone et al., 1998; Klein et al., 1999; Schutter et al., 2001; Knoch et al., 2006; Fitzgerald et al., 2007).

Relatively little research evidence has reported the time-span of the rTMS effect on emotional and attentional information processes. In depressed patients, effects were apparent for at least five hours after one session (e.g. Pascual-Leone et al., 1999; George et al., 1997) and even three days after five sessions

stimulation (Moser et al., 2002). In normal volunteers, there is evidence of effects from twenty minutes to eight hours after stimulation (George et al., 1996).

Because of anti-depressant effects, several meta-analyses have indicated the left DLPFC as being a stimulation target (e.g. McNamara et al., 2001, Burt et al., 2002; Martin et al., 2003).

Based on the original studies conducted (George et al., 1996; Pascual-Leone et al., 1999), a lot of studies to date have followed a standard procedure for the localization of the DLPFC, either in general or to Brodmann area 9/46 (e.g. Shajahan et al., 2002; Miniussi et al., 2005; Fitzgerald et al., 2006). First, the motor cortex was localized by evoking a response of the contralateral hand muscle, the abductor pollicis brevis muscle (APB). Then the coil was moved 5 cm rostrally, presumably targeting the DLPFC. The measure of 5 cm was derived from the Talairach atlas (Talairach, 1988). This method of coil placement is easy to perform but does not account for individual variations in the distance between motor areas and the DLPFC (for a review, see Fitzgerald, 2006).

Most important in our studies, before the rTMS procedure, the site of DLPFC (Brodmann area 9/46) stimulation site was defined under magnetic resonance (MRI) non-stereotactic guidance. On the first treatment trial, a stimulation intensity of 110% of the motor threshold (MT) at rest of the right abductor pollicis brevis (APB) muscle was established using EMG. Based on the anatomical MRI scan, the position for the DLPFC (Brodman 9/46) stimulation was adjusted to be over the middle frontal gyrus.

Anti-depressant effects of rTMS

Several studies have shown changes in cerebral blood flow and glucose metabolism induced by rTMS (eg. Siebner et al., 1998) and these findings acknowledge its therapeutic applications in neurological and psychiatric disorders (del Olmo, 2007).

Since the mid-1990s, the literature is rapidly accumulating with regard to the laterality- and frequency-dependent therapeutic anti-depressant effects of rTMS. It has been extensively studied as a treatment for depression, and many clinical

studies that applied rTMS to the prefrontal cortex report results superior to placebo (for a review, see Burt et al., 2002; Martin et al., 2003).

High-frequency stimulation (1 Hz to 20 Hz) was found to induce a beneficial mood effect in depressed patients when administered in multiple sessions over the left prefrontal cortex (George et al., 1996; Pascual-Leone et al., 1999). Later studies reported that multiple low-frequency (< 1 Hz) rTMS sessions over the right prefrontal cortex can also produce an anti-depressant effect (Klein et al., 1999; Schutter et al., 2001), demonstrating that the laterality of the anti-depressant effect is frequency-dependent (for a review see Gershon et al., 2003). This is in line with the imbalance hypothesis of depression, which presumes that a relative hypoactivity in the left relative to the right prefrontal cortex plays a critical role in the pathophysiology of depression (Davidson et al., 2002). Fast left prefrontal rTMS enhances and slow right prefrontal rTMS reduces the activity in the targeted brain areas, thus restoring normal balance between the hemispheres.

Effects on mood in depressed patients were obtained after at least one week of stimulation whereas no acute rTMS effects after only one session have been reported (e.g. for a review, see Burt et al., 2002).

Despite the majority of studies producing positive findings of beneficial effects of multiple sessions of rTMS on the DLPFC, considerable doubts have continued to be expressed about the clinical applicability of rTMS, predominately due to concerns about the magnitude of the clinical effects seen and the number of patients considered to meet clinical response criteria (for a review, see Martin et al., 2003).

In healthy subjects, primary research evidence suggests that changes in mood after prefrontal rTMS are the opposite of those in depressed patients. In healthy subjects, some studies have shown that a single session of high-frequency rTMS increases feelings of sadness when administered to the left prefrontal cortex but increases feelings of happiness if administered to the right prefrontal area (e.g. George et al., 1996; Pascual-Leone et al., 1999). However, these effects could not be replicated by other recent studies who used a more stringent methodology and larger groups of participants (Mosimann et al., 2000; Padberg et al., 2001; Baeken et al., 2006). Therefore, mood effects after a single rTMS session in

healthy volunteers are uncertain. Multiple rTMS sessions in healthy volunteers are not possible due to ethical aspects.

Using more stringent methodology for controlling shortcomings mentioned in other rTMS research, we used a sham (placebo)-controlled condition, a large time interval between the sham and rTMS sessions, stimulation of one single region per session (in order to exclude interaction with the previous stimulation), individual brain imaging (to determine the exact target of stimulation) and a large number of high-stimulation intensity pulses and a large uniform sample (Baeken et al., 2006).

Cognitive effects of rTMS

As a non-invasive tool for stimulation of the human cerebral cortex, rTMS not only influences mood measurements but can also influence cognitive functioning. In fact, rTMS can induce alterations of neuronal activity that may affect cognition (Moser et al., 2002) and becomes a promising technique to investigate causal connections between attentional processes and depression.

To investigate cognitive functioning, one rTMS session can reversibly interfere with the normal activity of a brain area to determine whether this area is essential for task performance (Hausmann et al., 2004).

Long-term safety of rTMS with regard to cognitive functioning is well established from open and controlled studies exploring its therapeutic efficacy. For example, safety studies convincingly suggest that rTMS does not result in long term cognitive impairments (Little et al., 2000; Schulze-Rauschenbach et al., 2005; Wassermann et al., 1996). A review of the literature reveals no major adverse cognitive effects of performance on any of the cognitive domains over the baseline-post rTMS period (e.g. Hausmann et al., 2004). Some studies have demonstrated a beneficial effect on cognitive functioning after multiple HF-rTMS (High Frequency rTMS) sessions (e.g. Moser et al., 2002), such as verbal memory (Padberg et al., 1999), verbal fluency (Triggs et al., 1999) and improvement on list recall (Little et al., 2000) following two weeks of 1 to 20 Hz rTMS over the left DLPFC in depressed subjects.

Surprisingly little research has been done on cognitive effects of rTMS immediately after cessation of one stimulation session. For example, direct disruptive effects on cognitive functions were demonstrated for speech

generation at high frequency (20 Hz) rTMS (Pascual-Leone et al., 1999) and for random number generation (Jahanshahi & Dirnberger, 1999). Nevertheless, the rTMS studies that have been carried out have methodological limitations (e.g. small samples, non-blind conditions, inaccurate stimulation localisation, relapses/ recurrences and inadequacy of placebo/control procedures).

To investigate the interaction between emotional and attentional information processing in the abovementioned dorsal circuit, the influence of a single rTMS session over the DLPFC on mood and attentional processes might be promising. These results could be compared to results after two weeks of rTMS with similar parameters.

rTMS in healthy volunteers and depressed patients

In order to gain a better understanding in the neural working mechanisms of depression, the fundamental attentional processes which are related to the dorsal circuit should be examined. Miniussi et al. (2005) highlighted the importance to investigate the general underlying neural architecture of the multiple and non-uniform elementary nature of the attentional mechanisms in order to gain a better understanding of these unique trajectories.

Therefore, we started conducting single session rTMS studies in healthy subjects focusing on acute rTMS effects. The goal of these experiments in healthy volunteers was to elucidate the specific acute rTMS influence after left and right dorsolateral frontal HF-activation through determination of behavioural effects.

We explored the precise influence of a single session of rTMS over the left and over the right DLPFC not only on cognition, but also on mood in healthy volunteers. According to Damasio (1996) mood should be well measured since it has an important influence on executive functioning.

After we could demonstrate that a single session of rTMS has a specific influence on cognitive functioning, the same tasks will be used in depressed patients. We will investigate the influence of a single session as compared to two weeks of daily HF-rTMS over the left DLPFC on executive functions in medication free depressed patients.

In order to trace possible functional acute effects of rTMS on cognitive functioning, we chose two well-established cognitive tasks known to involve

prefrontal brain activity, as evidenced by many neuroimaging studies. These studies have linked Stroop task performance and Task Switching performance to activity in the DLPFC (e.g. Hadland et al., 2001; Milham et al., 2003; Blasi et al., 2006; Loose et al., 2006).

Stroop task

An important aspect of cognitive control is selective attention, which plays a critical role in the ability to process task-related stimuli and to suppress task-unrelated stimuli in order to guide the execution of task-relevant responses (Cohen et al. 1990).

The Stroop interference effect remains a cornerstone of the investigation of human selective attention (Banich et al., 2001) and is one of the most frequently used tasks in cognitive psychology, clinical neuropsychology, and cognitive neuroscience to study interference and attention (e.g., Kornblum et al., 1999; MacLeod, 1991; MacDonald, 2000; Pardo et al., 1990; Stuss et al., 2001).

In a Stroop colour-naming task, participants have to name the ink colour of a colour name word. There is greater conflict for incongruent trials (e.g., naming the colour of a word printed in green ink when the word is "RED") than for congruent trials (the word "RED" printed in red ink) (Stroop interference effect).

Most neuroimaging studies that have examined the neural basis of these attentional systems by studying the Stroop or Stroop like tasks have identified the dorsolateral prefrontal cortex (PFC), anterior cingulate cortex (ACC), and posterior parietal cortex (PPC) as being central to overcoming this kind of interference (Banich et al., 2000; Barch et al., 2001; Bush et al., 1998; Carter et al., 1999; Fan et al., 2003; MacDonald et al., 2000; Milham et al., 2001, 2003; Pardo et al., 1990).

The DLPFC is assumed to select the relevant information by imposing an attentional set, or biasing information in posterior cortices by representing context (Banich et al., 2000; Miller & Cohen, 2001). This attentional implementation has been underpinned by neuroscience research as top-down regulative processes of cognitive control.

In contrast, the ACC is often thought to identify the presence of conflict and alert other systems to make use of control processes (Botvinick et al., 2001; Van

Veen & Carter, 2002). This attentional process has been marked the evaluative component of cognitive control.

Over the last seven decades, many Stroop variants have been developed in experimental neuroscience research (MacLeod, 1991).

At first, a classic Stroop task can be used in which subjects are asked to name the ink colour of coloured words. Congruent and incongruent trials are equally presented and the instruction is always the same. The simplest Stroop task makes use of two coloured words. We will use this classic Stroop task in our first study.

In more complex Stroop tasks, the intensity of conflict can be manipulated "by varying the proportions of congruent and incongruent trials". During this Stroop task, 80 % of all trials can be congruent trials and 20 % can be incongruent trials. This proportion of incongruent trials ensues a high conflict during incongruent trials (e.g., a high interference effect). In contrast, 20 % of all trials can be congruent but 80 % can be incongruent trials resulting in a lower conflict on incongruent trials. The instruction, to react to the colour of the word, is similar in both conditions. We will use this modified Stroop paradigm in our ERP research.

In an even more complex variant of the Stroop paradigm, subjects must keep in mind, or actively maintain, the instruction before the onset of each trial. This task cue has two different dimensions, namely the instruction to read the word (automatic process) and the instruction to name the colour of the word (strategic process) (MacDonald et al. 2000). In addition, subjects perform the Stroop task under the conditions "high expectancy" and "no expectancy" for incongruent stimuli by blocked manipulation of the frequency of incongruent trials (Carter et al. 1999). Top-down attentional processes will particularly be activated when strategic processes are engaged (after instruction "colour") and when expectancy for incongruent trials is high (anticipation for the upcoming event is possible in high expectancy blocks). These processes, associated to the DLPFC (Carter et al. 1999), facilitate a high degree of top-down control whereby the tendency to read the word should be overcome and conflict associated with responding to incongruent stimuli should be reduced. We will use this modified Stroop paradigm in our research investigating the effects of HF-rTMS over the left and right DLPFC.

Task Switching task

A second aspect of cognitive control involves cognitive flexibility. Cognitive flexibility largely defines successful human behaviour by initiating a change in the cognitive set to optimally adjust towards the novel demands of the environment (Woodward et al., 2006).

Task Switching investigates the ability to switch flexibly between two conditional response tasks with mutually incompatible response–selection rules (Woodward et al., 2006). Switching task blocks require enhanced executive and attentional control demands and greater cognitive flexibility than single-task blocks (Erickson et al., 2005) since the task rules change between the tasks and a constant need for the subjects to adjust to the currently relevant task set (Gruber et al., 2006).

A number of recent functional neuroimaging (fMRI) studies have highlighted functional activation of Task Switching processing within the human DLPFC (Rushworth et al., 2003) and posit that this cortical region is critically involved in implementing adaptive adjustments to the current task set (Luks et al., 2002; Sylvester et al., 2003; Smith et al., 2004; Woodward et al. 2006).

To isolate the effects of Task Switching processing, we employed a blocked design in which two trials (visual and auditory trials) were presented in isolation of one another during single blocks (repetitive blocks) and were randomly and unpredictably intermixed in a third block (mixed block). The two motor responses involved different modalities and therefore non-overlapping neural systems.

During a modified version of this abovementioned Task Switching task, a cue before the auditory switch trials was implemented. In this way, prospective and active reconfiguration for a new task was compared to a condition where task set was directly cued but with unpredictable task sequences. Most importantly, in this third block participants were instructed to pay constant attention to the visual stimuli to trigger attentional set implementation, whereas they were informed by a cue, just before stimulus onset, when a distracting auditory stimulus would appear. This task cue should trigger an intention to trigger response preparation.

rTMS research hypothesises

Cognitive interference and mental flexibility are attentional processes which can be related to activity in the cortico-subcortical circuit.

Previous findings of neuroimaging research demonstrated that the left DLPFC mediates top-down control by maintaining an 'attentional set'. The left DLPFC is known to play an important role in sustaining only task relevant representations of stimuli chosen from a large set of available stimuli so that attention can be effectively directed to achieve the task goals. Recent research revealed an essential role of the left DLPFC in task preparation (Dreher et al., 2003) and conflict predicting activity in interference tasks (Liston et al., 2006).

Neuroimaging brain studies of Task Switching reported increased activation of a bilateral DLPFC–parietal network for switch relative to repeat trials (Dreher et al., 2003). Sohn et al. (2000) found right lateralized prefrontal activation (the inferior part of DLPFC) when information about task repetition and task switch was available. These results are in line with several neuroimaging studies which observed greater activity for cue initiated preparatory processes, intentional set representations, in the right lateral prefrontal cortex (Brass & von Cramon, 2004; Dreher et al., 2002; Sohn et al., 2000).

Because of previous research (neuro-imaging or rTMS) and theoretical aspects (functional models of cognitive functioning), we expect significant cognitive changes after a single rTMS session. Since previous neuroimaging studies have shown the engagement of the DLPFC during Stroop tasks and Task Switching performance (Fassbender et al., 2006; Liston et al., 2006), we hypothesize that cognitive performance will benefit from HF-rTMS over the left and right DLPFC.

We hypothesize that HF-rTMS over the left and right DLPFC will have a beneficial influence on Stroop task performance. We will investigate Stroop task performance using a simple and a modified Stroop task. In our modified Stroop task, in line with research of MacDonald et al. (2000), we expect changes in RT latencies only after the colour instruction. Since attentional set representations should be increased after stimulation over the left DLPFC, we hypothesize no effects on the Stroop interference effect.

Since the right DLPFC is related to cue preparation and intentional set modifications, we expect a similar beneficial influence of HF-rTMS over the right DLPFC on the modified Stroop task.

For Task Switching performance, we expect a distinct but specific influence for HF-rTMS over the left and over the right DLPFC. Since the visual trials refer to attentional set representations, we hypothesize that visual switch trials will benefit from HF-rTMS over the left DLPFC due to endogenous task set reconfiguration and a general task preparation. Specifically, we hypothesized a decreased reaction time in the component of endogenous information processing, but not in the psychomotor speed component for visual trials.

Right DLPFC was found to be activated when information about task switches was available (Sohn et al., 2000). Since the right DLPFC is related to intentional set switching, we expected that after stimulation over the right DLPFC, the reaction time on the switch trial triggered by a direct cue-task association will decrease.

Thereafter, we will investigate the influence of one session and two weeks of HF-rTMS over the left DLPFC in depressed patients. We will only investigate HF-rTMS over the left cortex because of its well documented anti-depressant effects.

Because the performance of our modified Stroop task revealed to be to difficult for depressed patients based on a pilot study, we will only use the simple Task Switching task. In this simple Task Switching paradigm, no cue predicted the upcoming auditory switch trial. We expect beneficial switching performance after a single rTMS session in depressed patients. After two weeks of HF-rTMS, we expect additional positive changes in cognitive functioning.

Based on prior rTMS research, we expect no influence on mood measurements after a single HF-rTMS session in patients with a depressive disorder and healthy volunteers. After two weeks of HF-rTMS over the left DLPFC in depressed patients, we expect major anti-depressant effects as compared to baseline.

Based on the hypothesized relation between attention and mood in the abovementioned cortico-subcortical circuit, we would expect that anti-depressant effects of rTMS will correlate with the pre-post treatment change in attentional functions. Treatment changes will be measured after two weeks of HF-rTMS

over the left DLPFC in major depressed patients. Moreover, effects of one rTMS session could be predictive for the anti-depressant treatment outcome.

EVENT RELATED POTENTIALS

Emerging evidence from studies using various methodologies has revealed that depression may be associated with a disruption in the functional integrity of the abovementioned dorsal cortico-subcortical region underlying higher attentional control (Siegle et al., 2007). When exploring the biological vulnerability factor in depression, more insight should be obtained in the temporal and functional interactions of brain regions of this specific circuit.

Therefore, Event Related Potentials (ERPs) will be used as a second neuro-biological technique to investigate cognitive control processes associated to the cortico-subcortical network.

ERPs can be reliably measured using electroencephalography (EEG), a procedure that measures electrical activity of the brain through the skull and scalp. ERPs are signal-averaged EEG recordings that are time-locked to perceptual stimuli and to motor responses. These scalp recorded ERPs offer temporal resolution of neural processes, permitting a precise analysis of the time course of neural events supporting task performance (Kok et al., 2001).

When exploring the temporal interactions between several brain regions in depressed patients, studies must start with exploring baseline cognitive control in healthy volunteers.

Experimental evidence differentiates two main components in this cognitive control: as mentioned above, (a) an *evaluative component*, which is responsible for detecting a conflict and signalling when adjustments in control are necessary, and (b) a *regulative component*, which is in charge of the active maintenance and utilization of relevant information to guide task-appropriate attentional adjustments (Curtin et al., 2003).

These components, essential for adaptive behaviour, have been underpinned by neuroscience research revealing that the implementation of cognitive control is supported by a cortical fronto-dorsal network of interactive structures including the anterior cingulate cortex (ACC) for conflict evaluation and

dorsolateral prefrontal cortex (DLPFC) for conflict regulation (Blasi et al., 2006).

In healthy volunteers, an ongoing debate addresses the functional role of brain regions in the cortico-subcortical circuit when a conflict is expected and regulative adjustments in attentional control are required, (Liston et al., 2006).

The aim of this research was to investigate the nature and time course of neural activity supporting performance during a variant of the Stroop task in healthy volunteers.

Using a between-subject design, we manipulated the degree of conflict for incongruent trials during two attentional demanding task conditions. In the first task condition, 80 % of all trials were congruent trials and 20 % were incongruent trials ensuing high conflict during incongruent trials (e.g., a high interference effect). In the 'high conflict condition', dominant evaluative control should emerge during the processing of incongruent trials.

We compared the latter condition to a condition in which 20 % of all trials were congruent but 80 % were incongruent trials inducing a lower conflict on incongruent trials. This relatively lower conflict and associated smaller interference effect should result from adjustments in attentional control (e.g., regulative control processes).

In the Stroop task two modulations of the ERP, N450 and Sustained Potentials (SP) are consistently associated with both abovementioned components of conflict processing (e.g., Liotti et al., 2000; West & Alain, 2000; Houston et al., 2004).

Neurophysiological evidence shows an enlarged N450 when conflict is high and it is assumed that the evaluative processes detect the conflict.

On the other hand, attenuation (a more negative going) of the SP is associated to conditions where regulative attentional adjustments will decrease the cognitive conflict (e.g. Lansbergen et al., 2007).

At this point we are aware of only two studies which examined the effects of modulating the percentage of incongruent trials on ERP waves during a Stroop task (West & Alain, 2000; Lansbergen et al., 2007). Both studies used a within-subject design in which the frequency of incongruent trials alternated within separate blocks in one session.

One could question if the counterbalancing between the different expectancy blocks sorted out attentional set biases. When central evaluative processes emerged in one block, increased evaluative processes could bias the appearance of central regulative processes in a following block. This might imply that regularative and evaluative processes won't be registered purely and distinctively from each other. Therefore, we replicated these experiments using a between-subject design and with clear instructions before the start of the experiment producing an unambiguous task set manipulation.

ERP research hypothesises

We expected an attenuation of the SP (associated to activity in the DLPFC) reflecting regulative control processes within the low conflict condition (80 % incongruent trials).

Within the condition with 80% congruent trials, we expect an enhanced N450 (associated to activity in the ACC) because this condition elicits a high cognitive conflict. In contrast, we didn't expect a pronounced N450 in low conflict condition because evaluative control should not emerge because attentional adjustments should reduce the conflict.

CHAPTER OVERVIEW

To make each of the papers self-containing, partial overlap between the chapters may occur.

In **chapter one**, the influence of high-frequency rTMS over the left DLPFC on Stroop task performance in healthy female volunteers was investigated. More specifically, we examined possible selective attention changes after a single session of rTMS. We have used a basic Stroop task in which two coloured words (green and red) were randomly displayed, in their congruent colours (e.g. 'green' displayed in green ink) and their incongruent colour (e.g. 'green' displayed in red ink).

In **chapter two**, a modified Stroop task was applied to measure selective attention using similar stimulation parameters over the left DLPFC. We manipulated healthy female subjects' expectancies of incongruent stimuli using a within subjects design. In our new Stroop paradigm, before the onset of each

trial, subjects must keep the instruction in mind, namely the instruction to read the word (automatic process) or the instruction to name the colour of the word (strategic process). In addition, subjects perform the Stroop task under the conditions "high expectancy" (80% incongruent trials) and "no expectancy" (50% incongruent trials) for incongruent stimuli by within blocked manipulation of the frequency of incongruent trials.

In **chapter three**, using the same Stroop task, a single session of High Frequency (HF) rTMS was applied over the right DLPFC to investigate the precise role within top-down attentional control.

In **chapter four**, we explored the influence of HF-rTMS over the left DLPFC on top-down attentional control using a Task Switching paradigm. Participants were healthy right handed female volunteers. A Task Switching paradigm requires switching between two conditional response tasks with mutually incompatible response-selection rules. We used a Task Switching paradigm with three following conditions. During the first two blocks, repetitive auditory and visual trials were presented whereas in the third block switch trials were presented. In this third block, participants were instructed to be prepared for visual trials and that auditory trials were used as a distractor. Latencies on visual switch trials were used as an index of attentional task set representation. Cued auditory switch trials were used as an index of intentional set representations.

Using the same Task Switching paradigm in **chapter five**, the influence of rTMS over the right DLPFC was investigated.

In **chapter six**, we have measured ERPs during a variant of the Stroop task to investigate temporal correlates of underlying processes in conflict processing. The Stroop task used in this experiment was slightly different to the task used in study three. Using a between subjects design, we have manipulated conflict "by varying the proportions of congruent and incongruent trials". In the first task condition, 80 % of all trials were congruent trials and 20 % were incongruent trials ensuing high conflict during incongruent trials (e.g., a high interference effect). We compared the latter condition to a condition in which 20 % of all trials were congruent but 80 % were incongruent trials inducing a lower conflict on incongruent trials. To sort out all possible working memory components, we have used no instruction before each trial.

In **chapter seven**, the specific influence of a single HF-rTMS session on Task Switching performance and mood in medication free major depressed patients is explored. We used a Task Switching paradigm with three following conditions. In line with study four and five, participants were pretrained on two simple blocks of repetitive auditory or repetitive visual stimuli. The third block was different to the Task Switching task used in chapter four and five. In this previous paradigm, we chose to use an extra visual cue for auditory switch. The advantage of this cue presentation for optimal interference in one stimulus modality might however be questionable because auditory trials elicited an adequate amount of distracting attention by themselves. Therefore, in the third block (Task Switching block), participants alternated between two pretrained tasks (switch trials) or repeated the same task (repetitive trials). Consequently, they had no previous knowledge which task they had to perform and requires continuous task set inhibition.

Finally in **chapter eight**, we examined the immediate and post treatment effects of rTMS over the left DLPFC on performance of the same Task Switching paradigm and mood measurements in therapy resistant depressed patients. We have used a crossover design differentiating rTMS treatment responders and non responders.

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CHAPTER 1

THE INFLUENCE OF RTMS OVER THE LEFT DORSOLATERAL PREFRONTAL CORTEX ON STROOP TASK PERFORMANCE[1]

ABSTRACT

Several studies have demonstrated that repetitive Transcranial Magnetic Stimulation (rTMS) can improve cognitive processing. Neuroimaging studies have shown the engagement of the left dorsolateral prefrontal cortex (DLPFC) in executive functioning, and more specifically during selective attention.

In the present study, the influence of high frequency rTMS over the left DLPFC on Stroop task performance in healthy female volunteers was investigated.

As expected, reaction time on both the incongruent and congruent trials decreased significantly after stimulation with a smaller the Stroop interference effect. Mood remained unchanged after rTMS.

Such a pattern is consistent with the role of the left DLPFC in implementing top-down attentional control.

[1] Based on: Vanderhasselt, M.A., De Raedt, R., Baeken, C., Leyman, L., & D'haenen, H. (2006). The influence of rTMS over the left dorsolateral prefrontal cortex on Stroop task performance. *Experimental Brain Research, 18,* 1-4.

INTRODUCTION

Repetitive Transcranial Magnetic Stimulation (rTMS) induces alterations in neuronal activity that may affect mood and cognition and can provide more insight into the workings of the neural circuits involved in executive functioning, by modulating brain activity in controlled designs (Moser et al., 2002).

Previous research with depressed patients indicates that high frequency rTMS (>1Hz) over the left dorsolateral prefrontal cortex (DLPFC) results in an increase in several aspects of executive functioning (Martin et al., 2003). However, we are not aware of any studies regarding rTMS over the left DLPFC in healthy volunteers where mood was kept under control. This might be essential since mood has an important influence on executive functioning. Most notably, Damasio (1996) provides a systems-level neuroanatomical and cognitive framework for executive function and the influence on it by emotion, the somatic marker hypothesis, which has been underpinned by several studies (Bechara & Damasio, 2005). The basic idea of this hypothesis is that decision-making is influenced by marker signals that arise in bioregulatory processes, including those expressed in emotions and feelings.

Executive functioning is defined as a complex cognitive process that requires the co-ordination of several sub processes to achieve a particular goal (Lezak 2004). An important aspect of executive functioning is selective attention, which plays a critical role in the ability to process task-related stimuli and to filter out task-unrelated stimuli in order to guide the execution of task-relevant responses (Cohen et al., 1990). The Stroop interference remains at the cornerstone of investigation into human selective attention (Banich et al., 2001). The basic principle is that word reading- a highly potent learned ability- interferes with colour naming. This effect is most striking when a colour-word noun, e.g. the word ‘RED’ is printed in green ink and the task is to name the word’s ink colour. The Stroop interference is characterised by a slower response in naming these incongruent words as compared with the colour-congruent stimuli case (Stroop, 1935).

Studies using functional Neuroimaging techniques have linked selective attention to activity in the dorsolateral prefrontal cortex (DLPFC) (Hadland et al., 2001). However, the relative contributions of specific regions such as the DLPFC and the Anterior Cingulate Cortex (ACC) involved in performing the

Stroop task are a continuing source of debate (Rushworth et al., 2002). A number of neuroimaging studies have led to the hypothesis that the left DLPFC may be involved in representing and maintaining the attentional demands of the task, while response-related activity was found within the ACC (MacDonald 2000). This means that DLPFC would be involved in top-down attentional control.

Based on this research and on the literature concerning cognitive changes after rTMS (Milham et al., 2003), we hypothesised that, when high frequency-rTMS on the left DLPFC has a positive influence on selective attention by maintaining an attentional set, there should be a faster reaction time on *both* congruent and incongruent trials of the Stroop task as compared with a control placebo sham condition. Accordingly, there should be an influence on the Stroop interference effect in the rTMS condition.

MATERIALS AND METHODS

Participants

Twenty-eight right-handed female volunteers (mean age: 23; age range: 18-60, standard deviation: 4.4) were studied after they had given written informed consent to the study, which was approved of by the local ethics committee of the Academic Hospital of the Free University Brussels (A.Z.-V.U.B.). None of the subjects had any neurological, psychiatric or medical history. Nor did they have any contraindications to rTMS (Wassermann, 1998), as assessed through a medical screening before inclusion. They all underwent a physical examination, EEG and the Mini-International Neuropsychiatric Interview (M.I.N.I.) (Sheehan et al., 1998). Handedness was assessed with the Hand preference scale of Van Strien (Van Strien, 2001).

Design

A double blind, within subjects design by counterbalanced crossover sham (placebo) and active rTMS was used.

Procedure

On the day of stimulation, the investigation started with a baseline mood measurement using two different mood scales, the visual analogue scales (VAS)

and the Profile of Mood States (POMS) (Wald 1984). The POMS consists of subscales for depression (8 items), anger (7 items), fatigue (6 items), vigour (5 items) and tension (6 items). Each scale consists of adjectives followed by a five-point scale (0-4). The participants are asked to describe how they feel "at this moment". On the VAS scale, participants were asked to indicate on horizontal 10 centimetre lines whether they experienced the same five abovementioned mood states, from "totally not" to "very much".

Subsequently a computerised Stroop task was performed. The Stroop task was programmed in E-prime (Schneider et al., 2002) and was run on a DELL computer, OptiPlex GX110. Continuous series of coloured words (green and red) were randomly displayed, in their congruent colours (e.g. 'green' displayed in green ink) and their incongruent colour (e.g. 'green' displayed in red ink). Subjects were instructed to respond as quickly and as accurately as possible using the "F" and "J" keys on an AZERTY keyboard. They were asked to react to the ink colour in which the word was presented and not to pay attention to the semantic information of the word.

After the Stroop task, High Frequency (HF) rTMS was performed over the left DLPFC. All stimulations were performed using a MAGSTIM -high-speed stimulator (Magstim Company Limited, Wales, UK) with a figure-8-shaped coil. Motor threshold (MT) was determined individually before real and sham stimulation. Stimulation intensity was 110% of MT of the right abductor pollicis brevis muscle, stimulation frequency was 10 HZ (HF-rTMS) and intertrain interval was 26.1 s. Forty trains were applied in ca 20 minutes (1560 pulses per session). The left DLPFC (Brodmann area 9) stimulation site was defined under magnetic resonance (MRI) non-stereotactic guidance. Real and sham stimulation were performed at the same place on the scull, but for sham stimulation the figure-8-shaped coil was held at an angle of 90° only resting on the scalp with one edge. After stimulation, participants again completed both mood scales, followed by the Stroop task. After completing the Stroop task, mood was assessed for the last time. All subjects were stimulated between 9am and 12pm. There was a delay of 1 week between the two stimulation sessions. The same individuals were stimulated at the same moment of the day.

RESULTS

Mood effects

Analysis of variance (ANOVA) for repeated measurements was used to analyse the changes of mood. We used two 2X3 within subjects ANOVA's with stimulation (rTMS-SHAM) and time (pre - post1 - post2) as within-factors and mood scores evaluated with the VAS and the POMS as dependent variables. No significant interaction effects between time and stimulation were found [*F's* <1]. Therefore, we conclude that there were no mood changes from baseline caused by left prefrontal HF-rTMS compared to ratings immediately after stimulation and after the second Stroop task.

Reaction time on Congruent en Incongruent trials

Stroop effects were analysed using a mixed ANOVA. The basic design was a 2x2x2x2 factorial design with stimulation condition (rTMS-SHAM), time (pre-post) and type of trial (congruent-incongruent) as within-factors and the order of the stimulation condition as between-factor. The dependent variable was RT on congruent and incongruent trials. Latencies more than two standard deviations beyond each participant's mean were removed. The order of stimulation yielded no main effect and was not implied in any interaction effect [*F's* <1]. This factor was left out of all further analyses.

No main effect of "rTMS/SHAM" [F (1,27) =2.907, p = .100; *ns*] was found. However, we did find a main effect of "pre-post" [F (1,27) =4.961, p = .035] and "congruent-incongruent" [F (1,27) =23.583, p = .001]. The interaction between stimulation condition "rTMS/SHAM" and time "pre-post" [F (1,27) =3.375, p = .078] as well as the interaction between stimulation condition "rTMS/SHAM" and type of trial "congruent-incongruent" [F (1,27) =3.244, p = .085] were trend-significant. The interaction between time "pre/post" and trial "congruent-incongruent" was not significant [F <1]. However, the crucial three-way interaction between "rTMS/SHAM", "pre-post" and "congruent-incongruent" was significant [F (1,27) =4.293, p = .048].

This interaction effect was further analysed by paired-t-tests to test our specific hypotheses.

As predicted, in the SHAM placebo condition, there was no difference between both test moments neither for the congruent trials [t (27) = .242; ns], nor for the incongruent trials [t (27) = .006; ns].

In line with our hypothesis, we found a significant difference in the performance on the Stroop task between both test moments during active rTMS for congruent trials [t (27)= 2.033, *p*=.032], and incongruent trials [t (27)= 2.261, *p*=.042].

For a summary of these results, we refer to table 1.

Stroop interference effect

In addition to the main hypothesis, we also analysed the interference effect using a repeated measures ANOVA. The basic design was a 2x2 factorial design with stimulation condition (rTMS-SHAM), time (pre-post) as within-factors. The dependent variable was the Stroop interference effect (RT on incongruent trials minus RT on congruent trials).

The analyses yielded no main effects "rTMS/SHAM" [F (1,27) =2.907, *p* = .100; ns], but a significant main effect of "pre-post" [F (1,27) =4.961, *p* = .035]. Most crucial, the interaction effect was significant between "rTMS/SHAM" and "pre-post" [F (1,27) =4.293, *p* = .048]. Using paired t tests, this analysis yielded significantly smaller interference effects between congruent and incongruent trials after rTMS [t (27)=2.103, *p*=.045] but not after SHAM [t (27)=0.274, *p*=.786].

Stroop error analyses

We analysed the error data using repeated measures ANOVA. The basic design was a 2x2 factorial design with "stimulation condition" (rTMS-SHAM) and "time" (pre-post) as within-factors. The dependent variables were the Stroop error data. For these analyses, we did not find any main or interaction effects F's < .598.

Table 1

Mean Reaction Time latencies and approximate Standard Deviation of the Stroop task in a SHAM control and an active rTMS stimulation condition.

	SHAM		rTMS	
	PRE	POST	PRE	POST
Congruent trials	**409.07** (*46.83)*	**402.95** (*38.61)*	**436.30** (*68.95)*	**416.09** (62.96)*
Incongruent trials	**413.41** (*52.11)*	**411.64** (*46.34)*	**450.97** (*78.44)*	**424.22** (*67.70)***

*p<.05 and **p<.02

DISCUSSION

This study examined the effects of rTMS at the left DLPFC on selective attention. The results of the Stroop task can be evaluated independent of mood changes. The reaction times on both the incongruent and congruent trials decreased significantly after the stimulation over the left DLPFC, while no changes emerged after the placebo sham condition. The Stroop interference effect did significantly decrease after rTMS but not in the SHAM control condition. The order of stimulation condition implied no effect. In addition, no effects were found when analysing the Stroop error data.

An important observation that needs consideration is that the pre measurements of the Stroop Rt's of the rTMS stimulation condition and the SHAM (placebo) condition for congruent [t (27) = 2.301, *p*=. 039] and for incongruent [t (27) = 2.230, *p*=.042) trails are significantly different.

However, since the order of rTMS and SHAM was counterbalanced and, in addition, the same persons were used in the two conditions we can only conclude that these baseline differences can purely be attributed to a chance factor. The participants were slower on both congruent and incongruent trials before rTMS as compared to SHAM but each test person is its own control. Therefore, it is appropriate to compare rTMS versus SHAM based on the individual difference scores between pre and post, which results in a significant difference. For this reason, we can conclude that rTMS had a significant influence on the response times in contrast to the SHAM control condition.

However, since active rTMS might be more painful and could cause more discomfort than SHAM with the coil at 90 degrees to the scalp (Hoffman et al., 2000, Loo et al., 2000), consideration of non-cortical effects such as an increased alertness caused by painful stimulation of the scalp during rTMS might be essential. Although it is an important challenge to control for this in future research, the POMS subscale 'vigour' should have detected such a 'peripheral' effect (Wald 1984) since this scale contains items such as "Alert", "Energetic" and "Active". In addition, we found no changes on the POMS subscale 'fatigue' after the treatment with rTMS. There was no significant interaction effect between time and stimulation type on these subscales. Previous research concerning HF- rTMS over the left DLPFC could demonstrate that all patients tolerated the TMS procedure without significant cognitive adverse effects (Shajahan et al., 2002).

The fact that stimulation over the DLPFC has a positive effect on reaction times of *both* congruent and incongruent trials and decreased the Stroop interference effect, is consistent with the hypothesis that the left DLPFC plays a role in the implementation of control, by representing and actively maintaining the attentional demands of the task (imposing an attentional set) (Harrison et al., 2004). Accordingly, MacDonald et al. (2000) demonstrated that individuals who showed the most activation in the left DLPFC after the color-naming instruction showed the smallest Stroop interference effect.

It had already been demonstrated that the DLPFC and the ACC participate in a circuit that mediates higher attention functions (MacDonald et al., 2000). Recently it has been suggested that the ACC monitors conflict or errors in response pathways during initial task performance, which initiates the implementation of cognitive control in the DLPFC when selecting between alternative responses is difficult (Milham et al., 2003). This had hinged on observations during Stroop performance that the activity within the ACC decreases as the level of response conflict is reduced with practice and/or when control is strongly engaged in the DLPFC (Erickson et al., 2004). These results are based on a correlational design using brain-imaging techniques. The key findings of our study provide further support for the fact that the DLPFC mediates top-down control by maintaining an 'attentional set', by using an experimental manipulation of brain activity.

However, research combining rTMS with functional brain imaging is necessary for providing evidence of the differential involvement of the ACC and the DLPFC in the circuitry that is responsible for higher attentional control.

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CHAPTER 2

ACUTE EFFECTS OF RTMS OVER THE LEFT DORSOLATERAL PREFRONTAL CORTEX ON TASK SET IMPLEMENTATION[2]

ABSTRACT

The dorsolateral prefrontal cortex (DLPFC; Brodmann area 9/46), part of a prefrontal cortico-subcortical circuit, takes a central role in the activation and implementation of cognitive control. As a non-invasive tool to induce causal interference in the human cerebral cortex, repetitive Transcranial Magnetic Stimulation (rTMS) can be used to investigate the specific role of the DLPFC in this top-down attentional control.

We have used a modified Stroop task with an instruction to read the word or to name the colour before each trial and with two expectancy conditions. In the high expectancy condition, 80 % of all trials were incongruent. In the no expectancy condition, 50 % of all trials were incongruent. The influence of high frequency (HF) rTMS on Stroop task performance of healthy female volunteers was tested using a double blind within subjects design by counterbalanced crossover sham (placebo) and active rTMS over the left DLPFC.

We have found decreased RT's after colour naming for congruent and incongruent trials in both expectancy conditions. Stimulation over the left

[2] Vanderhasselt, M.A., De Raedt, R., Leyman, L., & Baeken, C. (2008). Acute effects of repetitive Transcranial Magnetic Stimulation over the left dorsolateral prefrontal cortex on task set implementation. Unpublished data.

DLPFC had a general influence on preparatory attentional set representations and resulted in task relevant information being continuously kept online.

INTRODUCTION

Cognitive control involves selective attention which plays a critical role in the ability to process task relevant stimuli. This makes it possible to filter out task-unrelated stimuli in order to guide the execution of correct responses (Cohen et al., 1990; Milham et al., 2003). A flourishing research in selective attention subsists in identifying the neural loci of attentional control processes and to reveal the contexts in which these processes are used to enhance selection (Miller et al., 2001).

A number of studies have shown that cognitive control is supported by a cortical network by means of functional specialization involving the dorsolateral prefrontal cortex (DLPFC), the ventrolateral prefrontal cortex (VLPFC), the dorsal cingulate (dACC) and the parietal cortex (PC; Miller & Cohen, 2001; Corbetta & Shulman, 2002; Banich et al., 2000).

In general, it has been proposed that the DLPFC responds to the need for control, created by interference from the outputs of task-irrelevant processing systems, by implementing top-down attentional control (Milham et al., 2003). However, findings remain restricted to correlation evidence based on neuro-imaging research and it has been pointed out that the crucial contributions of the DLPFC concerning strategic decision-making continue to be unclear (Corbetta & Shulman, 2002). Using repetitive Transcranial Magnetic Stimulation (rTMS), it is possible to investigate the precise and causal role of the dorsolateral prefrontal cortex in cognitive control. A typical paradigm to evaluate controlled attention selection is the Stroop task (Stroop, 1935). The logic behind this task is that word reading, which is a highly automatic ability, interferes with colour naming when a colour-word noun, e.g. the word “RED” is printed in green and the task is to name the word’s printed colour. The Stroop effect is characterised by a slower response in naming incongruent words as compared to colour-congruent words.

Previous research of our lab performed High-Frequency (> 1 Hz; HF) rTMS over the left DLPFC using a simple Stroop task in which subjects always responded to the colour of the stimulus. We demonstrated that RT on both

congruent and incongruent trials decreased with a smaller interference effect after rTMS (Vanderhasselt et al., 2006a). This is indicative for the improvement of attentional set implementation.

Moreover, prior research of Vanderhasselt et al. (2007) investigated the role of the right DLPFC within attentional control by a modified Stroop task. We developed a Stroop task with instruction 'colour' or 'word' prior to the stimuli and with two conditions during which subjects formed an expectancy or no expectancy for conflicting trials (80% or 50% incongruent trials respectively). After rTMS over the right DLPFC, decreased RT on congruent and incongruent trials were present only in the high expectancy conditions after the 'colour' instruction. This finding is in accordance with theoretical accounts relating the right DLPFC to attentional control implementation in conditions were conflict is highly expected and consequently conflict is reduced.

However, research evidence regarding the left DLPFC within context related top-down attentional control processes remains relatively unclear. An ongoing debate focuses on the range of the left DLPFC activity in high and low conflicting task contexts.

Therefore, the aim of this study was to investigate the role of the left DLPFC in selective attention by using an identical cued Stroop task as used in previous research over the right DLPFC (Vanderhasselt et al., 2007). A single session of HF- rTMS was applied to investigate the role of the left DLPFC within top-down attentional control. Top-down attentional processes will particularly be activated when strategic processes are engaged (after instruction "colour") and when expectancy for incongruent trials is high (anticipation for the upcoming event is possible in high expectancy blocks) (Carter et al., 1999; MacDonald et al., 2000). For that reason, we put forward that HF-rTMS over the left DLPFC will cause reduced reaction times for both incongruent and congruent trials after the instruction "colour" in "high expectancy" blocks compared to the "no expectancy" blocks. Because we expect an increased attentional set after DLPFC stimulation, we predict a smaller Stroop interference effect between congruent and incongruent trials after the colour instruction in the "high expectancy" conditions. After the "word reading" instruction, we expect no effects since in this condition no attentional control over automatic responses is required and effects in this condition would suggest general speeding effects of rTMS unrelated to the attentional set.

We also assessed mood changes at fixed moments during the procedure because mood can influence executive processes (Bechara et al., 2005).

MATERIALS AND METHODS

This study was part of a larger project investigating the influence of rTMS on neuro-cognitive functioning.

Subjects

Eighteen right-handed healthy female volunteers (mean age= 21.11 years, SD= 1.45 years) were enrolled in the study. The experimental protocol was approved by the Research Ethics Board of the University Brussels (UZ Brussel) and all subjects provided written informed consent after receiving a complete verbal description of the study. All subjects were naive to rTMS and had no personal history of psychiatric, neurological or physical illness as assessed through a thorough screening before inclusion. Prior medical screening also excluded volunteers with contraindications according to the safety guidelines for the rTMS (Wassermann, 1998). The Dutch version of the Beck Depression Inventory (BDI-II; Beck, Steer, & Brown, 1996; van der Does, 2002) was administered to screen for depressive symptomatology (cut-off score of 14). Right Handedness was assessed by the Van Strien Hand Preference Questionnaire (Van Strien, 2001). Subjects received 75 euros for their participation.

Design

A double blind, within subjects design with counterbalanced crossover sham (placebo) and active rTMS over the left DLPFC was used.

Procedure

To detect mood changes, mood was monitored prior to the rTMS session using the self rating Visual Analogue Scales (VAS) (McCormack et al., 1988). These VAS scales consisted of subscales for depression, anger, fatigue, vigour and tension. Mood measurements were performed at three time points (before the first rTMS, immediately after and approximately 45 minutes after each rTMS condition). After the mood assessment, subjects performed the computerized

Stroop task, used in previous research programmed with Presentation software © (Neurobehavioral Systems) and was run on a DELL computer, OptiPlex GX110.

Each subject performed a total of 280 trials. Each trial begun, positioned in the centre of the screen, with a 1500 ms instruction "word" indicating to respond to the meaning of the word, or the instruction "colour" indicating that participants should respond to the colour in which the word was printed. There was the same amount of both instructions randomly spread over all the trials. Subsequent, after a skittered time of delay (500msec - 3000msec), continuous series of coloured words (green, red) were randomly displayed in their congruent colours (e.g. 'green' displayed in green) and their incongruent colour (e.g. 'green' displayed in red). Each stimulus word was presented in coloured script on a black background.

Subjects performed the Stroop tasks under two conditions, namely "high expectancy" and "no expectancy" for incongruent trials. We made use of a blocked design (ABBABAAB), in which "no expectancy blocks" (BLOCK A) were alternated with "high expectancy blocks" (BLOCK B).

In the "no expectancy" block, half of the trials were congruent (the word was written in the same colour) and half were incongruent (the word was written in a different colour) (BLOCK A). In the "high expectancy" block, 80 % of the trials were incongruent (colour incongruence and word incongruence) and 20 % of the trials were congruent (colour congruence and word congruence) (BLOCK B).The maximal presentation time of the trial was 4000 ms but the stimulus disappeared when a response was given. The Inter Trial Interval was randomized between 1000 and 1500 ms.

Participants were presented one practice block (35 trials) followed by a total of eight blocks of each 35 trials. Before the start of the task, participants were instructed to respond as quickly and as accurately as possible. The appropriate colour of the specific response button was counterbalanced across subjects.

After performing the Stroop task, rTMS was applied using Magstim high-speed magnetic stimulator (Magstim Company Limited, Wales, UK) with a focal cooled figure-of-eight coil. All rTMS parameters, similar to parameters in our previous research, included a frequency of 10 Hz and an intensity of 110% of the individual motor threshold of the right abductor pollicis brevis muscle was determined individually using EMG.

In order to accurately target the left DLPFC (left middle frontal gyrus - Brodmann area 9/46), the position of the coil was anatomically determined using MRI non-stereotactic guidance. Perpendicular to this point the precise stimulation site on the skull was marked and stimulated. Subjects received forty trains of 3.9 s duration at 10 Hz, separated by an intertrain interval of 26.1 s (1560 pulses per session).

rTMS and sham protocols were identical apart from the figure 8-shaped coil that was held perpendicularly in the sham protocol preventing stimulation of the cortex. This procedure is in accordance to the sham guidelines of Loo et al. (2000) and safety guidelines of Anand & Hotson (2002).

During the stimulation, participants were instructed to sit at ease in a comfortable chair while wearing earplugs and being blindfolded. In this way, participants could not notice the difference between real and sham procedure.

After rTMS, a psychomotor task and an fMRI study (including a memory paradigm, an exogenuous cueing task and a categorization task for faces) were administered to the participants before the Stroop task was performed for the second time. These tasks are not used for the purposes of the current study. Because these extra tasks were not administered in our previous research, we cannot fully compare these data with previous research or analyse it in one overall analysis. The second Stroop task was administered approximately 50 minutes after stimulation.

There was a delay of 1 week between the two stimulation sessions. The same individuals were stimulated at the same time of the day.

RESULTS

Significance level was set at $p < .05$ for all statistical analyses which were conducted with SPSS 12.0.

Mood effects

Because of some missing values, four participants were left out of the analyses.

To examine possible mood changes, a 2X3 repeated measure ANOVA was performed for each VAS with stimulation (rTMS-SHAM) and time (Tpre –

Tpost – Tpost30) as within factors. Mood scores, evaluated with the VAS scales, were used as dependent variable for every ANOVA.

No significant interaction effects between time and stimulation were found for fatigue, anger, tension, vigour and depression scales F's < 1.39. We can therefore conclude that mood remained unaltered from baseline caused by left prefrontal HF-rTMS compared to ratings immediately after stimulation and after the second Stroop sequence.

Reaction time congruent and incongruent trials

Latencies more than 2.3 standard deviations beyond each participant's mean were removed. Using this criterion, a total of 54 trials (0.7 %) was excluded from the analysis.

Repeated measures ANOVA's including *stimulation* (sham-rTMS), *time* (pre-post), *condition* (A-B) and *trial type* (congruent – incongruent trials) were performed to analyse these data.

The first dependent variable was the mean reaction time after instruction "colour". Table 1 & 2 display the reaction times for congruent and incongruent trials within the 'expectancy' and 'no expectancy' blocks. We found a main effect for trial type [F (1,17)= 67.05, p=.0001] and for condition [F (1,17)= 8.23, p=.011]. The other main effects were not significant F's < 1.05.

The two way interaction between condition and trial type reached significance [F (1,17)=21.07, p=.0001]. The other interactions were not significant F's < 2.83.

Second, the same factorial design was used (2x2x2x2) after instruction 'word' and indicated a main effect for trial type [F (1,17)= 104.38, p=.0001], for condition [F (1,17)= 13.74, p=.002] and a marginal effect for time [F (1,17)= 3.49, p=.079]. Other main or interaction effects were not significant F's < 2.70. Data are presented in table 3&4.

Despite insignificant interaction effects, we further analyzed our data using paired t-tests to verify our a priori research hypotheses.

Most important, rTMS yielded a specific influence on RT's of congruent and incongruent trials after the instruction 'colour', independent of the expectancy condition. As compared to pre stimulation, RT of congruent [t (18)=2.461, p=.024; s] and incongruent [t (18)=2.306, p=.033; s] trials was significantly faster after the colour instruction during the expectancy condition. Surprisingly,

the same pattern was found in the no expectancy blocks for congruent [t (18)=2.718, p=.014; s] and incongruent [t (18)=2.239, p=.038; s] trials.

After instruction 'word', rTMS did not manage to have an effect on RT's in the expectancy blocks, all t's < 1.81. Sham didn't have an effect on reaction times in all conditions t's < 1.709.

In addition to our main hypothesis, we also explored the influence of rTMS on the interference effect. These analyses indicated no changes pre-post stimulation in every condition t's < 0.877. Most important, we obtained significant differences in reaction times between congruent and incongruent trials in every condition t's > 2.502 and p's < .022. To confirm the validation of our conclusions, differences between sham and rTMS before stimulation did not reach significance t's < 1.100.

Stroop error analyses

We analysed the error data using a repeated measures ANOVA's. The basic design was a 2x2x2x2 factorial design with *stimulation* (sham-rTMS), *time* (pre-post), *condition* (A-B) and *trial type* (congruent – incongruent trials) as within-factors. Using the mean Stroop error data, we did not find any main or interaction effects after the colour instruction F's < .953 and not after the word instruction F's < .685.

Table 1

Mean Reaction Time latencies and approximate Standard Deviation following the colour instructions on the Stroop task in a SHAM control condition. Responses are presented in msec.

	Expectancy		No expectancy	
	PRE	POST	PRE	POST
Congruent trials	**636,21** *(171,07)*	**620,27** *(146,89)*	**614,88** *(137,97)*	**647,49** *(136,34)*
Incongruent trials	**653,78** *(165,37)*	**647,49** *(136,34)*	**677,65** *(161,62)*	**620,27** *(146,89)*

Table 2

Mean Reaction Time latencies and approximate Standard Deviation following the colour instructions on the Stroop task after active rTMS stimulation. Responses are presented in msec.

	Expectancy		No expectancy	
	PRE	POST	PRE	POST
Congruent trials	**615.88** *(138.20)*	**566.74** *(124.04)*	**595.41** *(131.97)*	**553.66** *(102.44)*
Incongruent trials	**654.36** *(131.60)*	**614.63** *(137.98)*	**683.46** *(149.25)*	**627.09** *(109.26)*

Table 3

Mean Reaction Time latencies and approximate Standard Deviation following the word instructions on the Stroop task in a SHAM control condition. Responses are presented in msec.

	Expectancy		No expectancy	
	PRE	POST	PRE	POST
Congruent trials	**585.42** *(153.24)*	**566.62** *(142.66)*	**554.95** *(138.13)*	**549.70** *(110.75)*
Incongruent trials	**663.76** *(173.47)*	**646.23** *(157.71)*	**654.60** *(164.56)*	**633.96** *(151.79)*

Table 4

Mean Reaction Time latencies and approximate Standard Deviation following the word instructions on the Stroop task after active rTMS stimulation. Responses are presented in msec.

	Expectancy		No expectancy	
	PRE	POST	PRE	POST
Congruent trials	**578.50** *(124.24)*	**579.40** *(112.76)*	**558.42** *(105.15)*	**542.40** *(95.46)*
Incongruent trials	**658.95** *(119.04)*	**651.91** *(98.04)*	**625.61** *(124.81)*	**606.91** *(126.52)*

DISCUSSION

For investigating cognitive functioning, rTMS can reversibly interfere with the normal activity of a brain area to determine whether this area is essential for task performance (Hausmann et al., 2004). Behavioural changes in attentional control can be observed over a relative short period of time (Vanderhasselt et al., 2006b). Mood remained stable after HF-rTMS over the left DLPFC.

Repeated measures ANOVA's showed no crucial interaction effects that would be indicative of an effect on cognitive functioning. However, when performing specific a-priori t-tests, we found decreased reaction times on congruent and incongruent trials after the instruction 'colour'. We established these results in both expectancy conditions. We found no effects on Stroop error data. This might suggests that rTMS over the left DLPFC had no influence on task context manipulations for the expectancy of conflicting trials.

This result of decreased RT for congruent and incongruent trials for colour naming is in accordance with our previous rTMS research over the left DLPFC (Vanderhasselt et al., 2006). However, the Stroop interference effect did not change after stimulation which is not in line with previous research (MacDonald et al., 2000; Vanderhasselt et al., 2006). However, since reaction times for both congruent and incongruent trials significantly decreased, we can conclude that the general task set representation was improved for both trial types after the instruction colour.

Within neurocognitive research, researchers sometimes suggest that top-down executive control mechanisms further increase attention toward target stimuli when selection is made more demanding by distractor incongruency (e.g. Banich et al., 2000). If the DLPFC would only be related to processes of distractor incongruency, one could question why the RT latencies of Stroop congruent and incongruent trials were decreased in all three rTMS studies. Therefore, extending these theoretical accounts of this brain region, our results suggest that once expectancy for conflict increases (colour naming), the DLPFC enhances an attentional focus resulting in decreased RT latencies in congruent and incongruent trials. In the condition where participants don't prepare themselves for overcoming an automatic response (word reading), RT on congruent and congruent trials was not affected. These results are in accord with MacDonald et al. (2000) although these researchers did not discuss this issue. These researchers

concluded that the nature of context representations (colour or word instruction) seems to play an important role in the left DLPFC related increased attentional set (MacDonald et al., 2000). It seems that the DLPFC is not just activated by distractor incongruency, but more to the expectancy of conflicting information.

This expectancy for conflicting trials was manipulated using a trial by trial instruction but also by manipulating the amount of incongruent trials in separate blocks. In the current research, rTMS over the left DLPFC had a general influence on preparatory attentional set representations and resulted in decreased RT in both expectancy blocks. In contrast, after rTMS over the right DLPFC (Vanderhasselt et al., 2007), reaction time latencies were distinctively decreased after colour naming only in the high expectancy condition. Our data suggest that stimulation over the left DLPFC had a general influence on preparatory attentional set representations, also when task contexts have not triggered extra strategic processes to reduce the conflict.

An important shortcoming in this study is, because of different research procedures, that we are not allowed to compare the results of left and right rTMS studies. In the previous research (Vanderhasselt et al., 2007), strategic processes were investigated immediately after rTMS over the right DLPFC. In the current study, cognitive functioning was analyzed one hour after stimulation over the left DLPFC since this study was part of a larger study. Before the performance of the current Stroop task, participant's primary responded to a series of other cognitive tasks, which might have influenced the results. Therefore, no firm conclusions can be drawn concerning the lateralization effects in strategic processes associated to activity in the DLPFC.

Moreover, no interactions of TMS/sham and other factors in are omnibus test were found which could indicate that TMS had no reliable effect. We have to be cautious interpreting the post hoc analyses in the absence of an overall significant interaction effect.

Therefore, a replication and future controlled research combining rTMS with functional brain imaging is essential to further investigate the structural and functional activation within the left and right DLPFC in the circuitry that is responsible for higher attentional control.

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CHAPTER 3

THE INFLUENCE OF RTMS OVER THE RIGHT DORSOLATERAL PREFRONTAL CORTEX ON TOP-DOWN ATTENTIONAL PROCESSES[3]

ABSTRACT

Repetitive Transcranial Magnetic Stimulation (rTMS) provides a unique opportunity to study causal relationships between activity in the dorsolateral prefrontal cortex (DLPFC) and executive functioning, by modulating brain activity in SHAM controlled designs. We devised a new Stroop task paradigm in which subjects must engage in both strategic and automatic attentional processes. In the current experiment, we manipulated subjects' expectancies for incongruent stimuli. Previous research demonstrated that when subjects have a high level of expectancy that a stimulus will be incongruent, they are able to strategically adjust the relative influence of word reading on colour naming.

The effect of high frequency (HF) rTMS on Stroop performance of twenty right-handed healthy female volunteers was tested using a double blind within subjects design by counterbalanced crossover sham (placebo) and active rTMS over the right DLPFC.

[3] Based on: Vanderhasselt, M A., De Raedt, R., Baeken, C., Leyman, L., Clerinx, P., & D'Haenen, H. (2007). The influence of rTMS over the right dorsolateral prefrontal cortex on top-down attentional processes. *Brain Research, 1137(1),* 111-116.

Since mood remained unchanged after rTMS, the Stroop data could be evaluated independent of mood changes. Only in the high expectancy condition, we found a decreased response time to both congruent and incongruent trials on the Stroop task performance after HF rTMS. The SHAM placebo condition yielded no effects.

We conclude that high frequency stimulation over the right DLPFC has an effect on top-down attentional processes by modulating the attentional set.

INTRODUCTION

Repetitive Transcranial Magnetic Stimulation (rTMS) has been used as a non-invasive tool for stimulating the human cerebral cortex and, as a result, becomes a heuristic technique of neuronal depolarizing and altering underlying cortical physiology. This technique is capable of transiently disrupting local processing in neural networks in the brain. High-frequency rTMS (above 1 Hz) evokes increased excitability of the stimulated cortical region, an activation pattern that lasts for hours after stimulation (Muller et al., 2000; Wasserman & Lisanby, 2001; Pascual-Leone et al., 1994). rTMS provides a unique opportunity to study causal relationships between focal brain function and behaviour. It can provide more insight into the workings of the neural circuits involved in executive functioning, by modulating brain activity in SHAM controlled designs (Moser et al., 2002).

A well-studied behavioural paradigm of controlled attention selection is the Stroop task (Stroop, 1935). The principle is that word reading- a highly automatic ability- interferes with colour naming when a colour-word noun, e.g. the word “RED” is printed in green and the task is to name the word’s printed colour. The Stroop interference is characterised by a slower response in naming these incongruent words as compared to colour-congruent words.

Studies using functional neuroimaging techniques have linked Stroop task performance to activity in the dorsolateral prefrontal cortex (DLPFC) (Hadland et al., 2001).

Neuropsychological and neuroimaging studies revealed that the DLPFC implements top-down attentional control (Milham et al., 2003). Specific lateralized involvement of the DLPFC in cognitive control is becoming a latest source of debate. Although top-down attentional processes are commonly

associated to the left DLPFC (MacDonald et al., 2000), recent research revealed an essential role of the right DLPFC in task preparation (Vanderhasselt et al., 2006b, Brass and von Cramon, 2004; Dreher et al., 2002; Sohn et al., 2000) and conflict predicting in cued switching tasks (Liston et al., 2006).

We are aware of only one study to date in which the standard colour word Stroop performance has been compared before and after HF-rTMS over the DLPFC, while mood was kept under control (Vanderhasselt et al., 2006). The latter might be essential since mood has an important influence on executive functioning (Bechara et al., 2005). Results demonstrated the involvement of the left DLPFC in implementing top-down attentional set. To our knowledge, analogous research regarding rTMS over the right DLPFC has not yet been reported.

The aim of the present study is to investigate the role of the right DLPFC in imposing top-down attentional set. We constructed a novel behavioural Stroop paradigm, based on former research (Carter et al., 1999; MacDonald et al., 2000), to unambiguously activate top-down attentional processes, which have been associated to activity in the DLPFC (Milham et al., 2003).

In our new paradigm, before the onset of each trial, subjects must keep in mind, or actively maintain, the instruction. This task cue can have two different dimensions, namely the instruction to read the word (automatic process) and the instruction to name the colour of the word (strategic process) (MacDonald et al., 2000). In addition, subjects perform the Stroop task under the conditions "high expectancy" and "no expectancy" for incongruent stimuli by blocked manipulation of the frequency of incongruent trials (Carter et al., 1999). Top-down attentional processes will particularly be activated when strategic processes are engaged (after instruction "colour") *and* when expectancy for incongruent trials is high (anticipation for the upcoming event is possible in high expectancy blocks). These processes, associated to the DLPFC (Carter et al., 1999), facilitate a high degree of top-down control whereby the tendency to read the word should be overcome and conflict associated with responding to incongruent stimuli should be reduced. Therefore, we hypothesize that HF-rTMS over the right DLPFC will cause faster reaction time to incongruent trials after the instruction "colour" in "high expectancy" blocks compared to the "no expectancy" blocks. More specific, if HF-rTMS over the right DLPFC improves the attentional set, the strategic processes that are particularly involved in the

abovementioned condition will be facilitated and reaction time on incongruent trials will decrease (with a decreased Stroop interference effect). After the "word reading" instruction, we expect no effects since in this condition no attentional control over automatic responses is required. Effects in this condition would suggest general speeding effects of rTMS unrelated to the attentional set.

To our knowledge, attentional orientating combined with HF rTMS over the right DLPFC to investigate the influence on top-down attentional control, has not yet been performed. Comparable rTMS research where the influence of mood was taken under control is currently very scarce. In one former similar study, (Vanderhasselt et al., 2006) a regular Stroop paradigm was used after left DLPFC stimulation. However, a shortcoming of the regular Stroop task is that there is ambiguity regarding response selection because the stimuli indicate both the task and the response.

The Stroop task we used in the present study is more specific and unambiguously referring to strategic processes since an instruction and an expectancy condition were used. Given these variations between both Stroop paradigms, attentional outcomes of HF-rTMS over the right DLPFC and left DLPFC cannot be completely compared. To additionally control for shortcomings in earlier rTMS research, we used a sham-controlled condition, a long time interval between stimulation sessions, a large homogenous sample, stimulation of one single region per session in order to exclude interaction effects with the previous stimulation, structural magnetic resonance imaging (MRI) to determine the exact target of stimulation, and a large number of pulses at high stimulation intensity (Baeken et al., 2006). Since some gender differences in attentional processing have been demonstrated (e.g. Roalf et al., 2006) and for reasons of homogeneity, we only included female volunteers to investigate the role of the right DLPC in top-down attentional processing.

MATERIALS AND METHODS

Subjects

Twenty right-handed female normal volunteers (mean age: 24; age range: 18-25, standard deviation: 2.6) gave written informed consent prior to participation, after the nature of the procedure had been fully explained. The study was

approved by the local ethics committee of the Academic Hospital of the Free University Brussels (A.Z.-V.U.B.). None of the subjects had any neurological, psychiatric or medical history. Nor did they have any contraindications for rTMS (Wassermann, 1998), as assessed through a thorough screening before inclusion.

They all underwent a physical examination, EEG and the Mini-International Neuropsychiatric Interview (M.I.N.I.) (Sheehan et al., 1998). Handedness was assessed with the hand preference scale of Van Strien (Van Strien, 2001).

Design

A double blind, within subjects design with counterbalanced crossover sham (placebo) and active rTMS was used.

Procedure

On the day of stimulation, the investigation started with a baseline mood measurement using visual analogue mood scales (VAS). These VAS scales consisted of subscales for depression, anger, fatigue, vigour and tension. The participants were asked to describe how they felt "at that moment" by indicating on horizontal 10 centimetre lines whether they experienced the five abovementioned mood states, from "totally not" to "very much".

Subsequently a computerised Stroop task was performed. The experiment was programmed with Presentation software © (Neurobehavioral Systems) and was run on a DELL computer, OptiPlex GX110. For each subject, 280 trials were presented. Each trial begun with a 1500 ms instruction "word" indicating to respond to the meaning of the word, or the instruction "colour" indicating that participants should respond to the colour in which the word was printed. There was the same amount of both instructions and all colour combinations to all the trials. After a skittered time of delay (500msec - 3000msec), a continuous series of coloured words (green and red) were randomly displayed for 1500 ms, in their congruent colours (e.g. "green" displayed in green) and their incongruent colour (e.g. "green" displayed in red).

Subjects performed the Stroop tasks under two conditions, namely "high expectancy" and "no expectancy" for incongruent trials. We made use of a blocked design (ABBABAAB), in which "no expectancy blocks" (BLOCK A) were alternated with "high expectancy blocks" (BLOCK B).

In the “no expectancy” block, half of the trials were congruent (the word was written in the same colour) and half were incongruent (the word was written in a different colour) (BLOCK A). In the “high expectancy” block, 80 % of the trials were incongruent (colour incongruence and word incongruence) and 20 % of the trials were congruent (colour congruence and word congruence) (BLOCK B).

Participants were presented one practice block followed by a total of four blocks A and four blocks B. There were 35 trials in each combination of instruction and congruency. The order of stimulus type was counterbalanced across subjects, and the order of delay within stimulus type was randomized.

Subjects were instructed to respond as quickly and as accurately as possible using the “F” and “J” keys on an AZERTY keyboard. After the Stroop task, High Frequency (HF) rTMS was performed over the right DLPFC.

All stimulations were performed using a MAGSTIM –highspeed stimulator (Magstim Company Limited, Wales, UK) with a figure-8-shaped coil. Motor threshold (MT) was determined individually before real and sham stimulation. Stimulation intensity was 110% of MT of the right abductor pollicis brevis muscle, stimulation frequency was 10 HZ (HF-rTMS) and intertrain interval was 26.1 s. Forty trains were applied in ca 20 minutes (1560 pulses per session). The right DLPFC (Brodmann area 9**)** stimulation site was determined under MRI non-stereo tactic guidance. Real and sham stimulation were performed at the same place on the skull, but for sham stimulation the figure-8-shaped coil was held at an angle of 90° only resting on the scalp with one edge. After stimulation (post1), participants again completed the mood scale, followed by the Stroop paradigm. After completing the Stroop task, mood was assessed for the last time (post2). All subjects were stimulated between 9am and 12pm. There was a delay of 1 week between the two stimulation sessions.

The same individuals were stimulated at the same moment of the day.

RESULTS

Mood effects

Changes of mood were analysed using repeated measures ANOVA for each VAS scale with stimulation (rTMS-SHAM) and time (pre - post1 - post2) as within-factors and mood scores evaluated with the VAS as dependent variable.

The significance level was set at $p < .05$. No significant interaction effects between time and stimulation were found. Therefore, we conclude that there were no mood changes caused by right prefrontal HF-rTMS between baseline and immediately after stimulation and after the second Stroop task.

Reaction time congruent and incongruent trials

Statistical analysis was performed using repeated measures ANOVA's. Latencies more than 2.3 standard deviations beyond each participant's mean were removed. Using this criterion, a total of 43 trials (0,7%) was excluded from the analysis, no more than three per participant. The significance level was set at $p < .05$. The basic design was a 2x2x2x2x2 factorial design with stimulation condition (rTMS-SHAM), time (pre-post), expectancy (high expectancy-no expectancy) and type of trial (congruent-incongruent) as within-factors and the order of stimulation as between factor.

At first, the dependent variable was the mean reaction time (RT) after the instruction "colour" (the condition where control over automatic response is required). Since order of stimulation yielded no main effect and was not implied in any interaction, this variable was left out for the subsequent analyses.

We found a main effect of "rTMS/SHAM" [F (1,19) = 12,652; p = .002; s], "high expectancy/no expectancy" [F (1,19) = 6.070; p = .023; s] and "pre/post" [F (1,19) = 8,206; p= .010; s], but no main effect for "congruent/incongruent" [F (1,19) = ,749; p = .398; *ns*].

As expected, the interaction between "stimulation" and "expectancy" [F (1,19) = 15,021; p =.001; s] and "stimulation" and "pre/post" [F (1,19) = 13,944; p = .001; s] reached statistical significance. In addition, results revealed a trend significant two way interaction effect between "stimulation" and "type of trial" [F (1,19) = 3,521; p = .076; *ns*], but not a significant two-way interaction between "expectancy" and "type of trial" [F (1,19) = 2,720; p = .116; *ns*].

The three way interaction between "stimulation", "expectancy" and "type of trial" [F (1,19) = 27,867; p = .0001; s] showed a significant effect. No further two or three way interactions, neither the four way interaction reached statistical significance [$F's < 1$].

We further verified our a priori hypotheses using contrast analyses. After active stimulation, the reaction time in "high expectancy" blocks according to the instruction "colour" of both congruent [t (20)=2.246, p = .037; s] (see fig. 1)

and incongruent trials [t (20)=2.101, *p* = .049; s] (see fig. 2) was significantly faster as compared to before stimulation. In "no expectancy" blocks, behavioural changes after active stimulation did not reach statistical significance [*p's* >.05]. In addition, the reaction time to both congruent and incongruent trials in SHAM control conditions did not change in "high expectancy" nor in "no expectancy blocks" [*p'*s > .05].

For a summary of the results, we refer to table 1 and 2.

In addition to our main hypothesis, we also analysed the interference effect using a 2x2x2 factorial design with "stimulation" (rTMS-SHAM), "expectancy" (high expectancy-no expectancy) and delay (pre-post) as within factors. The dependent variable was the Stroop interference effect (RT on congruent trials minus RT on incongruent trials). We found a trend significant main effect "rTMS/SHAM" [F (1,19) = 3,521; p = .076; ns]. The interaction effect between "rTMS/SHAM" and "expectancy" was significant [F (1,19) = 27,867; p = .0001;s]. No other main or interaction effects reached statistical significance [F's < 1]. However, when using paired t tests, we have found no effects of rTMS on Stroop interference in the high expectancy condition (Mpre= -157; Mpost= -135) [t (20)=0,306 p=.763] and in the no expectancy condition (Mpre= 99;Mpost= 124) [t (20)=0,354 p=.727]. No effects in the sham condition were found t's < 1.10.

Second, the same factorial design (2x2x2x2x2) was performed, with the mean reaction time after the instruction "word" as dependent variable. No main or interaction effects reached statistical significance [*F's* < 1]. For a summary of the results, we refer to table 3 and 4.

Stroop error analyses

We analysed the error data using a repeated measures ANOVA's. The basic design was a 2x2x2x2 factorial design with *stimulation* (sham-rTMS), *time* (pre-post), *condition* (A-B) and *trial type* (congruent – incongruent trials) as within-factors. Using the mean Stroop error data, we did not find any main or interaction effects after the colour instruction [F's < .549], and not after the word instruction [F's < .447].

Table 1

Mean Reaction Time latencies and approximate Standard Deviation following the colour instructions on the Stroop task in a SHAM control condition. Responses are presented in msec.

	Expectancy		No expectancy	
	PRE	POST	PRE	POST
Congruent trials	**602** (*151*)	**590** (*142*)	**556** (*132*)	**541** (*141*)
Incongruent trials	**580** (*192*)	**577** (*140*)	**642** (*151*)	**689** (*152*)

Table 2

Mean Reaction Time latencies and approximate Standard Deviation following the colour instructions on the Stroop task after active rTMS stimulation. Responses are presented in msec.

	Expectancy		No expectancy	
	PRE	POST	PRE	POST
Congruent trials	**732** (*164*)	**594** (*182*)	**716** (*155*)	**615** (*163*)
Incongruent trials	**575** (*200*)	**455** (*163*)	**815** (*172*)	**739** (*162*)

Table 3

Mean Reaction Time latencies and approximate Standard Deviation following the word instructions on the Stroop task in a SHAM control condition. Responses are presented in msec.

	Expectancy		No expectancy	
	PRE	POST	PRE	POST
Congruent trials	**552** (*66*)	**537** (*76*)	**553** (*61*)	**595** (*68*)
Incongruent trials	**589** (*84*)	**572** (*66*)	**548** (*64*)	**576** (*74*)

Table 4

Mean Reaction Time latencies and approximate Standard Deviation following the word instructions on the Stroop task after active rTMS stimulation. Responses are presented in msec.

	Expectancy		No expectancy	
	PRE	POST	PRE	POST
Congruent trials	**590** (*65*)	**584** (*72*)	**561** (*73*)	**588** (*69*)
Incongruent trials	**571** (*78*)	**576** (*71*)	**547** (*85*)	**552** (*56)*

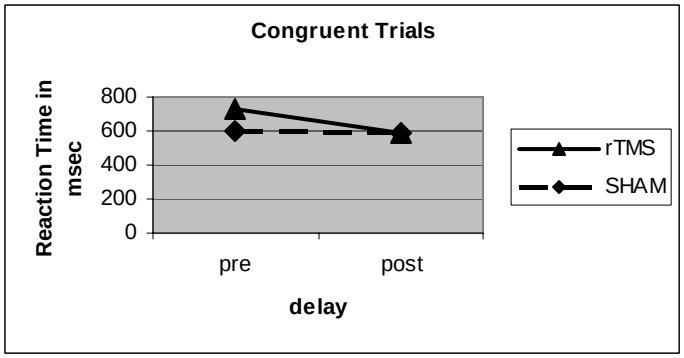

Figure 2. Mean reaction times of the congruent trials during the high expectancy blocks in the rTMS and the Sham control condition.

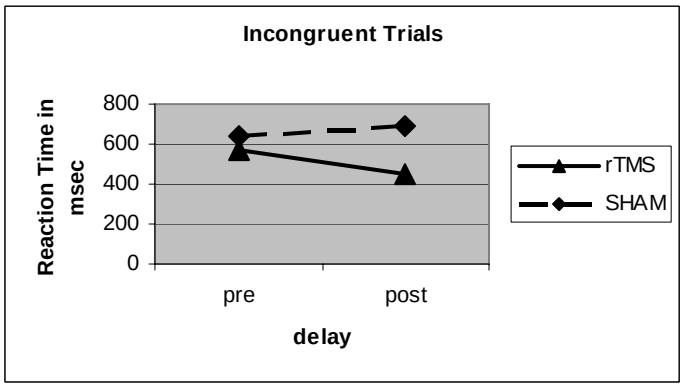

Figure 3. Mean reaction times of the incongruent trials during the high expectancy blocks in the rTMS and the Sham control condition.

DISCUSSION

This study examined the effects of HF-rTMS over the right DLPFC on top-down attentional control. Since stimulation had no effect on mood, the results of the Stroop task can be evaluated independent of mood changes. The order of stimulation condition implied no effect.

According to the instruction "colour", we found behavioural changes on Stroop task performance after HF-rTMS over the right DLPFC while no changes emerged after the SHAM placebo stimulation. More specific, in the "high expectancy" blocks the reaction time to *both* congruent and incongruent trials decreased significantly after HF-rTMS. In "no expectancy" blocks, this remarkable result was not found. As expected, according to the instruction "word", no behavioural changes on Stroop task performance were found so that general speeding effects could be excluded. Both instructions yielded no effects on the error data indicating no speed-accuracy tradeoff.. These results are in line with the assumption that strategic processes are only activated after the instruction "colour", when automatic reading needs to be overcome.

Our findings are indicative for the fact that subjects were forming expectancies for incongruent stimuli and engaged strategic top-down attentional processes that were increased after rTMS to reduce the conflict elicited by incongruent trials (Carter et al., 1999). Although we have found a significant interaction between stimulation and time, we should mention that the Stroop interference effect did not change significantly after rTMS (nor after SHAM) which does not follow the logic of an increased attentional set. However, we observed a decreased reaction time to congruent trials in "high expectancy" blocks compared to no variation in reaction time to congruent trials in "no expectancy" blocks. This is consistent with an improved attentional set in general and, as a result, the implementation of strategic processes during the "high expectancy blocks". Although the absence of a regular (or even reversed) incongruency effect in the high expectancy condition before stimulation is inconsistent with former research (e.g. Carter et al., 1999), it demonstrates that the 80/20 ratio in favour of incongruent trials used in our experiment unambiguously activated top-down attentional processes that we intended to increase after rTMS of the DLPFC.

Consideration needs to be given to the absence of a Stroop effect (Incongruent-Congruent reaction times) in the high expectancy condition during the pre-measurement, since faster reaction times only emerged on incongruent trials compared to congruent trials in the rTMS condition [t (19) = 2,981; p=.008; *s*] but not in the Sham reaction times condition [t (19) = 0,427; p=.674; *ns*]. This might challenge the conclusion of an expectancy based improved attentional set associated to rTMS over the DLPFC. However, since the order of rTMS and SHAM was counterbalanced and, in addition, the same persons were used over the two conditions as their own controls, it is appropriate to compare rTMS versus SHAM based on the individual difference scores between pre and post, which results in a significant difference. For this reason, we can conclude that rTMS had a significant influence on the response times in contrast to the SHAM control condition.

Interestingly, these results during the "high expectancy block" are similar to the results reported in a study using a standard Stroop after rTMS over the left DLPFC (Vanderhasselt et al., 2006). Therefore, consideration needs to be given to the lateralisation of brain areas to ensure the allocation of attentional resources to overcome the conflict occurring at different levels of processing. Van Veen (2005) suggested separate prefrontal cortex areas for resolving conflict at stimulus and response level. Milham et al. (2001) proposed that hemispheric differences in attentional control depend upon the level of processing at which the conflict occurs (e.g., response, stimulus). Based on a Stroop study under functional Magnetic Resonance Imaging (fMRI), they found that the involvement of the right prefrontal cortex in attentional control is primarily limited to situations of response conflict, while the involvement of the left prefrontal cortex extends to the occurrence of conflict at stimulus levels. Nevertheless, these results are a continuous source of debate (Van Veen et al., 2005). Liu and colleagues (2004) found that the Stroop interference effect typically arises from stimulus–stimulus conflict between the task-relevant and task-irrelevant dimensions and prior studies have shown that the degree of conflict experienced at the level of response decreases with expectancy because of the fact that the degree of attentional control increases (Carter et al., 1999). Based on decreased reaction time to both congruent and incongruent trials in "high expectancy" blocks, our results thus suggest that improved preparatory attentional processes at stimulus level were engaged to enhance the attentional

set in general. In this way, the right DLPFC seems to be involved in attentional processes at stimulus level.

Thus, previous research (Liu et al., 2004; Luks et al., 2002) and on our results of an improved attentional set in general after experimental manipulation through HF-rTMS over the right DLPFC are not in line with the correlational fMRI results of Milham et al. (2001) who linked the right DLPFC to attentional processes at response level. Based on these findings and on literature concerning attentional mechanisms (Liu et al., 2004), we conclude that stimulation over the right DLPFC has an effect on top-down attentional control when conflict is occurring at stimulus level. The key finding of an improved attentional set in general in the "high expectancy block" after HF-rTMS over the right DLPFC is similar to results of Vanderhasselt and co-workers (2006) where rTMS was performed over the left DLPFC. Based on the abovementioned studies (Vanderhasselt et al., 2006; Luks et al., 2002)**,** the left DLPFC and the right DLPFC seem to have a similar attentional mechanism concerning their predominant role in imposing an attentional set. In the abovementioned experiment (Vanderhasselt et al., 2006) the expectancy for incongruent trials was not manipulated. Consequently, subjects could not compare between variations of difficulty over separated blocks. The attentional set was improved in general, without further specifications. In the current experiment, behavioural changes in attentional control could only be observed in "high expectancy blocks" and not in "no expectancy blocks". This suggests that the DLPFC manipulates the attentional control relative to context related information. Braver et al. (1999) conceptualized context processing as voluntary behaviour by providing top-down activation when an automatic response must be controlled. Rahm et al. (2006) proposed, based on their MRI research, that context-appropriate evaluation is subserved by mid-dorsolateral PFC and may represent a later processing stage than target detection in response conflict. Our results suggest that once expectancy for incongruent trials increases, the right DLPFC enhances a permanent attentional focus compared to the condition where participants don't prepare themselves for overcoming an automatic response. The reverse Stroop effect, only found in the high expectancy conditions, additionally supports this assertion. This is in line with previous research where a positive correlation between the right DLPFC and increased context predictability was displayed (Bischoff-Grethe et al., 2001). However, given that only female volunteers were

included in our sample, these results are in need of replication in male population.

Research combining rTMS with functional brain imaging is necessary for providing further evidence for the specific involvement of left and right DLPFC in the circuitry that is responsible for higher attentional control.

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CHAPTER 4

COGNITIVE CONTROL AND THE DORSOLATERAL PREFRONTAL CORTEX: AN EXPERIMENTAL RTMS APPROACH[4]

ABSTRACT

The specific functional role of the Dorsolateral Prefrontal Cortex (DLPFC) is still under debate since tasks that are used in neuroimaging research are very heterogeneous. High Frequency repetitive Transcranial Magnetic Stimulation (HF-rTMS) has an excitatory effect on underlying neurons and can therefore be applied to determine whether a specific brain area is involved in task performance.

We investigated the influence of HF-rTMS over the left DLPFC on top-down attentional control using a switch task. Latencies on visual switch trials with an instruction prior to the task to activate general preparedness were used as an index of attentional task set representation. Auditory switch trials were used as distracters.

This study was conducted according to a double-blind, within-subjects design by counterbalanced crossover sham (placebo) and active rTMS.

Since mood was not influenced by stimulation, endogenous control mechanisms could be evaluated independent of mood changes.

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After HF-rTMS over the left DLPFC, attentional set reconfiguration for visual trials increased significantly. It appears that DLPFC activity can be related to an anticipatory component of attention, resulting in a regulatory strategy that can be employed whenever the task demands are known.

INTRODUCTION

Neuroimaging and neuropsychological data have drawn attention to the functional activation of the dorsolateral prefrontal cortex (DLPFC) as a key neural substrate of cognitive control, which has frequently been associated with Task Switching (Sohn et al., 2000; Loose et al., 2006). Based on recent research, it has been suggested that the DLPFC plays a role in the implementation of top-down attentional control for task maintenance (Milham et al., 2003; Johnston et al., 2007).

Notwithstanding interesting results of previous studies, the tasks used to investigate top-down strategic processes associated with the DLPFC are very heterogeneous, which can lead to misattributed activation variance in this region (Erickson et al., 2005). For example, some authors have postulated that Task Switching by itself requires the allocation of endogenous attentional control for the coordination and management of multiple tasks (Erickson et al., 2005). However, within Task Switching, attentional task preparation and task execution engage dissociated cognitive acts and neuropsychological components in cognitive control (Kieffaber et al., 2006). Neuroimaging research based on Task Switching paradigms revealed an important distinction between tasks that measure the switches of “intentional set” (reconfiguration of task appropriate stimulus response mappings) versus “attentional set” (a general perceptual preparation responsible for the discriminative selection of task-relevant information) (Rushworth et al., 2002). It has, however, proved complex to interpret the functional role of separate cortical brain activations when using functional magnetic resonance imaging studies (fMRI) given it’s impossibility to infer causality (Rushworth et al., 2003).

We therefore used High Frequency repetitive Transcranial Magnetic Stimulation (HF-rTMS) to influence - reversibly and transiently - the normal activity of the DLPFC. This technique temporarily stimulates local brain activity

and can be applied to determine whether a specific brain area is related to task performance (Rushworth et al., 2003).

The goal of our experiment was to elucidate the role of left dorsolateral frontal activation in cognitive control through the measurement of task performance on a Task Switching paradigm after rTMS versus placebo sham stimulation.

Active switching of attention reflects the highest executive control of attentional processes. It relies on the inhibition of a certain response and the initiation of another. Processes that are essential to execute the first task need to be neglected, and those that are essential for the second need to be established (McDowd & Shaw, 2000). Much of the research into this switching process has focused on tasks requiring the same input (usually visual, but with a different solution strategy) and the same output (for example, either a manual or a vocal response) (Banish et al., 2000; Nakahara et al., 2002). However, switching attention between different alternating visual stimuli does not require a switch between resources, whereas switching between visual and auditory impulses combined respectively with a manual and a foot response does require a switch between different input and output modalities (De Raedt & Ponjaert-Kristofferson, 2000). It may be important to use a task that relies on different and non-interfering input and output modalities, since there are performance limits when tasks contain the same modalities (Anderson, 1995).

We used a modified Task Switching paradigm with two different incompatible input and output modalities and three subsequent conditions. During the experiment, subjects are first pretrained on two simple tasks (blocks 1 & 2) afforded by a set of repetitive auditory and repetitive visual stimuli respectively. In the third block (Task Switching between visual and auditory trials), subjects mostly alternated between the two pretrained tasks (task switch between the auditory and the visual task) or repeated the same task (task repetition). Most importantly, in this third block participants were instructed to pay constant attention to the visual stimuli, whereas they were informed by a cue, just before stimulus onset, when a distracting auditory stimulus would appear. Participants were thus continuously prepared in advance for the visual stimuli, and this implies prospective and active attentional reconfiguration during the entire task, which refers to “attentional set” (Rushworth et al., 2005).

For visual trials, a component of endogenous information processing and a component of psychomotor speed were distinguished (Roberts & Pallier, 2001).

Previous neuroimaging studies have shown the engagement of the left DLPFC during top-down attentional control and maintaining task-relevant representation (Fassbender et al., 2006; Liston et al., 2006). We therefore hypothesized that visual switch trials will benefit from HF-rTMS over the left DLPFC due to endogenous task-set reconfiguration and a general task preparation. Specifically, we hypothesized a decreased reaction time in the component of endogenous information processing, but not in the psychomotor speed component for visual trials. Since our cued auditory trials do not refer to attentional set representation, but are associated more with intentional set reconfiguration (Vanderhasselt et al., 2006a) and serve in this experiment as distracters, we did not expect an influence on these trials.

To control for the shortcomings mentioned in other rTMS research, we used a sham-controlled condition, a large time interval between the sham and rTMS sessions, stimulation of one single region per session (in order to exclude interaction with the previous stimulation), individual brain imaging (to determine the exact target of stimulation) and a large number of high-stimulation intensity pulses and a large uniform sample (Baeken et al., 2006). We are aware that executive functioning is influenced by mood (Damasio, 1996), and we will therefore also assess whether any possible mood changes caused by HF-rTMS over the left DLPFC might moderate the effects.

Since gender differences in attentional processing have been demonstrated (e.g. Roalf et al., 2006), for reasons of group homogeneity we included only female volunteers.

METHOD

Participants

A total of 20 right-handed female volunteers were recruited ranging in age from 21 to 43 (M= 27.7; SD= 2.67). The study was approved by the local institutional ethics committee of the University Hospital Brussels (U.Z. Brussel), and written informed consent was obtained from all the participants. None of the subjects reported a neurological, psychiatric or medical history. Prior medical

screening excluded volunteers with contraindications according to the safety guidelines for the rTMS (Wassermann, 1998). All the participants underwent a physical examination, an EEG and a Mini-International Neuropsychiatric Interview (M.I.N.I.) (Sheehan et al., 1998). Handedness was assessed with the hand preference scale of Van Strien (Van Strien, 2001).

Design

This study was conducted according to a double-blind within-subjects design by counterbalanced crossover sham (placebo) and active rTMS.

Procedure

Mood was recorded at various stages of the experiment. Participants were asked to indicate their current mood state on Visual Analogue Scales (VAS). The VAS consisted of subscales for "depression", "anger", "fatigue", "vigor" and "tension". The participants were asked to describe how they felt "at that moment" by indicating on 10-centimeter horizontal lines whether they experienced the five abovementioned mood states, from "not at all" to "very much". During the experiment, three mood measurements were obtained: baselines (pre), immediately after rTMS (post 1), and after Task Switching performance (approximately 30 minutes after stimulation, post 2).

After the first mood measurement, the experiment began with a computerized self-paced switching task. The Task Switching control panel consisted of a slightly inclined board (connected to a personal computer) with a central pushbutton around which eight pushbuttons were positioned in a semicircle. Each pushbutton had a diameter of two centimeters, so that each light could be clearly seen when the participant's finger was on the pushbutton. In addition, a loudspeaker and a pedal were attached to the control panel. Subjects were instructed to respond as quickly and as accurately as possible.

This paradigm contains three blocks, two blocks of repetition trials and one block of switch trials. The first two blocks consist of repetitive tasks: one block with 28 visual stimuli and one block with 28 auditory stimuli. The two motor responses involved different modalities and therefore non-overlapping neural systems. During the first block, participants were told that when they saw a lit push-button, they had to remove their finger from the central pushbutton and put out the light. At each visual trial, one out of four of the eight pushbuttons could

light up at random. For visual trials, two components of the reaction time were recorded (Roberts & Pallier, 2001). Decision time (DT), a central (cognitive) component, reflects the time required to initiate a response and corresponds to the time that elapses between stimulus onset and the release of the central pushbutton. For attentional set, this cognitive component is most relevant, since it measures top-down strategic task preparation processes in the most straightforward way. Movement time (MT), a peripheral executive component, represents the motor activity or the time required to complete the response (Gorus et al., 2007).

In the second block, participants were instructed to press a pedal with their foot when they heard a buzzer. Participants were instructed to let their foot hover over the pedal during the entire experiment.

The third and last block, a double task condition, was an alternating switch trial block with 29 auditory and 28 visual stimuli in which 24 out of the 29 auditory signals and 25 out of the 28 visual signals were switch trials. Subjects did not know in advance whether the stimulus would be a light or a sound but were very explicitly instructed to focus their attention on the visual stimuli and to switch attention when the auditory stimuli appeared. Because we wanted an index for a general task representation and top-down attentional control, a cue did not precede the visual trials. Just before each auditory trial, the central pushbutton (cue) was lit for 150 msec.

As a manipulation check, we asked all the participants afterwards if they had noticed the cue that indicated the upcoming auditory stimulus. All the participants clearly did. It is important to state that the (visual) task in the repetition trial blocks did not differ from the (visual) task in the double task condition, because the central light used as a cue for the auditory trials was clearly separate from the target lights positioned in a semicircle.

After each response on a visual trial, subjects were asked to return their finger to the central pushbutton as quickly as possible, which triggered Stimulus Onset Asynchrony (SOA) for the next trial. After each auditory signal, they had to remove their foot from the pedal to trigger SOA for the next trial. SOA differed randomly between 3000 msec and 6000 msec. The same sequence was used for all the participants. If errors occurred, the stimulus was replaced by a new stimulus to obtain the same amount of correctly performed reactions for each participant.

Subsequently, after Task Switching performance HF-rTMS over the left DLPFC was performed using a MAGSTIM high-speed stimulator (supplied by Magstim Company Ltd., Wales, UK) with a figure-8-shaped coil. The motor threshold was determined individually using EMG before real and sham stimulation according to the procedure of Wassermann et al. (1998). Stimulation intensity was 110% of motor threshold of the right abductor pollicis brevis muscle, stimulation frequency was 10 HZ (HF-rTMS) and forty trains of 3.9 s duration were applied for approximately 20 min. The left DLPFC (Brodmann area 9) stimulation site was defined under magnetic resonance (MRI) non-stereotactic guidance.

Real and sham stimulation were performed at the same place on the skull, but for sham stimulation the figure-8-shaped coil was held at an angle of 90° only resting on the scalp with one edge according to the sham guidelines (Anand & Hotson, 2002). During stimulation, all the subjects wore earplugs and were blindfolded to ensure that subjects would not notice the difference between the placebo sham and the real rTMS procedure.

After the stimulation, the Task Switching paradigm (3 blocks) was presented a second time, approximately 10 minutes after stimulation.

There was a delay of 1 week between the two stimulation sessions. The same individuals were stimulated at the same time of the day. Debriefing after the experiment revealed that all the subjects believed they had received real rTMS on all occasions.

RESULTS

Mood effects

Changes of mood were analyzed using a 2X3 within-subject ANOVA with stimulation (rTMS-Sham) and time (pre - post 1 - post 2) as within-factor and mood scores, evaluated with the VAS scores as dependent variables. Because of some missing values during testing, data of only 19 participants were analyzed. For the subscales “anger”, “depression” and “vigor” we found no main effects on stimulation or time. We found a main effect on the subscale “fatigue” for stimulation [$F(1,18) = 5.706$, $p = .028$; s] and on the subscale “tension” for time [$F(2,18) = 3.694$, $p = .047$; s]. However, no significant interaction effects were

found between time and stimulation (*p's* < .05). We can therefore conclude that mood remained unaltered from baseline caused by left prefrontal HF-rTMS compared to ratings immediately after stimulation and after the second Task Switching sequence.

Reaction time on switch trials during the double task (third block)

Since the dependent variable of the visual switch trials is related to different processes as compared to the auditory switch trials, we tested our specific ad hoc hypothesis using separate paired t-tests for each component. The dependent variables were the median reaction time on auditory and visual switch trials (in milliseconds).[5]

Paired t-tests indicated a significantly decreased reaction time for *DT on visual switch* trials after the rTMS stimulation as compared to the pre task [$t(19) = 3.795$; $p = .001$; *s*] (see Fig. 1). For the sham placebo condition, we found no significant pre-post differences for this stimulus modality [$t(19) = 1.262$; $p = .222$; *ns*]. Furthermore, for the MT of the visual trials we found no significant changes in RT after rTMS [$t(19) = .748$; $p = .464$; *ns*] or after sham [$t(19) = .865$; $p = .398$; *ns*] (see Fig. 2).

As for the distraction trials, no significant differences in reaction time on *auditory switch trials* were found in the rTMS condition [$t(19) = .521$; $p = .609$; *ns*] or in the sham placebo condition [$t(19) = .360$; $p = .723$; *ns*](see Fig. 3). For the RTs, we refer to table 1.

Reaction time on repetitive trials during the single task (first and second blocks)

We also used t-tests to explore the influence of rTMS on the median reaction times during the two repetitive blocks. As predicted, in the sham placebo condition, there were no reaction time differences before to after treatment for the *auditory trials* [$t(19) = 0.024$; $p = .981$; *ns*] or for DT [$t(19) = 0.551$; $p = .588$; *ns*] or for MT [$t(19) = 1.022$; $p = .320$; *ns*] for the *visual trials*. Moreover, after active rTMS the reaction time for the *auditory trials* [$t(19) = 0.218$; $p =$

[5] We have also analyzed the switch trials, corrected for individual processing speed (RT of auditory and visual switch trials of block 3 minus RT on repetitive trials of block 2 and block 1, respectively). These analyses yielded similar results.

.829; *ns*] (see Fig. 3) or for DT [$t(19) = 0.309$; $p = .760$; *ns*] (see Fig. 1) or for MT [$t(19) = 1.022$; $p = .320$; *ns*] (see Fig. 2) for the *visual trials* did not differ significantly from the baseline.

The reaction times of the auditory trials and visual trials in the task repetition blocks are presented in table 2.

Reaction time during the single task (blocks 1 and 2) versus reaction time during the double task (block 3)

For visual trials, we found a significantly shorter median DT during the double task as compared to the single task in all stimulation conditions (see Fig. 1): $Sham_{pre}$ [$t(19) = 6.467$; $p = .0001$; *s*] and $Sham_{post}$ [$t(19) = 6.645$; $p = .0001$; *s*]; $rTMS_{pre}$ [$t(19) = 4.976$; $p = .0001$; *s*] and $rTMS_{post}$ [$t(19) = 7.454$; $p = .0001$; *s*]. These results are indicative for strong endogenous control mechanisms in the double task block (block 3).

On the other hand, we found significantly faster median MT only during the double task as compared to the single task in one condition (see Fig. 2): $Sham_{pre}$ [$t(19) = 3.556$; $p = .002$; *s*]. No differences were observed in the other conditions: $Sham_{post}$ [$t(19) = 2.018$; $p = .057$; *ns*] condition and $rTMS_{pre}$ [$t(19) = 1.055$; $p = .305$; *ns*] and $rTMS_{post}$ [$t(19) = 1.261$; $p = .223$; *ns*] conditions.

For the auditory trials (see Fig. 3), we found, as expected, faster median reaction times on repetitive trials compared to switch trials in the $Sham_{pre}$ [$t(19) = 3.272$; $p = .004$; *s*] and $Sham_{post}$ [$t(19) = 3.714$; $p = .001$; *s*] conditions and in the $rTMS_{pre}$ [$t(19) = 3.408$; $p = .003$; *s*] and $rTMS_{post}$ [$t(19) = 3.074$; $p = .006$; *s*] conditions. For the RTs, we refer to tables 1 & 2.

Table 1

Median Reaction Time latencies and Standard Deviation of switch trials (block 3) in a sham control and an active rTMS stimulation condition.

	rTMS		Sham	
	PRE	POST	PRE	POST
Auditory trials	**312.15** *(53.23)*	**306.65** *(65.13)*	**319.75** *(57.27)*	**316.10** *(46.14)*
Visual trials (DT)	**289.80** *(38.04)*	**264.05** *(40.84)*	**281.34** *(32.87)*	**287.87** *(36.20)*
Visual trials (MT)	**246.52** *(68.71)*	**257.4** *(64.45)*	**270.3** *(59.28)*	**261.07** *(64.54)*

Table 2

Median Reaction Time latencies and Standard Deviation of repetitive trials (blocks 1 & 2) in a sham control and an active rTMS stimulation condition.

	rTMS		Sham	
	PRE	POST	PRE	POST
Auditory trials	**248.5** *(43.18)*	**252.15** *(40.60)*	**238.12** *(64.06)*	**246.92** *(41.24)*
Visual trials (DT)	**348.35** *(34.01)*	**346.36** *(27.82)*	**345.90** *(35.50)*	**343.57** *(27.88)*
Visual trials (MT)	**227.01** *(46.63)*	**235.45** *(49.18)*	**223.43** *(40.67)*	**231.02** *(36.16)*

Auditory and visual trials of the respective repetitive blocks were compared before and after rTMS. No behavioral changes reached statistical significance.

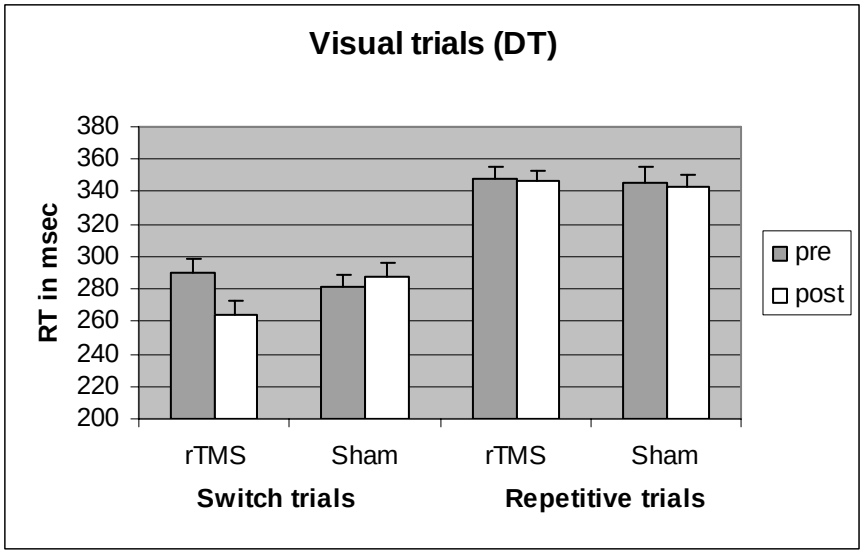

Figure 4. Median Decision Times and standard errors of visual switch trials (block 3) and repetitive trials (in block 1) before and after rTMS and sham stimulation.

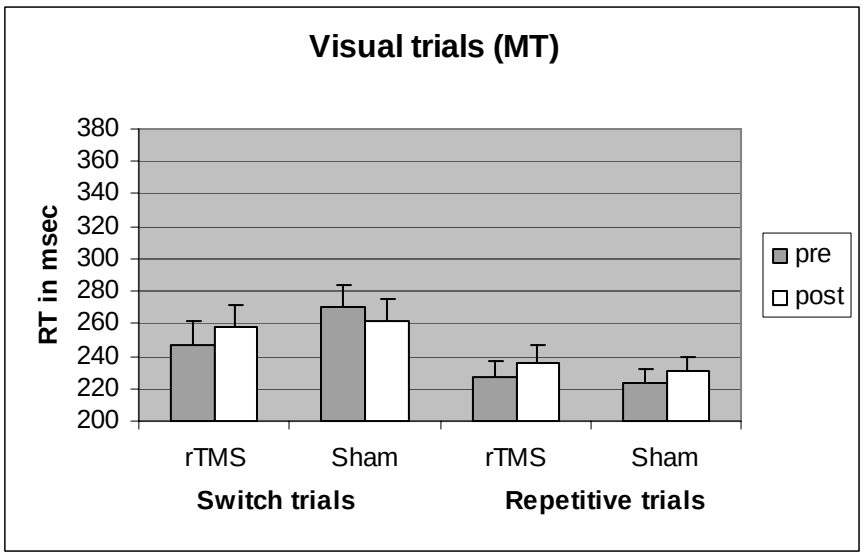

Figure 5. Median Movement Times and standard errors of visual switch trials (block 3) and repetitive trials (in block 1) before and after rTMS and sham stimulation.

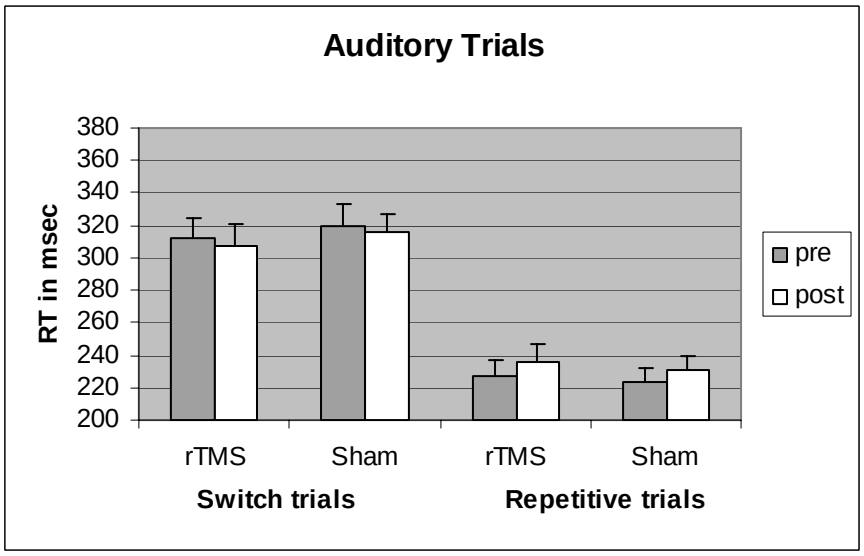

Figure 6. Median reaction times and standard errors of auditory switch trials (block 3) and repetitive trials (in block 2) before and after rTMS and sham stimulation.

DISCUSSION

Although previous neuroimaging and lesion studies have highlighted the importance of the dorsolateral prefrontal cortex (DLPFC) as being a key neural substrate of cognitive control, there remains an ongoing debate regarding the nature of the DLPFC's involvement in top-down preparedness for Task Switching (Luks et al., 2007). We investigated the role of the left DLPFC in endogenous control when prospective and active reconfiguration for a specific task was mixed with a condition where another task was directly cued and used as a distracter.

Because mood remained stable after stimulation, the results of the Task Switching paradigm can be evaluated independent of mood changes.

The decision time (DT) of visual switch trials decreased significantly after HF-rTMS over the left DLPFC, whereas no changes emerged after the placebo sham condition. In contrast, no significant differences in reaction time were found for movement time (MT) of visual switch trials, nor for cued auditory switch trials in the rTMS condition or in the sham placebo condition. Smith et al. (2004) proposed that motor components of switching set may be related to pre- and post-central gyrus and are thus independent of frontal control mechanisms.

Importantly, changes in reaction time to visual or auditory stimuli were not observed in the repetitive blocks either after sham placebo or after active rTMS. The significant effects cannot therefore be attributed to non-specific differences associated with stimulus and/or response mode or to effects attributed to general arousal.

Although one might question the unpredictable nature of the switch since most trials were switch trials, we found differential response patterns for the two modalities. During the switch block, most remarkably the DT (and not the MT) for visual trials (block 3) was significantly faster than the DT for repetitive visual trials (block 1) in all rTMS and sham conditions. The general decreased DT during switch blocks in our Task Switching paradigm suggests a successful general attentional task preparation for visual trials during the switch block representing endogenous task control. On the other hand, for the auditory trials, we found a faster reaction time on repetitive trials as compared to pre-cued switch trials, which indicates a normal switch cost for these stimuli in the switching block. This harmonizes with the results reported by Meiran et al.

(2000), who demonstrated reduced but not abolished switching costs when the participants were actively prepared for the upcoming trials with a preceding cue. This implies that, even with an alerting cue presentation for auditory switch trials, no anticipatory effects for these trials were observed.

Decision Time (DT) is related to the ability to prepare for specific task requirements. It can be regarded as a central aspect of cognitive control (Roberts & Pallier, 2001). Rogers and Monsell (1995) demonstrated an active "anticipatory" component of task-set reconfiguration which is endogenously triggered and which, given a "predictable switch", can be initiated prior to stimulus presentation during an alternating task-switching paradigm.

On the other hand, it still could be that with practice participants obtained a certain trade-off between fast reacting (lifting the finger from the central pushbutton and selecting and planning the movement to the lit pushbutton afterwards) versus movement planning before lifting the finger from the central pushbutton. Participants may have shifted from a careful 'plan-before-you-move strategy' in the repetition trials to a quick reaction strategy of 'first lift and later plan' in the double task condition. However, the MT for the repetition blocks did not reveal to be different compared to the MT for the switching block before and after rTMS.

Moreover, the manifestation of a trade-off pattern between MT and BT within visual switch trials after rTMS stimulation should result in a negative correlation between reactions times of both components. However, we found a positive correlation between MT and DT before rTMS [r = .438; p = .053; s] and no correlations between both components on the other stimulation moments: rTMS post [r = .259; p = .270; ns], Sham pre [r = .105; p = .659; ns] and sham post [r =.105; p = .661; ns]. Moreover, the rTMS effects doesn't seem to be related to a changed trade-off pattern, since the correlations of pre and post difference scores between DT and MT were not negative: rTMS [r = -.049; p = .836; ns] and sham [r = -.060; p = .800; ns]. This is indicative for the fact that no different response strategy was used after rTMS stimulation.

Importantly, most cognitive paradigms used to measure cognitive switching, such as the Wisconsin Card Sorting Task (WCST), lack the specificity that is required to explore the role of brain regions in cognitive processes and involve additional cognitive processes besides switching, in particular working memory (Smith et al., 2004). In contrast, our results demonstrate a specific top-down

preparedness for task-relevant information in a condition with unpredicted task sequences.

In line with our results, the recent research by Nicholson et al. (2006) demonstrated the activation of endogenous task set reconfiguration processes when switching between tasks.

In addition, Luks et al. (2007) demonstrated greater activity within the left DLPFC during preparatory allocation of attention and the employment of a regulatory strategy whenever the task demands are known. These authors suggested that the amount of preparatory activity may depend on the specificity with which task demands are identified and with which an attentional strategy can be organized in advance of stimulus presentation to facilitate stimulus processing and response selection.

In the present Task Switching paradigm, we used different response and stimulus modalities between the crucial target and distracter to minimize confounds for attentional set representation. One might question our decision to use a visual cue for auditory trials, since the (single) auditory signal had to be reacted to by pressing a foot pedal and could be clearly discriminated from the visual cues. However, because we were interested in endogenous task representation, maximum distraction was crucial. We therefore used a cue for an upcoming distracter which appeared in the same stimulus modality as the attentional set configuration but which was clearly discriminated from the visual switch trials. In addition, research has shown that some neurons in the DLPFC encode ongoing tasks (Asaad et al., 2000) or abstract task rules (Wallis et al., 2001) rather than the stimulus identity itself, resulting in goal-directing adaptive behavior appropriate to the given context (Tsujimoto & Sawaguchi, 2005). This means that the use of two stimulus modalities might be crucial to distinguishing the different context representations.

When combining our results with neuroimaging research results, we might conclude that DLPFC computations indeed serve to reactivate representations related to top-down attentional control processes and to represent the task context by providing top-down signals that favor task-relevant response pathways over competitors, as forwarded by Dreher and Grafman (2003).

There could arise a point of concern when investigating the contribution of the left DLPFC in maintaining an attentional set while there is no control showing that rTMS has specifically gained attentional set and not other

processes related to Task Switching. However, it is important to note that our research hypotheses are founded on explicit assumptions and preceding research with this task paradigm. Therefore, it was possible to conceptualize attentional set in a clear and unambiguous design in which subjects had to focus on specific stimuli and ignore other distracting stimuli.

In our previous research (Vanderhasselt et al., 2006a), we used an instruction with less emphasis on visual trials being the most important stimuli. Accordingly, we did not find a decreased DT for the visual trials in the switch block as compared to the repetitive block. Because DT is associated to the implementation of an attentional set, the comparison of both research results tends to additional evidence for a manipulation of this attentional process.

Moreover, it is possible that, although the majority of our female subjects used oral contraceptives, the menstrual cycle phase could have had an impact on mood measurements and cognitive functioning (Kirschbaum et al., 1999).

A next point of concern is the specificity of the effect of rTMS. It is generally believed that effects of rTMS are not strictly local given the high degree of connectivity to other cortical areas and subcortical nuclei. Recently, Esser et al. (2006) demonstrated that facilitatory rTMS effects are primarily found at the target areas of the projection from the stimulated region, taken into consideration that TMS primarily activates horizontally running axons. Moreover, it cannot be excluded that stimulating one hemisphere has effects on the other hemisphere via long-term potentiation of callosal projections. Therefore, stimulation of axons related to the modulatory brain systems will also result in widely distributed effects and research results should be interpreted with care.

Therefore, future controlled research combining rTMS with functional brain imaging is essential to further investigate the structural and functional activation within the left and right DLPFC in the circuitry that is responsible for higher attentional control.

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CHAPTER 5

THE INFLUENCE OF RTMS OVER THE RIGHT DORSOLATERAL PREFRONTAL CORTEX ON INTENTIONAL SET SWITCHING[6]

ABSTRACT

High Frequency (HF) Repetitive Transcranial Magnetic Stimulation (rTMS) has an excitatory effect on neurons of a specific brain area. The dorsolateral prefrontal cortex (DLPFC) has been associated with executive functions, such as task set switching. One important experimental paradigm for investigating such higher order cognitive control is the task-switching (TS) paradigm. A TS paradigm requires switching between two conditional response tasks with mutually incompatible response-selection rules. In the present study, the influence of HF rTMS over the right DLPFC in healthy female volunteers on a modified TS paradigm was investigated. As expected, reaction time on cued switching trials decreased significant after rTMS, as compared to non cued switch trials. No changes emerged after the placebo sham condition. Mood remained unchanged after rTMS. These findings demonstrate the role of the right DLPFC in cued intentional set switch initiation.

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INTRODUCTION

Repetitive Transcranial Magnetic Stimulation (rTMS) can be used as a non-invasive tool for stimulation of the human cerebral cortex, since it can reversibly interfere with the normal activity of a brain area to determine whether this area is essential for task performance. More specific, results from electrophysiological research suggest that high frequency (HF) rTMS has an excitatory effect on neurons (Pascual-Leone et al., 1994).

It is widely acknowledged that the prefrontal cortex plays a major role in executive functions, such as task-set switching. However, more precision is required in identifying which components of such high-level processes relate to which sub-regions of the brain (Forstmann et al., 2005). One important experimental paradigm for investigating such higher order cognitive control is the task-switching (TS) paradigm. The TS paradigm, which is regularly used to analyse 'executive control' processes in humans, investigates the ability to switch flexibly between two conditional response tasks with mutually incompatible response-selection rules (Wyllie et al., 2004). Moreover, human behaviour depends upon an interaction between our internal goals (top-down control such as anticipation) and our reactions to stimuli (bottom-up influences such as task repetition). Therefore it is most important to achieve this combination in Task Switching paradigms. Providing participants with time to prepare for a task switch typically leads to a reduction in switch costs (Rogers and Monsell, 1995). There is evidence that the observed reduction in switch costs is largely attributed to active preparation of control processes for the upcoming switch (Goschke, 2000). Research results of Sohn and colleagues (2000) demonstrated that endogenous preparation and exogenous adjustment for a task switch may be independent processes involving different brain areas. Their data indicated that voluntary goal-directed attentional shift is different from involuntary stimulus-dependent attentional shift.

Most event-related fMRI studies of Task Switching reported no specific brain region for switch trials, but an increased activation of a bilateral DLPFC–parietal network for switch relative to repeat trials (Dreher et al., 2003). Moreover, Sohn et al. (2000) found right lateralized prefrontal activation (the inferior part of DLPFC) when information about task repetition and task switch was available. In contrast, anterior regions in the prefrontal cortex are active when the need for

endogenous control is increased (Dreher et al., 2002; Forstmann et al., 2005). The specific involvement of right DLPFC in cued switching based on the abovementioned correlative fMRI analyses can also be tested by experimental manipulation of brain activity in the same crucial region. Therefore, we used rTMS over the right DLPFC to test the involvement of this brain structure in different components of intentional Task Switching.

To examine the neuronal specificity of the Task Switching effect, we used a Task Switching paradigm with three subsequent conditions. Subjects are first pretrained on two simple tasks (two separable blocks) afforded by a set of auditory and visual stimuli. In the third block (Task Switching block), subjects alternated between the two pretrained tasks (task switch) or repeated the same task (task repetition). In this third block of our experiment, two different switch conditions are included. In the switch-to-tone trials, subjects were informed by a cue when the auditory stimuli would appear. In the switch-to-light trials, participants have no idea when they had to switch to the visual stimulus. The former affects goal-driven or *top-down attention* processes, the latter engages *stimulus-driven attention* processes (van Veen et al, 2005). For visual trials, a component of endogenous information processing and a component of psychomotor speed were distinguished (Roberts and Pallier, 2001).

We hypothesised that the HF-rTMS, compared to sham placebo, over the right DLPFC has a specific influence on Task Switching performance. We expected that after stimulation over the right DLPFC, the reaction time on the switch trial triggered by a direct cue-task association (switch-to-tone trials) will decrease. Furthermore, we hypothesized that both components of the stimulus-related processes (switch-to-light trials) will not be influenced by the cerebral HF-stimulation. Moreover, we are not aware of similar attention-focused studies regarding rTMS over the right DLPFC in healthy volunteers where mood was kept under control. This might be essential since mood has an important influence on executive functioning (Damasio, 1996). Therefore, we will also evaluate if mood changes don't mediate the effects. To control for shortcomings mentioned in other rTMS research, we made use of a sham-controlled condition, a large time interval between stimulation sessions, a large uniform sample, stimulation of one single region per session in order to exclude interaction effects with the previous stimulation, and brain imaging to determine the exact

target of stimulation and a large number of pulses at high stimulation intensity (Baeken et al., 2006).

MATERIALS AND METHODS

Participants

Twenty two right-handed female volunteers (mean age: 23; age range: 18-25, standard deviation: 2.3) gave written informed consent prior to participation after the whole procedure had been fully explained. None of the subjects had any neurological, psychiatric or medical history. Nor did they have any contraindications to rTMS (Wassermann, 1998), as assessed through a medical screening before inclusion. They all underwent a physical examination, EEG and the Mini-International Neuropsychiatric Interview (M.I.N.I.) (Sheehan et al., 1998). Handedness was assessed with the Hand preference scale of Van Strien (Van Strien, 2001).

The study was approved by the local ethics committee of the Academic Hospital of the Free University Brussels (A.Z.-V.U.B.).

Design

A single blind, within subjects design by randomized crossover sham (placebo) and active rTMS was used.

Procedure

On the day of stimulation, the investigation started with a baseline mood measurement using visual analogue scales (VAS). Our VAS consisted of subscales for depression (8 items), anger (7 items), fatigue (6 items), vigour (5 items) and tension (6 items). The participants were asked to indicate on horizontal 10 centimetre lines whether they experienced the five abovementioned mood states, from “totally not” to “very much”.

Subsequently the Task Switching paradigm was performed. The task was run on a DELL computer, OptiPlex GX110. This task is a computerized self-paced version of a Task Switching paradigm (Gorus et al. in press and Gorus et al. in press) based on the original task of Van Zomeren (1981). Moreover, this task was modified to combine stimulus related and cue related switch tasks.

The device consist a board (connected to a computer) with a central pushbutton around which eight pushbuttons are positioned in a semicircle. In addition, a loudspeaker and a pedal are attached to the device. Participants were instructed to focus their attention to the visual stimuli and to switch attention when the auditory stimuli would appear. For visual trials, two components of the reaction time were recorded (Roberts & Pallier, 2001). Decision time (DT), a central (cognitive) component, reflects the time required to initiate a response and corresponds to the time that elapses between stimulus onset and the release of the central pushbutton. Movement time (MT), a peripheral executive component, represents the motor activity or the time required to complete the response (Gorus et al., 2007). For auditory trials, total reaction times were recorded.

Just before each auditory trial, the central pushbutton was illuminated (cue). As a manipulation check, we asked the participants if they had noticed the cue which indicated the upcoming auditory stimulus. All participants clearly did. Participants were instructed to respond as quickly and as accurately as possible.

This paradigm contains three blocks. The first two blocks consist of repetitive tasks (one block with 28 visual stimuli and one block with 28 auditory stimuli). Both motor responses involved different modalities and thereby non-overlapping neural systems.

During the first block, participants were told that, when they saw an illuminated pushbutton, they had to push out the light. At each visual trial one out of four of the eight pushbuttons could be illuminated randomly. In the next block, participants were instructed to press with their foot on a pedal when they heard a buzzer. The last block, the double task condition, was an alternating switch trial block with 29 auditory and 28 visual stimuli that were randomly mixed. During the switch block, 24 out of the 29 auditory signals and 25 out of the 28 visual signals were switch trials. After each response on a visual trial, subjects were asked to go back with their finger to the central pushbutton as quick as possible, which triggered Stimulus Onset Asynchrony (SOA) for the next trial. After each auditory signal, they had to remove their foot of the pedal to trigger SOA for the next trial. SOA differed randomly between 3000msec and 6000 msec. The same sequence was used for all participants.

After the Task Switching task, HF-rTMS was performed over the right DLPFC. All stimulations were performed using a MAGSTIM -high-speed

stimulator (Magstim Company Limited, Wales, UK) with a figure-8-shaped coil. Motor threshold (MT) was determined individually before real and sham stimulation. Stimulation intensity was 110% of MT of the right abductor pollicis brevis muscle, stimulation frequency was 10 HZ (HF-rTMS) and intertrain interval was 26.1 s. Forty trains were applied in ca 20 minutes (1560 pulses per session). The right DLPFC (Brodmann area 9**)** stimulation site was defined under magnetic resonance (MRI) non-stereotactic guidance. Real and sham stimulation were performed at the same place on the scull, but for sham stimulation the figure-8-shaped coil was held at an angle of 90° only resting on the scalp with one edge. After stimulation, participants again completed the mood scale (5 minutes), immediately followed by the second presentation of the Task Switching paradigm.

After completing the switching task, mood was assessed for the last time. All subjects were stimulated between 9am and 12pm. There was a delay of 1 week between the two stimulation sessions which were performed at the same moment of the day.

RESULTS

Mood effects

To evaluate mood changes, 2X3 within subjects ANOVA's with stimulation (rTMS-SHAM) and time (pre - post1 - post2) as within-factors and mood scores, evaluated with the VAS scales as dependent variables, were used. Because of some irregularities during testing, data of only 20 participants were analysed. No significant main or interaction effects between time and stimulation were found (p's $< .05$). Therefore, we conclude that there were no mood changes from baseline caused by right prefrontal HF-rTMS compared to ratings immediately after stimulation and after the second Task Switching task.

Reaction time on switch trials

Since switching from auditory to visual trials is a completely different process as compared to switching from visual to auditory trials, we tested our specific ad hoc hypothesis using separate paired t-tests for each component. The dependent variables were the mean reaction time on auditory and DT and MT of visual switch trials, corrected for individual processing speed [RT of auditory

and visual switch trials of block 3 minus RT on repetitive trials of block 2 and block 1 respectively]. The RT of the subjects was registered in milliseconds (msec).

Paired t-tests indicated a significant decreased reaction time for auditory switch trials after the rTMS stimulation as compared the pre task [t (22)= 2.381, p=.027]. For the SHAM placebo condition, we found no significant pre-post differences for this stimulus modality [t (22)= 1,472, p=.156]. Moreover, no significant differences in reaction time on visual switch trials were found in the rTMS condition for DT [t (22)= .647, p=.524], not for MT [t (22)= .437, p=.492]. The SHAM placebo condition yielded no differences for DT [t (22)= -.415, p=.683], and for MT [t (22)= .547, p=.444]. For a summary of these results, we refer to table 1.

Reaction time on repetitive trials

To further verify our specific a priori hypothesis, we used contrast analyses for the trials in the two repetitive blocks. As predicted, in the SHAM placebo condition, there was no difference between both test moments neither for the auditory trials [t (22)=0.713, p=.483; ns], for DT [t (22) = 0.852 p=.403; ns] or MT [t (22)= .296, p=.371] of the visual trials. Moreover, after active rTMS reaction time of auditory [t (22) = 0.431 p=.671; ns], visual trials DT [t (22) =0.819 p=.671; ns] and MT [t (22)= .512, p=.602] did not differ significantly. Reaction times of the auditory trials and visual trials in the task repetition blocks are presented in table 2.

Table 1

Mean Reaction Time latencies approximate Standard Deviation of the Task Switching block in a SHAM control and an active rTMS stimulation condition.

	rTMS		SHAM	
	PRE	POST	PRE	POST
Auditory switch trials	**331.89** *(66.45)*	**262.93** *(63.28)**	**270.33** *(56,46)*	**246.16** *(40.94)*
Visual switch trials (DT)	**358.51** *(47.95)*	**351.04** *(43.51)*	**352.65** *(33.89)*	**356.78** *(46.28)*
Visual switch trials (MT)	**254.35** *(23.47)*	**238.4** (*27.63)*	**365.9** *(47.45)*	**250.5** *(48.73)*

**p<.05 After rTMS, we found a significantly decreased reaction time for auditory switch trials. No other behavioural changes in response to active or placebo stimulation reached statistical significance.*

Table 2

Mean Reaction Time latencies and approximate Standard Deviation of the Task Repetition blocks in a SHAM control and an active rTMS stimulation condition.

	rTMS		SHAM	
	PRE	POST	PRE	POST
Repetitive Auditory trials	**334,89** *(26,40)*	**323,09** (*96,93)*	**292,69** (*55,02)*	**304,45** (*55,58*)
Repetitive Visual trials (DT)	**331,39** (*26,21)*	**308,54** (*77,07)*	**328,88** (*29,07)*	**337,45** (*29,25)*
Repetitive Visual trials (MT)	**289.14** *(34.33)*	**253.54** *(51.52)*	**219.63** *(69.27)*	**227.72** *(49.38)*

No behavioural changes reached statistical significance.

DISCUSSION

The present study aimed at investigating the role of the right DLPFC in endogenous control, when the task set was directly cued but with unpredictable task sequences. Since mood was not influenced by stimulation, the results of the Task Switching can be evaluated independent of mood changes. For reasons of homogeneity, we only included female volunteers to this research. Therefore, our results could not be generalised.

The reaction time on cued auditory switch trials significantly decreased after HF-rTMS over the right DLPFC, while no changes emerged after the placebo sham condition. In contrast, no significant differences in reaction time were found for DT and MT of the uncued visual switch trials in the rTMS condition, nor in the SHAM placebo condition. The reaction times of non switch trials in the switch block have not been analysed because only four visual non switch trials and six auditory non switch trials were presented. The mean baseline auditory and visual values between rTMS and SHAM groups did not reach statistical significance (p's > .05) suggesting that no systematic effect is responsible for the obtained results.

The reported results are in line with several neuroimaging studies which observed greater activity for cue initiated preparatory processes in the right lateral prefrontal cortex (Brass & von Cramon, 2004; Dreher et al., 2002; Sohn et al., 2000). The present findings indicate that the brain has a specific right lateralized mechanism to deal with task cue presentation to ensure the allocation of the appropriate attentional resources to overcome the conflicting switch trial. Analysis of reaction time changes across behavioural paradigms demonstrated the existence of more than one constituent process during set switching (Meiran et al., 2000). Intentional set switching requires subjects to change the rules by which they select between "motor responses" while attentional set switching requires subjects to change the rules by which they select between "sensory stimuli". There has been relatively little attempt to distinguish these components of Task Switching (Rushworth et al., 2005). The present experimental Task Switching paradigm recorded not only attentional set switching but also the reaction time following a cue which required intentional set switching. More specific, switch cues instructed subjects to switch the intentional set guiding response selection (van Veen et al., 2005).

Previous research demonstrated that cues instructing reconfiguration of an intentional set (stimulus–response mapping) elicited relative positive-voltage over midline frontal sites (Rushworth et al., 2002), whereas cues instructing reconfiguration of an attentional set (relevant perceptual feature for response) elicited relative negative-voltage that was lateralised over frontal regions (Rushworth et al., 2005; Miniussi et al., 2005). When comparing the present results with previous findings from neuroimaging (Rushworth et al., 2002; Milham et al., 2001) and behavioural task-cueing paradigms (Miniussi et al, 2005), the right DLPFC and left DLPFC seem to have a distinct role in attentional control. Previous findings of Vanderhasselt et al. (2006) using an experimental manipulation of brain activity demonstrated that the left DLPFC mediates top-down control by maintaining an 'attentional set'. Findings of the present research provide strong evidence for the assumption that the right DLPFC plays a dominant role in reducing the reaction time by intentional set switch initiation, after cue presentation.

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CHAPTER 6

ERP CORRELATES OF COGNITIVE CONTROL: EVALUATIVE AND REGULATIVE CONTROL[7]

ABSTRACT

Experimental evidence differentiates two main components in cognitive control, an evaluative component for conflict detection and a regulative component for attentional adjustments. A current debate addresses the temporal nature of the interactions between both cognitive control processes.

We have measured Event Related Potentials (ERP) during a variant of the Stroop task to investigate the time course of underlying processes in conflict processing. Using a between subjects design, we have manipulated conflict by varying the proportions of congruent and incongruent trials.

In the 'high conflict condition', dominant evaluative control processes should emerge. In the 'low conflict condition', a smaller interference effect is expected resulting from adjustments in attentional control (e.g., regulative control processes). Both attentional processes can be related to ERP components, the N450 and Sustained Potentials (SP) respectively.

Consistent with previous research so far, higher conflict resulted in more Stroop interference and enhanced the N450. In addition, we have found an

[7] Vanderhasselt, M.A., De Raedt, R., Wiersema, J.R., & Gevers, W. (2007). ERP correlates of cognitive control: Evaluative and regulative control processes. Manuscript submitted for publication.

attenuated SP when attentional control adjustments were required. However, we also found a clear negative going N2 in the low conflict condition but not in the high conflict condition.

Our results entail distinct modulations of the ERPs for the implementation of cognitive control arising at multiple stages of information processing. The relative dominance of a specific component in cognitive control is indicative for the temporal interactions between the components.

INTRODUCTION

Cognitive control is the ability to coordinate thoughts and actions related to internal goals (Miller & Cohen, 2001). Experimental evidence differentiates two main components of cognitive control: (a) an *evaluative component*, which is responsible for detecting a conflict and signalling when adjustments in control are necessary, and (b) a *regulative component*, which is in charge for the active maintenance and utilization of relevant information to guide task-appropriate attentional adjustments (Botvinick et al., 2001).

These components, essential for adaptive behaviour, have been underpinned by neuroscience research revealing that the implementation of cognitive control is supported by a cortical fronto-dorsal network of interactive structures including the anterior cingulate cortex (ACC) and dorsolateral prefrontal cortex (DLPFC) (Blasi et al., 2006). Recent studies on the contribution of the ACC to executive functions have linked this area to 'conflict evaluation' during cognitive processing (Braver et al., 2001). The DLPFC is thought to mediate regulative processes such as 'updating, implementation or manipulation' of information processing within the executive function system (Smith et al., 1999; Brass et al., 2005).

A flourishing research addresses the nature of interactions between ACC and DLPFC brain regions. Within this context, relatively few researchers have investigated the time course of related evaluative and regulative processes of cognitive control.

In cognitive science, one of the most extensively studied phenomena for cognitive control is the Stroop interference effect (Stroop, 1935). The principle is that word reading -a highly automatic ability- interferes with colour naming when a colour-word noun is printed in a colour differing from the colour

expressed by the word's semantic meaning. The Stroop interference is characterised by a delay in naming the colours of these incongruent words (e.g., RED in green) as compared to colour-congruent words (e.g., RED in red).

Conflict can be manipulated by the ratio of congruent and incongruent trials during a Stroop task. The need for *Evaluative control* can be manipulated by a low proportion of incongruent trials versus a large proportion of congruent trials resulting in higher conflict on incongruent trials (West & Alain, 2000). The demands placed on *regulative control* can be manipulated by varying the response-to-stimulus interval (Perlstein et al., 2006; West & Schwarb, 2006) or, by presenting for the most part incongruent trials, resulting in long-term task-set adjustment and a relatively lower conflict on incongruent trials (Carter et al., 2000).

Previous experimental research of Vanderhasselt and co-workers (2007) established a manipulation of regulative processes following repetitive Transcranial Magnetic Stimulation (rTMS) over the DLPFC during a modified Stroop task. After stimulation, results indicated solely decreased reaction times both for congruent and incongruent trials after colour naming. This is indicative for the fact that the DLPFC is related to situations where an adjustment in cognitive control is necessary and, as a result, regulative attentional processes must have been engaged.

Although rTMS can provide more insight into the workings of the neural circuits by modulating brain activity in controlled designs (Vanderhasselt et al. 2006), it adds modest information to the current debate on the temporal nature of interactions between regulative and evaluative processes respectively.

To determine the nature of these underlying component processes, scalp recorded event-related brain potentials (ERP) offer real-time temporal resolution of neural processes, permitting a precise analysis of the time course of neural events supporting task performance (Kok et al., 2001).

In the Stroop task two modulations of the ERP, N450 and Sustained Potentials (SP) have been consistently associated with conflict processing (e.g., Liotti et al., 2000; West & Alain 2000).

The N450, comparable to the N2 (Perlstein et al., 2006), reflects a phasic negative deflection with a fronto-central distribution and a reversed polarity over the lateral frontal regions. This component peaks between 400 and 500 ms after stimulus onset and is thought to be a neuro-electric marker of conflict detection

and monitoring (West & Alain, 2000). FMRI studies and ERP source localisation studies (Liotti et al., 2000) indicate the mid-dorsal regions of the ACC as the neural generators of the N450 component. This negative deflection is largest under conditions in which response conflict is high, such as infrequent incongruent Stroop trials, when the evaluative component of cognitive control is required (e.g. Liotti et al., 2000).

A second, more sustained potential (SP) is elicited about 600 ms after stimulus onset and reflects a sustained lateral frontal negativity and sustained positivity over the central-parietal regions. The SP is greater in amplitude for correct incongruent than for neutral or congruent trials and can be manipulated by a high proportion of incongruent versus congruent trials (West, 2000). Activity in lateral-frontal areas has been reported to generate the more negative sustained potentials. This activity seems to reflect the activity of neural generators within the DLPFC, supporting activation and implementation of conflict resolution processes (i.e., the regulative component of cognitive control) (e.g. West & Alain, 2000).

In sum, neurophysiological evidence shows an enlarged N450 when conflict is high and evaluative processes emerge. On the other hand, an attenuation (a more negative going) of the SP is associated to conditions where attentional adjustments were required resulting in a relatively lower cognitive conflict.

We have used ERPs during the performance of a modified Stroop task to investigate the time course of interactions within both components of attentional control. During the present Stroop task, we manipulated the degree of conflict for incongruent trials during two attentional demanding task conditions. In the first task condition, 80 % of all trials were congruent trials and 20 % were incongruent trials ensuing high conflict during incongruent trials (e.g., a high interference effect). In the 'high conflict condition', dominant evaluative control should emerge during the processing of incongruent trials. In a second condition, in which 20 % of all trials were congruent but 80 % were incongruent trials, a lower conflict on incongruent trials was induced. In this 'low conflict condition', a small interference effect should result from adjustments in attentional control (e.g., regulative control processes).

We are aware of only two studies which examined the effects of modulating the percentage of incongruent trials on ERP waves during a Stroop task (West & Alain, 2000; Lansbergen et al., 2007). Both studies used a within-subject design

in which the frequency of incongruent trials alternated within separate blocks in one task. Although this design adds important information to both attentional control components, one could question if the counterbalancing between the different expectancy blocks sorted out attentional set biases. When central evaluative processes emerged in one block, increased evaluative processes could bias the appearance of central regulative processes in a following block. This might imply that regularative and evaluative processes will not be registered purely and distinctively from each other. Indeed, West & Alain (2000) reported significant effects of order when the low conflict condition block was performed first. However, these possible effects were not interpreted in both studies. In addition, both studies were based on different populations (normal volunteers, high and low impulsivity persons). Therefore, we replicated these experiments using a between subject design and with clear instructions before the start of the Stroop task producing an unambiguous task set manipulation.

Based on a comparable Stroop task using rTMS (Vanderhasselt et al., 2007) and using ERP (West & Alain, 2000; Lansbergen et al., 2007), we expected a clear SP reflecting regulative control processes within the low conflict condition (80 % incongruent trials). Within the condition with 80% congruent trials, we expect an enhanced N450 because this condition elicits a high cognitive conflict. In contrast, we didn't expect a pronounced N450 in low conflict condition because evaluative control should not emerge because attentional adjustments reduced the conflict.

METHOD

Participants

Twenty-five students (nine male and sixteen female) of Ghent University volunteered to participate in this experiment with age ranging from 19 to 27 years (M = 22.6; SD = 2.36). Twelve participants were included in a condition with high attentional conflict and thirteen participants were included in a condition with low attentional conflict. The research protocol was approved by the local ethics committee. All subjects were right handed, had normal or corrected-to-normal vision and a self-reported no history of neurological and psychiatric conditions or alcohol abuse. The Dutch version of the Beck

Depression Inventory (BDI-II; Beck, Steer, & Brown, 1996; van der Does, 2002) was administered to screen out for depressive symptomatology (cut-off score of 14). Right handedness was assessed with the Hand preference scale of Van Strien (2001). Participants received a compensation of fifteen euros for their participation.

Procedure

After a brief description of the experiment, participants provided written informed consent, completed the BDI-II and the Van Strien Hand preference scale. Subsequently, participants were seated upright in a chair located in a sound-attenuated, electrically shielded chamber and the electrodes for recording electro-encephalographic (EEG) activity were applied.

Behavioural Stroop task

Participants performed a computerized version of a modified Stroop task which was programmed with E-Prime © (Schneider et al., 2002) and was run on a 17-inch colour screen of a Hewlett-Packard (Hp) computer, Pavilion f523.

Each subject performed a total of 320 trials. Each trial begun with a 1000 ms fixation point positioned in the centre of the screen. Subsequent, continuous series of coloured words (green, red and blue) were randomly displayed in their congruent colours (e.g., 'green' displayed in green) and their incongruent colour (e.g., 'green' displayed in red). Each stimulus word was presented on a black background.

The maximum presentation time of the trial was 4000 ms but the stimulus disappeared when a response was given. The inter trial interval was randomized between 1000 and 1500 ms.

Using a between subjects design, we manipulated subject's attentional adjustment for congruent and for incongruent trials, using a condition with high conflict condition (80 % congruent trials and 20 % incongruent trials) and a condition with low conflict condition (20 % congruent and 80 percent incongruent trials).

Participants were presented one practice block (20 trials) followed by a total of eight blocks of each 40 trials. Before the start of the task, participants were instructed to respond to the colour of the word and that most of the trials were congruent or, in the other group, were incongruent. They were asked to respond

as quickly and as accurately as possible with their right hand on three response buttons positioned on a response box. The correct response button for each specific colour was counterbalanced across subjects.

EEG procedure

Electro-encephalogram (EEG) (digitized at 1024 Hz) was recorded from an array of 32 tin electrodes sewn into an elastic electro-cap according to the International 10–20 system (at sites Fpz, Fz, FCz, Cz, CPz, Pz, Oz, Fp1, F3, FC3, C3, CP3, P3, O1, FP2, F4, FC4, C4, CP4, P4, O2, F7, FT7, T7, TP7, P7, F8, FT8, T8, TP8, P8) using Instep hardware- and software. The reference electrodes were positioned at the left and right mastoids. The ground electrode was linked to a frontal midline electrode. Eye blinks and -movements were monitored with electrodes at both outer canthi of the eyes (horizontal Electro-oculogram EOG), and above and below the right eye (vertical EOG). Impedance for all recording sites was 3 Kohm or less.

Raw EEG data were pre-processed offline and divided in epochs from 1000 ms of post-stimulus activity relative to a 200 ms pre-stimulus baseline. EEG was re-referenced to an average reference using a digitally low-pass filter at 30 Hz and high-pass filtered at 0.16 Hz. In addition, a notch filter of 50 Hz was applied.

All segments were screened visually and those with remaining artefacts were removed. Artefacts were removed from analysis if the standard deviation of any scalp electrode exceeded 20 μv within a sliding time window of 200 ms or when the standard deviation of the EOG within the same time window exceeded 40 μV (Turconi et al., 2004). Epochs containing eye movements were corrected by subtracting from the EEG the PCA-transformed EOG components from each electrode, weighted according VEOG propagation factors (computed via linear regression) (Mecklinger & Pfeifer, 1996).

For both conditions of congruency proportion, ERPs were averaged for correct trials as a function of stimulus type (i.e., congruent, incongruent).

RESULTS

Behavioural Data

Data were analyzed with a 2x2 mixed ANOVA, with trial type as within-subjects factor (congruent-incongruent) and attentional conflict as a between-

subjects factor (high conflict – low conflict). The dependent variables were mean reaction time on correct trials (in ms). Latencies less then 200 ms and more then 1000 ms were removed. Using this criterion, no more then 3.2% of each participant's data was excluded from the analysis. The significance level was set at $p<0.05$.

As expected, the main effect of trial type was significant [$F(1,23)=87.82$; $p<.001$]. The main effect of congruency proportion was not significant [$F(1,23)=0.01$; $p=.96$; ns], but we obtained a highly significant interaction effect [$F(1,23)=27.14$; $p<.001$] between both factors. The interference score (incongruent trials-congruent trials) for the high conflict condition ($M=212.90$) is stronger as compared to the low conflict condition ($M=60.75$) (see figure 1).

Paired t-tests between congruent and incongruent trials in each condition revealed significant contrasts. More specific, both for the high conflict condition, [$t(1,11)=7.57$; $p<.001$], and for the low conflict condition, [$t(1,12)=5.63$; $p<.001$], reaction times for congruent trials were faster as compared to incongruent trials.

In addition, we used an independent t-test to analyse the differences between congruent and incongruent trials between both conditions. Congruent trials in the high conflict condition were significantly faster as compared to the same trials in condition with low conflict [$t(1,23)=2.64$; $p<.05$]. On the contrary, incongruent trials in the condition with high conflict were marginal significantly slower as compared to the same trials in condition with low conflict [$t(1,23)=1.85$; $p=.077$].

The error data were submitted to a mixed repeated 2 (trial type) x 2 (attentional conflict) ANOVA with the proportion of errors as dependent variable. Congruency yielded a significant main effect [$F(1,23)=8.58$; $p=.008$] indicating a lower proportion of errors for congruent trials. However, the main effect of conflict condition [$F(1,23)=2.78$; $p=.109$; ns], and the interaction effect [$F(1,23)=2.08$; $p=.162$; ns] were absent indicating no effects on error rates.

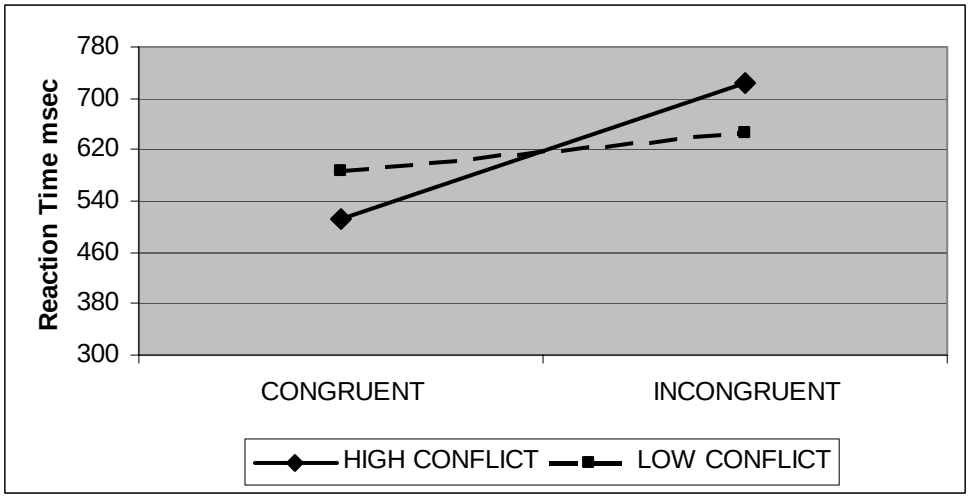


Figure 1. Mean reaction times on congruent and incongruent trials during high and low conflict conditions.

Electrophysiological Data

Because of a high amount of ERP artefacts, data of two participants were removed from the analyses. The grand average ERPs for congruent and incongruent trials in both congruency conditions at frontal, central and parietal electrodes are presented in Figure 2. The ERPs for each electrode are representative of the Stroop effects in their individual cluster.

For the modulation of these factors, there are three stimulus locked waveforms which can be clearly observed, N2, N450 and SP. Consistent with previous research, latencies of these components were determined as the maximum deflection within the time windows derived by visual inspection of the grand average potentials. The N2, N450 and SP were quantified as the mean voltage between 240-300 ms, 440-510 ms and 650-750 ms respectively.

For data reduction, we have clustered specific electrodes over areas of interest identified in previous work of West (2005) and Perlstein (2006): frontal-central cluster (electrodes FPz, Fz, FCz), left frontal cluster (electrodes FP1, F3, FC3), right frontal cluster (electrodes FP2, F4, FC4) for N2 and N450. For the SP we have also grouped electrodes in a parietal cluster (P3, Pz, P4).

Voltages were averaged across all electrodes per cluster prior to analyses.

For each cluster, a 2X2 mixed ANOVA was used with trial type (congruent-incongruent) as a within-subjects factor and attentional conflict as a between-subjects factor (high conflict – low conflict). The dependent variables were the mean amplitude for each cluster (in μV).

In addition, significant interaction effects were further analysed using interference effects of our Stroop manipulation (e.g., Lansbergen et al., 2007). Stroop interference effects were analysed using potentials associated with incongruent trials minus potentials associated with congruent trials.

The same rejected data in the behavioural data were also removed from the analyses in the electrophysiological data. In total, 5.5% of trials were rejected from averaging because of errors and EEG artefacts. Statistical tests were performed using the univariate F-ratio at the $p < .05$ level of significance.

N2 component

In the analysis of the phasic N2, the interaction effect between congruency proportion and trial type was significant over fronto-central sites [$F(1,21)=4.59$; $p < .05$]; left fronto-lateral sites [$F(1,21)=5.97$; $p < .05$] and right fronto-lateral sites [$F(1,21)=5.32$; $p < .05$]. These results were reflected by more negativity in the low conflict condition over all scalp sites. It is important to note that the main effects were not significant [F's<1].

We have used paired t-tests to investigate the interference of electro cortical activity between congruent and incongruent trials in both conflict conditions. In the high conflict condition, we have found significant differences between both trial types in this time range over fronto-central sites [$t(1,11)=2.255$; $p < .05$], trend significant over left fronto-lateral sites [$t(1,11)= 1,957$; $p=.079$] and over right fronto-lateral sites [$t(1,11)=2.131$; $p=.059$]. For these comparisons, electro cortical amplitudes were more negative for congruent trials.

In low conflict conditions, we have found no differences in amplitude between both trial types over all scalp regions during this time range [t's < .814] & [p's > .435].

N450 component

In the analysis of the phasic N450, the interaction effect of congruency proportion and trial type was significant over fronto-central sites [$F(1,21)=5.21$; $p < .05$], marginal significant over the left fronto-lateral sites [$F(1,21)=4.09$;

p=.057] but not significant over the right fronto-lateral sites [F (1,21)=2.14; p=.159; ns]. These results were reflected by more negative waveforms in the high conflict condition over fronto-central and left fronto-lateral sites. All main effects of the analysis were not significant [F's>1].

Using paired t-tests in the high conflict condition, we have found significant interference between both trial types in this time range over fronto-central sites [t (1,11)=4.072; p< .05], over left fronto-lateral sites [t (1,11)= 3,985; p=<.05] and over right fronto-lateral sites [t (1,11)=3.914; p=<.05]. For these comparisons, electro cortical amplitudes were more negative for congruent trials.

In low conflict conditions, we have found no differences in amplitude between both trial types over all scalp regions during this time range [t's < 1.688] & [p's > .122].

SP component

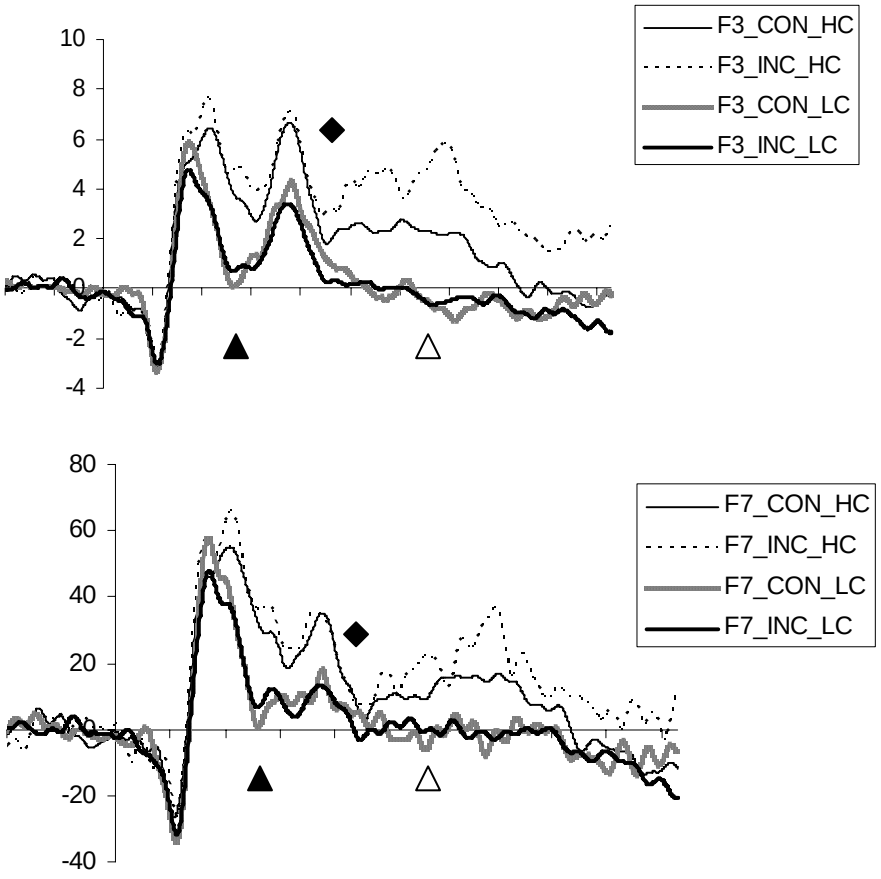
In the analysis of the sustained slow potentials, the main effect of congruency proportion indicated, as predicted, a stronger negativity for the low conflict condition as compared to the high conflict condition for fronto-central sites [F(1,21)=15.34; p <.001]and for left frontal sites [F (1,21)=13.77; p <.001]. All other main effects were not significant F's < 1.71.

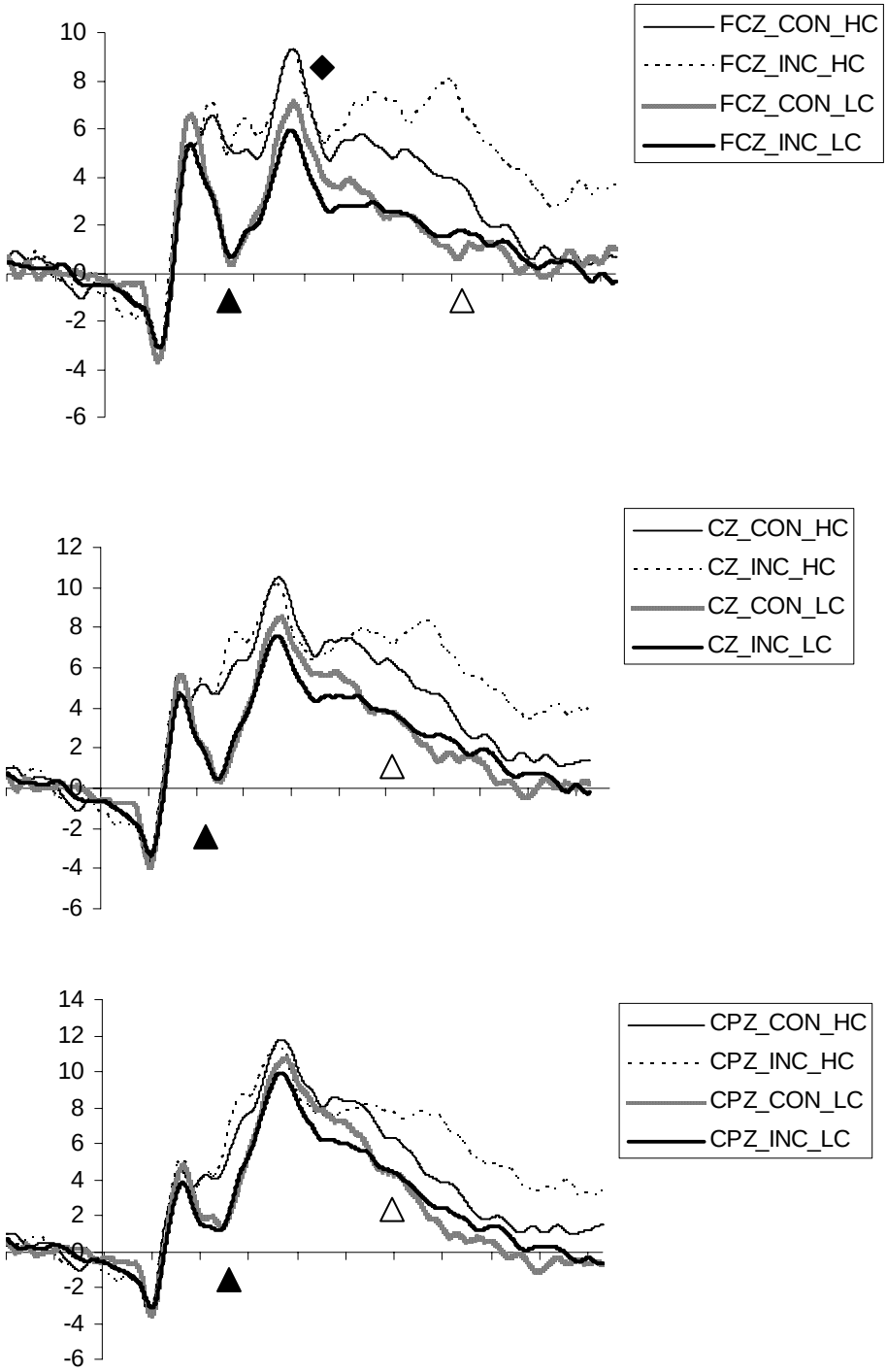
The interaction effect of congruency proportion and trial type was significant over left fronto-lateral sites [F (1,21)=4.09; p=.051] and parietal sites [F (1,21)=5,452; p <.05], marginal significant over the fronto-central sites [F (1,21)=4.01; p=.058] but not significant over right fronto-lateral sites [F (1,21)=1.41; p=.247; ns]. This effect was reflected by positive waveforms on incongruent and congruent trials in the high conflict condition over all scalp sites. During the low conflict condition, these waveforms were positive over fronto-central and parietal sites but negative over left and right fronto-lateral sites.

Using paired t-tests in the high conflict condition, we have found significant interference between both trial types in this time range over fronto-central sites [t (1,11)=2.506; p< .05], over left fronto-lateral sites [t (1,11)= 2,729; p=<.05], over parietal sites [t (1,11)=2.875; p< .001] but marginal significant over right fronto-lateral sites [t (1,11)=1.897; p=.087]. For these comparisons, electro cortical amplitudes were more negative for congruent trials.

In low conflict conditions, we have found no differences in amplitude between both trial types over all scalp regions during this time range [t's < 0.981] & [p's > .338].

In order to investigate possible correlations between the abovementioned ERP components in each condition, correlation coefficients were calculated. However, no significant correlations between components within each condition emerged [p's > .05].

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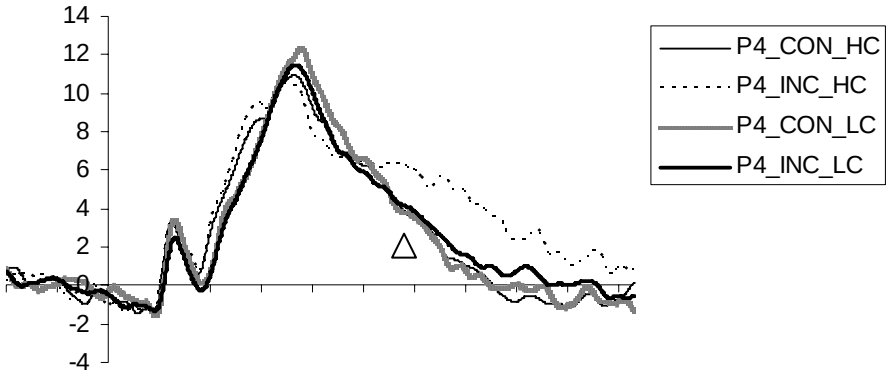

Figure 2. Grand-average ERPs for the low conflict (LC) and the high conflict (HC) condition elicited by incongruent and congruent stimuli. The N2 is marked by a closed triangle and the Sustained Potentials are marked by an open triangle. The N450 is marked by a closed square. Every tic is 100 ms.

DISCUSSION

We investigated the time course of the interactions between evaluative and regulative processes of cognitive control, using a modified Stroop paradigm in which the degree of conflict for incongruent trials was manipulated.

Behavioural data reveal a large interference effect (incongruent minus congruent trials) when incongruent trials are infrequent. This condition is characterized by high evaluative control (Carter et al., 2000). When the proportion of incongruent trials is low, participants may enlarge their attentional system towards word reading and, as a result, conflict during incongruent trials is high. In contrast, the interference effect was significantly smaller when incongruent trials were frequent. In this condition, regulative processes would reduce the attentional conflict.

ERPs were recorded to investigate brain correlates of Stroop interference (N450 and SP), which have been suggested to reflect evaluative and regulative elements of cognitive control, respectively (e.g. Liotti et al., 2000; West et al., 2000). ERP correlates revealed a modulation of frontal N450 at around 440 ms and a SP from 650 to 750 ms. Consistent with previous comparable ERP

research (West & Alain, 2000; Lansbergen et al., 2007), more Stroop interference resulted in a clear N450 ERP correlate.

Most interesting but not expected, we also found a clear negative going fronto-central N2 at around 270 ms in the low conflict condition but not in the high conflict condition. This primary frontally distributed phasic ERP modulation, the N2, which peaks at about 200 ms post stimulus seems to be associated with conflict detection (van Veen & Carter, 2002; Nieuwenhuis et al., 2003). According to the conflict detection theory of Botvinick et al. (2001), conflict detection is part of the evaluative component of cognitive control. Within this context, the amplitude of the N2 has been found to correlate with the degree of conflict, being greater when conflict is high than when it is low (Kopp et al., 1996).

One would expect that, if the N2 is related to conflict detection processes (e.g., van Veen & Carter, 2002), this component should be enlarged in the high conflict condition. However, when conflict was high, we observed a rather small N2 for both trial types with electro-cortical interference between congruent and incongruent trials. Nevertheless, we found an enlarged N2 in the low conflict condition for both congruent and incongruent trials with absent electro-cortical interference. Because a clear negative going of the N2 is related with no electro-cortical interference, it adds support for a role of this ERP correlate in conflict monitoring. This effect seems to be related to the task context and will be discussed later on.

The absence of the N2 component during the abovementioned comparable Stroop studies (e.g., West & Alain, 2000; Lansbergen et al., 2007) is possibly due to suboptimal interference control related to a within blocked design. When subjects have to change their attentional set every time a different task block is presented, it could be that the attentional set adjustments are biased because of the frequent modifications. On the other hand, inspection of the average waveforms of Lansbergen et al., (2007) and additional analyses in the paper also revealed a negative deflection around 290 ms post stimulus at fronto-central scalp sites (electrode FCz).

As a second component within our research, the amplitude of the N450 was modulated by the degree of conflict between colour and word information for incongruent trials in the Stroop task. These results are in line with the association between this ERP component and evaluative control in high conflict conditions.

In accordance to previous research (West & Alain, 2000), the negative going of this component was stronger for congruent trials as compared to the incongruent trials. This N450 component was also found, although less pronounced, in the low conflict condition and seems to be contradictory to the data of West and co-worker (2000) who observed only a N450 in the ERPs in the high conflict condition. However, our research findings are comparable with research of Lansbergen et al. (2007). Overall, the negative going waveforms over the N450 time window in the low conflict condition of the current study seem to correspond to the beginning of the subsequent SP.

A third feature of the data is a sustained positive activity during the high conflict condition versus a continuous negative activity over the fronto-lateral and front-central scalp regions in the low conflict condition. Overall, consistent with previous research, fronto-lateral scalp sites resulted in relatively more negative amplitudes of the slow waves with a reversed polarity over the parietal scalp sites (West & Alain, 2000).

In accordance with West and co-workers (2000), we observed a SP in both task conditions with a difference between congruent and incongruent electro-cortical signals only when conflict was high. In contrast, when conflict was low, this electro-cortical interference was absent and might reflect regulative processes.

The electrophysiological pattern for congruent and incongruent trials in both Stroop conditions was identical for the N2 and SP correlates. When comparing the SP with the behavioural results, less Stroop interference due to regularative processes leads to no differences in the neurophysiological signal for congruent and incongruent trials in later information processing. When the behavioural Stroop interference is more manifest, differences between congruent and incongruent trials in continuous slow waves remain significant. This pattern of results provides further support for the slow wave to reflect the engagement of regulative processes for both trial types (Curtin et al., 2003) and that those attentional processes are more activated when attentional adjustments are required.

Our results entail three distinct and specific modulations of the ERPs related to the implementation of cognitive control. When attentional adjustments are required, there seems to be a relation (although not a significant correlation) between the N2 and the SP. After an attenuated N2 for incongruent and

congruent trials, sustained negative amplitudes for congruent and incongruent slow waves emerged in this condition. These slow waves can be associated to regulative processes reducing the attentional conflict. Hence it seems that, when regulative processes have been increased for the implementation of a task-relevant attentional set, the conflict detection appears early in information processing (cfr. enhanced N2).

In the condition when conflict is high and evaluative control emerges, there is no fronto-central N2 for congruent and incongruent trials but there are, on the other hand, significantly different positive slow waves for both Stroop trials. Liotti et al., (2000) also demonstrated a prolonged positive wave between 500 and 800 ms after stimulus onset over the left superior temporo-parietal scalp. The amplitude and duration of this modulation have been proposed to index the slow processing of colour information in a perceptual level system when conceptual level information cannot guide a response (i.e., to guide a response on incongruent trials) (West & Alain, 2000). In addition, in this high conflict condition, an enhanced N450 component was observed.

To summarize, early conflict detection (cfr. N2) preceded control implementation processes (cfr. SP) in the low conflict condition (80% incongruent trials). In the high conflict condition (80% congruent trials), conflict detection (cfr. N450) emerged later in information process, approximately 470 ms after stimulus onset, but preceded regularative processes (cfr. SP). When conflict is expected and regulative processes emerge, conflict was detected earlier in the information process as compared to a condition when no regulative processes emerge.

Evidence regarding the functional significance of the N2 to cognitive control tends to be inconsistent and unclear. Research evidence linked the N2 component, as well as the N450 component, to activity in the ACC (van Veen & Carter, 2002). Therefore, researchers regularly match the N2 and N450 and link them to similar attentional components (e.g., Perlstein et al., 2006). However, our study shows that both components are divergent and appear in different conflict situations (e.g., West et al., 2005). Moreover, we found no correlations between the N2 and the N450 over all scalp sites entailing additional confirmation for separate roles of both ERP components. Further research should investigate the specific role of the N2 and the N450 within evaluative and regulative attentional processes in cognitive control. Research should focus on

the differences and similarities between both components concerning their relation in conflict monitoring.

Overall, our results show that within the process of cognitive control, series of ERP modulations arise at multiple levels of information processing (West et al., 2004), and support the assertion that the temporal course of information processing in cognitive control is related to the relative dominance of evaluative and regulative processes.

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CHAPTER 7

A SINGLE SESSION OF RTMS OVER THE LEFT DORSOLATERAL PREFRONTAL CORTEX INFLUENCES ATTENTIONAL CONTROL IN DEPRESSED PATIENTS[8]

ABSTRACT

Depressed patients are impaired in the ability to shift their focus of attention. This attentional control process is related to dysfunctions in the dorsolateral prefrontal cortex (DLPFC). It has been proposed that a dorsal circuit plays an important role in the interaction between emotional and attentional information processing.

However, because the different emphasis of fundamental cognitive neuroscience research and clinical research of repetitive Transcranial Magnetic Stimulation (rTMS) over the DLPFC, little research has been done on the effects of rTMS on cognitive functioning after a single stimulation session to explore the neural systems underlying depression.This study was conducted as a double-blind, placebo-controlled, crossover, within subjects design. Sixteen depressed patients performed a modified Task Switching paradigm, before and after receiving high frequency (HF) versus placebo rTMS over the left DLPFC.

[8] Vanderhasselt, M.A., De Raedt, R., Baeken, C., Leyman, L., & D'Haenen, H. (2007). A single session of rTMS over the left dorsolateral prefrontal cortex influences attentional control in depressed patients. *The World Journal of Psychiatry*. In press.

One session of HF- rTMS over the left DLPFC had a specific beneficial effect on Task Switching performance whereas mood remained stable. Antidepressant effects of rTMS could be related to the same neurochemical changes that underlie cognitive functioning. Therefore, Task Switching performance may provide a unique window into the extent of antidepressant effects which can be considered as second-order long-term effects possibly related to primary alternations in cognitive functioning.

INTRODUCTION

As a non-invasive technique to influence brain circuits, repetitive Transcranial Magnetic Stimulation (rTMS) induces alterations of neuronal activity that may affect mood and cognition (Moser et al., 2002). Although rTMS revealed to be an interesting tool to investigate cognitive functions in healthy subjects (Vanderhasselt et al., 2006a), much rTMS research has merely focused on the effects of rTMS as a treatment procedure for major depression. Regarding the antidepressant effects, research using rTMS over left dorsolateral prefrontal cortex (DLPFC) yielded promising results (for a review see Burt et al., 2002). A meta-analysis of Kozel et al. (2002) showed substantial clinical improvements in self reported mood measurements in left prefrontal rTMS studies. On the contrary, a rTMS meta-analysis of Martin et al. (2003), reported inadequate and inconsistent evidence for the antidepressant evidence in depression. They concluded that more specific research is required concerning its underlying working mechanisms.

Cognitive functioning could represent the underlying fundamental working mechanism of rTMS. However, research on the effects of rTMS on cognitive functioning in depressed patients shows inconsistent findings. We are aware of a small number of rTMS studies where improved cognitive performance was found in depressed patients (Moser et al., 2002). Triggs and co-workers (1999) found an improvement in neuropsychological performance following left-frontal rTMS after ten weeks as well as after three months. Other researchers (Loo et al., 2001) reported trends for improvement in neuropsychological performance after four weeks of active rTMS. However, as the authors mentioned, these effects could be due to practice effects since they used no placebo control condition. On the other hand, an absence of cognitive effects after several weeks of daily rTMS

in depressed patients has frequently been reported (e.g. Speer et al., 2000). In some cases, cognitive improvement was found in combination with no therapeutic effect of rTMS (e.g. Padberg et al., 1999).

In contrast, O'Connor and co-workers (2005) found that rTMS over a 2-week period improved performance on cognitive tasks and that these cognitive effects were greater in those patients who showed a significant antidepressant effect of rTMS. Given the interaction between cognition and emotion, the causal status of the improved cognitive effects could not be demonstrated because it is widely recognised that improved mood also influences cognitive functions (e.g. Boggio et al., 2005). There has recently been an increased interest in the study of cognitive performance as a marker of brain pathology in affective disorders (Stuss et al., 2003). However, support for cognitive functioning as underlying working mechanisms of depression, have been inconclusive to date (for a review see Martin et al., 2003). Since studying the interface between cognition and emotion becomes more prominent, research regarding immediate changes in cognition after rTMS in depressed patients, is most important. Studies investigating the influence of a single rTMS session on mood and cognition are very scarce.

Depression has been related to dysfunctions in specific aspects of executive processes, such as strategic attentional processes and selective set shifting, whereas relative automatic processes remain intact (Hartlage et al., 1993). Austin (2001) demonstrated that depressed patients are impaired in their ability to shift the focus of attention. This attentional process can be studied using a Task Switching paradigm that requires participants to rapidly switch between two or more tasks across consecutive trials (Arbuthnott and Frank, 2000).When subjects switch between tasks, they must both inhibit the previous relevant task and re-engage in a different task. We refer to the latter process as task set inhibition (Arbuthnott and Frank, 2000).

Functional magnetic resonance imaging (fMRI) studies have reported decreased activation of the left DLPFC in depression (Mayberg et al., 1999). Executive functions such as task-set inhibition are thought to depend on the left DLPFC (MacDonald et al., 2000). Using task-switching paradigms, several neuroimaging studies have shown that the lateral prefrontal cortex is more active on task-switch then on task-repetition trials (Sohn et al., 2000; Crone et al., 2006). In addition, rTMS research has pointed out the role of the DLPFC in

overcoming inhibition of a previously performed task during Task Switching in healthy volunteers (Vanderhasselt et al., 2006b). However, analogous and controlled neuropsychological rTMS research within a depressed population is limited (Bermpohl et al., 2006).

The aim of the present study was to evaluate the specific influence of a single session of rTMS on Task Switching and mood in depressed patients. We used a Task Switching paradigm with three following conditions. During two separate blocks of repetitive trials, the participants were pretrained on two simple tasks afforded by a set of auditory or visual stimuli. The responses of these stimuli required mutually incompatible response demands. In the third block (Task Switching block), participants alternated between the two pretrained tasks (switch trials) or repeated the same task (repetitive trials). During this block, they had no previous knowledge which task they had to perform, which requires continuous task set inhibition.

In line with several lesion studies (Aron et al., 2004), neurophysiological studies (Garavan et al., 2002) and analogous studies in healthy subjects (Vanderhasselt et al., 2006a) , we predicted that high frequency (HF)-rTMS over the DLPFC in depressed patients, compared to sham placebo, would have a primary influence on attentional control processes. More specific, we expected that after stimulation over the left DLPFC, the reaction time on the switch trials in the Task Switching block, in contrast to the trials in the first repetitive blocks, would decrease. We are aware that mood mediates executive functioning (Damasio, 1996) and that this understanding is of great importance when studying subjects with major depression. Therefore, we will also evaluate if possible mood changes mediate the effects. Based on evidence from recent studies, (e.g. Bermpohl et al., 2006), we predicted that there would be no mood changes after a single session of HF-rTMS over the left DLPFC.

To control for shortcomings mentioned in other rTMS research, we made use of a sham-controlled condition, a large time interval between stimulation sessions, stimulation of one single region per session in order to eliminate interaction effects with the previous stimulation, brain imaging to determine the exact position of stimulation, a large number of pulses at high stimulation intensity and a large uniform sample (Baeken et al., 2006; Baeken et al., 2007).

METHOD

This study was part of a larger project investigating the influence of rTMS on different neuro-cognitive markers.

Participants

A total of sixteen right-handed depressed patients (10 women and 6 men, mean age = 42 years; SD = 11,20) were enrolled in the study, which has been approved by the ethics committee of the hospital (U.Z. Brussel). After the nature of the procedure had been fully explained, all participants gave written informed consent before inclusion. They all underwent a physical examination and an EEG. All patients fulfilled the DSM-IV criteria for major depression as confirmed by the Mini-International Neuropsychiatric Interview (M.I.N.I.) (Sheehan et al., 1998). Depression severity was measured using the 17-tem Hamilton Depression Rating Scale (HDRS) (score at least >16). Right-handedness was evaluated by the van Strien hand preference screening questionnaire (Van Strien, 2001). Patients were all free of antidepressant medication. Some patients were washed out for at least14 days (and for minimally 3 weeks if they were on Fluoxetine) before the start of the study, other patients did not use psychotropic medication. Only patients who didn't need rescue medication or concomitant therapies during this period were included in the study. Importantly, they had regularly contact with a psychiatric to evaluate possible deterioration of their mood.

An overview of demographic and clinical characteristics of every patient is presented in table 1.

Design

This study was conducted as a double-blind, placebo-controlled crossover, within subjects design, in which participants received 20 minutes of real (10-Hz) or placebo (sham) rTMS over the left DLPFC.

Procedure

On the morning of stimulation, the investigation started at around 9 am with a baseline mood measurement. Patients were asked to indicate their current mood state on Visual Analogue Mood scales (VAS). These VAS scales consisted of

subscales for ‘depression’, ‘anger’, ‘fatigue’, ‘vigour’ and ‘tension’. The participants were asked to describe how they felt “at that moment” by indicating on horizontal 10 centimetre lines whether they experienced the five abovementioned mood states, from “totally not” to “very much”.

Afterwards, participants performed a computerised self-paced switching task, programmed in Delphi. The device consists of a board (connected to a computer) with a central pushbutton around which eight pushbuttons are positioned in a semicircle. In addition, a loudspeaker and a pedal are attached to the device. For a sketch of the experiment, we refer to figure 1.

This paradigm contains three blocks, in which the first two blocks consist of repetitive tasks (one block with 28 visual stimuli and one block with 28 auditory stimuli) and the last block consists of switch trials. Both motor responses involved different modalities and thereby non-overlapping neural systems.

During the *first* block, participants were told that, when they saw an illuminated pushbutton, they had to remove their finger from the central pushbutton and push out the light. At each visual trial, one out of four of the eight pushbuttons could illuminate randomly. For visual trials, two independent components of the reaction time were recorded. Decision time (DT), a central cognitive component, reflects the time necessary to initiate a response and corresponds to the time that elapses between stimulus onset and the release of the central pushbutton. Movement time (MT), a peripheral executive component, represents the motor activity or the time that is required to complete the response (Gorus et al., 2006). In the *second* block, participants were instructed to press their foot on a pedal when they heard a buzzer. Participants were instructed to let their foot hover over the pedal during the entire experiment. In this task, only total reaction times can be recorded.

The *third* block, the double task condition, was an alternating switch block with 29 auditory and 28 visual stimuli that were randomly mixed. During the switch block, 24 out of the 29 auditory signals and 25 out of the 28 visual signals were switch trials (only switch trials were analysed). Because of a technical problem, the first trials were lost and only 22 auditory and 22 visual switch trials could be recorded. Patients were instructed to focus their attention to the visual stimuli and to switch attention when the auditory stimuli would appear. After each response on a visual trial, they had to return their finger to the central pushbutton as quick as possible, which triggered Stimulus Onset Asynchrony

(SOA) for the next trial. After each auditory signal, they had to remove their foot of the pedal to trigger SOA for the next trial. In each of the three tasks, SOA differed randomly between 3000 msec and 6000 msec. The same sequence was used for all participants.

The participants were instructed to respond as quickly and as accurately as possible. If errors occurred, stimuli were replaced by a new stimulus in order to obtain the same amount of correctly performed reactions for every participant. Delayed reactions time latencies (> 3000msec) were removed from the analyses. For a timeline of the experiment, we refer to figure 2.

Subsequently, HF-rTMS over the left DLPFC was performed using a Magstim high-speed magnetic stimulator (Magstim Company Limited, Wales, UK), connected to a specially designed figure-eight-shaped coil. Before rTMS application, the motor threshold (MT) of each subject was determined individually using EMG. Stimulation intensity was 110% of MT of the right abductor pollicis brevis muscle, stimulation frequency was 10 HZ (HF-rTMS). Forty trains of 3.9 s duration, separated by an intertrain interval of 26.1 s (1560 pulses per session) were applied. The total stimulation time was approximately 20 min. The precise left DLPFC (Brodmann area 9/46) stimulation site and position of the coil was defined under magnetic resonance (MRI) non-stereotactic guidance. Perpendicular to this point, the precise stimulation site on the skull was marked and stimulated. Safety guidelines, based on recent available safety studies on rTMS, were followed (Wasserman, 1998; Anand and Hotson, 2002).

Afterwards, approximately 10 minutes following stimulation, the Task Switching paradigm was again administered.

Real and sham stimulation were performed at the same place on the skull, but for sham stimulation the figure 8-shaped coil was held at an angle of 90% only resting on the scalp with one edge, following recent SHAM guidelines (Anand & Hotson, 2002). Because the nature of the procedure had been explained in the informed consent before the start of the study, subjects were fully aware that one of the sessions was placebo. During stimulation, all participants wore earplugs and were blindfolded to guarantee that they couldn't see the difference between the placebo sham and the real rTMS procedure. The order of the stimulation conditions sham (placebo)-real was counterbalanced with a delay of 1 week

between the two stimulation sessions. The same individuals were stimulated at the same moment of the day.

The mood scales (VAS) were used to record mood at various stages of the experiment, respectively at baseline (pre) – immediately after rTMS (post1) and after Task Switching performance (+/- 30 minutes post stimulation, post 2).

Table 1

Demographic and clinical characteristics of the depressed patients.

Subject	Age	Gender	Duration current episode	At least failed trial	Psychotropic medication during rTMS
1	35	F	1 year	1,00	none
2	22	F	2 months	0,00	none
3	38	M	5 months	3,00	none
4	55	F	1 year	1,00	none
5	51	F	1 year	1,00	none
6	51	F	2 year	3,00	none
7	35	M	3 year	2,00	none
8	61	M	2 year	1,00	lendormin
9	34	M	7 year	5,00	none
10	52	F	5 year	3,00	none
11	45	F	2 year	3,00	none
12	48	F	5 year	3,00	regulton, pantozol
13	25	M	2 year	3,00	none
14	34	M	11 year	3,00	none
15	42	F	4 year	3,00	none
16	53	F	2 months	1,00	none

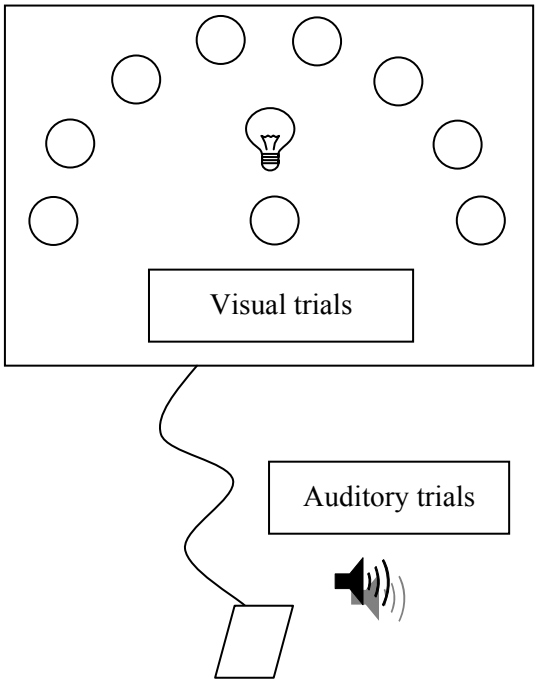

Figure 7. A sketch of the Task Switching experiment.

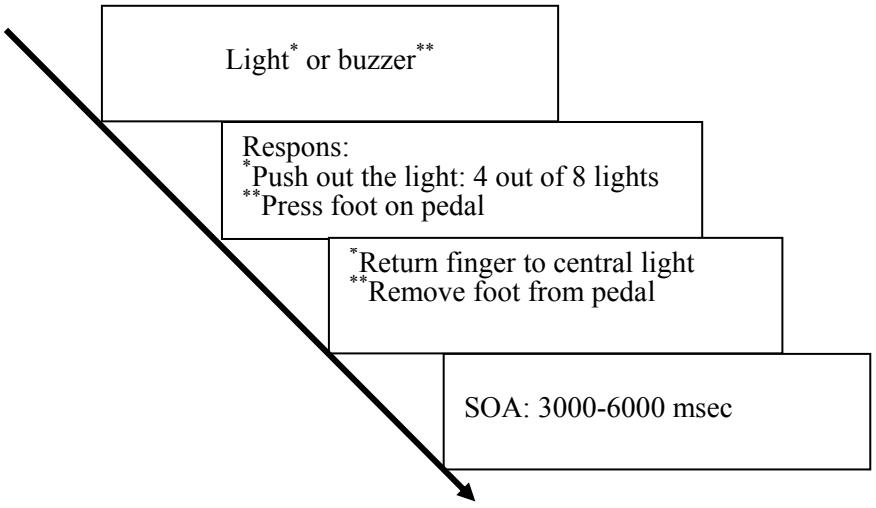

Figure 8. Timeline of the task switching experiment

RESULTS

All patients tolerated the experimental procedure well, only two reported mild headaches after the real stimulation procedure. Debriefing after the experiment revealed that participants tended to believe after each session that this particular session was the real stimulation.

Significance level was set at $p<.05$.

Mood effects

Analysis of variance (ANOVA) was used to analyse mood changes. Because of some missing values on the mood scales, data of only fourteen patients were analysed. We used a 2x3 within subjects ANOVA's with *stimulation* (rTMS-SHAM) and *time* (pre, post1, post2) as within-factors and mood scores, evaluated with the different VAS scales, as dependent variables. As expected, no main effects reached significance, neither the crucial interaction effects between time and stimulation: [$F_{anger}(2,12) =1.994$, $p = .18$; *ns*], [$F_{vigor}(2,12) =0.119$, $p = .89$; *ns*], [$F_{fatigue}(2,12) =1.087$, $p = .37$; *ns*], [$F_{tension}(2,12) =2.080$, $p = .17$; *ns*], [$F_{depression}(2,12) =0.509$, $p = .62$; *ns*].

Therefore, we conclude that there were no mood changes from baseline caused by left prefrontal HF-rTMS compared to ratings immediately after stimulation and after the second Task Switching task.

Reaction time on switch trials during the double task (third block)

Switch effects were analysed using mixed ANOVA's. The basic design was a 2x2x2 design with *stimulation condition* (rTMS-SHAM), and *time* (pre–post) as within-subjects factors and the *order of the stimulation condition* as between-subjects factor. The dependent variables were the mean reaction time (in milliseconds) on auditory and visual (both DT and MT) switch trials, corrected for individual processing speed (RT of auditory and visual switch trials of block 3 minus RT on repetitive trials of block 2 and block 1, respectively). The order of stimulation yielded no main effect and was not implied in any interaction effect [$F(2,14) =2.614$, $p = .12$; *ns*]. Consequently, this factor was left out in all further analyses.

Regarding our a-priori assumptions, the crucial interactions between stimulation condition ''rTMS/SHAM'' and time ''pre–post'' for DT [$F(1,15)$

=5.157, p = .04; *s*] as well as the interaction between stimulation condition ‘‘rTMS/SHAM’’ and time ‘‘pre–post’’ for ART [F(1,15) = 7.261, p = .02; *s*] were significant. The interaction between stimulation condition ‘‘rTMS/SHAM’’ and time ‘‘pre–post’’ for MT [F(1,15) =3.318, p = .09; *ns*] was not significant.

The significant interaction effects were further analysed by paired t tests to test our specific a priori hypotheses. Paired t tests indicated a significant decreased reaction time for both auditory switch trials [t (15)=3.301, p =.01; *s*] and for the DT of the visual switch trials [t (15)=3.457, p =.01; *s*] after the rTMS stimulation as compared the pre rTMS task. For the SHAM placebo condition, we found no significant pre–post differences for the visual stimulus modality [t (15)=0.474, p =.64; *ns*] nor for the auditory stimulus modality [t (15)=0.35, p =.73; *ns*]. For RT’s, we refer to Tables 2 and 3.

Reaction time on repetitive trials during the single task (first and second block)

To further verify our specific hypothesis, we additionally explored the influence of rTMS on the reaction times during the two repetitive task blocks, using ANOVA’s. The basic design was a 2x2 factorial ANOVA with *stimulation condition* (rTMS-SHAM), and *time* (pre–post) as within-subject factors. The dependent variables were the mean reaction time (in milliseconds) on auditory and visual repetitive trials.

The only significant main effect was for DT, showing faster latencies in the SHAM condition [F(1,15) =9.353, p = .008; *s*]. However, the crucial interaction effects between stimulation condition ‘‘rTMS/SHAM’’ and time ‘‘pre–post’’ for DT [F(1,15) =3.130, p = .10; *ns*], for ART [F(1,15) =1.988, p = .18; *ns*] and for MT [F(1,15) =1.596, p= .23, *ns*] were not significant. Reaction times of the auditory trials and visual trials in the task repetition blocks are presented in Table 3.

Table 2

Mean Reaction Time latencies approximate Standard Deviation of the Task Switching block in a SHAM control and an active rTMS stimulation condition.

	rTMS		SHAM	
	PRE	POST	PRE	POST
Auditory switch trials	**420,13** *(110,26)*	**363,94** *(76,36)**	**439,35** *(92,95)*	**419,67** *(47,77)*
Visual switch trials DT	**442,48** *(67,76)*	**425,47** *(75,81)**	**414,34***(58,42)*	**400,99** *(37,54)*
Visual switch trials MT	**282,33** *(64,98)*	**279,42** *(51,92)*	**290,03** *(50,70)*	**310,39** *(45,79)*

*For both auditory and visual switch trials, RT's before and after rTMS/SHAM were compared. *RT for visual and auditory switch trials (DT) was decreased after rTMS at $p < .05$. No other behavioural changes in response to rTMS or SHAM reached statistical significance.*

Table 3

Mean Reaction Time latencies and approximate Standard Deviation of the Task Repetition blocks in a SHAM control and an active rTMS stimulation condition.

	rTMS		SHAM	
	PRE	POST	PRE	POST
Repetitive Auditory trials	**313,82** *(67,69)*	**327,23** *(79,01)*	**359,38** *(103,46)*	**332,62** *(66,20)*
Repetitive Visual trials; DT	**362,21** *(48,35)*	**401,46** *(80,93)*	**342,89** *(41,97)*	**335,19** *(31,61)*
Repetitive Visual trials; MT	**311,02** *(63,68)*	**312,73** *(62,05)*	**298,21** *(57,09)*	**315,12** *(74,24)*

Auditory and visual trials of the respective repetitive blocks were compared before and after rTMS. No behavioural changes reached statistical significance.

DISCUSSION

The influence of HF-rTMS in medication free depressed patients might offer new avenues to study the relationship between basic cognitive processes and depression. To our knowledge, this is the first study to explore the influence of a single session HF- rTMS over the left DLPFC on mood and Task Switching performance in depressed patients.

We found that one session of HF- rTMS over the left DLPFC had a beneficial effect on Task Switching. These results are in line with previous rTMS research that related Task Switching performance of healthy volunteers to activity in the DLPFC (Vanderhasselt et al., 2006b). More specifically, we found that reaction time latencies of switch trials during the Task Switching block for both visual and auditory trials significantly decreased after rTMS whereas sham yielded no effects. No differences on the repetitive trials of the single task blocks were found, which indicates that our results are not caused by a general increased arousal. Moreover, peripheral movement time was not influenced by the rTMS procedure, which means that the effects are related to central cognitive functioning. Since we used a sham controlled crossover design, the improved cognitive performance associated with HF rTMS could not be related to a non-specific effect.

As predicted, after a single session of HF-rTMS in depressed patients, no mood effects were found, indicating that the beneficial cognitive effects are not related to an immediate antidepressant effect of rTMS. In line with the imbalance theory of depression, which is based on findings of a hypo-activity of the left relative to the right prefrontal cortex in the pathophysiology of depression (Drevets et al., 2000), other studies reported that successive sessions of HF-rTMS over the left DLPFC transiently increase mood (Kozel & George, 2002).

The current study provides a contribution to the literature on cognitive control and attentional processes that might be related to the underlying antidepressant effect of rTMS, administered with parameters typically used in clinical studies of major depression.

Our results are in line with research from Haussmann and co-workers (2004) who used multiple sessions of unilateral rTMS (HF over the left DLPFC) as well as bilateral combined rTMS (HF over the left DLPFC and low frequency over

the right DLPFC). They reported mild beneficial effects on attention partly independent of its antidepressant efficacy.

Wagner and co-workers (2006) stated that, as there is good clinical evidence for a relationship between stimulation intensity of rTMS over the left DLPFC and its antidepressant efficacy (Padberg et al., 2002), analyses of cognitive effects would be particularly interesting. They suggest that increased attentional control processes after rTMS might not be limited to a period immediately after stimulation but may possibly reflect primary neurochemical alterations and, as a result, may be a sensitive cognitive measure to trace short-term effects of rTMS in humans (Wagner et al., 2006). Corresponding to this consideration, recent findings by Pogarell and colleagues (2006) demonstrated an increased dopaminergic neurotransmission in the striatum as an acute neurobiological antidepressant action of left dorsolateral rTMS.

In addition, Bermpohl and colleagues (2006) recently suggested that, given the link between emotional and cognitive functions, a switch task could be used as a rough indicator for the general clinical state of depressed patients. This implies that cognitive tasks may serve as a valuable tool for studying acute rTMS effects in depressed patients (Bermpohl et al., 2006).

A study of Möller and co-workers (2006) found that the P300, a major endogenous brain Event-Related Potential (ERP) component which has been found to be reduced in patients with depression, was significant increased in amplitude after rTMS over the left prefrontal cortex compared to sham stimulation. An increase in P300 amplitude is indicative of improved attentiveness (Sommer and Matt, 1990; Picton, 1992 in Möller et al., 2006). However, no significant antidepressant effects after five days of stimulation were found in this study. Nevertheless, similar rTMS procedures administering this treatment over a longer period reported a clear antidepressant outcome (Gershon et al., 2003).

One could thus suggest that primary to the antidepressant effect of rTMS, cognitive changes emerge.

In addition, neuroimaging studies demonstrated functional changes in blood flow within the DLPFC and connected regions after HF-rTMS (Kimbrell et al., 1999; Speer et al., 2000; Paus and Barrett, 2004). The antidepressant effects of rTMS might be related to the same neurochemical changes in the neurocircuitry that underlie cognitive attentional control processes. It has already been

demonstrated that this dorsal circuit plays an important role in the interaction between emotional and attentional information processing (Taylor and Fragopanagos, 2005) and that dysfunctional activation in this area of the brain may possibly contribute to the development of affective disorders (George et al., 1994).

In sum, the use of Task Switching paradigms may provide a unique window into the extent of antidepressant effects (Wagner et al., 2006) which can be considered as second-order long-term effects possibly caused by primary alternations in cognitive functioning.

Future research combining rTMS with functional brain imaging is necessary for providing evidence of these cognitive changes as a marker of antidepressant effects.

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CHAPTER 8

ACUTE NEUROCOGNITIVE EFFECTS OF REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION PREDICT ANTIDEPRESSANT TREATMENT OUTCOME[9]

ABSTRACT

Repetitive Transcranial Magnetic Stimulation (rTMS) applied on the dorsolateral prefrontal cortex (DLPFC) is a new treatment procedure that holds promise to gain more insight into the pathophysiology of depression because the DLPFC might occupy an important role in the interplay between emotional and attentional information processing. The aim of the present study is to investigate whether acute neurocognitive effects of repetitive Transcranial Magnetic Stimulation predicts antidepressant treatment outcome.

We examined the immediate and post treatment effects of rTMS over the left DLPFC on cognition and mood in therapy resistant depressed patients using a crossover design differentiating rTMS treatment responders and non responders. A Task Switching paradigm was used to measure cognitive functioning. The study period started in January 2005 and ended in May 2007.

After two weeks of High Frequency (HF) rTMS over the left DLPFC, depressive symptoms improved in more than half (57%) of our therapy resistant population. After a single HF- rTMS session, mood did not improve but

[9] Vanderhasselt, M.A., De Raedt, R., Leyman, L., & Baeken, C. (2007). Acute neurocognitive effects of repetitive Transcranial Magnetic Stimulation predict antidepressant treatment outcome. Manuscript submitted for publication.

attentional functioning was solely increased within our group of treatment responders.

Cognitive reactivity after a single rTMS session can be related to beneficial treatment outcome. Moreover, within this group of responders, changes in attentional functioning were correlated with changes in depressive symptoms. This means that attentional processes might be related to identical neurophysiological changes that underlie successful antidepressant treatment.

INTRODUCTION

Repetitive Transcranial Magnetic Stimulation (rTMS), a non-invasive method for neuronal depolarization of specific areas of the human brain, is a rather new technology that holds promise for therapeutic advances and insights into the pathophysiology of depression (Loo et al., 2005).

To date, numerous open and controlled clinical trials demonstrated that high-frequency (HF; >1Hz) rTMS, when applied over the left dorsolateral prefrontal cortex (DLPFC) or low-frequency (LF; <1Hz) rTMS when applied over the right DLPFC has antidepressant benefits (for a review see Gershon et al., 2003). On the other hand, a detailed review of the literature reveals that the data so far are still inconsistent. These inconsistencies can be related to the use of diverse stimulus parameters and methodological limitations such as non-blind conditions, inaccurate stimulation localisation, diverse output measures and inter-individual differences in participants (Bermpohl et al., 2006). For example, Fregni et al. (2006) recently showed that after 10 daily sessions of rTMS (20 Hz stimuli at 110% of the threshold over the left DLPFC), subjects' scores on the Hamilton Depression Rating (HAMD) were improved. On the contrary, comparable studies with a similar treatment procedure could not establish these antidepressant effects (for a review, see Loo & Mitchell, 2005).

Because of these contradictory results, the efficacy of rTMS remains a topic of debate. Although it seems desirable to further assess the assumption of antidepressant effects of HF- rTMS over the left DLPFC (Burt et al., 2002), a promising avenue for further research might be to investigate characteristics of treatment responders versus non responders. This makes it possible to search for markers of rTMS effects and to investigate possible working mechanisms underlying its therapeutic efficacy. Recently, it has been argued that the

heterogeneity of research findings might be due to a high variability across depressed patients in their response to rTMS (Bermplohl et al., 2006). Whereas previous research mainly focussed on exogenous stimulation parameters, one could thus investigate endogenous features predicting treatment outcome.

Positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) studies have established a regulative role for a specific cortico-subcortical circuit in mood disorders (Mayberg et al., 1999) and, accordingly, have postulated that this dorsal circuit would occupy an important role in the interplay between emotional and attentional information processing (Taylor & Fragopanagos, 2005).

The aim of the present research is to explore underlying attentional mechanisms related to the outcome of rTMS antidepressant treatment, starting with non-emotional stimuli. Although rTMS is currently used as a new tool for neuropsychological research in healthy subjects (e.g. Vanderhasselt et al., 2007), cognitive functioning in studies investigating clinical populations are frequently viewed as simply epiphenomena (Martis et al., 2003). The most common observation of previous studies is that rTMS has no major detrimental cognitive effects over the baseline-post period after several weeks of daily rTMS in depressed patients (e.g. Janual et al., 2005). Some of these studies have found improvement on a number of cognitive tests, such as verbal memory (Padberg et al., 1999), verbal fluency (Triggs et al., 1999) and improvement on list recall (Little et al., 2000) following two weeks of 1 to 20 Hz rTMS over the left DLPFC in depressed subjects.

Research from our lab could demonstrate that one session of placebo controlled HF- rTMS over the left DLPFC in medication free depressed patients had a beneficial effect on Task Switching performance but not on mood in depressed patients (Vanderhasselt et al., 2007). Stimulation was administered with parameters typically used in clinical studies with an antidepressant treatment outcome. As a result, one could suggest that primary to the antidepressant effect of rTMS, cognitive changes emerge and later changes in depressive symptoms might be a secondary effect. Accordingly, these primary cognitive effects might predict anti-depressant treatment outcome. Therefore, immediate effects of rTMS on cognition and mood should be investigated using a placebo controlled design differentiating responders and non responders (e.g. Brakemeier et al., 2007).

In the abovementioned study of our lab (Vanderhasselt et al., 2007), medication free patients with a major depressive disorder were included in the study. In the current study, a homogeneous group of medication free therapy resistant depressed patients who had failed to respond to at least two antidepressant medications were included, to investigate the influence of a single rTMS session as compared to two weeks of daily HF-rTMS over the left DLPFC.

Cognitive flexibility during Task Switching performance, a core function of the DLPFC, has been well documented to be impaired in depression (Austin et al., 2001). A Task Switching paradigm, the same paradigm that was used in our previous single session rTMS research (Vanderhasselt et al., 2007), was used to measure cognitive functioning before and after the antidepressant rTMS treatment. We tested cognitive performance before, after a single session and finally after two weeks of rTMS treatment.

Given our previous results and based on the existing literature, the predictions of this study are twofold. Concerning depressive symptoms, we predict that rTMS will have a significant beneficial effect on depressive symptoms only after two weeks of treatment. Secondly, we predict that positive effects on Task Switching performance after one session of HF-rTMS will differentiate treatment responders and non responders. We define responders as those showing a 50% or more reduction in their Hamilton Depression Rating scores after treatment. Furthermore, we predict that, after two weeks of rTMS treatment, cognitive improvements will only be observed in treatments responders. Non responders will not change in cognitive performance after rTMS treatment. Moreover, based on the hypothesized relation between attention and mood, we would expect that the treatment effect in the group of responders correlates with the pre-post treatment change in attentional functions.

METHODS

This study was part of a larger project investigating the influence of rTMS on different neuro-cognitive markers.

Participants

Fifteen (Mean age=45.6; SD=5.87) right handed patients (6M/9F) with refractory depression were recruited from in- and outpatient facilities of the University Hospital of Brussels (UZ Brussel) from January 2005 to May 2007. An overview of the demographic and clinical characteristics of all participants at baseline is presented in table 1. The data of five of these patients were also included in a former study on the effects of one session of rTMS (Vanderhasselt et al., 2007).

The study protocol was approved by the local medical Ethics Committee of the University Hospital. After a full description of the experiment, all subjects gave written informed consent to participate in the study.

A diagnosis of a therapy resistant major depressive episode with melancholic features was confirmed using the structured Mini International Neuropsychiatric Interview (MINI - Sheehan et al., 1998; Dutch version of Van Vliet et al., 2000) and a detailed examination by a psychiatrist. For ten of the patients, the depressive episode was diagnosed for the first time more than 3 years ago and they had been unresponsive to at least 2 prior anti-depressant medication trials (i.e. Stage III of therapy resistance (TR) based on criteria of Thase and Rush (1995)). Five patients were classified into stage V of TR (i.e. failure of a course of bilateral electroconvulsive therapy).

Additionally, their score on the 17-item Hamilton Depression Rating Scale (HAMD, Hamilton, 1960) had to be at least 21 (and no symptoms scoring 0). Participants also administered the Dutch version of the Beck Depression Inventory (BDI; Beck, 1961; Dutch version Bouman, Luteijn, Albersnagel, & van der Ploeg, 1985), and were selected according to a BDI cut-off score above 21.

All subjects were right handed, according to the Van Strien Hand Preference scale (2001).

None of the patients had received rTMS before and all met safety criteria for rTMS (Wassermann, 1998). Patients were excluded if they had any history of physical illness likely to affect brain physiology, head injury, co morbid psychiatric conditions including alcohol or substance abuse, bipolar disorder or contraindications to rTMS.

Patients who used antidepressants and anti-psychotropic medications were tapered from their medications for at least two weeks prior to receiving rTMS. If the patients were using Fluoxetine, they had to be free of anti-depressant pharmacotherapy for at least three weeks. Benzodiazepines were permitted during the study on a steady dose. Only patients who did not need rescue medication or concomitant therapies during this period were included in the study. Because patients discontinued antidepressant medications before entering the experiment, patients were carefully followed by a trained psychiatrist.

All subjects underwent a physical and neurologic examination (EEG) and a structural three-dimensional brain MRI for a non-stereotactic identification of the stimulation site (Brodmann area 9/46 (left DLPFC)).

Stimulation protocol

The rTMS stimulation parameters were well within the established safety guidelines (Wasserman, 1998). Magnetic stimulation was performed by a high-speed magnetic stimulator MAGSTIM (Magstim Company Limited, Wales, UK), united with a cooled figure-eight shaped coil.

On the first treatment trial, a stimulation intensity of 110% of the motor threshold (MT) at rest of the right abductor pollicis brevis (APB) muscle was established using EMG. Correspondent to the precise DLPFC site using MRI, the skull was marked and stimulated through a fixed position of the coil over all rTMS sessions.

Ten HF-rTMS sessions (10 Hz) were delivered daily (Monday–Friday) within a period of two weeks, using following parameters per session: 40 trains of 3.9 seconds duration, separated by an intertrain interval of 26.1 seconds resulting in 1560 pulses per session. The total stimulation time was approximately 20 min.

At the start of their rTMS treatment of 10 sessions, each subject also received one sham placebo stimulation session. The order of the first stimulation session, being real rTMS stimulation or sham stimulation, was assigned by a crossover design. Sham stimulation was performed at the identical place on the skull, but the figure eight-shaped coil was held at an angle of 90 only resting on the scalp with one edge, following recent SHAM guidelines (Anand & Hotson, 2002).

During stimulation, all participants wore earplugs and were blindfolded to guarantee ‘optimal’ blinding.

Clinical mood assessments

Anti-depressant treatment efficacy was diagnosed by the HAMD and BDI at baseline and also after a period of two weeks of rTMS treatment. Both measures were used as objective outcome measures. Patients were considered to be responders to treatment if the HAMD score after treatment had decreased by 50% or more from baseline (Brakemeier et al., 2007).

To evaluate immediate subjective mood changes, patients were asked to indicate their current mood state on Visual Analogue mood Scales (VAS). These VAS consisted of subscales for 'depression', 'anger', 'fatigue', 'vigour' and 'tension'. The participants were asked to describe how they felt "at that moment" by indicating on horizontal 10 centimetre lines whether they experienced the five abovementioned mood states, from "totally not" to "very much". The mood scales (VAS) were used to record mood at various stages of the experiment, respectively at baseline (T_{pre}) – immediately after rTMS (T_{post}) and approximately 30 minutes after the first real rTMS/placebo sham session (T_{post30}) and at the end of the rTMS treatment period ($T_{posttreatment}$).

Task Switching paradigm

Participants performed a computerised self-paced switching task. The device consists of a board (connected to a personal computer) with in the middle a pushbutton and eight pushbuttons positioned in a semicircle around the central button. In addition, a speaker and a pedal are connected to the device.

This paradigm includes three continuous task blocks, in which the first two blocks consist of repetitive tasks (one block with 28 visual stimuli and one block with 28 auditory stimuli) and the last block consist of switch trials. Both motor responses involved different stimulus modalities and thereby non-overlapping neural systems.

During the *first block*, subjects were told that, when they saw an illuminated pushbutton, they had to remove their finger from the central pushbutton and push out the light. At each visual trial, one out of four of the eight pushbuttons could illuminate randomly. For visual trials, two components of the reaction time were recorded. Decision time (DT), a central cognitive component, reflects the time necessary to initiate a response and corresponds to the time that elapses between stimulus onset and the release of the middle pushbutton. Movement time (MT), a

peripheral executive component, represents the motor activity or the time that is required to complete the response (Gorus et al., 2006).

In the *second block*, participants were instructed to press their foot on a pedal when they heard a buzzer. In this task, only total reaction time can be recorded. The participants were instructed to hold their foot above the pedal waiting for the signal and to respond as quickly and as accurately as possible.

The *third block*, the double task condition, was an alternating switch block with 29 auditory and 28 visual stimuli that were randomly mixed. During the switch block, 24 out of the 29 auditory signals and 25 out of the 28 visual signals were switch trials (only switch trials were analysed). Because of a technical problem, the first trials were lost and only 22 auditory and 22 visual switch trials could be recorded.

Patients were instructed to focus their attention to the visual stimuli and to switch attention when the auditory stimuli would appear. Following each response on a visual trial, they had to return their finger to the central pushbutton as quick as possible, which triggered Stimulus Onset Asynchrony (SOA) for the next trial. After every auditory signal, they had to remove their foot of the pedal to trigger SOA for the next trial. In each of the three tasks, SOA differed randomly between 3000 ms and 6000 ms. The same trial sequence was used for all participants. If errors occurred, stimuli were replaced by a new stimulus in order to obtain the same amount of correctly performed reactions for every participant.

Table 1

Mean (SD) demographic and clinical patient characteristics at baseline.

VARIABLE	
Age	45.6*(5.87)*
Gender ratio (M/F)	6/9
Hamilton Depression Score (HAMD)	23.3*(3.44)*
Beck Depression Inventory score (BDI)	32.23*(7.28)*
Age at onset of first depressive episode	38.13*(16.4)*
Failed antidepressant trials	3
% Hospitalisationduring the study	54%
% Suicide risk at the start of the study	46%

RESULTS

All patients tolerated the experimental procedure well. Only two subjects reported a mild headache just after stimulation. Significance level was set at $p < .05$ for all statistical analyses which were conducted with SPSS 12.0.

Effects of rTMS on mood and depressive symptoms: short term effects on mood

Analysis of variance (ANOVA) was used to analyse short term mood changes after a single session of HF-rTMS. Because of some missing values on the mood scales, two subjects were removed from analysis. For separate VAS scales, we conducted 2x3x2 mixed ANOVA's (multivariate approach) with *stimulation* (rTMS-SHAM) and *time* (T_{pre}, T_{post}, T_{post30}) as within-factors and *treatment response* (responder-non responder) as between factor.

Mood scores, evaluated with the different VAS scales, were used as dependent variables. An overview of the VAS measures before (Tpre), immediately (Tpost) and 30 minutes after (Tpost30) after rTMS are presented in table 2.

No main effects for stimulation reached significance: $F_{vigor}(1,12)=1.097$, $p=.316$, $F_{anger}(1,12)=1.087$, $p=.375$, $F_{tension}(1,12)=1.080$, $p=.319$, $F_{depression}(1,12)=1.195$, $p=.296$ or fatigue $F<1$. No significant overall effects of time were found: $F_{anger}(1,12)=2.682$, $p=.113$, $F_{tension}(1,12)=1.554$, $p=.254$, $F_{depression}(1,12)=1.314$, $p=.270$, or for fatigue and vigor F's <1. In addition, no main effects of treatment response were found on the different VAS measurements F's<1. No two way interaction effects were found F's< 1.47.

Finally, the interaction effects between stimulation, time and treatment response yielded no significant effects $F_{vigor}(2,24)=0.119$, $p=.889$, $F_{anger}(2,24)=1.201$, $p=.345$, $F_{tension}(2,24)=2.089$, $p=.171$, $F_{depression}(2,24)=1.238$, $p=.327$ or $F_{fatigue}(2,24)=0.336$, $p=.718$.

As a result, we conclude that there emerged no short term mood changes from baseline caused by left prefrontal HF-rTMS compared to ratings immediately after stimulation or after 30 minutes for responders and non responders.

Effects of rTMS on mood and depressive symptoms: treatment response on depressive symptoms

Treatment outcome was diagnosed by reports on the HAMD. Eight out of fifteen patients (57 %) reported a reduction of 50% of their scores on the HAMD after two weeks of rTMS treatment. An overview of the group data is presented in table 3.

To further explore these separate results within groups of responders and non responders after rTMS treatment, Wilcoxon Signed-Rank nonparametric tests were used to be as conservative as possible within the context of our small group sizes.

Reports on the BDI revealed a significant lower score after rTMS treatment for responders ($z=2.52$, $p=.012$) but not for non responders ($z=0.593$, $p=.553$). At baseline, both groups did not significantly differ on their BDI scores ($z=0.001$, $p=1.00$). In contrast, after two weeks of rTMS treatment, the BDI showed significant lower scores for the responder group as compared to the non-responder group ($z=2.371$, $p=.018$).

Effects of rTMS on Task Switching: short term effects

Three sets of mixed repeated measures ANOVA's were performed to analyze the immediate effects of rTMS on cognition for all participants.

The three dependent variables, respectively for each ANOVA, were the mean reaction time (in milliseconds) on auditory (total reaction time) and visual (decision time - DT and movement time - MT) switch trials, corrected for individual processing speed (RT of auditory and visual switch trials of block 3 minus RT on repetitive trials of block 2 and block 1, respectively). Delayed reaction times (> 3000 ms) and very short reaction latencies (< 200 ms) were removed from the analyses.

A distinction was made between responders and non responders to analyze immediate mood effects. Therefore, the basic design was a 2x2x2x2 design with *stimulation condition* (rTMS-SHAM), and *time* (T_{pre}–T_{post30}) as within-subjects factors and *treatment response* (responders-non responder) and *order* (first sham - first rTMS) as between-subjects factors. Because the factor order was not implied in any main or interaction effect F's <1.4, this factor was left out in all subsequent analyses.

For an overview of the data, we refer to tables 4 and 5.

As predicted, our crucial three way interaction was significant for short term effects of rTMS on decision time (DT) of visual reactions times $F(1,13)=5.369$, $p=.039$.

The main effect of time $F(1,13)=6.105$,$p=.029$, and the two way interaction between stimulation condition and time $F(1,13)=4.976$, $p=.046$, also reached statistical significance

The other main or two way interactions yielded no significant effects (F's < 2.98 & p's > .110).

To further explore these results within groups of responders and non responders separately, two sets of Wilcoxon Signed-Rank nonparametric tests were used.

Within our group of responders, in contrast to sham placebo stimulation ($z=$ 0.420, $p=.674$), difference scores for DT significantly decreased after rTMS ($z=2.308$, $p=.017$). Within our group of non responders, no changes were found ($z=.943$ $p=.345$).

Movement time (MT) of visual switch trials yielded no main or interaction effects $F < 1.18$. The three way interaction $F(1,13)=0.003$, $p=.957$, is indicative for no effects of rTMS or sham stimulation on this component of visual RT, neither for responders or non responders.

For auditory reaction times (ART), the crucial three way interaction $F(1,13)=3.308$, $p=.094$, yielded only a marginally significant effect but given our a priori hypotheses based on previous research (Vanderhasselt et al., submitted), we further analysed this interaction. The other main or interaction effects were not significant F's < 1. Wilcoxon Signed-Rank nonparametric tests demonstrated that reaction times on auditory switch trials decreased nearly significantly after rTMS ($z=1.820$, $p=.069$) within our group of responders but not within our group of non responders ($z=0.105$, $p=.917$). After sham placebo, attentional processes did not change (z's < .700; $p > .05$).

To sort out a non-specific influence of rTMS on cognitive functioning, we also tested the same factorial design for repetitive trials. However, no main or interaction effects reached statistical significance F's < 1.3.

In order to directly investigate the predictive utility of DT, which revealed to be the variable that differentiated responders from non-responders after two weeks of rTMS in the most significant way, a binary logistic regression analysis

was performed. Treatment response (responders – non responder) served as the dependent variable and the independent variable was the difference in DT before and after a single session of rTMS.

Analyses of the model revealed reasonable goodness-of-fit by a non significant Hosmer and Lemeshow test, [chi]2(6, N = 15) = 8.274, p=.219. The omnibus test of model coefficients was significant, [chi]2(1, N = 15)=7.459, p=.006 (Nagelkerke R2=.523).

An overall classification rate of 86,7% of participants correctly classified as either responders (6/8, 75%) or non responders (7/7, 100%) was obtained.

Effects of rTMS on Task Switching: Treatment response

Again, three sets of mixed ANOVA's were performed to analyze the treatment effects of two weeks of rTMS on measures of cognitive processing. A 2x2 factorial design was used including *time* (pre-post$_{treatment}$) as within factor and *treatment response* (responders-non responders) as between factor. Pre-measures of cognitive processing were for each subject based on their first administration of Task Switching performance (which was either before active or sham stimulation). The three dependent variables, respectively for each ANOVA, were the mean reaction time (in milliseconds) on auditory (total reaction time) and visual (decision time - DT and movement time - MT) switch trials, corrected for individual processing speed (RT of auditory and visual switch trials of block 3 minus RT on repetitive trials of block 2 and block 1, respectively). For a summary of the data, we refer to table 4.

As predicted, the two way interaction between time and treatment response was significant F(1,13)=6.191, p=.027 for DT of visual trials. The main effect of time was not significant F < 1, in contrast to the highly significant main effect of treatment response F(1,13)=9.134, p=.01.

For MT of visual trials, neither the main nor the interaction effect reached statistical significance F's<1.

In accordance to our expectations, the two way interaction between time and treatment response for auditory reaction trials was also significant F(1,13)=14.088, p=.002. Both main effects were not significant F's < 2.61.

In order to further explore the significant interaction effects, changes in cognitive functioning were separately investigated within groups of responders and non responders using Wilcoxon non-parametric tests. Within our group of

responders, two weeks of rTMS treatment significantly decreased DT (z=2.240, p=.025) and MT (z=1.960, p=.05) for visual trials, and for auditory reaction time (z=2.521, p= .012).

On the contrary, for non responders, cognitive functioning did not change for both components of visual and auditory reaction times z's < 1.014, p's > .310.

Most important within this design, reaction times of responders and non responders did not significantly differ during their first Task Switching performance: for DT (z=1.154; p=.247), for MT (z=0.694; p=.487), and for ART (z=0.581; p= .329). Moreover, after rTMS treatment, both groups established significantly different reaction times on DT (z=2.199; p=.029) and ART (z=2.315; p=.021) but not on MT (z=0.347; p=.779).

We also tested the same factorial design for repetitive trials. However, no main or interaction effects reached statistical significance F's < 1.2.

Correlations between mood measurements and cognitive functioning

To investigate whether the improvements in depressive symptoms and the progress in cognitive functioning are related, correlations between both measures are essential. Therefore, correlation coefficients between clinical improvements and changes in attentional processing were analysed in treatment responders and non-responders (post treatment minus pre-treatment for symptoms and Task Switching performance).

A marginal significant correlation was found between changes in BDI scores and changes in decision time (DT) of visual switch trials (r=.51; p=.06). However, changes in movement time and auditory reaction times did not reach statistical significance p's >.05. Also treatment changes in repetitive trials did not correlate to changes in mood scores p's >.05. In non responders, no significant correlations emerged (all p's >.47).

Table 2

Mean ratings and standard deviations for the VAS measures before, immediately after and after 30 minutes of rTMS or SHAM stimulation.

	ACTIVE rTMS			SHAM PLACEBO		
	T_{pre}	T_{post}	T_{post30}	T_{pre}	T_{post}	$\mathbf{T_{post30}}$
VAS						
Depression	**5.65**	**5.56**	**5.76**	**6.54**	**5.63**	**5.53**
	(3.62)	*(2.57)*	*(3.14)*	*(3.12)*	*(3.36)*	*(3.62)*
Anger	**1.56**	**0.86**	**0.65**	**1.22**	**0.43**	**0.74**
	(2.24)	*(1.24)*	*(0.84)*	*(1.37)*	*(0.42)*	*(0.52)*
Tension	**4.99**	**4.34**	**4.56**	**4.65**	**4.85**	**4.63**
	(2.57)	*(2.37)*	*(4.05)*	*(2.15)*	*(3.33)*	*(3.97)*
Fatigue	**6.12**	**6.98**	**7.98**	**7.54**	**6.83**	**7.69**
	(3.42)	*(2.01)*	*(2.36)*	*(1.62)*	*(1.17)*	*(2.96)*
Vigor	**1.45**	**1.67**	**1.53**	**1.45**	**1.73**	**1.65**
	(2.01)	*(2.07)*	*(1.45)*	*(1.53)*	*(0.69)*	*(2.01)*

Table 3

Group means on the Hamilton Depression rating scale (HAMD) and Beck Depression Inventory (BDI) before and after rTMS treatment for responders and non responders.

	HAMD		BDI	
	PRE rTMS	POST rTMS	PRE rTMS	POST rTMS
Responders (n= 8)				
Mean (SD)	**21.5** *(8.26)*	**7.25** *(2.76)*	**30.37** *(7.99)*	**15.5** (*5.47)*
Non responders (n= 7)				
Mean (SD)	**24.14** *(2.73)*	**20.42***(7.13)*	**32.42** (*9.39)*	**29.71** *(7.29)*

Table 4

Mean Reaction Time latencies and Standard Deviation of switch trials of the Task Switching in a SHAM and rTMS condition

RESPONDERS					
	SHAM		rTMS		
	PRE	POST	PRE	POST	POST TWO WEEKS
ART	**441.76**	**420.96**	**447.98**	**414.46**	**385.14**
	(32.85)	*(43.70)*	*(29.40)*	*(53.25)*	*(38.87)*
VT; DT	**447.05**	**399.67**	**467.30**	**409.81**	**355.51**
	(49.04)	*(20.42)*	*(47.10)*	*(58.46)*	*(74.39)*
VT; MT	**310.88**	**360.18**	**313.82**	**308.66**	**336.67**
	(35.23)	*(46.30)*	*(36.86)*	*(32.47)*	*(29.22)*
NON RESPONDERS					
	SHAM		rTMS		
	PRE	POST	PRE	POST	POST TWO WEEKS
ART	**465.14**	**422.78**	**440.63**	**436.59**	**500.25**
	(68.54)	*(34.99)*	*(56.68)*	*(52.10)*	*(83.54)*
VT; DT	**438.84**	**429.77**	**442.07**	**441.29**	**482.41**
	(51.67)	*(46.23)*	*(38.88)*	(37.20)	*(100.18)*
VT; MT	**305.07**	**326.44**	**300.12**	**299.71**	**309.23**
	(36.15)	*(52.53)*	*(23.31)*	*(25.65)*	*(30.50)*

ART = Auditory switch trials; VT = Visual switch trials; DT = Decision Time; MT = Movement Time

DISCUSSION

Evidence suggesting that rTMS might be a promising treatment procedure with rapid onset of action has aroused growing interest. However, inconsistencies in rTMS treatment outcome research necessitate investigating possible underlying working mechanisms and characteristics of treatment responders (Kimbrell et al., 1999).

Therefore, we performed rTMS in a homogeneous research group of therapy resistant medication free depressed patients. We stimulated over the left DLPFC, as being a typical stimulation target in mood disorders, and measured depressed mood symptoms and attentional functioning before rTMS, after one rTMS session, and after 10 rTMS sessions.

Subjective mood reports did not change after a single session of HF-rTMS. Positive treatment outcome was measured using the HAMD and verified with the BDI, two well validated questionnaires. More then half (57%) of our therapy resistant population showed a decrease of at least 50% of their HAMD score after two weeks of daily HF-rTMS over the left DLPFC.

Within our group of treatment responders, we observed a significant improvement in Task Switching performance after one double blind placebo controlled rTMS session. We could demonstrate that a specific component of visual switch trials, i.e. decision time, and reaction times on auditory switch trials were improved after HF-rTMS. Movement time of visual switch trials, as being the motor component of switching, was not influenced by rTMS. These current findings are in accordance with previous research of our lab indicating that a single session of rTMS increases Task Switching performance in healthy volunteers (Vanderhasselt et al., 2006; Vanderhasselt et al., 2007) and in depressed patients (Vanderhasselt et al., 2007).

The enhancement in switching performance after a single session of placebo controlled HF-rTMS over the left DLPFC is in line with the involvement of the DLPFC in the representation of goal-directed behaviour. The DLPFC has been identified to occupy a key role in sustaining task-relevant representations of non emotional as well as emotional stimuli to accomplish the task goals (Taylor & Fragopanagos, 2005).

The acute effect of rTMS on cognition in depressed patients is in accordance with previous studies (Bermpohl et al., 2006, see below), but in contrast to other

studies (e.g. Loo et al., 1999). As compared to this latter experimental research, we have used a relatively intensive treatment protocol (10 Hz, 110% of Motor Threshold, 1560 pulses per session) which can explain the rapid attentional improvements. On the other hand, because the attentional improvements only emerged in the group of treatment responders when no mood effects did yet arise, cognitive effects are specific and interpretable, holding intriguing implications for clinical practice.

Our data show that increased cognitive performance after a single session of HF-rTMS is predictive of the antidepressant treatment outcome. The binary logistic regression model displayed an overall hit rate of 86.7 % and indicates that DT serves as a significant predictor for treatment response to rTMS. The regression model correctly assigned 6/8 of the responders (a sensitivity of 75%) and 7/7 of the non-responders (specificity of 100%) to their final response group. In line with these observations, the correlation between changes, pre and post treatment, in depression scores and changes in attentional performance reached significance for decision time, a specific switching component associated with attentional set representations

These results highlight a link between higher attentional and emotional information processing, both processing pathways within the same dorsolateral cortico-subcortical network.

Gradually, neuroimaging studies are beginning to unravel the underlying dynamics of these affective processing pathways. Reduced left DLPFC functioning, within a fronto-subcortical network, is thought to play a pivotal role in the pathophysiology of depression and connects emotional and cognitive information processing (Drevets et al., 2002).

Importantly, neuroimaging research faces the critical problem of understanding cause and effect whereas rTMS can demonstrate causal relations in information processes. In psychiatry, however, rTMS has mainly been studied as a potential antidepressant treatment. Only limited research has been reported on cognitive effects of rTMS immediately after termination of stimulation, probably because cognitive effects have mainly been investigated to evaluate treatment safety aspects (Wagner et al., 2006).

Our results are indicative for the assumption that a single session of rTMS primary manipulates attentional processes with secondary effects, after two weeks of rTMS, on depressive symptoms. To our knowledge, we are not aware

of other controlled studies investigating the predictive role of specific attentional processes on treatment outcome (Leyman et al., 2007). Nevertheless, prior studies investigated acute changes after rTMS that may trigger antidepressant outcome.

Wagner and co-workers (2006) investigated the effects of one session of rTMS in healthy volunteers using a divided attention task. Based on their results, these researchers proposed that the acute effects of rTMS on cognition maybe produced by identical neurochemical changes that underlie successful antidepressant treatments. However, the fact that the study was based on a group of healthy volunteers, made it difficult to link attentional changes during the hours after an rTMS session with the neurochemical changes underlying the antidepressant treatment.

Shajahan et al. (2002) demonstrated an increased perfusion in the ACC after the first rTMS session in depressed patients, but reported no improvements of verbal fluency. However, verbal fluency might not be an optimal choice to represent processes associated to the DLPFC and the left dorso-lateral circuit. In line with our results, a study of Möller and co-workers (2006) found that the P300, a major endogenous brain Event-Related Potential (ERP) component which has been found to be reduced in patients with depression, was significant increased in amplitude after rTMS over the left prefrontal cortex compared to sham stimulation. An increase in P300 amplitude is indicative of improved attentiveness (Picton, 1992 in Möller et al. 2006). Most important, no significant antidepressant effects after five days of stimulation were found in this study. Finally, Bermpohl et al. (2006) suggested that the AGN, an affective Go/NoGo task, may be employed for its predictive value on behalf of the general clinical state of depressed patients during rTMS treatment. Given the linkage between emotional and cognitive functions, the latter affective/cognitive task might serve as a rough indicator for clinical treatment response.

However, in the current study we started using a non-emotional task focussing on attentional goal representations and our results suggest that Task Switching performance might hold promise as a predictor for the response of patients to multiple sessions of rTMS applied as a therapeutic instrument. Moreover, attentional functioning seems to play an important role in the progress of mood disorders. Our results suggest that rTMS primary influences higher attentional functioning. However, future research combining rTMS with

functional brain imaging is necessary for providing further evidence of these cognitive changes as a marker of antidepressant effects.

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GENERAL DISCUSSION

Although it has been well documented that depressive disorder is related to a reduced activity in brain structures that play a unique role in the interplay between emotional and higher attentional control processes, the underlying mechanisms remain unclear.

A review of the literature – in an attempt to explain these mechanisms – highlights the relevance of the interplay between cognitive and biological vulnerability factors in depression. The cognitive vulnerability factor describes the process of elaboration of negative schemata (e.g. Teasdale et al., 1988). The biological vulnerability factor describes a linear cascade process and emphasizes the mediation of impaired prefrontal functioning and cognitive control processes in the elaboration of these negative schemata (e.g. Fales et al., 2007).

The dorsolateral prefrontal cortex (DLPFC; Brodmann area 9/46) takes a central role in the activation and implementation of cognitive control.

The aim of this dissertation was to provide more insight in the pathophysiology of prefrontal functioning, as a part of the biological vulnerability factor of mood disorders. This dissertation is based on theories concerning the functional interactions of brain regions in the cortico-subcortical network.

We made use of two neurobiological techniques, a causal interference repetitive Transcranial Magnetic Stimulation (rTMS) technique and a correlational Event Related Potentials (ERP) technique to investigate the neuro-circuitry of cognitive control in healthy volunteers and depressed patients. The combination of these techniques provides a powerful tool to determine the functional interaction in brain regions important in mood and cognitive functioning.

This section presents an integrated overview of the main research findings. Theoretical implications and a discussion of limitations are presented. Finally, suggestions for future research are presented.

MAIN FINDINGS

Influence of rTMS over the left and right DLPFC on cognitive control in healthy volunteers

DLPFC activity seems to play a central role in the neural circuitry of cognitive control (top-down attentional control). Therefore we started our research using High Frequency repetitive Transcranial Magnetic Stimulation (HF-rTMS), a non invasive interference technique, to investigate the role of the DLPFC in specific aspects of cognitive control in healthy, right handed female volunteers. We have used two experimental paradigms, a Stroop task and a Task Switching paradigm to investigate the effects of rTMS on cognitive control. For these experiments, we made use of a double blind, within subjects by crossover sham (placebo) and active rTMS design.

For a number of years, top-down attentional control was thought to reflect the integrity of left frontal cortex functioning (Swick et al., 2002). However, recent literature on cognitive control regarding DLPFC activity shows a more heterogeneous picture of lateralisation (Kerns et al., 2004).

Therefore, different aspects of cognitive control could be involved that are related to left or to right DLPFC processing (Stürmer et al., 2007). Most important, the lateralisation of control processes seems to be task-specific (Rubia et al., 2006; Miller & Cohen, 2001). Also in our studies, stimulation over the left and over the right DLPFC posits a specific effect on Stroop task and Task Switching performance. Therefore, the acute stimulation effects on both experimental tasks will be discussed separately and will be integrated at the end of this section.

Influence on Stroop tasks

Using a regular Stroop task with two colours (red and green), one session of HF-rTMS over the left DLPFC had a beneficial effect on colour naming. Specifically, reaction times on both the incongruent and congruent trials decreased significantly after stimulation while no changes emerged after the placebo sham condition. Most important, although the Stroop interference effect was small, this effect was significantly decreased after rTMS and not after SHAM. Specifically, incongruent trials benefited more from stimulation as

compared to congruent trials, which is completely in line with an improved attentional set. Incongruent trials - as compared to congruent trials - benefit more from an enhanced attentional set because these trials require more attention for correct performance.

After exploiting a regular paradigm, we developed a modified Stroop task with two colours (red and green), with an instruction (word reading or colour naming) and with two expectancy conditions (no expectancy or expectancy for incongruent trials; with 50% or 80% incongruent trials respectively). After one session of HF-rTMS over the left DLPFC, we observed decreased RT for congruent and incongruent trials (with a regular Stroop effect) after colour naming but not after word reading. Most surprisingly, the interference effect was not decreased after stimulation. However, because both congruent and incongruent trials were decreased only after colour naming, this might indicate an increased general attentional set. We established these results in both expectancy conditions. This suggests that rTMS over the left DLPFC had no influence on task set adjustments concerning the expectancy of conflicting trials. Yet, no interactions of TMS/sham and other factors in the omnibus test were found which could indicate that TMS had no reliable effect. We have to be cautious interpreting the post hoc analyses in the absence of an overall significant interaction effect.

We have evaluated Stroop performance using the same modified paradigm before and after stimulation over the right DLPFC. After HF over the right DLPFC, RT was decreased in colour naming solely in the "expectancy" condition, whereas performance after the word instruction was not influenced. When expectancy for conflicting trials was not triggered, latencies for colour naming and word reading were not affected. Within the high expectancy condition, we have found a reversed Stroop effect. We can not explain why the Stroop interference effect was different in our rTMS study over the left DLPFC in contrast to over the right DLPFC. In all three experiments, error analyses reported no effects on task accuracy after rTMS. This excludes a speed-accuracy trade-off which is sometimes an explanation for inconsistent and unexplainable data patterns. But, as mentioned, we should be cautious in interpreting the data after stimulation over the left DLPFC.

This reversed effect after rTMS over the right DLPFC is can be explained because, if one expects incongruent trials, a congruent trial is an outlier and

reaction times are higher. Although this interference effect was involved in an interaction between stimulation and pre/post, this effect was not significantly changed after stimulation. This result does not follow the logic of an increased attentional set after colour naming.

Nevertheless, since RT's for both congruent and incongruent trials were decreased only after colour naming in all three experiments, we might conclude that the left and right DLPFC play a role in the implementation of cognitive control. This control is set by representing and actively maintaining the attentional demands of the task (imposing an attentional set) (Harrison et al., 2004). According to the "word" instruction, no behavioural changes on Stroop task performance were found, suggesting no general speeding effects of rTMS unrelated to the attentional set.

Within neurocognitive research, researchers have suggested that top-down executive control mechanisms further increase attention toward target stimuli when selection is made more demanding by distractor incongruency (conflict between target and distractor stimuli) (e.g. Banich et al., 2000). It is important to mention that, although incongruent trials benefited more from stimulation as compared to congruent trials using a regular Stroop task, reaction times on both Stroop trials decreased after stimulation. If the DLPFC would only be related to processes of distractor incongruency, one could question why the RT latencies of Stroop congruent trials were decreased in all three rTMS studies. Therefore, extending the theoretical accounts of this brain region, our results suggest that once expectancy for conflict increases (colour naming), the DLPFC enhances an attentional focus resulting in decreased RT latencies in congruent and incongruent trials. In the condition where participants don't prepare themselves to overcome an automatic response (word reading), RT on incongruent and congruent trials were not affected. These results are in accord with MacDonald et al. (2000) although these researchers did not discuss this issue. These latter researchers concluded that the nature of context representations (colour or word instruction) seems to play an important role in an increased attentional set which can be related to the left DLPFC (MacDonald et al., 2000). It seems that the DLPFC is not just activated by distractor incongruency, but more to the expectancy of conflicting information.

This expectancy for conflicting trials was manipulated using a trial by trial instruction but also using a task block instruction. Following left and right

DLPFC stimulation, we have found different Stroop results related to the task expectancy indicating a lateralisation for specific task processes.

Relatively few scientists have addressed this lateralisation question for strategic cognitive control in Stroop task performance. First we will consider left lateralized effects on cognitive control and subsequently right lateralized effects will be discussed.

Egner & Hirsch (2004) demonstrated that cognitive control in Stroop tasks is implemented by left medial and left lateral prefrontal cortices that bias processes in regions that have been implicated in high-level perceptual and motor processes. Banich et al. (2001) found robust left DLPFC activation when the attentional set was difficult to impose. In addition, using ERP's, Lansbergen et al. (2007) also established a crucial role of the left DLPFC in Stroop performance.

In our research, stimulation over the left DLPFC induced a general effect after the colour instruction since rTMS established an effect in both expectancy conditions. It might therefore be that the left DLPFC also keeps top-down attentional control on line in conditions where strategic processes are less triggered and therefore difficult to impose. However, because of some shortcomings in this study, we have to be cautious in interpreting the results. Nevertheless, using a regular Stroop task with colour naming, the beneficial effects of rTMS over the left DLPFC on both congruent and incongruent trials are in accordance with main research findings of MacDonald et al. (2000).

Wagner and co-workers (2001) demonstrated, using an event-related fMRI study, that the right DLPFC is essential in monitoring and selecting goal relevant representations. Kerns et al. (2004) established a positive correlation between Stroop accuracy and activation in the right DLPFC and suggested that response conflict engages right DLPFC. Within this context, the right DLPFC seems to be specifically activated in conditions where attentional control is elicited for reducing the conflict (Kerns et al., 2004). This is in accord to our research demonstrating that stimulation over the right DLPFC affected response latencies after a cue (colour naming) alerting for the upcoming conflict. This emerged only in conditions where strategic processes are highly engaged for optimal task performance (high expectancy condition). It seems that right DLPFC activation is more confined in cognitive control processes. Only when preparatory strategic processes are triggered in the expectancy conditions and an instruction alerts for

extra strategic attention (colour instruction), the right DLPFC seems to be activated.

Influence on Task Switching tasks

We have used a Task Switching paradigm with two blocks of either repetitive visual or repetitive auditory trials. During a third block, participants were prepared for visual trials and a distracting cue alerted for the upcoming auditory switch trial.

For visual trials, a component of endogenous information processing (Decision Time; DT) and a component of psychomotor speed (Movement Time; MT) were distinguished. For auditory trials, total reaction times were registered after an alerting cue.

After a single session of HF-rTMS over the left DLPFC, DT of visual switch trials was decreased. No effects on MT of visual switch trials or on auditory switch trials were found in this placebo controlled design. On the other hand, reaction time on cued auditory switching trials decreased significant after rTMS over the right DLPFC. Cues instructed subjects to switch attention from visual trials to reaction to auditory trials.

Because both trial types in our Task Switching paradigm made use of different modalities, some caution is warranted regarding conclusions concerning lateralisation effects on set switching. Nevertheless, previous research has successfully investigated lateralization effects of the DLPFC in Task Switching performance. A recent lesion study with patients with right frontal and left frontal lesions found that both groups showed larger switch costs, but apparently for different reasons (Aron et al., 2004).

Patients with lesions in the left frontal cortex, more specifically the left middle frontal gyrus, reported problems with top-down attentional control for the maintenance and the establishment of a task-set (Aron et al., 2004). Luks et al. (2007) demonstrated greater activity within the left DLPFC during preparatory allocation of attention and the employment of a regulatory strategy whenever the task demands are known. These authors suggested that the amount of preparatory activity may depend on the specificity with which task demands are identified and with which an attentional strategy can be organized in advance of stimulus presentation to facilitate stimulus processing and response selection.

These results are in line with our research demonstrating effects of stimulation over the left DLPFC on DT in visual switch trials. In our data, it seems that the left DLPFC plays a role in endogenous control when prospective and active reconfiguration for a specific task (DT) has been augmented.

Lesions to the right prefrontal cortex, more specifically the right inferior frontal gyrus, manifest itself in impairments in the inhibition of task sets and/or responses. Several neuroimaging studies have observed greater activity for cue initiated preparatory processes in the right lateral prefrontal cortex (Brass & von Cramon, 2004; Dreher & Berman, 2002; Sohn et al., 2000). Right DLPFC was found to be only activated when information about task switches was available (Sohn et al., 2000).

Our results suggest a specific right lateralized mechanism to deal with task cue presentation to ensure the allocation of the appropriate attentional resources to overcome the conflict in switch trials.

When conceptualizing the results of all abovementioned task switching lateralisation studies, left and right Task Switching performance can be interpreted in the light of attentional and intentional set (Rushworth et al., 2005). "Endogenous preparation" (attentional set implementation) and "adjustment in response to the external stimulus" (intentional set switching) engage dissociated cognitive acts and neuropsychological components in cognitive control. In the paradigm we used, we manipulated attentional set by the explicit task instruction to be prepared for visual trials, and cued auditory trials were used as a distractor requiring intentional set switching. Latencies on visual switch trials were used as an index of attentional task set representation and we found only effects on visual DT after left stimulation. Cued auditory switch trials were used as an index of intentional set representations and we found only rTMS effects on RT of auditory trials after right stimulation.

On the other hand, one should be cautious in interpreting the significant effects of rTMS on DT of visual trials. Given a possible trade-off between DT and MT ("first lift and later plan strategy") of visual trials, it is challenging to disentangle both components of visual trials (Fisher, 2003). In order to warrant this manipulation between DT and MT, catch trials (trials in which a cue but not a target is presented) would be used. The reaction times on those visual trials should correspond to DT of visual trials and counter a possible trade-off between DT and MT. These catch trials were not used in the current experiments and

might put into question the validity of the results. However, the manifestation of a trade-off pattern between DT and MT within visual switch trials after rTMS stimulation should result in a negative correlation between reaction times of both components. However, we found a positive correlation between DT and MT before rTMS and no correlations between both components on the other stimulation moments. This might indicate that no different response strategy was used after rTMS stimulation.

Another point of discussion is that only 5 auditory and 3 visual trials out of 29/28 trials in the switch blocks were repetitions. The amount of repetitive and switch trials is not sufficient for analysing repetitive and switch trials separately in the switch block (block 3). Therefore, we did not evaluate the comparison within switch blocks between repetitive and switch trials. We have chosen to consider the switch costs, more specific auditory and visual switch trials (in milliseconds), correcting by individual speed processing [RT of auditory and visual switch trials of block 3 minus RT on repetitive trials of block 2 and block 1 respectively], as the dependent variables. Although one might question the unpredictable nature of the switch since most trials were switch trials, we did find differential response patterns for both modalities. Rogers and Monsell (1995) demonstrated an active "anticipatory" component of task-set reconfiguration which is endogenously triggered and that, given a somewhat predictable switch in task and time, can be initiated prior to stimulus presentation during an alternating task-switching paradigm.

So it seems that stimulation over the DLPFC has triggered an anticipatory attentional component to facilitate reactions to switch trials in the third switch block. Most interesting, after stimulation over the left DLPFC, we have found faster reaction times on visual switch trials of block three as compared to repetitive trials in the first two blocks. We are not aware of similar data patterns in the literature which makes the interpretation of these data difficult. One could argue that anticipatory control was so high that, even at baseline, it resulted in very fast reactions to switch trials. However, this could also indicate a speed-accuracy trade-off because subjects responded faster (too fast) possibly resulting in a lot of mistakes. It was the case that the task instruction during the left rTMS study putted more emphasis on the difficulty and importance of the visual trials in the third block. This could have triggered the motivation of participants, but could also lead to more errors. For sorting out this speed-accuracy trade-off

explanation, we should analyze the error data. However, because of technical problems, the registration of errors was not accurate. This is a major shortcoming because inconsistent data patterns can not be explored in depth. Further research should ensure that the error registration is correct and interpretable.

Moreover, we have to mention a conceptual problem concerning this task switching paradigm. In a strict sense, this paradigm is not a switching task paradigm. The reason is that the auditory task consists of only one stimulus-response mapping. A task usually consists of at least two stimulus-response mappings. In this paradigm, the auditory trials were used as a distractor. However, because only switch auditory trials were used where the interference with visual trials was maximal, switch costs on these trials can nevertheless be analysed.

Conclusions

Since mood was not influenced by HF-rTMS, potentional effects of rTMS on cognitive functioning could be investigated.

The key findings of our rTMS studies provide support for the fact that the DLPFC mediates top-down attentional control that favours task relevant response pathways over competitors. These conflict reducing attentional processes can be labelled as the regularative component of cognitive control. This brain region is thought to implement an attentional set that is related to context representations to prepare for conflicting trials (Banich et al., 2000; Miller & Cohen, 2001).

Most interesting, we have used two different experimental tasks, the Stroop task and the Task Switching task, to measure the concept of ‘cognitive control’. Both tasks seem to display a similar effect on cognitive control while using different experimental methods.

Stimulation over the left DLPFC had a general influence on preparatory attentional set representations and resulted in task relevant information being continuously kept online. In Stroop tasks, this resulted in general decreased RT’s in colour naming for both congruent and incongruent trials in both high and no expectancy conditions. In Task Switching, this resulted in decreased DT on

visual switch trials, an endogenous component also related to a general preparatory response.

On the other hand, stimulation over the right DLPFC had a specific influence on cued switch trials, when temporal strategic processes are online to reduce the attentional conflict. In Stroop tasks, this implied that RT's on congruent and incongruent trials were decreased, only in the high expectancy blocks, which is also the condition during which people are prepared to resolve conflict. In Task Switching, this was reflected by an intentional set when a cue announced the upcoming switch. Therefore, the right DLPFC plays a crucial role when participants have foreknowledge of the upcoming switch because of task context representations.

Because our rTMS results are in line with neuroimaging data that relate DLPFC activity to top-down attentional control processes, it provides experimental proof that a single session of HF-rTMS in healthy volunteers can influence cortico-subcortical functioning. However, no conclusions can be drawn from the interactions between brain regions within the cortico-subcortical circuit. Given the importance of this network in the biological vulnerability for depression, research should focus on its temporal and functional working mechanisms.

ERP correlates of cognitive control in healthy volunteers

Neuroscience research revealed that the implementation of cognitive control is supported by a cortical fronto-dorsal network of interactive structures including the anterior cingulate cortex (ACC) and dorsolateral prefrontal cortex (DLPFC) (Blasi et al., 2006), which have been related to evaluative and regulative control respectively.

More insight is necessary to determine the temporal aspect of these two attentional components within cognitive control. Scalp recorded event-related brain potentials (ERP) offer temporal resolution of neural processes, permitting a precise analysis of the time course of neural events supporting task performance (Kok et al., 2001).

Therefore, we investigated ERP components during Stroop task performance. Using a modified Stroop task (high and low conflict condition) with no prior instruction before each trial, our behavioural data showed a large interference effect when incongruent trials are infrequent and evoke evaluative control during

this high conflict condition. In contrast, the interference effect was significantly smaller when incongruent trials were frequent (low conflict condition) and indicate that regulative processes reduced the attentional conflict. These results are in line with other studies (e.g. Carter et al., 2000).

ERP correlates revealed an unexpected modulation of frontal N2 at around 270 ms, and expected modulations N450 at around 440 ms and a SP from 650 to 750 ms. The N450 component has been related to evaluative processes (associated to ACC activity) and the Sustained Potentials (SP) seem to reflect regulative processes (related to DLPFC activity) (e.g. West et al., 2000; Liotti et al., 2000). The N2 is supposed to reflect conflict detection and could be associated to activity in the ACC (Van Veen & Carter, 2002).

It seems that early conflict detection (cfr. N2) preceded control implementation processes (cfr. SP) in the low conflict condition (80% incongruent trials). In the high conflict condition (80% congruent trials), conflict detection (cfr. N450) emerged later in information process, approximately 470 ms after stimulus onset, but preceded regularative processes (cfr. SP). When conflict is expected and regulative processes emerge, conflict was detected earlier in the information process as compared to a condition when no regulative processes emerge.

Research evidence linked the N2 component, as well as the N450 component, to activity in the ACC (van Veen & Carter, 2002). When the N2 and the N450 component are linked to the same neural generator, it might suggest that activation of the ACC preceded activation of the DLPFC for reducing further attentional conflict. These conclusions are comparable to research evidence of Botvinick et al. (2001) and will be discussed in the theoretical implications of this chapter.

Cognitive control in depressed patients

In healthy volunteers, we could demonstrate that a single session of rTMS can influence cognitive control processes related to the cortico-subcortical circuit involved in depression. An important next step was to use a similar design and analogous stimulation parameters to investigate attentional mechanisms in depressed patients before and after rTMS.

In our first exploratory study, we could demonstrate that one session of HF-rTMS over the left DLPFC in medication free depressed patients had a beneficial

effect on Task Switching performance. More specifically, we found that reaction time latencies of switch trials during the Task Switching block for both visual and auditory trials significantly decreased after rTMS whereas sham yielded no effects. No differences on the repetitive trials of the single task blocks were found, which indicates that our results are not caused by a general increased arousal.

For visual switch trials, in contrast to peripheral movement time (MT), Decision Time (DT) was influenced by the rTMS procedure. In addition, latencies on auditory switch trials were also decreased. This implies that the acute stimulation effects are related to central cognitive functioning. Since we have used a sham controlled crossover design, the improved cognitive performance associated with HF rTMS could not be related to a non-specific effect.

In a second more specific study, we investigated the influence of a single rTMS session as compared to two weeks of daily HF-rTMS over the left DLPFC in a homogeneous group of medication free therapy resistant depressed patients who had failed to respond to at least two antidepressant medications.

Subjective mood reports did not change after a single session of HF-rTMS. However, more then half (57%) of our therapy resistant depressed population showed a decrease of at least 50% of their HAMD score after two weeks of daily HF-rTMS over the left DLPFC (positive treatment response).

Only within our group of treatment responders, we observed a significant improvement in Task Switching performance after one double blind placebo controlled rTMS session. We could demonstrate that a specific component of visual switch trials, i.e. decision time (DT), and reaction times on auditory switch trials were improved after HF-rTMS. Movement time (MT) of visual switch trials, as being the motor component of switching, was not influenced by rTMS. Most importantly, beneficial changes in DT after one session of HF-rTMS were predictive for beneficial mood effects after two weeks of rTMS in treatment responders.

One could argue that an improved mood of the group of responders is likely to have a facilitatory effect on cognitive set switching. Keedwell et al. (2005) looked at the effects of positive mood induction on switching in two separate tasks: alternating fluency (switching between retrieval of words from two different categories) and alternating Stroop performance (switching between

naming the ink colour of a word and reading the word from one stimulus to the next). In both switching tasks, positive mood caused poorer performance compared to neutral mood. In contrast, we demonstrated that a positive mood was associated with an increased task performance. As abovementioned, we found that positive changes in Task Switching performance were correlated with and even predictive for future beneficial mood changes.

Other researchers have also reported correlations between a positive mood development and cognitive progress. For example, studies have shown that impaired executive function in patients with major depressive disorder (Elliott et al., 1998; Murphy et al., 2001) was correlated with depression severity (Smith, 1994) and illness duration (Borkowska & Rybakowski, 2001). These studies add evidence for the relationship between emotional and attentional information processing.

Consequently, negative mood impairs cognitive performance (e.g. Borkowska & Rybakowski, 2001), but as in our research, cognitive improvements are also related to later mood improvements.

We are aware of two controlled studies investigating the immediate effects of DLPFC brain stimulation on cognitive tasks in depressed patients. Boggio et al. (2007) observed performance improvement in an affective go-no-go task (AGN) after one single session of anodal transcranial direct current stimulation (tDCS) of the DLPFC in depressed patients. In accordance, Bermpohl et al. (2006) showed that a decrease in the activity of the right dorsolateral prefrontal cortex, using low frequency rTMS, also enhances the performance in the same AGN task in depressed patients (Bermpohl et al., 2006). In both studies, activity in the left dorsolateral prefrontal is expected to increase directly (via anodal tDCS of the left DLPFC; Boggio et al., 2007) and indirectly (via inhibition of the right DLPFC; Bermpohl et al., 2006).

Boggio et al. (2007) found no correlation between performance in the AGN task and depression improvement after 10 days of tDCS treatment. These results suggested that the effects of a single session of tDCS on cognitive performance cannot be used to predict the impact of repeated sessions of tDCS on mood improvements. In addition, Bermpohl et al. (2006) also failed to find a correlation between the effects of a single session of rTMS on attentional processes and mood measurements.

In accordance to Boggio et al. (2006) and Bermpohl et al. (2006), other researchers proposed that cognitive changes might occur independently from mood changes (Wagner et al., 2006). Moreover, other studies showed improvements in executive functioning, after five sessions of HF-rTMS of the left DLPFC (Moser et al., 2002) and effects on working memory after tDCS of the left DLPFC in depressed patients (Fregni et al., 2006), that were not correlated to mood improvement.

In contrast, our data show that increased DT, associated with attentional set representations, after a single session of HF-rTMS, has predictive value for the antidepressant treatment outcome. In line with these observations, the correlation between pre and post treatment changes in depression scores and changes in DT reached significance.

From both a psychological and neurobiological perspective, selective attention and top-down control are heterogeneous constructs. Therefore, when exploring the interplay between attentional and emotional functioning, it might be that very specific components of cognitive control must be investigated. When looking at the cognitive tasks used in the abovementioned studies (Boggio et al., 2007; Bermpohl et al., 2006), it might be that only general aspects of working memory were involved in performing these executive tasks. The selection of the specific task we used was based on our studies in healthy volunteers.

In our healthy volunteer's research, when investigating cognitive functioning related to the left DLPFC, we could demonstrate that specific aspects of imposing an attentional set are affected after stimulation. rTMS over the left DLPFC influenced strategic attentional set implementation processes in order to reduce the upcoming conflict.

Our results highlight a linkage between higher attentional and emotional information processing, both processing pathways within the same dorsolateral cortico-subcortical network. This is indicative for a central role of these attentional processes in the antidepressant development. These findings are in accord with the overview of the literature in the introduction which highlights the mediation of higher attentional processes, as part of a biological vulnerability, on the elaboration of negative schemata.

THEORETICAL IMPLICATIONS

Cortico-subcortical circuit: functional interactions in healthy volunteers

Given the ERP correlates (in chapter six), which demonstrate that ACC activity plays a specific role in conflict detection, we present an overview of the role of ACC in cognitive control. Thereafter, we implement our rTMS findings concerning the role of the DLPFC in cognitive control processes (chapter one to five). Finally, we integrate these findings into functional interactions between the DLPFC and ACC in the cortico-subcortical circuit in order to extend the conflict monitoring hypothesis.

The conflict monitoring scheme proposed that the DLPFC is important in implementing cognitive control and maintaining an attentional set (Botvinick et al., 2001). The ACC contributes to executive functions by evaluating the level of conflict and indicating the degree to which top-down control needs to be engaged (conflict detection) (Botvinick et al., 2001). A meta-analysis of Botvinick et al. (2004) established an increase in the activity of the dorsal (cognitive) division of the ACC during high-conflict/low-control trials relative to the congruent trials, concluding that it is more closely tied to conflict detection than to top-down control.

Nevertheless, the function of the ACC in conflict processing appears to be more complex than is postulated by the conflict monitoring scheme (Ruff et al., 2001). These latter researchers demonstrated that the nature of the ACC activation does not correspond to the magnitude of conflict as measured by RT differences.

In addition, Magno et al. (2006) recently demonstrated ACC activation when subjects rejected (i.e. they were allowed to “pass” on) difficult trials. These researchers proposed that the ACC may not simply detect conflict but is rather active relative to the degree to which cues predict the need to inhibit a response.

This corresponds to our ERP data, emphasising a different role for ACC in conflict detection in high and low conflict conditions (cfr. N450 & N2 component respectively). In both Stroop conditions, conflict detection emerged before the implementation of top-down regulative processes (Sustained Potential (SP) component). When conflict is expected (80% incongruent trials) and regulative processes decrease the degree of the conflict, ACC activity emerged earlier in the information process as compared to a condition when no regulative

processes emerge. In the high conflict condition, with 80% congruent trials, conflict detection emerged later in the information process as compared to the low conflict condition.

Overall, if the ACC is related to cognitive processes over and above pure conflict detection, these cognitive processes might be associated with prior inhibition of dominant S-R mappings resulting from top-down processes (Ruff et al., 2001). Therefore, ACC interaction with DLPFC activity, both crucial in cognitive control, should be discussed.

Following our rTMS research, DLPFC activity is related to the strategic implementation of an attentional set for reducing the conflict. Most important within our studies, DLPFC activity can be triggered when presenting mostly incongruent trials and results in reduced RT on congruent and incongruent trials. In addition, our ERP data confirm the DLPFC function within regulative processes and top-down attention implementation within the low conflict condition (80% incongruent trials).

Although an ongoing debate addressed the precise role of ACC and DLPFC activity (as above discussed), current questions arise regarding the functional and temporal interaction between both brain regions in the cortico-subcortical circuit.

As put forward in our ERP research, ACC activity seems to precede DLPFC top-down processes. However, both brain regions establish a reciprocal interaction, which makes it difficult to conclude 'which region comes first' (Markela et al., 2006). Nevertheless, our stimulus locked ERP results supply evidence for the negative loop interaction between DLPFC and dorsal ACC activity in the cortico-subcortical circuit. This negative loop has an influence on temporal features of ACC activity and depends on the amount of strategic processes that have been implemented.

When an incongruent trial is encountered within series of congruent trials, conflict is high. However, this incongruent trial is again followed by series of congruent trials which do not require cognitive control. This means that on every incongruent trial, the interference is high and regulative processes are low. Therefore, since regulative processes have not been organized for reducing the conflict during incongruent trials, conflict evaluation emerges later in the information process as shown by the N450.

On the other hand, when regulative processes (related to DLPFC activity) have increased the attentional set, it results in fast conflict detection (as shown

by the N2 which is related to ACC activation). It might be that activity in the DLPFC alerts the ACC for early conflict detection and results in reduced interference between congruent and incongruent trials in subsequent trials. This can be confirmed by our rTMS studies in healthy volunteers demonstrating decreased RT latencies in congruent and incongruent trials after the colour naming instruction.

To summarize, after the presentation of a stimulus, activity in the ACC always precedes DLPFC activity. However, the nature and functional interaction of the ACC depends upon the DLPFC activity that has been elicited. So it seems that the question of "which comes first" is less relevant as compared to the temporal aspects of ACC activity (early or later conflict detection) which depends on the amount of conflict.

Regulative processes result in early conflict detection making the interference between congruent and incongruent trials lower. Most important, DLPFC activation seems to play a central role within these interactions for cognitive control.

Cortico-subcortical circuit: functional interactions in depressed patients

Impaired cortico-subcortical functioning in depressive disorder reflects structural abnormalities leading to a miscommunication of two reciprocal neural systems: (1) a "ventral system" important for the identification of the emotional significance of a stimulus, and for the production of both normal and abnormal affective states; (2) a "dorsal system" important for executive function, including selective attention, planning, and effortful regulation of affective states involved in the performance of cognitive tasks and the regulation of affective states (Mayberg et al., 1999).

In the following paragraphs, we will discuss the specific role of brain regions (DLPFC, dorsal and ventral ACC, and amygdala) in the cortico-subcortical circuit and integrate our results within the model of Taylor and Fragapanos (2005).

Within our rTMS research in healthy volunteers and depressed patients, the DLPFC seems to be related to top-down attentional set implementation in order to strategically reduce the expected conflict. In these studies, we have used non-emotional stimuli. Nevertheless, the DLPFC area, traditionally thought of as a

pure cognitive system, can be modulated by the emotional value of the material being processed (Gray et al., 2002; Perlstein et al., 2001; Sergerie et al., 2005).

An overview of the literature demonstrates that the DLPFC region (Brodmann area 9/46) is sensitive to emotional and cognitive significant aspects of stimuli (Hikosaka & Watanabe, 2000). DLPFC has been found to be involved in affective processing in electroencephalography (EEG) studies (Davidson & Henriques, 2000) in emotional judgment when compared to non-emotional judgment (Keightley et al., 2003) and in a range of emotional functioning alterations in schizophrenia (Perlstein et al., 2001). Moreover, León-Carrión et al. (2007) showed recently that an increment in subjective arousal leads to direct activation within the DLPFC. This might imply that when tasks are (expected to be) difficult and challenging, subjective arousal leads to activation in DLPFC which even persists after stimulus cessation and this does not occur with non-arousing stimuli.

All together, these research findings imply that the DLPFC can regulate, besides task relevant information, the identification and registration of emotional stimuli.

Within the theoretical model of Taylor and Fragapanos (2005), this identification and registration of the emotional valence of stimuli is related to the ventral circuit, consisting the ventral ACC, orbitofrontal cortex and amygdala. Shalitz et al. (2006) indicated that activation within ventral ACC can be modulated by the emotional valence of stimuli. Overall, this brain region is preferentially engaged for sadness but not for happiness. In addition, increased activity within the amygdala, important for the identification of the emotional significance of a stimulus and production of affective states, may result in an increase of experience of specific negative emotions (Shalitz et al., 2006).

All together, the dorsal regions can regulate the attentional processes but the registration and identification of emotional stimuli is related to ventral cortices.

Within this context, an overview of the literature reveals that the source of the negativity bias is unclear. This negativity bias may reflect a top-down deficit in the control of attention. This means that the feedback of dorsal (cognitive) regions to ventral (emotional) regions is more ore less absent. Alternatively, this bias may reflect an enhanced bottom-up response to negative emotional stimuli that automatically dysregulates cognitive control mechanisms (e.g. Fales et al., 2007).

Most interesting in our research, increased attentional set representation after a single session of HF-rTMS in therapy resistant treatment patients is predictive for the antidepressant treatment outcome after two weeks of rTMS. rTMS over the DLPFC might activate cognitive control and, in doing so, primarily repairing the balanced and reciprocal interaction between dorsal and ventral brain regions. This increased attentional set might be crucial for the regulation of emotional processing.

Structural and functional impairments in dorsolateral and dorsal anterior cortices are associated with impairments in regulation of affective states and behaviour.

We can suggest that, because the antidepressant effects seem to be modulated by attentional processes, this mood dysregulation might be the consequence of a top-down attentional bias. Both psychological and neurobiological studies have investigated this negativity bias.

From a psychological view, it has been shown that depression is associated with deficits in cognitive inhibition (Joormann, 2004), working memory, and episodic memory (Joormann et al., 2007). More specific, depressed individuals have difficulty disengaging attention from emotionally negative material, inhibiting representations of negative material in working memory, and resisting their propensity to selectively retrieve negative memories from long-term storage.

In accordance to this top-down attentional bias, researchers in our lab recently found maintained attention for negative stimuli after long stimulus presentation in an Exogenuous Cueing Task (1500 msec) (Leyman et al., 2007), and problematic inhibition of negative material during a Negative Affective Priming (NAP) task that could be observed 2000 ms after the prime trial (Goeleven et al., 2006) in depressed individuals. This suggests that later elaborative attentional processes in stead of early identification processes seem important for the regulation of negative emotions, related to top-down schema driven cognitive control. Based on these results, Goeleven et al. (2006) concluded that impaired inhibition of negative affect, found in depressed patients, could be an important construct in cognitive theories on depression linking cognitive biases to neuropsychological impairments in depression.

Joormann et al. (2007) argued also that difficulties in mood regulation play an important role in emotional disorders, and that there are important individual

differences in the effectiveness of mood-regulation processes. This impairment in the regulation of negative stimuli and emotions could reflect a vulnerability factor in depression.

From a neurobiological point of view, Fales et al. (2007) recently confirmed that a failure in recruiting the cognitive control related to DLPFC activity suggests that patients are not able to suppress unattended negative distracters. These researchers suggested that the negativity bias has multiple sources, implicating both top-down and bottom-up dysfunctions. Our research can only confirm the central implications of attentional functioning as being a top-down dysregulation in the DLPFC.

Research evidence has shown that the success of an antidepressant treatment is different for each individual. Recently, it has been argued that the heterogeneity of research findings might be due to a high variability across depressed patients in their response to rTMS (Bermplohl et al., 2006). Our research suggests that the registration of specific processes related to attentional set improvements might be predictive for the success of the antidepressant treatment effect of rTMS.

LIMITATIONS

Besides limitations that were already mentioned in each of the preceding chapters, some general limitations regarding this project must be mentioned.

In the context of the Stroop task, the Conflict Monitoring theory (Botvinick et al., 2001) predicts that strong ACC engagement should be followed by behaviour reflecting relatively focused attention (strong top-down control), and weak ACC engagement by less focused behaviour.

A striking confirmation of this observation was reported by Kerns and colleagues (2004). They found that, when incongruent trials were associated with high ACC activity, relatively low interference was observed on the subsequent trial. This fits well with the idea that strong ACC engagement leads to a reinforcement of top-down control and predicts DLPFC activity in the upcoming trial. Accordingly, following trials with strong ACC engagement, there was relatively strong activation in dorsolateral prefrontal cortex, a brain region closely associated with cognitive control (Botvinick et al., 2004).

Moreover, using TMS over the left DLPFC in right handed volunteers, Stürmer and co-workers (2007) recently demonstrated interruptions in processing context-dependent modulations after a preceding conflict in an interference task. In line with these biological comments, Mayr et al. (2003) documented a stimulus-response transition which makes it challenging to discuss decreased reaction times patterns. Decreased reaction times can be a result of top-down attentional set but also a result of bottom-up priming of the previous trial. This is most important in our two colour Stroop tasks in which every trial had a repetitive feature, at stimulus or response level.

Therefore, using the modified Stroop paradigm as used in chapter 2 and 3, we should have questioned whether switching to incongruent colour naming would lead to disproportionately stronger Stroop interference only after previous congruent word reading. These extra analyses might have been informative about the influence of rTMS on the interaction between ACC and DLPFC brain regions.

In addition, researchers have observed that DLPFC activity is related to the conflict level and brings this information to the following trial for the adjustment of cognitive control (Mansouri et al., 2007). In a challenging environment, we need to optimize the usage of our limited cognitive resources, and the DLPFC might support an adaptive and dynamic tuning of our cognitive control processes by maintaining information of recent cognitive challenges. It also seems that the DLPFC maintains information regarding previously experienced conflict necessary for conflict-induced behavioural adjustment.

This implies that in our ERP research, incongruent trials after incongruent trials would display decreased RT latencies as compared to a preceding congruent trial. However, these sequential behavioural effects have not been reported because of non-significant results. The reason for these null findings might be that in our Stroop design, the number of incongruent trials following congruent trials is very limited in the low conflict condition, which limits the power to detect differences. Therefore, sequential effects on electro-cortical data have not been analysed. However, it could be that, also with no effects on behavioural data, electro-cortical data can reveal the functional adaptation of DLPFC and ACC activity.

FUTURE RESEARCH DIRECTIONS

Cognitive deficits cause considerable impairments and restraints in daily life and have become one of the major clinical and research foci in recent years. According to our work using a Task Switching paradigm, specific aspects of cognitive control seem to be particularly relevant for the anti-depressant development. As being the regulative component of cognitive control, preparatory task set implementation revealed to be predictive for the antidepressant treatment outcome.

Within the context of cognitive control, related to the cortico-subcortical circuit, the question raised whether aberrant target regulative and evaluative processes might represent an underlying working mechanism in depression. However, the core phenomena of attention are brief and require fast resolution to accurately reflect timing and intensity and are best detected with sensitive neurophysiological indices (Kok et al., 2001). Therefore, the implication of attentional processes as a possible vulnerability factor for depression could be investigated measuring explicit ERP correlates in both currently and formerly depressed individuals, compared with healthy controls (no previous depression), to further demonstrate difficulties in regulative and evaluative processes. As compared to the abovementioned Task Switching paradigm that was used in our current experiments in depressed patients, regulative and evaluative components of cognitive control can be manipulated during the modified Stroop paradigm.

In our ERP research with healthy volunteers using this modified Stroop paradigm, we demonstrated that the N2/N450 ERP components (evaluative control) and the ERP slow wave (regulative control) can be manipulated through the amount of conflict for congruent and incongruent. More specifically, within the low conflict condition, we demonstrated very pronounced slow waves indicating regulative control interacting with early conflict detection.

There have been several studies, although presenting inconsistent results, of ERP in depression. To our knowledge, there have been no previous ERP studies investigating fundamental aspects of attentional control in major depression. Therefore, ERP correlates should be investigated in patients with a major depressive disorder. Executive impairments have been well documented in depressed patients. Given the hypoactivity within the dorsal prefrontal region in major depressive disorder, the temporal interactions between regulative and

evaluative processes might be impaired. These subtle indices could be used as a marker for an underlying working mechanism and a vulnerability factor in depression.

Another research topic concerns the measurement of ERP correlates during this modified Stroop paradigm in formerly depressed patients. Research should investigate if the amount of depressive episodes has an effect on attentional processes. If cognitive control processes represent a biological scar vulnerability factor, there should be a negative correlation between depressive episodes and regulative processes.

Most important, researchers so far have not focused on the precise effect of an antidepressant treatment on attentional control. Within this context, the influence of HF-rTMS over the left DLPFC on ERP correlates would be particularly interesting. Explicit attentional control processes should be analyzed before and after rTMS using ERP registration during Stroop task performance. Research should focus on both acute effects but also effects after two weeks of rTMS on ERP correlates of cognitive control.

However, we suggest that a pilot study should primary investigate the effects in healthy volunteers after a single HF rTMS session using the same modified Stroop task with a high and low conflict condition.

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CONCLUDING SUMMARY

A review of the literature emphasizes the interplay between cognitive and biological vulnerability factors in depression. The cognitive vulnerability factor describes the process of elaboration of negative schemata (e.g. Teasdale et al., 1988). The biological vulnerability factor emphasizes the mediation of impaired prefrontal functioning and cognitive control processes in the elaboration of these negative schemata (e.g. Fales et al., 2007). Cognitive control implementation is related to the dorsolateral prefrontal cortex (DLPFC; Brodmann area 9/46), a structure within the cortico-subcortical circuit.

The aim of this dissertation was to provide more insight in the pathophysiology of prefrontal functioning, as a part of the biological vulnerability factor of mood disorders.

We made use of repetitive Transcranial Magnetic Stimulation (rTMS) as a causal interference technique and Event Related Potentials (ERP) as a correlational technique to investigate the neuro-circuitry of cognitive control in healthy volunteers and depressed patients.

The key findings of our rTMS studies in healthy volunteers provide support for the fact that the DLPFC mediates top-down attentional control to implement an attentional set. These regulative processes are related to context representations to prepare for conflict trials (Banich et al., 2000; Miller & Cohen, 2001). Our stimulus locked ERP results in healthy volunteers supply evidence for the negative loop interaction between DLPFC and dorsal ACC activity in the cortico-subcortical circuit. This negative loop has an influence on temporal features of ACC activity and depends on the amount of strategic processes that have been implemented. Based on these results, we further investigated cognitive control processes in depressed patients.

After two weeks of HF-rTMS over the left DLPFC in depressed patients, depressive symptoms were improved in more then half of our therapy resistant population. After a single rTMS session, mood remained unchanged but we observed increased cognitive control in the group of rTMS responders. Most important, the influence of a single session of HF-rTMS on task switching

performance in therapy resistant treatment patients was predictive for the antidepressant treatment outcome after two weeks of rTMS.

Our results highlight a link between attentional and emotional information processing within a dorsolateral cortico-subcortical network. This is indicative for a central role of these attentional processes in the antidepressant development. These findings are in accord with current literature highlighting the mediation of higher attentional processes on the elaboration of negative schemata.

NEDERLANDSTALIGE SAMENVATTING

Een overzicht van de literatuur geeft aan dat de interactie tussen cognitieve en biologische kwetsbaarheidfactoren een belangrijke rol speelt in depressie. De cognitieve kwetsbaarheidsfactor is gerelateerd aan het proces van een sterker wordende associatie tussen stressoren en negatieve schema's bij opeenvolgende depressieve episodes. De biologische kwetsbaarheidsfactor is gerelateerd aan het proces van een verlaagd cortico-subcorticaal prefrontaal functioneren en daaraan gerelateerde verminderde cognitieve controle bij de verdere verwerking van deze negatieve schema's in depressie. De implementatie van cognitieve controle wordt gerelateerd aan de Dorsolateraal Prefrontale Cortex (DLPFC, Brodmann gebied 9/46), een structuur die, samen met de dorsale Anterieure Cingulate Cortex (dACC, Brodmann gebied 24/32) deel uitmaakt van het corticaal-subcorticaal prefrontaal netwerk.

De doelstelling van dit project is om inzicht te verkrijgen in de pathofysiologie van het corticaal-subcorticaal functioneren dat deel uitmaakt van de biologische kwetsbaarheidsfactor binnen stemmingsstoornissen. We maakten gebruik van een causale repetitieve Transcaniële Magnetische Stimulatie (rTMS) techniek en een correlationele Event Related Potentials (ERP) techniek om het hersenfunctioneren met betrekking tot de cognitieve controle in gezonde vrijwilligers en depressieve patiënten te onderzoeken.

rTMS-studies in een groep van gezonde vrijwilligers konden aantonen dat de DLPFC gerelateerd is aan strategische aandachtscontrole door het reguleren van de aandachtscontrole. De aandachtscontrole wordt opgewekt door de voorbereiding op conflicterende trials. ERP-correlaten bij gezonde vrijwilligers hebben een centrale rol voor regulatieve processen aangetoond binnen een negatieve interactie tussen regulatieve (DLPFC) en evaluatieve (dACC) activiteit in het prefrontaal circuit. Gegeven deze resultaten bij gezonde vrijwilligers, hebben we verder cognitieve controle processen onderzocht in een groep van depressieve patiënten.

Onderzoek bij depressieve patiënten heeft aangetoond dat na een periode van twee weken hoogfrequente (> 1 Hz, HF)-rTMS ter hoogte van de linker DLPFC,

depressieve symptomen verbeterden in meer dan de helft van een therapieresistente populatie (rTMS-responders). Meer specifiek konden we aantonen dat na een eenmalige rTMS-sessie de stemming stabiel bleef, met een verbeterde cognitie enkel in de respondersgroep. Deze verbeterde cognitieve controle na één stimulatiesessie bleek voorspellend te zijn voor de antidepressieve werking van rTMS na twee weken.

Deze resultaten tonen aan dat er een link bestaat tussen aandachts- en emotionele informatieverwerking binnen het corticaal-subcorticaal prefrontaal netwerk en dat regulatieve processen een cruciale rol spelen in deze interactie. Deze bevindingen stemmen overeen met de literatuur die aangeeft dat afwijkende regulatieve controle gerelateerd is aan de ontwikkeling en het behoud van negatieve schema's.