Full title:

The role of the left DLPFC in endogenous task preparation: an experimental repetitive Transcranial Magnetic Stimulation study

Running head:

Cognitive effects of rTMS of the left DLPFC

Marie-Anne **Vanderhasselt** [1], Rudi **De Raedt** [1], Lemke **Leyman** [1], Chris **Baeken** [2]

[1] Ghent University, Department of Psychology, Henri Dunantlaan 2, B-9000 Ghent, Belgium.

[2] Department of Psychiatry, University Hospital Brussels (U.Z. Brussel), Laarbeeklaan 101, B-1090 Brussels, Belgium.

Characters (including spaces) = 30 034

Corresponding author:

Marie-Anne Vanderhasselt
Ghent University
Department of Psychology
Henri Dunantlaan 2,
B-9000 Ghent,
Belgium.
Tel.: +3292648612;
Fax: +3292646489.
Email address: MarieAnne.Vanderhasselt@UGent.be

This research was supported by a grant from the Scientific Fund W. Gepts UZ-Brussels and funded by Grant BOF-01J08107 from Ghent University. Dr Vanderhasselt is a postdoctoral fellow of the Research Foundation _ Flanders (FWO) (FWO08/PDO/168).

Authors report no conflicts of interest.

ABSTRACT

The precise role of the Dorsolateral Prefrontal Cortex (DLPFC) in attentional set activation is still not entirely clear. Hence, repetitive Transcranial Magnetic Stimulation (rTMS) can be applied to interfere with neural processing to determine whether a specific brain area is required in task performance.

In this study, the influence of one session of High Frequency (HF)-rTMS of the left DLPFC on a reaction task using visual and auditory trials was investigated. Participants were instructed to pay constant attention to the visual stimuli, whereas they were informed that distracting auditory stimuli could also appear. Participants had to respond to both stimuli.

Results indicate that after one session of HF-rTMS of the left DLPFC, performance was improved for the primary task, but not for the distracters. Specifically, we found decreased RT for an endogenous component of attentional control which embodies the online representations of task relevant information.

To conclude, the current results highlight a specific role of the left DLPFC in actively preparing for a specific task in the presence of a distracting task.

Key words:

rTMS - dorsolateral prefrontal cortex – attentional set – top down

INTRODUCTION

Attentional control can be described as 'goal-driven allocation of attention towards the processing of task-appropriate stimuli and responses, and away from distracters' [1, p792]. Commonly considered as a hallmark aspect of attentional control, 'attentional set' refers to the maintenance of an online task appropriate representation to strategically overcome as much as possible interference of distracters.

Overall, numerous neuroimaging studies have been performed to highlight the role of the Dorsolateral Prefrontal Cortex (DLPFC) in attentional control[2]. Although the left DLPFC has been found to be implicated in distracter incongruency (for example incongruent Stroop trials) [3], recent studies indicate that this brain area seems to be specifically related to strategically keeping task relevant representations online (for example being prepared to name the color of a color noun)[4]. This foreknowledge about task relevant information and the associated cognitive adjustments can be labeled as an increased attentional set.

The association between DLPFC and attentional set activation has been established using various cognitive tasks designs, but mostly using a trial by trial cue to prepare subjects to deal with possible upcoming distracters. The way that participants increase the attentional set depends on the context of the cue, but is based on fast working memory recruitment to strategically prepare for task relevant representations and possible distracters[5]. However, instead of this cue by cue instruction, a general instruction before the start of an experiment can also indicate the primary task and the possible appearance of distracters. In this case subjects are prepared to enhance their attentional set for executing this primary task, but are aware that they also have to respond to unexpected distracters. If the left DLPFC is related to this type of attentional set, increased DLPFC activation should be related to an increased potential to execute the primary task. Yet, to the author's knowledge, this has not been investigated in previous research.

Despite fundamental research so far, neuroimaging research cannot conclude on causality in the specificity of DLPFC activation patterns. However, repetitive Transcranial Magnetic Stimulation (rTMS), a non-invasive means of stimulating nerve cells in superficial areas of the brain [6], can be used to experimentally influence DLPFC activity. During the rTMS procedure, an electrical current passes through a coil placed close to the participants head and depolarizes underlying neurons. Using aggressive stimulation parameters (more than 10 Hz stimulation), effects of rTMS on information processing can last for many hours [7].

In this study, we have used High Frequency (HF; 10 Hz) rTMS to increase -reversibly and transiently- the normal activity of the left DLPFC. The aim of this study was to elucidate the specific role of left DLPFC activation in attentional set using a reaction task with a primary and an interfering distracter task.

In this task, we made use of two different input and output modalities during three successive blocks with fixed order. Subjects were first 'pretrained' on two simple tasks afforded by a set of visual (block 1) and auditory (block 2) stimuli respectively. In a third mixed block, both visual and auditory trials were presented randomly with different stimulus onset asynchronies and participants had to react to both trials. In this last block, however, participants were instructed to pay constant attention to the visual stimuli, whereas they were informed by a cue, just before stimulus onset, if a

distracting auditory stimulus would appear. For maximum interference, the distracting cue was visual and closely related to the visual characteristics of the principal task.

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. For visual trials, we used a four choice reaction time task, distinguishing between a component of endogenous information processing (decision time) and a component of psychomotor speed[8]. Because the distracting task was a simple RT task implying no decision processes, only total reaction times were registered.

If the left DLPFC is involved in the regulation of an active attentional set to strategically prepare for a task, HF-rTMS of the DLPFC would have an effect on the decision time of visual trials. Specifically, we hypothesized a decreased reaction time in the component of endogenous information processing, but not in the psychomotor speed component for visual trials. In contrast, we anticipated no effects on auditory trials because participants are not actively prepared for this stimuli but performance relies on the presentation of an external cue.

METHOD

Participants

Because gender differences in attentional processing have been demonstrated, for reasons of group homogeneity we included only female volunteers. A total of 20 healthy 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 medical institutional ethics committee of the University Hospital Brussels (U.Z. Brussel), which is in accordance with the recommendations laid down in the current version of the Declaration of Helsinki.

Before the start of the study, written informed consent was obtained from all the participants. All the participants underwent a standard physical and mental examination performed by a trained psychiatrist, including the evaluation of current and past history of medical and psychiatric disorders. The psychiatric diagnosis was completed by the structured Mini-International Neuropsychiatric Interview (based on the DSM-IV-TR criteria)[9], In addition, to exclude epileptic activity every participant underwent an EEG, inspected by a neurologist. Magnetic Resonance Imaging (MRI) was performed to screen for abnormal structural brain tissues or tumors. Based on these measurements, none of the subjects demonstrated neurological, psychiatric or medical history or current problems. This prior medical screening also excluded volunteers with contraindications according to the safety guidelines for rTMS [10].Right Handedness was assessed through a well validated Dutch scale of Van Strien [11].

Procedure

Subjective mood ratings were recorded on Visual Analogue Scales (VAS) [12] at time points: baseline (pre), immediately after rTMS (post 1), and after task performance (approximately 30 minutes after stimulation, post 2). The VAS consisted of subscales for “depression”, “anger”, “fatigue”, “vigor” and “tension”. 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".

A reaction time task was performed before and after rTMS. This task made use of a device with a central pushbutton and eight pushbuttons around positioned in a semicircle. In addition, a pedal was attached to the device.

This paradigm contained three task blocks with fixed order, in which the two fist blocks served to train two simple motor tasks. During the first block (28 trials), participants were told that when they saw a light turning on in one of the eight push-buttons, they had to remove their finger from the central pushbutton and push out the light in the lit button (but only four lights could turn on). In the second block (28 trials), participants were instructed to let their foot hover over the pedal and to press that pedal with their foot when they heard a buzzer. In the third block (28 visual and 29 auditory trials), participants were instructed to respond to both visual and auditory trials (with the same sequence for every participant). Although participants mostly alternated between stimuli (45 out of 57), they did not know in advance whether the stimulus would be a light or a sound. They were very explicitly instructed to focus their attention on the visual stimuli but that auditory stimuli would interfere during the block. Because we wanted an index for a general task preparation, the visual trials were not preceded by a cue. For visual trials, two components of the reaction time were recorded [8]. 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, because 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 [13].

For maximum interference, just before each auditory trial, the central pushbutton (cue) was lit for 150 msec with visual characteristics closely related to the primary task. 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.

Stimulus Onset Asynchrony differed randomly between 3000 msec and 6000 msec.

Subsequently after task performance, HF-rTMS of the left DLPFC was performed using a MAGSTIM high-speed stimulator (supplied by Magstim Company Ltd., Wales, UK) with a figure-8-shaped coil. In order to correct individual anatomical differences and to avoid stimulation of other cortical areas besides the left DLPFC, all subjects underwent a T1-weighted MRI (3D-TFE, voxel size 1x1x1 mm) of the brain using a 1.5T Intera MR scanner (Philips, Best, the Netherlands). We located the left DLPFC visually on the 3D surface rendering of the brain based on the subject's own gyral morphology and we marked the centre of the middle frontal gyrus as the target site, which is anatomically localized in the centre of the DLPFC (Brodmann area 9/46; Talairach coordinates -50, 34, 34). The corresponding coil position was found by determining the perpendicular projection of this point on the scalp. On the 3D-reconstruction of the head, we marked 4 reference points - right ear, left ear, vertex and nose – which were connected by two reference axes: one from nose to atlas and one between the two ears. A fifth reference point, the projection of the DLPFC on the scalp, was defined by the crossing of the two axes. For a visualisation of the coil position on a individual's head, we drew these reference axes on a cap by using the geodetic distance from nose to top, from right ear to top and

from top to the coil position, yielding the same stimulation point for the two sessions of each individual (for more information, we refer to the paper of Peleman et al. [14]).

We used following stimulation parameters: 110% of motor threshold (stimulation intensity), 10 HZ (stimulation frequency), 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 minutes.

This study was conducted according to a double-blind within-subjects design by counterbalanced crossover sham (placebo) and active rTMS. 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 [15]. During stimulation, all the subjects wore earplugs and were blindfolded to ensure blindness of the stimulation procedure. There was a delay of 1 week between the two stimulation sessions. Debriefing after the experiment revealed that all the subjects believed they had received real rTMS on all occasions. This experiment was part of a larger project investigating also other neuro-cognitive markers.

Statistical Analyses

Changes of mood were analyzed using 2X3 within-subjects ANOVAs 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.

For changes in reaction times, a priori hypotheses were based on existing literature. We tested our specific ad hoc hypothesis using separate paired t-tests. Because the reaction to visual trials is a completely different process as compared to the reaction to auditory trials, we performed separate t-tests for each component. The dependent variable was the median reaction time (RT), registered in milliseconds. *First*, we analyzed RT to visual trials (principal task) that were preceded by auditory trials (distracters). *Second*, we analyzed RT to auditory trials (distracters) that were preceded by visual trials (principal task). *Third*, we used t-tests to explore the influence of rTMS on median RT during the first two training blocks. In these blocks, no attentional control is required because RT's are based on stimulus repetitions. *Finally*, because we noticed that the difference of RT between the training block and the task block was different for the principal task and for the distracters, we performed additional t-tests.

Because error rates were extremely low (only a few errors occurred), no accuracy analyses were performed. Significance level was set at $p < .05$ for all the statistical analyses that were conducted with SPSS 15.0. Cohen's *d* effect sizes were calculated based on the standard differences between means (using mean and standard deviation). For an overview of all median RT's, we refer to table 1.

RESULTS

Effects on mood

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 crucial significant interaction

effects were found between time and stimulation (p's < .05). We can therefore conclude that mood remained unchanged after left prefrontal HF-rTMS.

Effects on cognition

1. *Reaction times on Visual trials during the mixed reaction block (block 3)*

Paired t-tests indicated a significantly decreased DT on visual trials after rTMS stimulation as compared to pre task [t(19) = 3.795; p = .001; cohen's *d* = .65]. In the sham placebo condition, we found no significant pre-post differences [t(19) =1.262 ; p = .222; cohen's *d* =.18]. Furthermore, for MT we found no significant changes in RT either after rTMS [t(19) = .748; p = .464; cohen's *d* =.16] or after sham [t(19) = .865; p = .398; cohen's *d* =.14].

2. *Reaction times on Auditory trials during the mixed reaction block (block 3)*

As for these trials, no significant differences in RT to auditory trials were found either in the rTMS condition [t(19) =.521; p = .609 ; cohen's *d* =.09] or in the sham placebo condition [t(19) =.360; p = .723; cohen's *d* =.07].

3. *Reaction times on the visual and auditory trials in the training blocks (1 & 2)*

As predicted, in the sham placebo condition, there were no RT differences before to after treatment either for the auditory trials [t(19) = 0.024; p = .981; cohen's *d* =.16], for DT [t(19) = 0.551; p = .588; cohen's *d* =.07] or MT [t(19) = 1.022; p = .320; cohen's *d* =.19] of visual trials. Moreover, after active rTMS RT for either auditory trials [t(19) = 0.218; p = .829; cohen's *d* =-.08], DT [t(19) = 0.309; p = .760; cohen's *d* =.06] or MT [t(19) = 1.022; p = .320; cohen's *d* =.17] for the visual trials did not differ significantly from the baseline. This indicates that rTMS did not simply influence reaction speed.

4. *Reaction time during the training (blocks 1 and 2) versus reaction time during the mixed task block (block 3)*

For visual trials, we found a significantly shorter median DT during the mixed reaction block as compared to the training block in all stimulation conditions: $Sham_{pre}$ [t(19) = 6.467; p = .0001; cohen's *d* =1.86] and $Sham_{post}$ [t(19) = 6.645; p = .0001; cohen's *d* =1.54]; $rTMS_{pre}$ [t(19) = 4.976; p = .0001; cohen's *d* =1.68] and $rTMS_{post}$ [t(19) = 7.454; p = .0001; cohen's *d* =2.34]. These results are indicative for strong endogenous control mechanisms in the mixed block (block 3).

We found significantly faster median MT only during the mixed reaction block as compared to the training block in the baseline of the placebo condition: $Sham_{pre}$ [t(19) = 3.556; p = .002; cohen's *d* =.92]. No other differences were observed: $Sham_{post}$ [t(19) = 2.018; p = .057; cohen's *d* =0.57] condition and $rTMS_{pre}$ [t(19) = 1.055; p = .305; cohen's *d* =.33] and $rTMS_{post}$ [t(19) = 1.261; p = .223; cohen's *d* =.38] conditions.

For the auditory trials (distracters), we found faster median reaction times on the training block compared to the mixed reaction block in $Sham_{pre}$ [t(19) = 3.272; p = .004; cohen's *d* =1.34] and $Sham_{post}$ [t(19) = 3.714; p = .001; cohen's *d* =1.58] conditions and in $rTMS_{pre}$ [t(19) = 3.408; p = .003; cohen's *d* =1.31] and $rTMS_{post}$ [t(19) = 3.074; p = .006; cohen's *d* =1.00] conditions.

Role of age on attention

For excluding the possible effects of age on attentional performance during this reaction time task, we analyzed the correlation between age and RT, DT and ART in all blocks, both for sham and rTMS conditions. We did not find any significant correlation (all p's >.05) which indicates that age was not related to attentional performance.

DISCUSSION

Using HF-rTMS, we investigated the role of the left DLPFC in attentional set activation when subjects were prospectively prepared to perform a specific task while a second task was used as a distracter. In a mixed reaction task, subjects were instructed to primary pay attention to a one task (i.e. visual task) whereas the other task was conceived as a distracter task (i.e. auditory task). Because mood remained stable after stimulation, the results could be evaluated independent of mood changes [16].

Behavioral data of the mixed reaction task indicated significantly decreased DT of visual trials after HF-rTMS of the left DLPFC, whereas no changes emerged for MT. This suggests that rTMS had an effect on the ability to prepare for certain task requirements by keeping task relevant representations online. Indeed, no significant differences in RT were found for auditory trials that are considered as being distracters. The fact that, compared to the simple training tasks, only the DT of the visual tasks decreased in all the mixed conditions (pre/post/rTMS/SHAM), suggests that task relevant representations can be set by the context, in this case being the task instruction prior to the mixed reaction task. This decreased visual DT in the mixed reaction task is indicative for an increase of endogenous task control. For the auditory distracting trials, we found faster median reaction times on the training block trials compared to the mixed block trials. Based on this task context, rTMS of the left DLPFC increased performance for a primary task but did not affect RT of the distracters. The observation that rTMS of the left DLPFC only influenced DT in the mixed reaction task points to a crucial role of the left DLPFC in attentional set representations. Important to mention is that both tasks were appearing with the same frequency in the mixed reaction task.

Behavioral data indicated no changes after placebo sham stimulation, which indicates the specific effect of active stimulation. Moreover after active rTMS, RT of visual and auditory training blocks were not changed. This indicates that the significant effects on the visual trials cannot be attributed to non-specific differences associated with stimulus and/or response mode (visual vs auditory) or to effects attributed to general arousal or general speeding (training vs mixed reaction task). Moreover, because of the important role of age in attentional performance, we analyzed its possible effects. In this group of subjects ranging in age from 21, to 43 years old, we found no effects of age on attentional performance on this task.

However, it is still possible 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 training blocks to a quick reaction strategy of 'first lift and later plan' in the mixed reaction block. However, the MT in training blocks did not reveal to be different compared to the MT for the mixed

reaction block before and after rTMS. Moreover, the manifestation of a trade-off pattern between MT and DT within the mixed reaction task block after rTMS stimulation should result in a negative correlation between RT 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]. All together, this suggests no different response strategy after rTMS stimulation, which indicates that the DLPFC is specifically related to an increased cognitive preparedness and not to a changed motor strategy. This is in line with the idea that activation of top down attentional control provides signals that favor task-relevant response pathways over competitors [17].

Being principal psychometric concepts, validity and reliability are important regarding the specificity of the conclusions and the generality of research results. One might raise questions about the validity of the task we used, referring to the degree to which this paradigm accurately reflects the concept of attentional set. However, using this paradigm, 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. This design is in accordance with the definition of how to measure attentional control [1, p 792] and attentional set [4]. The second psychometric aspect, reliability, addresses whether repeated measures provide consistent results given the same circumstances. Because every participant received both a sham and real stimulation session, we can conclude about the extent to which the results are consistent. Using a counterbalanced order between both sessions, we could compare the two baseline performances before stimulation/sham. Statistical analyses did not demonstrate a difference in baseline performance ($p \geq .61$], showing that RT measurements in this task are reliable. This implies that decreased DT after rTMS, as compared to no differences after sham, can be attributed to the stimulation.

A limitation of this research is that it is generally believed that effects of rTMS are not strictly local because of a high degree of connectivity to other cortical areas and subcortical nuclei [18]. Moreover, it cannot be excluded that stimulating one hemisphere has effects on the other hemisphere via long-term potentiation of callosal projections. Being a subsequent limitation of this research, we have no information concerning the IQ of every participant. This might be important because fMRI research demonstrated that those individuals who showed resistance to distracters during a demanding working memory task had both a higher IQ and increased prefrontal activity [19]. Future rTMS research should take this variable into account when stimulating the prefrontal cortex.

To conclude, the current results point to a crucial role of the left DLPFC in the active and endogenous preparation for performing a well defined task as compared to performance based on an external cue presentation. This goal-driven allocation of attention towards the processing of task-appropriate stimuli has been labeled as an increased attentional set [1]. Neuroimaging research has frequently associated this goal driven attentional control to left DLPFC computations [20, 21] but this is, to our best knowledge, the first study to demonstrate the crucial role of this brain area in task set manipulation in favor of a specific task in a mixed reaction task. The task context was set by instructions that enhanced attention for a specific task and made a second task a distracter task.

Importantly, conclusions of this study were based on post hoc tests testing a-priori hypotheses. This might be considered as a drawback for the interpretation and reliability of the current results.

Therefore, although the effects size of the results shows an important effect, the results should be interpreted with caution and further research into the effect of rTMS on cognitive control processes is warranted. Therefore, future research combining rTMS with functional brain imaging is essential to further investigate the structural and functional activation within the left DLPFC in the circuitry that is responsible for higher attentional control.

ACKNOWLEDGEMENTS

The authors wish to thank Prof. Dr. R. Luypaert and P. Van Schuerbeeck from the Department of Radiology of UZ Brussel for the technical assistance in MRI data analysis. The authors would like to thank M. Moens & M. Vercauteren for the development of the computer version of the task switching paradigm (www.subliemservice.be). The authors wish to acknowledge the contribution of Professor Hugo D'haenen for his assistance with the design of the study and to express their sorrow with his sudden death.

REFERENCES

1. Luks TL, Simpson GV, Feiwell RJ, Miller WJ: Evidence for anterior cingulate cortex involvement in monitoring preparatory attentional set. Neuroimage 2002;17:792-802.
2. Banich MT, Milham MP, Atchley RA, Cohen NJ, Webb A, Wszalek T, Kramer AF, Liang ZP, Barad V, Gullett D, Shah C, Brown C: Prefrontal regions play a predominant role in imposing an attentional 'set': Evidence from fmiri. Cognitive Brain Research 2000;10:1-9.
3. Banich MT, Milham MP, Jacobson BL, Webb A, Wszalek T, Cohen NJ, Kramer AF: Attentional selection and the processing of task-irrelevant information: Insights from fmri examinations of the stroop task; Vision: From neurons to cognition, 2001, vol 134:459-470.
4. Aarts E, Roelofs A, Van Turennout M: Anticipatory activity in anterior cingulate cortex can be independent of conflict and error likelihood. Journal of Neuroscience 2008;28:4671-4678.
5. Sandrini M, Rossini PM, Miniussia C: Lateralized contribution of prefrontal cortex in controlling task-irrelevant information during verbal and spatial working memory tasks: Rtms evidence. Neuropsychologia 2008;46:2056-2063.
6. Pascual-Leone A, Tormos JM, Keenan J, Tarazona F, Canete C, Catala MD: Study and modulation of human cortical excitability with transcranial magnetic stimulation. Journal of Clinical Neurophysiology 1998;15:333-343.
7. George MS, Wassermann EM, Post RM: Transcranial magnetic stimulation: A neuropsychiatric tool for the 21st century. Journal of Neuropsychiatry and Clinical Neurosciences 1996;8:373-382.
8. Roberts RD, Pallier G: Individual differences in performance on elementary cognitive tasks (ects): Lawful vs. Problematic parameters. Journal of General Psychology 2001;128:279-314.
9. Sheehan DV, Lecrubier Y, Sheehan KH, et al. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. Journal of Clinical Psychiatry 1998; 59(Suppl 20); 22–33;quiz 34–57. M.I.N.I. Plus (Nederlandstalige vertaling, Van Vliet, Leroy & Van Megen, 2000).
10. Wassermann EM. Risk and safety of repetitive transcranial magnetic stimulation. In: Report and suggested guidelines from the International Workshop on the Safety of Repetitive Transcranial Magnetic Stimulation. Clinical Neurophysiology 1998; 108(1): 1–16.
11. Van Strien A. Handvoorkeur en taaldominantie. Neuropraxis 2001; 2: 10–15.
12. McCormack HM, Horne L, Sheater S. Clinical applications of visual analogue scales: a critical review. Psychological Medicine 1988; 18, 1007-1019.
13. Gorus E, Lambert M, De Raedt R, Mets T: The influence of galantamine on reaction time, attention processes, and performance variability in elderly alzheimer patients. Journal of Clinical Psychopharmacology 2007;27:182-187.
14. Peleman K, Van Schuerbeek P, Luypaert R, Stadnik T, De Raedt R, De Mey J, Bossuyt A, Baeken C. Using 3D-MRI to localize the dorsolateral prefrontal cortex in TMS research. World J Biol Psychiatry 2009; 26:1-6.

15. Anand S, Hotson J. Transcranial magnetic stimulation: Neurophysiological applications and safety. Brain and Cognition 2002; 50(3): 366-386.
16. Damasio AR. The somatic marker hypothesis and the possible functions of the prefrontal cortex. Philosophical transactions of the royal society of London series B. Biol Sci 1996; 351(1346):1413– 1420.
17. Dreher JC, Berman KF: Fractionating the neural substrate of cognitive control processes. Proceedings of the National Academy of Sciences of the United States of America 2002;99:14595-14600.
18. Esser SK, Huber R, Massimini M, Peterson M J, Ferrarelli F, Tononi G. A direct demonstration of cortical UP in humans: A combined TMS/EEG study. Brain Research Bulletin 2006; 69(1): 86-94.
19. Gray JR, Chabris CF, Braver TS. Neural mechanisms of general fluid intelligence. Nat. Neurosci 2003; 6(3): 316–22.
20. Milham MP, Banich MT, Barada V. Competition for priority in processing increases prefrontal cortex's involvement in top-down control: an eventrelated fMRI study of the stroop task. Cognitive Brain Research 2003; 17(2): 212-222.
21. Johnston K, Levin HM, Koval MJ, Everling S. Top-down control signal dynamics in anterior cingulate and prefrontal cortex neurons following Task Switching. Neuron 2007; 53(3): 453-462.

Table 1: Mean Reaction Time latencies *(and Standard Deviation)* in the mixed reaction task before and after sham control and active rTMS.

	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: Mean Reaction Time latencies *(and Standard Deviation)* in the two training blocks before and after sham control and active rTMS.

	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)*