Clinical EEG and Neuroscience
43(4) 285-290

DOI: 10.1177/1550059412445657
http://eeg.sagepub.com

Effects of Transcranial Magnetic Stimulation on the Cognitive Event-Related Potential P300: A Literature Review

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Abstract

The objective of this study was to perform a systematic review regarding the effects of transcranial magnetic stimulation (TMS) on the cognitive event-related potential P300. A search was performed of the PubMed database, using the keywords "transcranial magnetic stimulation" and "P300." Eight articles were selected and, after analysis of references, one additional article was added to the list. We found the comparison among studies to be difficult, as the information regarding the effects of TMS on P300 is both scarce and heterogeneous with respect to the parameters used in TMS stimulation and the elicitation of P300. However, 7 of 9 studies found positive results. New studies need to be carried out in order to understand the contribution of these variables and others to the alteration in the latency and amplitude of the P300 wave.

Keywords

transcranial magnetic stimulation, event-related potential, P300

Received July 5, 2011; revised September 28, 2011; accepted October 3, 2011.

Introduction

Studies focusing on the effect of TMS on cognitive functioning of the human brain are limited in number. The aim of this review was to summarize the P300 event-related potential (ERP) changes from noninvasive magnetic stimulation of the cortex by means of TMS and to determine whether there are consistent patterns of changes reported in healthy individuals and neuropsychiatric populations. Another aim of this review was to present suggestions for future research.

Cognitive Event-Related Potentials

A cognitive ERP is a representation of brain responses to a specific stimulus during its cognitive processing.[1] These responses can be evoked by novel or deviant stimuli.[2] They do not depend on physical characteristics of the stimuli, such as the shape and size of a given visual pattern or the duration and intensity of an auditory stimulus; rather, they can be influenced by the contextual properties of the event, such as its probability, discriminatory difficulty, or novelty.[3] The early responses are related to the sensation, perception, and discrimination of the presented stimuli, the later ones to cognition and activation of memory resources. The classically recognized auditory evoked potentials are P50, N100, mismatch negativity, P200, N200, and P300.[4] These ERPs have latencies around 35-70, 60-140, 100-200, 160-260, 200-300, and 280-450 milliseconds, respectively.[5-7]

The so-called P300 potential represents processing of information at advanced cognitive levels, such as a shift of attention, context-updating, or orienting to a relatively novel or deviant stimulus.[8] The P300 waveform of the auditory or visual ERPs is a positive deflection peaking around 300 milliseconds from stimulus onset in response to rare, novel, or deviant stimuli in an oddball paradigm. Its amplitude is proportional with the amount of attentional resources allocated to the task and memory performance.[3] P300 potentials are generated when the stimulus unexpectedly gains significance and hence can be seen as reflecting the ability of the CNS to ''gate in'' important information.[9]

Some models suggest that the P300 response is not a single component, but in fact represents the sum of the activities that

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arise from neural structures distributed in several regions that process different types of information.[10] A P3a component over the frontal and central regions has been linked to novel stimuli in general and can be activated within 250-280 milliseconds of the stimulus, while a P3b component over parietal regions is activated by target "oddball" stimuli, related to a task such as pressing a button when the target is seen.[3] The latency of P3b varies from 250 to 500 milliseconds or more depending upon the task.[3] In regard to the P300 responses, it is believed that the latency reflects the time spent for cognitive processing of the stimulus and the amplitude is related to the quantity of attentional resources allocated during the task.[11]

In essence, elicitation of the P300 cognitive ERP is an easily conducted procedure that can be informative about the processes that involve cognitive activity in normal individuals as well as in psychopathological situations.[12,13]

Transcranial Magnetic Stimulation

TMS is a noninvasive, painless, and safe technique, capable of inducing focal electrical currents in the human cortex using a pulsed magnetic field.[14,15] It can be applied in single pulses or repeated pulses (rTMS). The first method is capable of evoking neural depolarization, but its long-term effects are limited. With repeated applications, there is an alteration of cortical activity for a prolonged time, leading to long-term effects on observable behavior.[16]

rTMS has an excitatory effect on the cortex, when the pulses have a frequency of >1 Hz, and has an inhibitory effect, when the pulse frequency is $\leq$1 Hz. However, the exact mechanisms of these effects are still a matter of research.[17] rTMS effects will depend on several parameters such as the pulse frequency, number of stimuli in a train, the intertrain interval, total number of stimuli, duration of treatment, and cortical location to be stimulated.[18,19]

Considering that TMS is a safe tool capable of inducing electrical currents in the human cortex, interfering with brain activity, and that the evaluation of cognitive ERPs is an objective way of assessing the neuronal electrophysiological activity during the processing of new information, these 2 methods can complement each other in the investigation of brain functioning in both healthy individuals and those with neuropsychiatric disorders. TMS may be used not only in probing information processing as reflected by ERPs but also in spatially probing neural contributors to the ERP signal. With this in mind, the objective of this article was a literature review of studies that performed analyses of the P300 response prior to, and after, TMS.

Materials and Methods

A systematic review was performed, using the PubMed database. Keywords used were "transcranial magnetic stimulation" and "P300" The inclusion criteria were (1) articles written about the effects of TMS on P300 and (2) articles available in English. Titles and abstracts of these articles were evaluated in order to determine which ones would properly fit the inclusion criteria of this review. References in these papers were also searched for other articles that fitted the criteria, but not found in the initial search. We then reviewed full texts of the selected manuscripts and summarized the parameters used in TMS stimulation. Elicitation of ERP P300, and the observed effects, reported in these studies are provided in Tables 1 and 2.

Results

The initial search in PubMed resulted in 14 articles, 6 of which did not meet inclusion criterion 1. References in the remaining 8 articles identified 1 additional article (Evers et al[20]). The reviewed articles had recent publishing dates from 2001 to 2011. Two articles (both by Jing et al[5,6]) documented different aspects of the same study, resulting in some redundancy.

Of the 9 studies, 4 used low frequency TMS (1 Hz), 3 studies used high frequency TMS (2 of them at 10 Hz and 1 at 20 Hz), and 2 studies used single pulse TMS. The most frequently stimulated area was the left dorsolateral prefrontal cortex (l-DLPFC); within 3 studies, this area was stimulated to the exclusion of others. Two studies applied stimulation over both left and right cortices, 1 stimulated only the right dorsolateral prefrontal cortex (r-DLPFC). One study omitted specification beyond the "prefrontal cortex," and 1 applied stimulation over the left supramarginal gyrus (Table 1).

The total number (N) of individuals that participated in these experiments was relatively small: 6 studies had an N less than 15 and only in 2 studies an N is greater than or equal to 15 (Table 1).

To elicit the P300, 6 articles used the auditory and 2 the visual oddball paradigm. One of them used a distractor stimulus that elicited a P3a wave separate from the classical P300 (P3b) in a patient with post-traumatic stress disorder (Table 2). The most utilized response to the target stimulus was a button press. This technique was used in 4 studies, and mental counting of target stimuli was used in 2 other studies. Two studies had no mention of a task (Table 2).

The effects of TMS on P300 varied significantly. Among the 4 studies that conducted the low-frequency stimulation, 1 found a reduced amplitude and an increased latency of P300 after a 15-minute but not after a 10-minute stimulation; another found only a reduction of the P3a; amplitude. The other 2 studies applying low-frequency stimulation found no significant changes in P300 measures. Among the 3 studies that used high-frequency stimulation, 1 found a reduction of the latency, another found increased latency, and a third found an increase of P300 amplitude. Of the 2 studies using single-pulse TMS, 1 found increased latency and the other found increased amplitude (Table 1).

Discussion

Three findings can be underscored from this review: one is that the first publication dates to 2001 and, therefore, it is about a new line of research.[20] The second is that in a 10-year period, only 8 articles investigated the effects of TMS on P300, so data

Table 1. Sample Size, Parameters Used for TMS, and Effect on P300 as Given in Different References

References	Individuals/n/control	Frequency and intensity	Stimulated area	Application	Effect on P300
Evers et al[20]	Healthy individuals/n = 14/14 active and 14 sham	20 Hz and 1 Hz; 95% of MT	r-DLPFC and lDLPFC	20 Hz—3 trains, 5 s interval, 1 min intertrain 1 Hz—2 consecutive min	Reduction in latency with 20 Hz rTMS to the left DLPFC No statistical relevance in other conditions
Jing et al[5]	Healthy individuals/n = 29/15 active and 14 sham	10 Hz; 100% of MT	l-DLPFC	2 Trains of 30 pulses with intertrain interval of 05 min	Changes in direct coherence (information flow) in medial frontal region and left parietal
Jing et al[6]	Healthy individuals/n = 15/15 active	10 Hz; 100% of MT	l-DLPFC	2 trains of 30 pulses with intertrain interval of 5 min	Increase in latency; amplitude reduction
Hansenne et al[7]	Healthy individuals/n = 17	1 Hz; 100% of MT	l-DLPFC	1st session—10 min active 2nd session—15 min active 3rd session—12.5 min sham Interval of 1 week between sessions	Increase in latency after 15 min of active stimulation No statistical relevance in other conditions
Price[21]	Healthy individuals/n = 1	Single Pulse TMS	PFC	Application of single pulse to create a deep pattern EEG	Significant increase in amplitude
Möller et al[22]	Depressive individuals/n = 10/7 active and 3 sham, Observed: 1 active quit	10 Hz; 100% of MT	l-DLPFC	5 Sessions in consecutive days. Each session with 40 trains of 5 s and intertrain interval of 25 s.	Amplitude increase Changes in latency did not have statistical relevance
Cooper et al[23]	Healthy individuals/n = 8	1 Hz; 110% of MT	r-DLPFC	15 min of continuous stimulation	No significant alterations in latency and amplitude were found in P300
Iwahashi et al[24]	Healthy individuals/n = 6	Single pulse TMS; 80% of MT	Left supramarginal gyrus	Single pulses after 150 ms, 200 ms and 250 ms after target sounds of oddball paradigm	Increase in latency of P300 with stimuli at 200ms and 250ms after target sounds of oddball paradigm
Tillman et al[25]	Individuals with PTSD/n = 1	1 Hz; 100% of MT	r-DLPFC and l-DLPFC	1st session—20 min in RPFC interval of 1 week 2nd session—20 min LPFC	Amplitude reduction of P3a after stimulation of the right DLPFC

Abbreviations: TMS, transcranial magnetic stimulation; PTSD, post-traumatic stress disorder; l-DLPFC, left dorsolateral prefrontal cortex; r-DLPFC, right dorsolateral prefrontal cortex; LPFC, lateral prefrontal cortex; RPFC, EEG, electroencephalograph; PFC, prefrontal cortex; MT, motor threshold; EOG, electrooculogram.

Table 2. Parameters Used to Elicit and Capture P300 as Given in Different References

References	Paradigm	Bandpass Filter	Ratio of tones, pattern:target (%)	EOG artifacts control	Electrodes	Characteristics of stimuli	Average of trials	Task
Evers et al[20]	Visual oddball	0.1-70 Hz	80:20	Nonspecific	Pz	White flash—pattern Red flash—target	20	Press a button on target stimulus
Jing et al[5]	Auditory oddball	0.1-30 Hz	80:20	In both lower corners	F3; F4; C3; C4; P3; P4; T3; T4; T5; T6; Fz; Cz; Pz; Oz	1000 Hz—pattern 2000 Hz—target Intensity: 80 dB	50	Press a button on target stimulus
Jing et al[6]	Auditory oddball	0.1-30 Hz	80:20	In both lower corners	F3; F4; C3; C4; P3; P4; T3; T4; T5; T6; Fz; Cz; Pz; Oz	1000 Hz—pattern 2000 Hz—target Intensity: 80 dB	50	Press a button on target stimulus
Hansenne et al[7]	Auditory oddball	0.05-35 Hz	80:20	Left lower corner	Fz; Cz e Pz	1000 Hz—pattern 2000 Hz—target Intensity: 70 dB	30	Press a button on target stimulus
Price[21]	Auditory oddball	0.1-30 Hz	75:25	Not specified	32 channels	1000 Hz—pattern 2000 Hz—target Intensity not mentioned	Not specified	Mental counting
Möller et al[22]	Auditory oddball	0.1-30 Hz	80:20	Right upper and lower corners	Cz	1000 Hz—pattern 2000 Hz—target Intensity: 80 dB	Not mentioned	Not mentioned
Cooper et al[23]	Auditory oddball	0.05-30 Hz	80:20	Above and below the left eye and on the outer canthus of each eye	Cz	1000 Hz—pattern 2000 Hz—target Intensity: 80 dB	40	Mental counting
Iwahashi et al[24]	Auditory oddball	0.1-200 Hz	80:20	Not mentioned	60 channels	1000 Hz—pattern 2000 Hz—target Intensity not mentioned	Not mentioned	Not mentioned
Tillman et al[25]	Visual oddball	0.03-100 Hz	20%: target 20%:pattern 60%: distractor	Not specified	F3; F4; P3; P4	Images	20	Press a button on target stimulus

about this area of research are scarce. The third is that these articles present studies with heterogeneous designs, producing heterogeneous results.

From clinical studies, it is known that increases in latency of P300 are associated with cognitive deterioration. Also, several studies already demonstrated that high frequency TMS to l-DLPFC improves cognitive function.[26-29] Thus, it may be hypothesized that high frequency TMS to l-DLPFC should produce a reduction on the latency and/or increase in the amplitude of the P300. Nevertheless, among the studies that used high frequency TMS, 1 study found a reduction in the latency of the P300, another found an increase in the latency, and a third found no significant effect.[5,20,22] These conflicting results may be explained by the heterogeneity of the methodology. For example, Both Jing et al[5] and Möller et al[22] used rTMS at a frequency of 10 Hz. However, the first studied healthy individuals in a single day of TMS application, whereas the second studied depressed patients over 5 consecutive days. Both Jing et al[5] and Evers et al[20] used healthy individuals. However, the first stimulated l-DLPFC at 10 Hz, whereas the second stimulated it at 20 Hz. It is important to point out that all 3 studies used an active stimulation coil as placebo and changed only its positioning or angle. This may also have influenced the results.

The studies that used low frequency to l-DLPFC would be expected to produce the opposite effect on P300: an increase in latency and a reduction in amplitude. In the study of Hansenne et al,[7] using 1-Hz frequency, no significant alteration of P300 was found after 10 minutes of continuous stimulation. However, after 15 minutes, a reduction of amplitude and an increase of latency was found, supporting the hypothesis that inhibitory stimulation in l-DLPFC causes an inhibitory effect on cognition.[7] However, Cooper et al,[23] also used a frequency of 1 Hz and a 15-minute continuous stimulation, but neither latency nor amplitude of the P300 was affected. While both studies used healthy individuals, Cooper et al[23] stimulated the r-DLPFC instead of the left one.[2]

Evers et al[20] used both high and low frequency stimulation with 20 Hz over l-DLPFC and 1 Hz over l-DLPFC and r-DLPFC. There were no alterations in amplitude or latency after low frequency TMS. However, stimulation was for only 2 minutes.[20] Thus, this finding is in accordance with the results from Hansenne et al.[7]

The fourth study, that used stimulation at 1 Hz (Tillman et al[25]), was of a Vietnam veteran with chronic post-traumatic stress disorder (PTSD). Both prefrontal cortices were stimulated in alternating fashion for 20 minutes. The result was a reduction only in the amplitude of the P3a when stimulation occurred over r-DLPFC. There was no significant alteration of the other parameters.[25] However, this was a case study. In addition, individuals with PTSD often exhibit hyper-surveillance and a corresponding increased amplitude in P3a when compared with healthy individuals.[30,31]

All studies in this review have small sample sizes, prejudicing external validity of the conclusions. This, together with the heterogeneity of methodologies, poses more questions than answers. It is difficult, to explain that in 2 articles, one using excitatory TMS (10Hz) and the other using inhibitory TMS (1Hz), applied to l-DLPFC of healthy individuals, both found the same result (an increase in P300 latency).[6,7] The authors of one of these articles,[6] argued that the fact that the stimulation of healthy individuals could have contributed to such discrepancy. However, a study by Evers et al,[20] using 20 Hz TMS in healthy individuals, found a significant reduction of P300 latency and concluded that the facilitating effect of rTMS in cognitive processing could be objectively measured by the cognitive evoked potential P300.[20]

Despite discrepancies in the methodology, all studies but one (from Cooper et al[23]) found a TMS effect on P300.[23] In the mentioned single study the subjects were healthy individuals and were stimulated in the r-DLPFC with suprathreshold stimuli (110% of MT) at a rate of 1Hz for 15 minutes. This review provides evidence that the effect of TMS on cognition can be evaluated in an objective way using the P300 ERP. On the other hand, the divergence in findings allows the supposition that other variables can confound the results. One study[21] has showed that the pattern of brain electrical activity can interfere with P300 results. It used an interactive technique, in which single-pulse TMS increased the probability of creating a specific pattern of electrical activity, instead of disorganized electrical activity.[21] This way, Price found a significant increase in the amplitude of P300. Thus, he suggests that another variable—the basal cortical electrical activity—may interfere with the results while probing the effects of TMS on cognition.

Some negative findings are in agreement from these studies: high frequency stimulation with few trains, a long intertrain interval and applied only in one session seems to have little effect on the P300, as do low-frequency stimulation at r-DLPFC of healthy individuals for of few minutes.

Conclusion

This review shows that TMS can enhance or impair the function of the cognitive networks as assessed by P300 measures. However, the contribution of TMS parameters, and other variables, remains poorly understood. It is important that new studies use moderate to large sample sizes, as well as sham coil placebo control conditions. In addition, P300 measures must be assessed over the course of many TMS sessions, as its effects on brain plasticity may take days to manifest. Differences between stimulation of r-DLPFC and l-DLPFC seem to exist and warrant further investigation. Another area of interest is difference in response between healthy individuals and those with neuropsychiatric disorders. Finally, the role of other variables such as deep cortical electrical activity should be elucidated.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

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