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Impact of Low-Frequency Transcranial Magnetic Stimulation on Brain Automatic Information Processing

A Mismatch Negativity Study

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Abstract: Repetitive transcranial magnetic stimulation (rTMS) is considered a powerful method for the study of the relationships between cortical activity and cognitive processes. Previous ERPs studies that focused on P300 response have shown that inhibitory/excitatory effects on prefrontal cortex (PFC), induced by low- and high-frequency rTMS, were able to modulate controlled but not automatic information processing. The present study assessed the impact of inhibition over left and right PFC induced by rTMS on mismatch negativity (MMN), which is known to represent automatic cerebral processes for detecting change. Auditory MMN was recorded in 20 subjects before and after application of left and right PFC 1-Hz rTMS for 15 min. MMN was also recorded before and after a sham-occipital 1-Hz rTMS as control condition. Results showed that 1-Hz rTMS induced no modification to either MMN latency or amplitude. In addition, N100 and P200 components to the frequent tones were not affected by rTMS. These results are consistent with previous findings showing that rTMS over both PFC is unable to disrupt automatic information processing. However, since two sites were stimulated in the present study, no definite conclusions about the inability of rTMS to disrupt automatic processing can be made.

Keywords: rTMS, MMN, automatic information processing, ERPs

Introduction

Repetitive transcranial magnetic stimulation (rTMS) is a useful, noninvasive, and relatively painless tool enabling modulation of neuronal activities in the human brain (Jahanshahi & Rothwell, 2000; Hallett, 2000; Anand & Hoston, 2002). Although the effects of rTMS on cortical excitation are mostly related to studies of the motor system with controllable outputs such as motor-evoked potentials (Gerschlager, Siebner, & Rothwell, 2001; Pascual-Leone, Valls-Sole, Wassermann, & Hallett, 1994; Peinemann et al., 2004), several lines of evidence suggested that similar excitatory/inhibitory effects of rTMS are observed in other cortical regions, in particular the prefrontal cortex (PFC), despite the anatomical differences between the motor areas and other cortical areas (Pascual-Leone et al., 1999).

Over the past 10 years, several studies have shown that rTMS can induce modulations of cognitive functions both in healthy and pathological subjects. For instance, rTMS has been reported to produce speech arrest and counting errors (Pascual-Leone, Gates, & Dhuna, 1991), alteration of visual perception (Kammer & Nusseck, 1998), enhancement and impairment of memory function (Pascual-Leone et al., 1999), significantly slower picture naming (Stewart, Meyer, Frith, & Rothwell, 2001), and enhancement of performance in a mental rotation task (Klimesch, Sauseng, & Gerloff, 2003). These various effects, which can last longer than the stimulation time itself, reflect the ability of rTMS to increase or decrease cortical activity (depending on the stimulation frequencies used). Actually, it is generally admitted that cortical excitation is induced by high-frequency rTMS ($\leq$ 1 Hz), whereas cortical inhibition is provoked by low-frequency rTMS (= 1 Hz; Chen, 2000; Pascual-Leone et al., 1994). With its ability to focally disrupt neuron activity, this method is useful to investigate the functional role of brain areas (Cohen et al., 1997).

While the effects of rTMS on neuropsychological functioning are well documented, only a few studies have investigated the effects of rTMS on cognitive event-related potentials (ERPs). The ERP studies that have been conducted have focused specifically on the impact rTMS on the P300 component of the PFC (Jing et al., 2001; Evers, Böckermann, & Nyhaus, 2001; Hansenne, Laloyaux, Mardaga, & Ansseau, 2004). The rational of these studies was based on the fact that P300 has been used extensively for the study of cognitive processes and psychopathology. Jing et al. (2001) have reported increased P300 latency after 10-Hz rTMS delivery over the frontal area in healthy subjects without any modification of P300 amplitude. In contrast, P300 latency and reaction time were significantly decreased after 20-Hz rTMS over the left but not over the right dorsolateral PFC, but a short 1-Hz single TMS did not have any significant impact on P300 component (Evers et al., 2001). Hansenne et al. (2004) found that P300 latency was significantly prolonged after 1-Hz rTMS over the left PFC but only when the stimulation duration was 15 min. In contrast, late ERP components (i.e., N100, P200, and

N200) were not altered by rTMS. Taken together, these findings could suggest that cortical inhibition induced by slow rTMS over PFC could affect principally the controlled cognitive processes (i.e., P300).

In order to test if the rTMS could affect automatic information processing, we investigated the impact of magnetic stimulations on the mismatch negativity (MMN) component. The MMN (Näätänen, Gaillard, & Mäntysalo, 1978) is a late latency component of ERPs elicited whenever a sound violates some regular aspect of the preceding sound sequence (for reviews see Näätänen & Winkler, 1999; Picton, Alain, Otten, Ritter, & Achim, 2000). This component can be observed in a simple oddball paradigm in which infrequent sounds (deviants) differing in some characteristics (usually frequency or duration) from repetitive sounds (standards) elicit the MMN. The MMN is a negative peak in the latency range between 100 and 250 ms from stimulus onset with frontal and central distribution (Näätänen et al., 1978). It is thought to be generated by a mismatch process between the incoming sound and some short-term memory (sensory memory) record representing the regularities of immediate history of auditory stimulation (Näätänen, 1992). Recent findings have also suggested that the transient auditory sensory memory representation underlying the MMN is facilitated by a long-term memory representation of the corresponding stimulus. This means that some characteristics of the sensory memory traces involved in the elicitation of this component are stored in a more durable representation and that these memory traces can be reactivated (Winkler, Cowan, Csépé, Czigler, & Näätänen, 1996; Winkler & Cowan, 2005). It seems that memory representations underlying MMN elicitation are linked to some elements of long-term memory storage. Because MMN occurs even in the absence of attention, it has been argued that this component represents an automatic cerebral process for detecting change. Nevertheless, Näätänen and Winkler (1999) have argued that the sensory memory information involved in the process generating the MMN could correspond to the experienced contents of conscious perception. Furthermore, studies have suggested that the process reflected by the MMN is a part of a chain of processes leading to voluntary discrimination of stimulus change (for complete review see Näätänen & Winkler, 1999). MMN is regularly followed by the P3a component, which is considered to reflect a switch of the focus of attention. Nevertheless, it seems that the stimulation must be sufficiently deviant to elicit a P3a after MMN. Indeed, only highly deviant sounds seem to elicit a large-amplitude P3a suggesting that this novel event has automatically captured attention. Since the MMN can be elicited by both slightly and highly deviant sounds and the P3a can only be elicited by a highly deviant sound, the MMN component does not appear to reflect the involuntary capture of attention or orienting but the P3a does (Escera, Alho, Schröger, & Winkler, 2000; for review see Friedman, Cycowicz, & Geata, 2001). P3a can be differentiated from P3b by several variables affecting its elicitation, its relatively shorter latency (peaks 60-80 ms earlier than P3b) and its scalp topography. P3b, which is thought to be the proper P300, occurs when a subject detects an informative, relevant stimulus in an active-task situation and shows its maximal amplitude over parietal scalp areas. In comparison the P3a component can be elicited by rare or novel stimuli even when these stimuli are irrelevant to the task performed and shows its maximal amplitude over frontocentral scalp areas. P3b (P300) reflects memory updating (Donchin & Coles, 1988), or context closure (Desmedt, 1981; Verleger, 1988), and it may represent the transfer of the relevant information to consciousness (Picton, 1992) and the memorization processes (Fabiani, Karis, & Donchin, 1986). In contrast, P3a reflects automatic, orienting central response to novel or sufficiently deviant stimuli.

As regards the physiological aspects of the MMN and its association with cortical networks, several studies have suggested that two main generators exist; first, the supra-temporal plane of the auditory cortex (Alho et al., 1998; Giard, Perrin, Pernier, & Bouchet, 1990), reflecting the preconscious detection of a change in the signal, and second, the frontal areas (Deouell, Bentin, & Giard, 1998; Giard et al., 1990; Rinne, Alho, Ilmoniemi, Virtanen, & Näätänen, 2000) reflecting the orienting of attention toward the detected change. It has been suggested that the supratemporal component would activate the frontal component, which, in turn, would lead to an involuntary switching of the subject's attention away from the primary task toward the deviation, and, further, its conscious detection (Näätänen & Michie, 1979; Giard et al., 1990; Rinne et al., 2000).

The aim of this study was to determine whether the inhibition induced by rTMS could have an impact on the frontal generators of the MMN. Thus, we wanted to explore whether specific brain areas underlying the automatic information processes could be modulated by rTMS as has been reported for specific brain areas underlying the controlled processes (i.e., P300 modulation by PFC stimulation). In the current study we chose to stimulate the right and the left PFC for several reasons. First, as mentioned above, source localization studies indicate that apart from the supratemporal plane of the auditory cortex, another important generator has also been identified in the frontal cortex. Second, since previous ERP studies used stimulations over frontal areas (Jing et al., 2001; Evers et al., 2001; Hansenne et al., 2004), the same areas were chosen in order to directly compare the collected data. Third, PFC is easier to localize than supratemporal plane. Indeed, a well-known procedure using M1 as reference position can be used to easily localize PFC. To our knowledge, an equivalent procedure to localize the supratemporal plane does not exist. In addition, this stimulation site was actually more comfortable

for the subjects, because application of rTMS in the proximity of the ears (temporal cortex) induces greater noise (which is very loud: 120-130 dB at 10 cm from the coil) perception from the apparatus.

Method

Subjects

Twenty healthy subjects (10 men and 10 women) aged between 21 and 28 years (mean age of 24.1, *SD* = 1.86) were recruited. Subjects were all naïve to rTMS and unaware of the aim of the study. They all underwent a medical interview to exclude psychiatric or somatic disorders, and more particularly personal and familiar epileptic antecedents. This interview was based on clinical examination and past history. No intake of drugs was allowed during the 3 weeks of the experiment, including 2 weeks before. Data from one participant were excluded as the result of excessive artifacts in the EEG recording. The remaining data from the sample of 19 participants were then analyzed. The Ethical Committee of the University of Liège Medical School approved the protocol and all subjects provided written informed consent prior to the study.

ERP Recording and Data Analysis

ERP recording was carried out in a sound-attenuated room. The subjects were tested until a total of 180 trials was obtained after rejecting trials which contained eye movements or other artifacts. ERPs were elicited by a passive auditory oddball paradigm with 80% frequent stimuli (1000 Hz, 80 dB, 5 ms rise/fall and 50 ms duration) and 20% rare stimuli (1050 Hz, 80 dB, 5 ms rise/fall and 50 ms duration). The auditory stimuli were presented binaurally at the rate of one trial every second. To be sure that all the subjects were distracted from the oddball task, they were instructed to ignore the auditory stimuli while watching a silent movie on a monitor at a distance of about 70 cm.

The EEG was recorded using silver-silver chloride electrodes attached at Fz, Cz, and Pz using linked earlobes for reference and right forehead for ground. All sites were cleaned with acetone and abraded to maintain a resistance below 5 kΩ. EOG was recorded from above the left eye. Amplifier gains were set at 10,000, with a band pass of 0.05-35 Hz. The EEG was digitized at 250 samples/s for 500 ms with a 50 ms prestimulus baseline. Trials on which the EEG or EOG exceeded 50 μV were rejected automatically. There were no other rejection criteria, and the individual curves were not visually inspected for artifacts.

MMN amplitude and latency were determined from all 3 electrodes as the difference in voltage between the baseline and the most negative sample between 100 and 250 ms after stimulus onset on the difference signals obtained by subtracting frequent tone ERPs from deviant tone ERPs. N100 and P200 components elicited by the frequent tones were also investigated, and they were defined as the most negative and most positive values within the latency windows of 60-140 and 120-220 ms from all 3 electrodes, respectively.

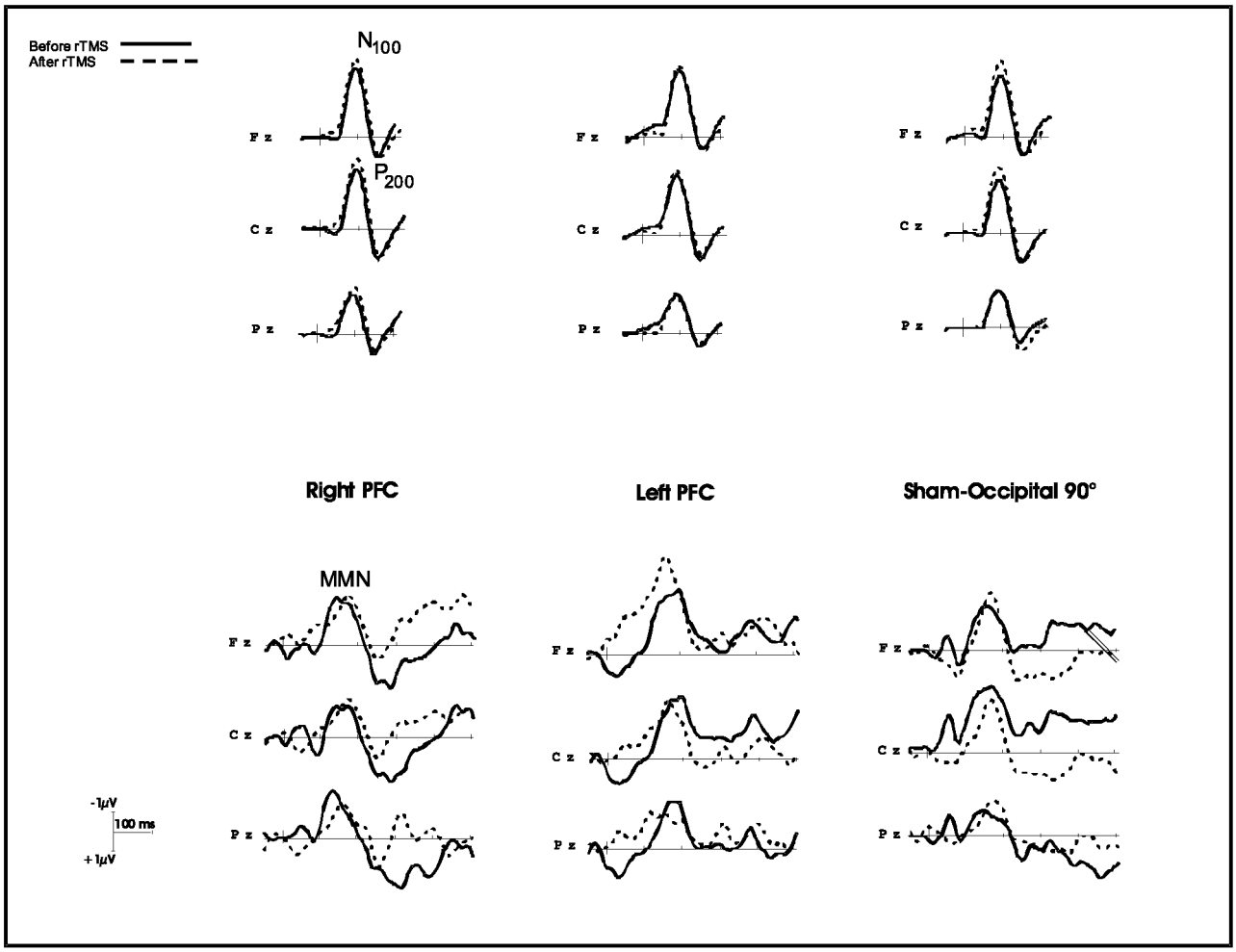
TMS Application and Procedure

rTMS was performed by using a Magstim superrapid magnetic stimulator (Magstim Company Ltd, UK) with four booster modules equipped with a 70-mm figure-eight-shaped flat coil. This device produces highly efficient triphasic sine wave pulses with a rise period of 60 μs and 250 μs duration. A biphasic device produces short efficient pulses and is faster than a monophasic device but it is possibly less accurate than the stimulator used here (Jalinous, 2002). The peak discharge current was 7 kA, with a peak magnetic field of 2 Tesla. rTMS was applied over left and right PFC measured respectively as 5 cm anterior to the left and to the right motor cortex according to several research and clinical studies (e.g., Jing et al., 2001; Martis et al., 2003). The left motor cortex (Ml) was located by methodically moving the coil across the left frontal-parietal region of the scalp (about 5 cm lateral and anterior to the vertex at an angle of 45 degrees) until the motor cortical response to right abductor pollicis brevis (APB) muscle was visually observed. The intensity of power output was initially fixed at 45% of maximum output of the stimulator, and successively increased by 2% until the threshold point for the activation of APB was found. Consequently, the lowest threshold point was determined. The same procedure was used to localize the right motor cortex; moving the coil across the right frontal-parietal region until response of the left APB muscle was visually observed.

The intensity of stimulations was 100% of the motor threshold (MT) of the right (left) APB muscle for the left (right) PFC according to the safety guidelines recommended by Wassermann et al. (1996). The MT was defined as the stimulus intensity that reliably (at least 6 times out of 10 stimuli) produced visibly observable right or left APB muscle contractions. The average intensity of the stimulation for the left PFC was 52.3% *(SD* = 1.98) of

maximum output of the stimulator and it was 52.2% *(SD* = 1.99) for the stimulation of the right PFC. During the delivery of the stimulation, the experimenter manually maintained the figure-eight-shaped flat coil tangentially to the prefrontal cortex (5 cm anterior to the motor cortex) in the experimental condition and at 90 ° to the occipital cortex in the sham condition. The subjects were seated in a comfortable armchair and asked to avoid moving their head. The points of prefrontal stimulation were marked with an indelible skin marker to be sure to maintain the coil at the precise location. The handle of the coil was pointed toward the occiput for all stimulation conditions. No particular instructions were given during the sham stimulation, and the sound of stimulation was comparable in all conditions.

Figure 1: *Upper traces: Grand-average waveforms (19 subjects) obtained by the frequent tones for each condition (right PFC, left PFC, and sham-occipital 90°) for the three midline electrodes (Fz, Cz, and Pz). Lower traces: Grand-average difference waveforms (19 subjects) obtained by subtracting ERPs to standard stimuli from those to deviant stimuli for each condition (right PFC, left PFC, and sham-occipital 90°) for the three midline electrodes (Fz, Cz, and Pz). Solid lines represent ERPs obtained before rTMS, and dashed lines represent ERPs obtained after rTMS.*



Subjects were assigned to randomly start with one of three interventions: 1-Hz stimulation of the left PFC continuously for 15 min (900 pulses), 1-Hz stimulation of the right PFC continuously for 15 min (900 pulses), and the sham condition which was 1-Hz stimulation of the occipital cortex for 15 min (900 pulses) with the coil oriented at 90 °. The choice of 15 min was based on a previous study (Hansenne et al., 2004). Subjects received the three interventions at a 1 week interval, and the order was randomized to prevent any sequence effect. The procedure was performed identically in each session. First, a baseline MMN was recorded. Immediately following the baseline MMN, real (left or right PFC) or sham (occipital 90 °) rTMS was applied across 15 min. Immediately after rTMS application a MMN was recorded again. MMN recording was, thus, done before and after each rTMS stimulation period.

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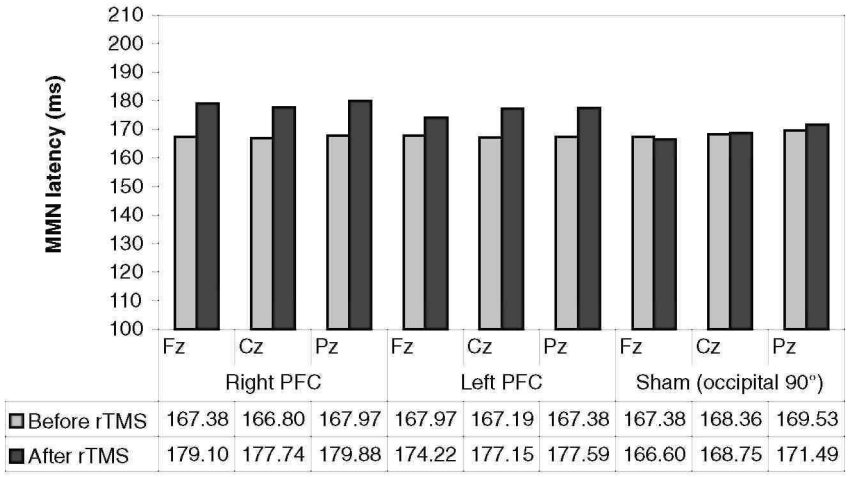
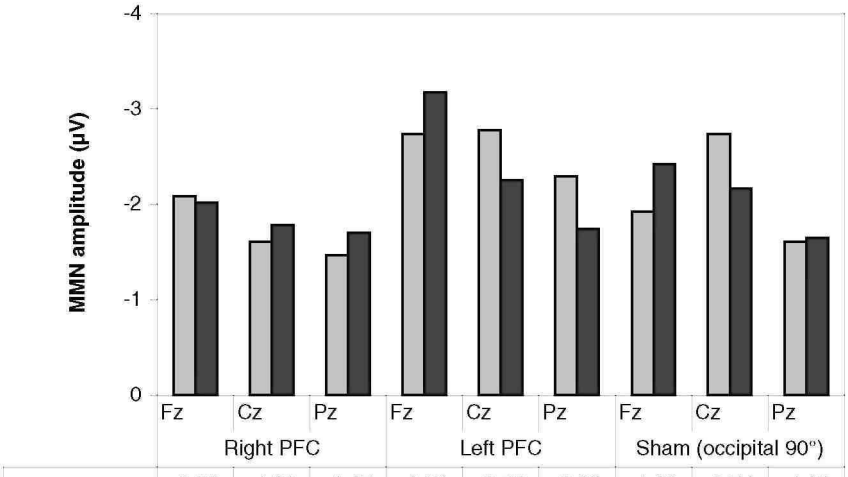
Statistical Analysis

The statistical analyses were carried out using Statistica (6.0) for Windows (Statsoft Inc., 2002). A three-way repeated-measures analysis of variance was performed with the factors of 3 Conditions (left PFC, right PFC, and sham) x 2 Sessions (before and after rTMS) x 3 Electrode Positions (Fz, Cz, and Pz). Greenhouse-Geisser epsilon correction for lack of sphericity was applied to interactions involving electrode as a factor. Planned comparisons (LSD tests) were used for subgroup comparisons. All statistical tests were two-tailed using a 5% level of significance.

Figure 2: *MMN latencies (left) and amplitudes (right) before and after the three rTMS conditions (right PFC, left PFC, and sham-occipital 90°) for the three midline electrodes (Fz, Cz, and Pz). No differences were statistically significant as revealed by LSD tests.*



	Fz	Cz	Pz	Fz	Cz	Pz	Fz	Cz	Pz
Before rTMS	167.38	166.80	167.97	167.97	167.19	167.38	167.38	168.36	169.53
After rTMS	179.10	177.74	179.88	174.22	177.15	177.59	166.60	168.75	171.49



	Fz	Cz	Pz	Fz	Cz	Pz	Fz	Cz	Pz
Before rTMS	-2.09	-1.60	-1.47	-2.74	-2.78	-2.29	-1.93	-2.74	-1.61
After rTMS	-2.02	-1.78	-1.70	-3.17	-2.25	-1.74	-2.42	-2.17	-1.65

Results

Figure 1 shows the responses to frequent tones and the grand average subtraction signals, showing the MMN responses at the Fz, Cz, and Pz electrodes before and after rTMS. With MMN latency as the dependent measure, a three-way repeated-measures analysis of variance showed no significant main effect of conditions, $F(2, 36) = 0.31$, p = ns, no significant main effect of sessions, $F(1, 18) = 2.39$, p = ns, and a tendency for an effect of electrode positions, $F(2, 36) = 2.74$, $p < .07$. No interactions were revealed to be statistically significant; Conditions x Sessions: $F(2, 36) = 0.63$, p = ns; Conditions x Electrode Positions: $F(4, 72) = 0.76$, p = ns; Sessions x Electrode Positions: $F(2, 36) = 1.16$, p = ns; Conditions x Sessions x Electrode Positions: $F(4, 72) = 0.31$, p = ns. The planned comparisons (LSD test) revealed no significant differences between MMN latencies before and after rTMS for separate electrodes (Figure 2).

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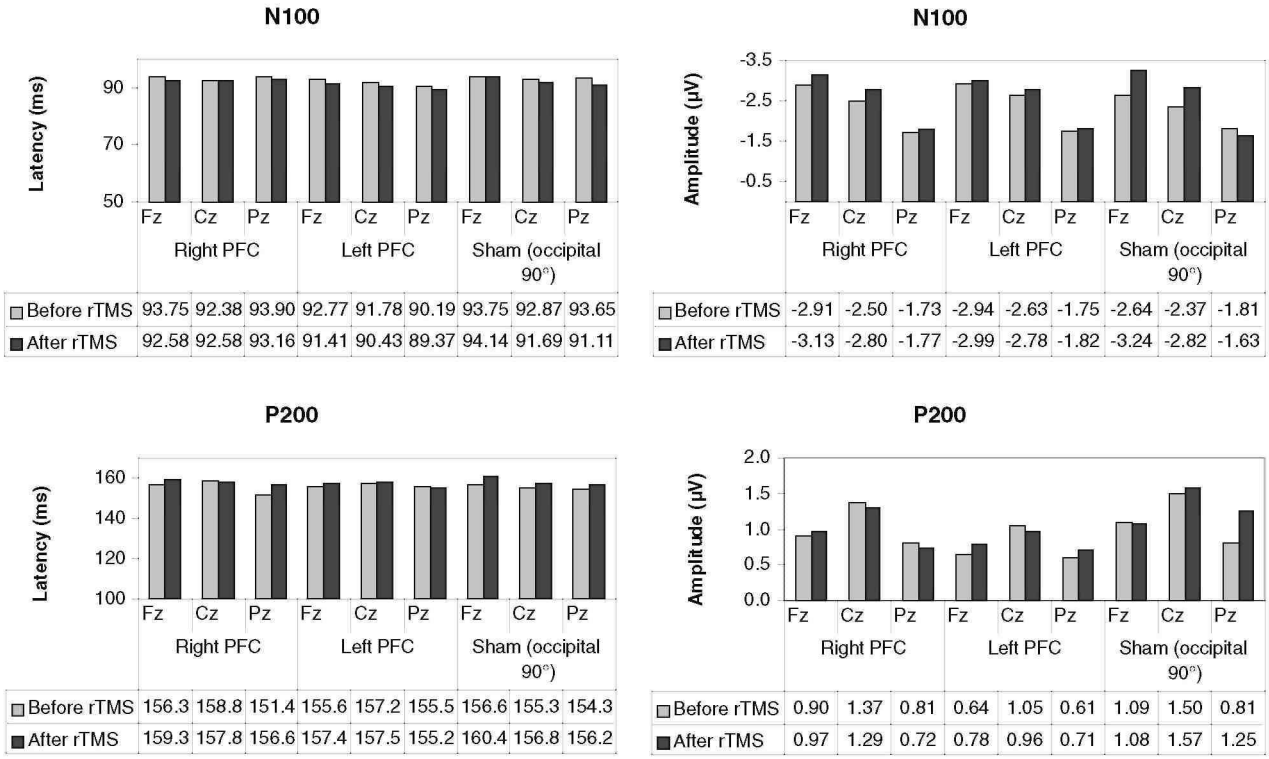
With MMN amplitude as the dependent measure, a three-way repeated-measures analysis of variance showed no significant main effect of conditions, F(2, 36) = 2.51, p = ns, no significant main effect of sessions, $F(1, 18)$ = 0.02, p = ns, and a significant main effect of electrode positions, $F(2,36) = 6.40$, $p < .004$. No interactions were statistically significant; Conditions x Sessions: $F(2,36) = 0.07$, p = ns; Conditions x Electrode Positions: $F(4,72)$ = 1.39, p = ns; Sessions x Electrode Positions: $F(2,36) = 1.49$, p = ns; Conditions x Sessions x Electrode Positions: $F(4,72) = 0.95$, p = ns. Despite the fact that Figure 1 suggests higher MMN amplitude after rTMS at left PFC, planned comparisons (LSD test) revealed no significant differences between MMN amplitudes before and after rTMS for separate electrodes (Figure 2).

Figure 3: *N100 and P200 latencies (left) and amplitudes (right) before and after the three rTMS conditions (right PFC, left PFC, and sham-occipital 90°) for the three midline electrodes (Fz, Cz, Pz). No differences between before and after rTMS were statistically significant as revealed by LSD tests.*



Analyses of ERPs elicited by standard stimuli revealed no significant changes in neither N100 and P200 amplitudes nor latencies after rTMS (Figure 3).

The inspection of Figure 1 shows a P300-like effect before rTMS over the right PFC and after the sham application. Unfortunately, these effects were not analyzed because P300 components were developed only in a minority of subjects. So, the effects suggested in Figure 1 are not representative.

Discussion

The results of the study, using only two sites on stimulation, show that neither right nor left PFC rTMS disrupt automatic cognitive processes as reflected by the MMN. In addition, N100 and P200 components from the frequent tones are not affected by rTMS. These findings are consistent with previous studies which have shown no significant modifications of early ERP components after rTMS over both PFC. Indeed, Evers et al. (2001) did not find any modification of N200/P200 latencies and amplitudes after rTMS at both 20-Hz and 1-Hz frequencies over the left and right frontal areas. Further, Hansenne et al. (2004) did not find any modification of N200/P200 latencies and amplitudes after 1-Hz rTMS over the left PFC whereas P300 latency was significantly increased. Based on these different findings, it could be argued that cortical inhibition of PFC caused by rTMS could affect controlled (i.e., P300) but not automatic (i.e., MMN, N200, and P200) cognitive processes.

The absence of significant rTMS effects found in the present study could be explained by the possibility that stimulations did not reach the MMN generators. It could be argued that the stimulation over the PFC operates on

weak or secondary MMN generators leaving main MMN generators fully active (i.e., the supratemporal plane). If we suppose that the frontal generators of the MMN have been reached, the lack of variation of either latency or amplitude of this negative component could suggest that PFC generators are not crucial for its generation, which supports the idea of a distributed network underlying the sound-duration change-detection processes, some of which are probably partly reflected in the MMN (Schall, Johnston, Todd, Ward, & Michie, 2003). It has been proposed that the supratemporal plane generator could activate the frontal one, leading to a switch of attention to conscious detection, suggesting that the frontal area acts as a secondary generator (Rinne et al., 2000). Jemel, Achenbach, Muller, Ropcke, and Oades (2002) provided additional evidence supporting the interactions between the MMN activity generated in the frontal and in the temporal cortices. Consequently, if PFC is not a crucial generator of the MMN, it may play a role in its generation. This point of view is supported by recent findings from intracranial recordings in which most electrodes with MMN signals were located in or close to the temporal lobe, but that MMN was also observed at frontal locations in some subjects, giving evidence for a participation of the frontal cortex in MMN generation (Rosburg et al., 2005). In contrast, P300, which has more widespread generators, is more directly altered by frontal rTMS (Jing et al., 2001; Hansenne et al., 2004). Unfortunately, since the MMN paradigm does not elicit a clear P300 component, it is not possible here to conclude whether the absence of a MMN effect is specific or not. Indeed, even if Figure 1 suggests a clear P3-like effect over the right PFC, it was impossible to analyze P300 responses because a P3a component was not easily identified (i.e., only few subjects exhibited a clear P3a component). This reflects that the sounds for MMN elicitation were chosen so that no P3a, or a very small one, would be expected. To see a larger P3a a larger difference between the standard and deviant would be needed. Previous studies have already clearly demonstrated the impact of rTMS on the P300 component (Jing et al., 2001; Evers et al., 2001; Hansenne et al., 2004).

Another possible explanation of the negative results gathered here could be that rTMS is only able to stimulate nerve cells in superficial brain areas. Indeed, the strength of the magnetic field produced by the stimulating coil falls exponentially with the distance from its center so that the depth of the targeted neural tissue considerably determines magnetic (and induced electric) field strength at a brain site (Ilmoniemi, Ruohonen, & Karhu, 1999). In the present study, a figure-eight coil with a depth of stimulation lying between 11.5 and 24.8 mm was used (Barker, 2002), but the depth of the MMN generators was not determined. Thus, it could be suggested that the depth of stimulation was not sufficient to reach and disrupt subcortical MMN generators. Recent studies have shown that the right inferior frontal gyrus (IFG; Opitz et al., 2002) and the left anterior cingulate gyrus (ACG; Oknina et al., 2005) could be good candidates to be frontal MMN generators. Considering the depth of those brain areas, we can see that the IFG (BA 10) lies between 9 and 55 mm and the ACG (BA 24) between 36 and 70 mm. But as seen above, TMS penetration depth lies between 11.5 and 24.8 mm. So, it seems that our TMS was unable to reach the ACG and could only reach some neurons lying between 9 and 24.8 mm in the IFG.

It is assumed that TMS activates only the tangentially oriented neurons and not the radially oriented ones (Pascual-Leone et al., 1998; Ruohonen & Ilmoniemi, 2002). Rinne et al. (2000), in a combined EEG and MEG study, found that no frontal activity was detected by MEG, however, this frontal activity was recorded by EEG. These authors assumed that this absence of frontal activity "suggests that the source of the frontal MMN component is either located deeper in the brain or is radially oriented" (Rinne et al., 2000, p. 19). Since a frontal MMN generator seems to be composed of radial neurons or lies in deep brain areas, it appears that TMS would find it difficult to influence these neurons.

Considering this evidence, this technique may not be suited for the study of a frontal MMN generator. Nevertheless, as the supratemporal plane is implicated for the MMN generation, further studies should be conducted with stimulations over this area to assess whether the absence of rTMS effect observed in this study was the result of the inability of rTMS to suppress the activity of neural structures involved in automatic information processing.

In the present study, rTMS was applied before the second MMN recording. It is possible that the effects of rTMS might have lasted only for a few seconds and, therefore, were not observed in our experimental design. Another way to investigate the impact of PFC rTMS on automatic information processing would be to use an "on-line" rTMS paradigm. This "on-line" paradigm consists in applying stimulations while a task is performed. However, this paradigm is not optimal because of the noise and sensations produced by rTMS application, inducing nonspecific behavioral and attentional effects, which sometimes lead to difficulties in the interpretation of the results. However, several studies have clearly demonstrated that the effects of rTMS upon behavior and, probably, cognition outlast the time of stimulation itself (Maeda, Gangitano, Thall, & Pascual-Leone, 2002; Touge, Gerschlager, Brown, & Rothwell, 2001, Muellbacher, Ziemann, Boroojerdi, & Hallett, 2001; D'Alfonson, 2000). In these studies, the rTMS effect fluctuated between 10 and 15 min after the end of the

stimulation. Therefore, it could be postulated that the effect of the stimulations used in the present study would still be effective during the MMN recording. Nevertheless, it would be interesting for further studies to use a shorter MMN paradigm (see Grau, Escera, Yago, & Polo, 1998; and Näätänen, Pakarinen, Rinne, & Takegata, 2003) or to perform a separate average of the first half of the deviants.

In conclusion, this study shows that slow rTMS over either left or right PFC does not disrupt the MMN. These findings support and extend previous evidence suggesting that rTMS over PFC does not appear to affect automatic information processes. Divergent effects of the PFC rTMS on controlled and automatic processes could be explained by the possibility that the brain areas involved in automatic processes are more subcortically located than those associated with controlled processes. However, behavioral experiments seem to be necessary to verify this assertion. Further, since only two sites were stimulated here, no definitive conclusions about the inability of rTMS to disrupt automatic processing can be drawn. As it has been discussed earlier, stimulation of other sites could have had an effect. Lastly, the preliminary nature of presented results with respect to the limited sample and procedure (only frontal stimulation) must be underlined. Further studies should also separate the temporal and frontal MMN subcomponents from each other on the basis of nose-referenced Fz and mastoid ERP. The mastoid-MMN is believed to represent the activity of only the temporal generators of MMN, while the Fz-recorded MMN shows the sum of temporal and frontal components (Alho, 1995; Näätänen, 1995). Moreover, the lack of MRI localization of the prefrontal cortex, the lack of a fixation apparatus to maintain the coil at the precise location, and the restricted number of electrodes (no lateral electrodes although both left and right prefrontal areas were stimulated) limits the conclusions of the study.

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