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Impact of low frequency transcranial magnetic stimulation on event-related brain potentials

Michel Hansenne[a], Olivier Laloyaux[a], Solange Mardaga[a], Marc Ansseau[b]

[a] *Department of Cognitive Sciences, Faculty of Psychology, University of Liège, 5 Boulevard du Rectorat (B32), B-4000 Liège, Belgium*
[b] *Department of Psychiatry, University of Liège, Liège, Belgium*

Abstract

Contradictory findings exist concerning the inhibitory function of low frequency repetitive transcranial magnetic stimulation (rTMS). Therefore, the study examines the impact of different duration of low frequency rTMS on ERPs. In 17 subjects, auditory ERPs were measured before and after 1 Hz rTMS delivered over the left prefrontal cortex during l0min (600 pulses) and 15min (900 pulses). Results showed that 15 min of 1 Hz rTMS induced a significant increase of P300 latency. There was no effect for early ERP components (N100, P200 and N200). This study confirms and extends that 1 Hz rTMS produces a real inhibitory effect only when the duration of the stimulation is about 15 min. The data suggest that rTMS modifies the speed of cognitive processing rather than the energetical aspect of information processing, and that cortical inhibition induced by the magnetic stimulation affects principally the controlled cognitive processes and not the automatic ones.

Keywords: Transcranial magnetic stimulation; P300; Event-related potentials; Cognition

1. Introduction

Since the last 10 years, transcranial magnetic stimulation (TMS) has emerged as a very interesting method either as a therapeutic procedure or as a unique investigating tool to assess the relationship between cortical activity and cognitive processes (Daskalakis et al, 2002; George et al., 1999; Jahanshahi and Rothwell, 2000; Pascual-Leone et al., 1999a,b, 2000).

From a clinical perspective, many studies have demonstrated that left prefrontal repetitive TMS (rTMS) improves significantly the core symptoms of depression, and it is regarded as a safe procedure without side effect (George et al., 1995). More particularly, in open trials, rTMS over the left prefrontal cortex and electroconvulsive therapy (ECT) are reported to be equally efficacious for patients having depression without psychosis (Hasey, 2001). A recent study suggests also that administration of 1 Hz rTMS to left temporoparietal cortex reduced auditory hallucinations in patients with schizophrenia or schizoaffective disorder (Hoffman et al., 2003).

From an experimental point of view, TMS allows painless stimulation of the brain through the scalp of normal conscious subjects. TMS studies have provided interesting results that contribute to a better understanding of the relationship between brain and behavior. Short-term effects of rTMS on cognitive processes have been reported in different studies including induction of speech arrest and counting errors (Pascual-Leone et al., 1991), alteration of visual perception (Kammer and Nusseck, 1998), enhancement and impairment of memory function (Pascual-Leone et al., 1999b), and significantly slower picture naming (Stewart et al., 2001).

Few studies have investigated the impact of rTMS on the P300 event-related brain potential (ERP). P300 is a positive deflection that occurs when a subject detects an informative task-relevant stimulus, and it is particularly interesting to the study of cognitive processes in normal subjects and in psychopathology (Donchin and Coles, 1988; Picton, 1992). P300 reflects memory updating (Donchin and Coles, 1988), or context closure (Desmedt, 1981; Verleger, 1988), and it perhaps represents the transfer of relevant information to consciousness (Picton, 1992). As regards the physiological aspects of P300 and its association with cortical networks, various studies have suggested that several cortical generators of P300 could co-exist: the medial temporal lobe, the temporo-parietal junction, and the medial and lateral frontal lobes (Johnson, 1993; Halgren et al., 1995a,b; Baudena et al., 1995; Reinsel et al., 1995; Linden et al., 1999). Jing et al. (2001) have reported an increase of P300 latency after 10 Hz rTMS delivery over the frontal area in healthy subjects without any modification of P300 amplitude. Furthermore, the P200 component showed a trend of decreasing latency. Evers et al. (2001) showed that P300 latency and reaction time were significantly decreased after 20 Hz rTMS over the left but not over the right dorsolateral prefrontal cortex. In contrast, 1 Hz single TMS did not have any significant impact on P300

component (Evers et al., 2001).

It is generally admitted that cortical excitation is induced by high frequency rTMS (i.e. 20 Hz), whereas cortical inhibition is provoked by low frequency (i.e. 1 Hz) (Pascual-Leone et al., 1999a,b). However, several studies did not report any modification after 1 Hz rTMS on either motor or cognitive functions. Although naming latency is facilitated only immediately after Wernicke's area stimulation at a frequency of 20 Hz, trains of 1 Hz failed to influence naming latencies (Sparing et al., 2001), and single session of 1 Hz TMS over the right or the left prefrontal areas did not interfere with neuropsychological functioning in normal volunteers (Koren et al., 2001). Furthermore, 1 Hz rTMS used continuously for 2 min of right or left prefrontal cortex did not modify P300 latency whereas 20 Hz rTMS applied in three trains of 5 s duration of left prefrontal cortex reduced significantly P300 latency (Evers et al., 2001). It could be argued that the duration of the 1 Hz stimulation used in these studies was too short to induce a lasting inhibition. Indeed, Evers et al. (2001) applied single TMS during 2 min. In contrast, Rossi et al. (2000) reported that 15 min of 1 Hz rTMS over the motor cortex produced a significant amplitude decrement of the negative slope of the Bereitschaftspotential.

Therefore, it is still unknown what is the optimal duration of low frequency TMS application. In order to clarify this point, the aim of the present study is to evaluate the effect of different duration of low frequency rTMS on P300. More precisely, we will assess the impact of 1 Hz rTMS overthe left prefrontal cortex during 10 min and 15 min onP300. The site of stimulation was chosen according to different studies that found significant effects of rTMS over left prefrontal cortex (Jing et al., 2001; Evers et al., 2001) and according to the intracranial generators of P300 (Johnson, 1993).

2. Method

2.1. Subjects

The study was conducted in 17 healthy subjects who were not familiar with either psychophysiological methods or rTMS. The sample comprised 10 women and 7 men aged between 18 and 35 years (mean age of 24.1 years, S.D. 5.6). They all underwent a medical interview to exclude psychiatric or somatic disorders, and more particularly epileptic antecedents. This interview was based on clinical examination and past history. No intake of drugs was allowed during 3 weeks of the experiment, including 2 weeks before. The Ethical Committee of the University of Liège Medical School approved the protocol and all subjects gave their informed consent.

2.2. ERP recording and data analysis

ERP recording was carried out in a sound-attenuated room. ERPs were elicited by an auditory oddball paradigm with 80% non-target stimuli (1000 Hz, 70 dB and 40 ms duration) and 20% target stimuli (2000 Hz, 70 dB, 40 ms duration). The auditory stimuli were presented binaurally at the rate of one trial every second. The subjects were asked to press a button for the rare stimuli as quickly as possible and to keep their eyes open and avoid blink. The subjects were tested until a total of 150 trials was obtained after rejecting trials for eye movement or other artifacts. The task duration was approximately 2 min, and few trials (5-12) were rejected due to eye movements or other artifacts.

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 sample/s for 900 ms with a 200 ms prestimulus baseline. Trials on which the EEG or EOG exceeded 50 μV were rejected automatically. There were no other rejection criterion, and the individual curves were not systematically inspected visually for artifacts.

N100, P200, N200 and P300 components were defined as the maximum negative or positive peaks within the latency windows of 60-140, 100-200, 160-260 and 280-450 ms, respectively from the target stimuli.

2.3. TMS application and procedure

rTMS trains were administrated with an 8-shaped flat coil (Magstim Company Ltd., UK). This device produces highly efficient biphasic sine wave pulses through the 8-shaped flat coil. The rise period of each pulse is 60 ms and the duration is 250 ms. The peak discharge current is 7 kA, with a peak magnetic field of 2 T. rTMS was applied over the left prefrontal cortex (measured as 5 cm anterior to the motor cortex). The motor cortex 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°) until the motor cortical response to right abductor pollicis brevis muscle was observed. The intensity of stimulation was 100% of the motor threshold of the right abductor pollicis brevis muscle according to the safety guidelines recommended by Wassermann et al. (1996). The motor threshold was defined as the stimulus intensity that reliably (at least six times out of 10 stimuli) produced visibly observable right abductor pollicis brevis muscle contractions. The average intensity of the stimulation was 53.2% of maximum output of the stimulator. During the delivery of the stimulation, the experimenter maintained manually the 8-shaped flat coil tangentially to the prefrontal cortex for the real condition and at 90° to the same site for the sham condition. The subjects were seated in a comfortable armchair and they were requested to avoid head movements. The point of prefrontal stimulation was marked with an indelible skin marker to be sure to maintain the coil at the precise location. The handle of the coil was pointed towards the occiput. No particular instruction was given during the sham stimulation, and the sound of stimulation was comparable in all the conditions.

Subjects were assigned to three conditions: 1 Hz stimulation continuously for 10 min (600 pulses), 1 Hz stimulation continuously for 15 min (900 pulses), and the sham condition (1 Hz stimulation continuously for 12.5 min). Each subjects received the three conditions at a week of interval, and the order of 10 min, 15 min or sham stimulation was randomized. The procedure was identical all the times. At first, baseline ERPs were recorded. Immediately following baseline ERPs, real (10 or 15 min) or sham rTMS over the left prefrontal cortex was applied. At once after rTMS application ERPs were recorded again. Therefore, ERP recording was done before and after each TMS stimulation period.

2.4. Statistical analysis

The statistical analyses were carried out using Statistica (4.5) for Windows (Statsoft Inc., 1993). A four-way repeated-measures analysis of variance was performed with the factors of three conditions (10 min, 15 min, and sham) x two sessions (before and after rTMS) x three electrode positions (Fz, Cz and Pz) x four components (N100, P200, N200 and P300). Greenhouse-Geisser epsilon correction for lack of sphericity was applied to interactions involving electrode as a factor. A two-way repeated-measures analysis of variance was performed for the reaction time (three conditions x two sessions). Least significant difference (LSD) method was used for post-hoc tests. All statistical tests were two-tailed using a 5% level of significance.

3. Results

Fig. 1 presents the grand average ERPs for the Fz, Cz, Pz electrodes elicited by target tones before and after rTMS. Reaction time ranged from 255 to 429 ms (mean reaction time of 328.8 ms, S.D. 41.3). Results showed no significant main effect of conditions ($F_{2,20} < 1$) and sessions ($F_{1,20} = 3.11$, $P = 0.10$), and no significant conditions x sessions interaction ($F_{2,20} = 1.29$, $P = 0.29$) for the reaction time.

Concerning ERP latencies, the four-way repeated-measures analysis of variance showed a significant main effect of components ($F_{3,39} = 831.8$, $P < 0.001$), a significant sessions x components interaction ($F_{3,39} = 4.71$, $P = 0.01$), a significant conditions x sessions x components interaction ($F_{6,78} = 2.95$, $P = 0.01$), and a significant conditions x sessions x electrodes interaction ($F_{4,52} = 3.52$, $P = 0.02$). LSD post-hoc comparisons showed that P300 latency was significantly increased after 15 min rTMS application ($F_{1,13} = 7.99$, $P = 0.014$), although no differences were displayed after 10 min rTMS or after the sham stimulation (Fig. 2). More precisely, LSD post-hoc comparisons showed that P300 latency increased after rTMS delivered for 15 min for the three electrode positions ($F_{1,13} = 9.01$, $P = 0.01$ at Fz; $F_{1,13} = 5.4$, $P = 0.03$ at Cz; $F_{1,13} = 9.29$, $P = 0.009$ at Pz) (Fig. 3).

Concerning ERP amplitudes, the four-way repeated-measures analysis of variance showed main effect of sessions ($F_{1,13} = 11.65$, $P = 0.004$), components ($F_{3,39} = 64.85$, $P < 0.001$) and electrode positions ($F_{2,26} = 24.94$, $P < 0.001$). There was no significant main effect of conditions ($F_{2,26} < 1$). All the interactions were not statistical significant.

4. Discussion

The main finding of the present study was that low frequency rTMS applied over the left prefrontal cortex induced an increase of P300 latency when the duration of the stimulation was of 15 min and do not when the duration was of 10 min. This means that 1 Hz rTMS can really inhibit cognitive processing, as reflected here by P300, only when the duration is at least of 15 min. This elucidates why 2 min of 1 Hz TMS over left or right prefrontal cortex did not induce an impact on P300 latency or amplitude (Evers et al., 2001).

Other studies have demonstrated that l Hz rTMS during 15 min produced significant inhibition. Rossi et al. (2000) found a significant amplitude decrement of the negative slope of the Bereitschaftspotential after 1 Hz rTMS applied over the motor cortex. Chen et al. (1997) studied the effects of low-frequency TMS on motor cortex excitability in humans: stimulation at 0.1 Hz for 1 h did not change cortical excitability, whereas stimulation at 0.9 Hz for 15 min (810 pulses) led to a mean decrease in motor evoked potential (MEP) amplitude of 19.5%. Moreover, they found that the decrease in cortical excitability lasted for at least 15 min after the end of the 0.9 Hz stimulation. The mechanism underlying this decrease in excitability is probably similar to long-term depression (LTD).

Fig. 1: *Grand average of the event-related potentials for targets before and after (dashed lines) the three rTMS conditions (sham, l0 min, and 15 min).*

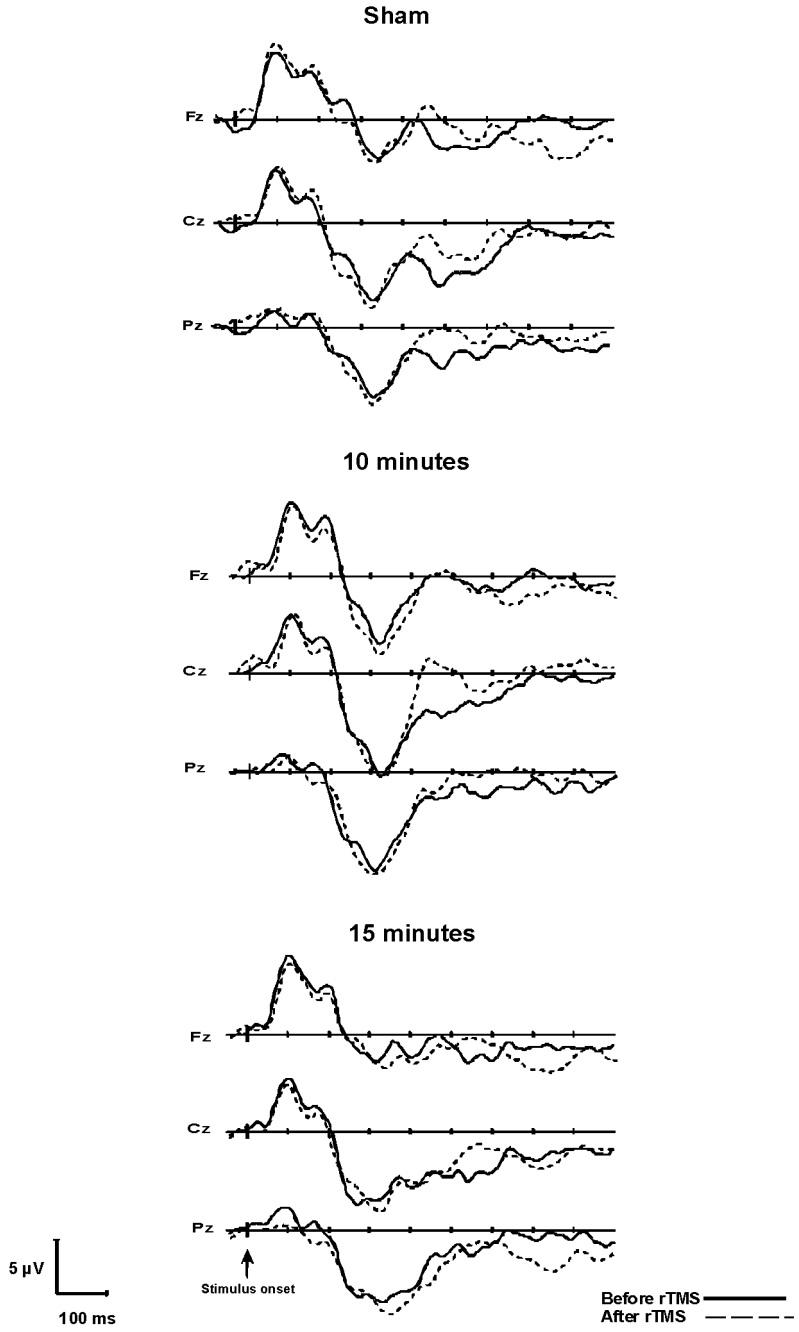
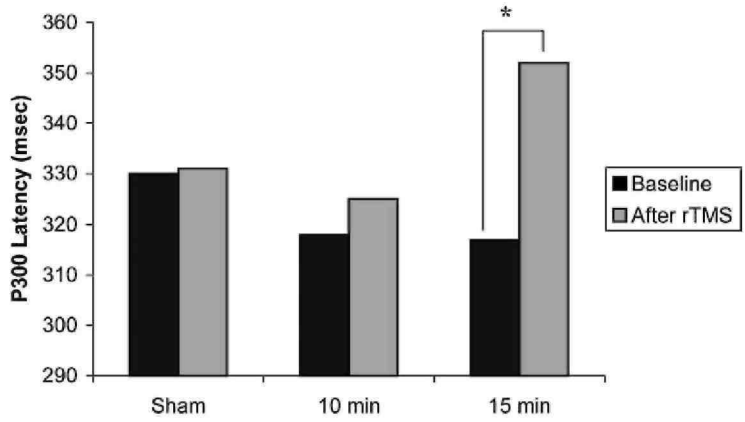


Fig. 2: *P300 latency before and after the three conditions; 1 Hz rTMS during 15 min, 1 Hz rTMS during l0 min, and sham application. (*) Significant difference (P = 0.02) between P300 latency before and after 15 min rTMS.*



Jing et al. (2001) showed that two trains of 3 s over the left prefrontal cortex separated by 5 min at 10 Hz delayed the P300 latency. The explanation of this result is unclear. Several studies demonstrated that 10 Hz rTMS improved cognitive functions; this means that 10 Hz is considered as an excitatory frequency (Pascual-Leone et al., 1999a,b). Jing et al. (2001) argued that both stimulation procedure and subjects (healthy volunteers) could contribute to the discrepancies between the studies.

Interestingly, Jing et al. (2001) found that the increasing of P300 latency was more obvious in the frontal and central areas. We did not report topographical effect in our study, but the ERP recording procedure was performed with only three median electrodes and not 14 electrode sites as it was the case in the study of Jing et al. (2001). Unfortunately, Evers et al. (2001) reported only results from Pz electrode.

The impact of low frequency rTMS on P300 component is limited to latency. We do not show any effect on P300 amplitude. The two other studies applying a similar procedure did not report significant modifications of P300 amplitude too (Jing et al., 2001; Evers et al., 2001). One of them found that the amplitude of P300 decreased at most electrode sites, but that did not reach the statistical level of significance (Jing et al., 2001). Taken together, these data suggest that rTMS affects the speed of cognitive processing rather than the energetical aspect of information processing.

In the present study, N100, P200 and N200 components were not altered by rTMS. This result is partly in agreement with those reported by Jing et al. (2001), in which only latency of P200 was decreased after rTMS. Evers et al. (2001) did not find any modification of N200 and P200 latency after rTMS at both 20 Hz and 1 Hz frequencies. The fact that early components of ERPs are not modified by rTMS suggests that cortical inhibition caused by the magnetic stimulation affects principally the controlled cognitive processes (i.e. P300) and not the automatic ones. In consequence, it could be possible that automatic indices of cognitive processes would be unchanged after rTMS. A study with the Mismatch Negativity (Näätänen, 2001) could clarify this point. Furthermore, although previous studies that have examined the impact of rTMS on P300 have focused only on P3b, further studies could evaluate the respective impact of rTMS on both P3a and P3b components.

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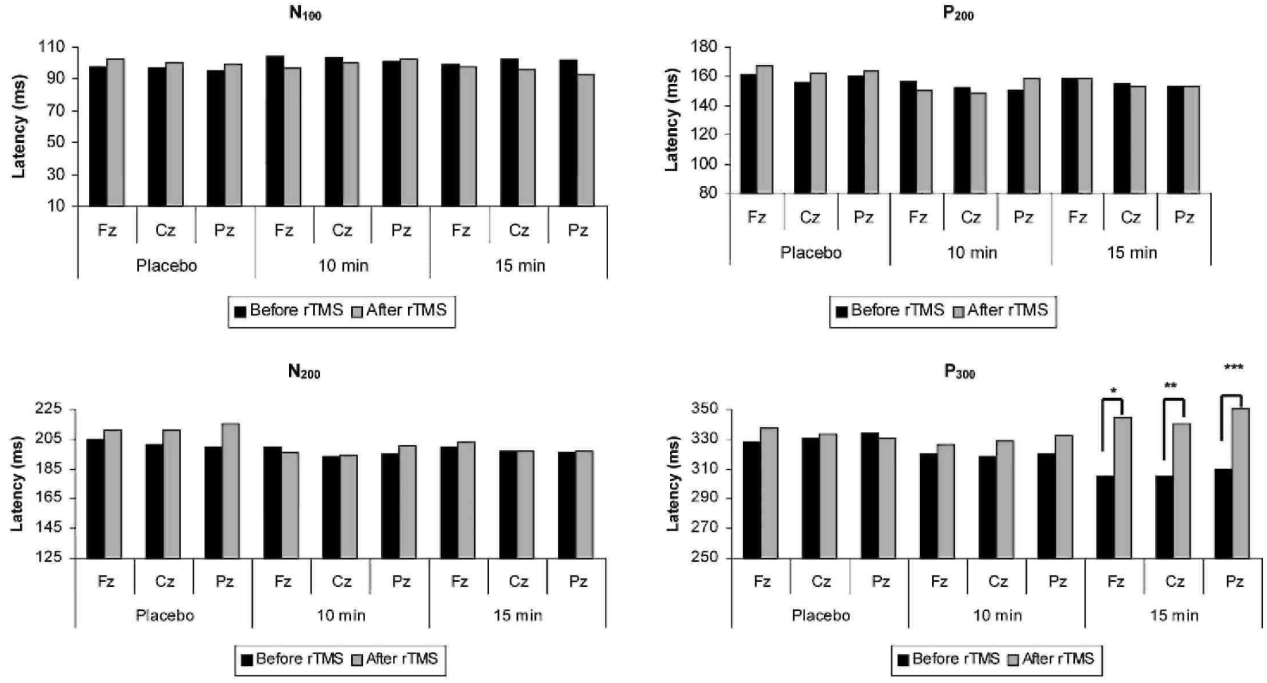
Fig. 3: *N100, P200, N200 and P300 latencies before and after the three conditions of rTMS (sham, l0 min, and 15 min) for the three midline electrodes. P300 latency was significantly enhanced at Fz (*) (P = 0.01), Cz (**) (P = 0.03), and Pz (***) (P = 0.009) after 15 min of rTMS.*



In contrast to P300 latency, reaction time was not modified after 1 Hz rTMS over the left prefrontal cortex applied for 15 min. Due to the limitation of the apparatus employed, Jing et al. (2001) were unable to record reaction time, but Evers et al. (2001) reported that reaction time significantly decreased after 20 Hz rTMS over the left prefrontal cortex. It could be argued from the present result that 1 Hz rTMS induces a delay of stimulus processing but not a delay on motor execution. In other words, a possible cortical effect of rTMS is evident in the electrophysiological response of the brain as measured with scalp electrodes and this appears despite any effect on overt behavior. Perhaps the electrophysiological response of the brain is a more sensitive measure of the effects of rTMS than cognition. Nevertheless, this result shows that it is possible to induce a delay in the processing of the stimulus without affecting the motor execution processes, probably because the task was relatively easy, and confirms that P300 is independent of the motor processes (McCarthy and Donchin, 1981; Smulders et al., 1995), although this debate is not close (Verleger, 1997).

The site of stimulation in the present study was chosen according to different studies that found significant effects of rTMS over left prefrontal cortex (Jing et al., 2001; Evers et al., 2001) and according to the intracranial generators of P300 (Johnson, 1993). However, we could question the use of only unilateral frontal stimulation to affect a component with temporal and parietal—most likely bilateral—generators (Halgren et al., 1995a,b). In consequence, the results found here reflect an inhibition of only one part of the brain responsible for the generation of P300; the other generators are probably not affected by the stimulation. To assess this point, further studies should be conducted with temporal and parietal stimulations.

In conclusion, this study confirms and extends that 1 Hz rTMS produces a real inhibitory effect of the central nervous system only when the duration of the stimulation is about 15 min. However, the preliminary nature of the presented results with respect to the limited sample and the procedure (only left TMS application, limited number of electrodes) must be underlined. 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 fact that possible head movements relative to the coil were not taken into account limit the conclusions of the study. Then, further studies with larger sample and more sophisticated procedure should be conducted to replicate these findings.

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