

Protocols

EEG-dependent ERP recording: using TMS to increase the incidence of a selected pre-stimulus pattern

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Abstract

EEG dependent event-related potential (ERP) recording (interactive ERP) is an extension to ERP paradigms whereby stimuli are initiated in response to a selected pattern of background EEG. This form of recording is critically dependent upon the incidence of the particular pattern of interest. We introduce here a process that modifies the EEG in a predictable manner so as to increase the incidence of a particular pattern. Transcranial magnetic stimulation (TMS) stimuli are applied in response to a selected pattern of pre-TMS activity, and the post-TMS response is characterized by the incidence of a defined pattern of EEG activity. Analysis of validation test results obtained with the TMS modification part of the process verifies an increased incidence of the response pattern after TMS stimuli, compared with placebo stimuli. The TMS modification procedure is then combined with interactive ERP recording in a two step process to affect the ERP response to sensory stimuli. The post-TMS pattern from the first step becomes the pre-stimulus pattern of the interactive ERP recording in the second step. The TMS modified interactive ERP (TMIERP) process is illustrated here using an auditory oddball paradigm. The amplitude of the P300 peak obtained using this process was significantly higher than that obtained using the standard auditory oddball paradigm.

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1. Type of research

Interest in the effects of background EEG upon behavioral and event-related potential (ERP) measures has developed in several forms. Microstates [15], oscillatory neuro-electric activity [4], selective averaging [24], and interactive ERP [20] are all forms of investigation based on the same premise: that the background EEG at the time of stimulus can have an effect upon the ERP feature under test. EEG-based delivery of stimuli, arising from this premise, is an extension to the ERP paradigm whereby stimuli are applied in response to a selected pattern of background EEG activity. Previous EEG-based ERP recording (herein collectively termed interactive ERP) has shown an increase in P3 amplitude with increasing theta and alpha activity [24], an increased VEP with theta activity [3], and with alpha phase [25], as reviewed by Intriligator [10]. Previous work at our

unit using interactive ERP recording likewise showed a significant effect of pre-stimulus EEG activity [20,21]. A major difficulty with all these forms of interactive ERP recording is the possibility of a low incidence of the particular EEG pattern of interest. A process was developed that attempts to increase this incidence.

Several studies have investigated the intermediate and long term effects of transcranial magnetic stimulation (TMS) on the background EEG and ERP. Wassermann [33] found no long-term (weeks and months) changes in the EEG in a review and meta analysis. Jing [12] showed medium-term (2 and 10 min) changes after rTMS in EEG and ERP data. Fewer investigators have studied the short-term (<1 s) effects on stimulus-locked oscillations commensurate with ERPs. Izumi [11] found an effect on EEG in this period, although an electrical artifact from the TMS pulse was questionable. TMS was thus selected as a means of modifying the EEG in the short term.

Interactive TMS stimulation was used because of concerns that the background EEG may affect the TMS effect in

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an unknown manner. There is growing evidence of such an EEG effect on sensory ERPs, as discussed earlier. It is also known that the motor-evoked response is usually initiated [19] and inhibited [32] in association with synaptic activation, which is likewise the basis of EEG activity. Finally, it has been shown that the effect of TMS is facilitated or suppressed by activity of the cortical region at the time of stimulus [16], showing a possible linkage to background EEG. We have thus far only found one study that specifically investigated the effect of background EEG on TMS features using retrospective correlation analysis. Rossini [26] found that MEP values, in response to TMS were lower amplitude and more often absent, when the EEG was dominated by alpha and theta activity. Interactive initiation of TMS pulses controls for these unforeseen EEG effects on the TMS response.

The TMS effects on EEG are therefore used as a means of altering the low incidence of a pattern of interest. A process that modifies the EEG in a predictable manner so as to increase the incidence of an EEG pattern that is subsequently used in interactive ERP recording is described. The TMS-modified interactive ERP process (TMIERP) is illustrated using the auditory oddball (P300) paradigm.

2. Time required

The process is applied as an adjunct to a traditional ERP paradigm and as a replacement for interactive ERP recording, so it is difficult to estimate the exact time impact. If, for example, a standard auditory oddball paradigm took 20 min (excluding set up time), then using this process might increase the time to 40 min. However, previous interactive recordings [21,24] allowed stimulus onset to vary by up to three times the standard ISI in order to stimulate during the pattern of interest. Using the described process might thus decrease the testing time by 30%.

3. Materials

Apart from the interactive aspect, TMS application and ERP recording are fairly standard. Only minimal detail will be provided on materials for these components unless such details are relevant to the process. Equipment for the process comprised a TMS machine (Magstim), an EEG/ERP machine (Scan), and a separate computer (Control) to carry out interactive processing, as well as to manage the combined process.

3.1. Interactive processing

Software was developed (C++) to receive EEG data transmitted by the Scan unit. A data array was continually updated, then processed and compared with a predetermined EEG pattern using a syntactic analysis algorithm.

Syntactic pattern recognition [5] attempts to classify a response pattern in the post-stimulus EEG, based on a set of extracted features, and an underlying model (grammar) for the generation of these patterns. The method was chosen as it does not require the response to be time locked to the stimulus, is able to recognize a complex pattern, and does not require stationarity. There are two distinct patterns involved in this protocol description, that are independent of the described process, and will be described as materials. The pre-TMS grammar as used in Section 4.2 and the TMS-response pattern, which is used as a pre-ERP pattern in Section 4.3. The association between these patterns is addressed in Section 4.1. Unfortunately, syntactic analysis makes a simple description of the pattern difficult, as recognition is based on the complete set of rules derived recurrently from the corresponding grammar. However, a heuristic summary can be made. In both cases a set of two to five templates (with individual correlation thresholds) for each of alpha, theta, beta, and delta primitives, plus an absolute threshold for a desynchronised primitive, comprise the building blocks for the pattern's grammar [5]. The pre-TMS grammar could be described as an "alpha" grammar, matching any permutation of two or more alpha primitives while ignoring desynchronised activity. The TMS-response grammar is heuristically the "opposite" of that pattern, with matching keyed to an absence of alpha activity, as identified by acceptance of alternative primitives. It must be stressed, however, that these simple descriptions are not intended to impute functionality to the patterns. For the purpose of this protocol described, the grammars are intended as no more or less than a means of identifying an EEG pattern that can be responded to.

3.2. Transcranial magnetic stimulation

TMS pulses were delivered by a Magstim Model 200 machine. A 90-mm stimulus coil delivered a monophasic pulse up to 2.0 T. The level for a supra-liminal TMS pulse at the motor cortex was established by the initiation of a Complex Motor Action Potential (CMAP) as indicated by EMG recording and by a visible muscle twitch. Sub-liminal TMS pulses, which were set at 90% of the supra-liminal motor threshold, were then used for testing. In a comparable ERP study, Evers [8] used a figure-8 coil over the pre-frontal area. As our circular coil has a less focussed pulse, the stimulus area was less specific but included the sites previously suggested. Sub-liminal stimuli were applied with the coil centered on and tangential to the Fz electrode. TMS pulses were initiated by the Control unit via the Magstim unit's "Trigger Input" socket.

3.3. ERP recording

Neuroscan's Scan 4.2 software, with Synamps, was used for EEG data acquisition and recording. This program

simultaneously sent (SOURCE Mode) a copy of the acquired data to the Control computer for interactive analysis. ERP stimuli were generated by Control and incorporated in the EEG recording via markers sent to the Synamps's "Trigger" port. Data was recorded from 32 channels (standard 10–20 system plus HEOG and VEOG), from Ag–AgCl electrodes referenced to linked mastoids, and using Synamps amplifiers (DC) from Neuroscan. All channels had a gain of 75 000 with a 0.1–30 Hz band pass filter and were sampled at 200 samples per second.

This report describes a process for controlling the timing of stimuli in an ERP paradigm, but the actual paradigm and stimulus features are incidental to that process. They are thus included as material, rather than distracting from the methods of the TMIERP process. In the illustrative application, the described process was incorporated in an auditory oddball paradigm with stimuli consisting of an 80-member 3:1 oddball sequence (1000 Hz/2000 Hz). A series of 12 recording pairs was made over four recording sessions, with a single subject, for whom the effect of TMS stimuli had been previously verified. Each recording pair consisted of a TMIERP recording, wherein both non-target and target tones are applied using this process, followed by a standard ERP recording [18] using the same sequence of stimuli but without regard to the background EEG. The subject reported a mental count of stimuli, but no further behavioral data was acquired. Statistical analyses were carried out at Fz, the TMS site.

3.4. Chemicals and reagents

Only standard ERP materials for cleaning, preparation, and electro-conduction were used in this process.

4. Detailed procedure

The process involves repeated loops comprising interactive TMS to modify the EEG, and interactive stimuli to utilize the modified EEG in an interactive ERP paradigm.

4.1. Validate a predictable effect of TMS for a particular pre-TMS pattern

While this step is not strictly a component of the TMIERP process, it is necessary to verify that the TMS pulses are actually having a predictable effect on the EEG. This step is especially important while introducing the process, but is also necessary before any intended application.

A single subject was used with six recording sessions (one training and five test sessions) at the same time of day on different weeks. Each session comprised 4 recordings (5 for the training session) of 39 TMS and 41 placebo stimuli (13–23 min per recording). The Hospital Ethics

Committee approved the procedure, and informed consent was obtained.

Verification of the TMS effect involved a training session, and then five test sessions. Recognition of the post-TMS pattern was developed using sweeps recorded in the training session. Criteria for the response pattern were subjectively selected from the first training recording, then tested against the other four. Analysis of the response to TMS was based on the detection of a predicted pattern via the syntactic analysis algorithm. The presence or absence of a specified pattern is clearly a categorical variable. The marginal incidence of this pattern (matched or not matched) in the two situations (TMS or placebo) was tested for independence in the resulting 2×2 table. The single subject study design induces a repeated measure across the entire sample. This has been accounted for in the analysis by using conditional logistic regression for binary responses as described in Diggle [7].

The pattern recognition algorithm derived was used, unchanged, for all subsequent sensory ERP test sessions.

4.2. Interactive TMS

The pre-TMS pattern used in this study comprised a combination of alpha and theta waveforms and desynchronized EEG, which had been found to meet several criteria in previous (non-interactive) single sweep TMS analysis. It was easily identifiable, short lasting (~ 1 –5 s), and of reliable incidence. While details of the pre-TMS pattern are clearly relevant (and described in Section 3), its importance in this methodology study was simply to standardize the pre-TMS EEG, and so control for unknown effects due to variations in EEG.

4.3. Interactive ERP

The EEG pattern in response to TMS was then used as a pre condition for an ERP stimulus. It should be noted that interactive processing in this instance is looking for a pattern putatively induced by the TMS-modifying pulse. The interactive ERP based on that pattern is, at this point, completely unknown. This situation is different to the normal interactive ERP paradigm whereby the stimulus pattern has previously been associated with an effect on the ERP.

4.4. Timing control

The post-TMS pattern recognition step is repeated several times, at increasing delays after the TMS stimulus. This is because the EEG modification is not always apparent immediately after the TMS pulse. A maximum delay for this process (2 s in this illustration) prevents the process from looping indefinitely. If the predicted pattern is not found in that time, the interactive ERP step is abandoned and the TMS-modifying step restarts. This means, of course, that there is not direct correspondence between the two steps.

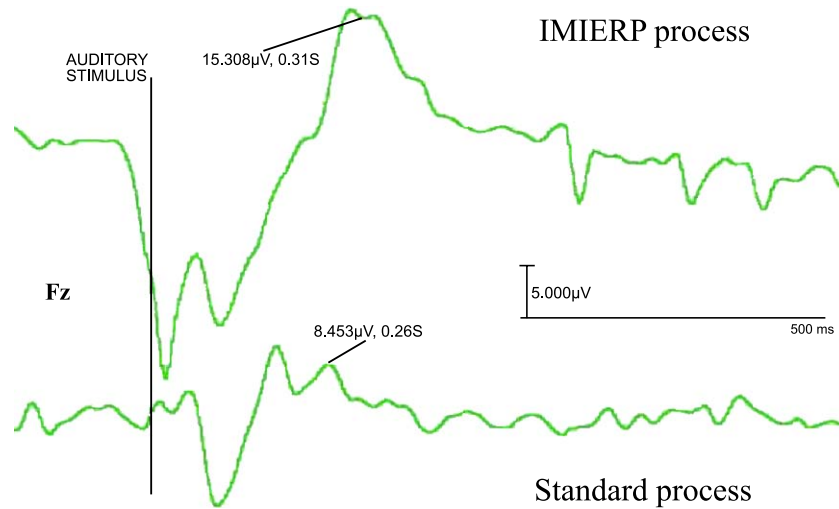


Fig. 1. Averaged P300 paradigm responses (Fz) using TMIERP and Standard processes as an illustrative application. Stimuli were delivered at the “Auditory Stimuli” point. TMS pulses were not marked, but were prior to this point.

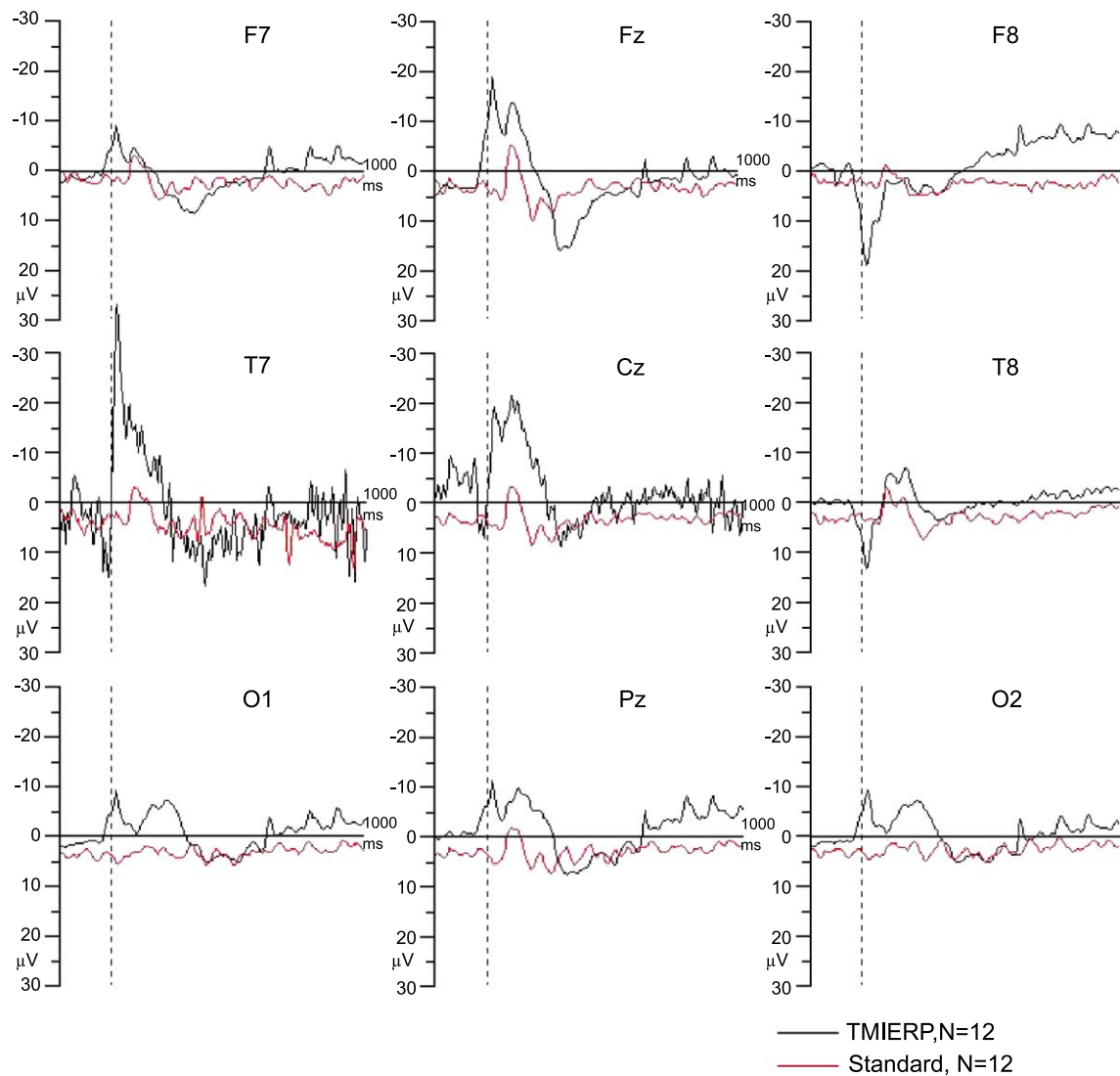


Fig. 2. Topography of the P3 peak from the TMIERP and Standard processes used in the illustrative application.

More TMS pulses were applied than sensory stimuli. After a loop through both interactive steps, the software checks whether any more ERP stimuli need to be delivered. If so, then the process begins again. If not, then the acquisition phase is completed.

4.5. TMIERP analysis

To illustrate the process, 24 sensory ERP recordings were carried out comprising alternate TMIERP and standard recordings. The resulting sweeps from both processes were averaged for targets and non-targets. The amplitudes of the P3 peak (highest voltage in the 250–400 ms range) from both processes were compared using a *t* test.

5. Results

5.1. Validate a predictable effect of TMS for a particular pre-TMS pattern

Odds ratio analysis (Mantel–Haenszel) of the post-TMS EEG indicates that the odds of a pattern match under TMS are approximately twice the odds under the placebo (OR = 1.71; 95% CI = 1.34–2.17; $p < 0.01$), a significant increase in incidence after TMS.

These results show that interactive application of a TMS leads to a predictable modification of the EEG in a significant proportion of stimuli.

5.2. TMIERP analysis

The grand average over 12 recordings, of responses (Fz) to target tones, for the TMIERP process and for the standard process are shown in Fig. 1. The topography of the P3 peak from the TMIERP process is shown in Fig. 2. This figure shows no obvious differences in topography (P3 or N1) between TMIERP and standard waveforms. In each of the 12 recording pairs, the P3 amplitude from the TMIERP process was greater than that from the standard process. There was a significant group difference ($t = 4.97$, $df = 22$, $p < 0.001$) between the TMIERP values ($17.84 \pm 6.4 \mu\text{V}$) and standard values ($7.5 \pm 3.4 \mu\text{V}$).

These results show that the TMS modified interactive ERP process, as described produces an ERP significantly different to that produced using random application of stimuli.

6. Discussion

The first part of the results showed an increased incidence of the selected response pattern after TMS. Thus, interactive application of a TMS pulse does indeed lead to a predictable modification of the EEG for the pre- and post-TMS patterns as selected. This was a necessary condition for the operation of the complete TMIERP process. Appli-

cation of the TMIERP process to an auditory oddball paradigm showed a significant effect upon a sensory ERP. The TMIERP based response has higher amplitude than the response based on the standard recording process. The TMS effects on EEG have therefore been used to facilitate the operation of an interactive ERP paradigm, with a consequent effect on ERP amplitude. Variations of the process may be applied to facilitate the operation of any interactive ERP paradigm by increasing the incidence of a background pattern that is of interest but rare, by standardising the timing of a common pattern of interest, or by introducing completely novel patterns. The utility of this facilitation, and thus the gain for ERP research in general, of course, will still depend on current and potential benefits inherent in interactive ERP recording (Section 1).

Theoretical justification for the use of interactive recording, and hence for the development of the described process, lies in the proposed links between EEG activity, ERP responses, and cognition. That cognition affects EEG has been clearly shown [1,9], while ERP links with cognition are also well established [22,23]. In addition, several authors have also proposed a role for oscillatory processes (EEG) in influencing cognition [2]. Initially based on functional correlates of alpha activity such as attention [28] and cognition [14], recent work has extended the process to attention-related gamma (40 Hz) activity [31] and higher frequencies [4]. The effect of theta activity on cognition (episodic memory processes) is also established [13], while delta activity has been related to signal detection and decision making [29]. Each of these studies was carried out using retrospective analysis, with no control over the timing of stimuli or responses, making it difficult to infer causality. Using interactive ERP recording, a causal effect of background EEG can be argued, rather than simple correlation, but variable stimulus timing weakens the argument. Using interactive ERP recording, incorporating the TMIERP process, the variations in stimulus timing can be minimised. Each of the above studies could be replicated prospectively to test for a causal effect of background EEG on cognition. Almost any current ERP paradigm, in fact, may prove to be enhanced by the incorporation of the described process to test for an effect of background EEG.

Obviously, the results in this study hold for a particular TMS-modifying pattern, for a particular pre-ERP pattern, and for particular stimuli in a particular ERP paradigm. However, the process is completely general in its application, it is methodologically novel and may well prove to be a useful technique in electrophysiological brain research.

6.1. Trouble shooting

TMS typically produces a large stimulus artifact making it difficult to record background EEG for several seconds after stimulation [6]. This artifact was minimized by arranging the leads perpendicular to the coil, and by using the Synamps's de-blocking feature whereby the input to the amplifiers is

disconnected for 10 ms around the TMS stimulus. The individual sweeps were assessed manually for eye movement, muscle artifact, and excessive TMS artifact. Any sweeps, which contained such artifact within 1500 ms post stimulus, were discarded. The amplifiers were blocked for 10 ms, which meant that early data was not available. In addition, in about 5% of cases, the sweep contained evidence of residual charge from the TMS pulse. Several suppliers are producing quick reset amplifiers that can be turned off and on for a shorter period, and are less likely to be affected by residual TMS charge on the amplifier. Unfortunately, these would not be expected to overcome difficulties with residual TMS induced currents from the head.

The magnetic flux distribution from TMS, and its effect on the cortex are poorly understood, but are relevant in the verifying an effect of interactive TMS when compared with placebo. Current methods of producing a TMS placebo [27] reduce but do not eliminate the flux. This placebo flux is of greater concern in the described process, as the site of activation of the EEG is not well known. To address these concerns, this study uses a placebo that delivers completely artificial sound and sensation stimuli, with zero magnetic flux component. A prerecorded click sound was played through headphones (plus ear plugs as a safety measure) to mimic the TMS click. The placebo “sensation” was generated by applying a brief (100 μ s) electrical current (20 mA) between two points (2 cm apart) on the scalp (under coil center). The loudness of the click placebo and current, time, location, and spacing parameters for the “sensation” placebo were adjusted subjectively to match the TMS characteristics in each recording session. Distinguishing the placebo from TMS was possible with effort (mainly by the location of sound), so an endogenous effect of this information cannot be ruled out. This form of placebo has not been well validated, and needs further development.

Variations in interstimulus interval (ISI) are known to affect ERP data, so care was taken to match the ISI of interactive TMS and placebo stimuli wherever possible. When interactive recording is carried out, it is clearly not possible to use a set ISI value. For each recording, however, the ISI from each interactive TMS stimulus was stored and replicated for a subsequent placebo stimulus to ensure against a bias ascribable to ISI methodology. An ISI maximum of 45 s was set to ensure a degree of continuity in the sequence. If the pre-stimulus pattern was not matched after 45 s of testing, a TMS stimulus was applied by default (and also a matched ISI placebo). These TMS stimuli were discarded from processing. Despite these efforts, it is still possible that systematic variations in ISI may confound results. This is, however, a problem with interactive recording in general rather than with our described process.

In this description of the process, the TMERP version of a protocol was compared with non-interactive version. No attempt was made compare it with a non-TMS modified but still interactive version of the protocol. This comparison will be investigated in future studies.

6.2. Alternative and support protocols

Many of the myriad ERP paradigms currently used in neurophysiological research can be modified to use the TMERP process. In a sense, these are all alternative protocols to the auditory oddball protocol described. If the fixed ISI is of particular interest (e.g., P50 paradigms [17]), if the ISI value is too small for meaningful analysis and modification (e.g., Auditory Brainstem paradigms [30]), or if the stimulus is already dependent upon some other feature (e.g., readiness potentials), then, obviously, the process cannot be applied.

Less trivially, it is also possible to apply the process using any of a number of different pre-TMS patterns. If the process proves useful, then the development of optimal pattern recognition parameters would become important. The obvious limitation being that the pattern selected needs to have a reasonable incidence. The situation is analogous to the current search for optimal rTMS parameters. Similar investigations of stimulus parameters such as site, morphology, and even repetition need to be made for the described process.

7. Quick procedure

The TMS-modified interactive ERP process only is described in this section. Procedures for ERP acquisition and analysis and for TMS stimulation are standard [18,33], and will not be described.

(i) Validate a predictable effect of TMS for a particular pre-TMS pattern.

Identify pre-TMS pattern, and post-TMS predicted pattern. Verify that interactive TMS substantially produces the predicted pattern.

Start Loop

(ii) Interactive TMS

Step 1. Continuously monitor the subject's EEG pattern.

Step 2. Compare the monitored pattern with pre-selected criteria for a TMS-modifying pulse.

Step 3. If the pattern does not substantially meets the pre-selected modification criteria, then return to Step 1.

Step 4. If the pattern substantially meets the pre-selected modification criteria, initiate a TMS-modifying pulse.

(iii) Interactive ERP

Step 5. Continuously monitor the subject's EEG pattern, post TMS.

Step 6. Compare the monitored pattern with pre-selected criteria for an ERP initiation.

Step 7. If the pattern substantially meets the pre-selected ERP initiation criteria, initiate an ERP stimulus and go to Step 10.

(iv) Timing control

Step 8. If the time limit is not reached then go to Step 5.

Step 9. If the modified EEG pattern does not meet the pre-selected ERP initiation criteria within a certain time limit, then give up and go back to the start of the process at Step 1.

Step 10. If all the ERP stimuli have not been delivered, then go back to the start of the process at Step 1.

End Loop

(iv) TMIERP Analysis

After all stimuli have been delivered, process the recording of brain wave activity to extract the electrophysiological response for further analysis.

8. Essential references

[4,20,24]

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