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On the challenge of measuring direct cortical reactivity by TMS-EEG

Since its introduction in 1997 by Ilmoniemi and colleagues [1], the combination of TMS and EEG has been proposed as a new and unique method of characterizing brain reactivity and connectivity [2]. However, shortly after its introduction it became clear that this combination brings new technical problems. At the beginning, researchers' attention was focused on the saturation of the EEG amplifiers caused by the TMS pulse, which has led to the introduction of several TMS-compatible recording systems (for a more extensive description see Ref. [3]) and to the definition of the ideal recordings parameters with the attempt to maximally reduce the artifact duration [3,4]. Beside recording settings, several off-line procedures have been proposed to solve the artifact issue such as subtraction approaches, filtering methods, principal component analysis (PCA) and independent component analysis (ICA). Unfortunately, these methods are not established standard procedures to remove the magnetic artifact and thus have not been further applied. Therefore, the best possibility so far to reduce the artifact duration is selecting the right recording parameters, with independent groups reporting a reasonable loss of EEG signal, that is 5–6 ms from the pulse delivery [3,4].

More recently, researchers have focused on the EEG signal recorded after the magnetic artifact, namely the TMS-evoked potentials (TEPs) recorded in the first milliseconds following the pulse delivery (in the first 5–10 ms following pulse), as spurious extracortical sources may contribute to the generation of these components. The debate about the short latency TEPs started when several groups reported a huge bipolar waveform recorded between 5 and 10 ms (P5, N8) after TMS pulse [4–6], mainly evoked when the stimulation was performed over lateral scalp positions. Despite the source of this waveform is unknown, it has been interpreted as muscle activity [5], huge cortical response or as a combination of cortical and extra-cortical signals [6,7]. The first conclusion is mainly supported by a recent work by Mutanen et al. [5], nicely showing that the amplitude of the biphasic response is highly dependent on coil distance, orientation and tilt angle relative to cranial muscles. In particular, its amplitude decreased when the coil, or even its wings, was moved toward central sites and it was no longer recorded when TMS was applied over the midline. To further explore the nature of these early responses, Rogasch et al. [4] and Veniero et al. [6,7] tried to manipulate its amplitude by means of TMS protocols known to modulate cortical excitability. However, Rogasch et al. [4] found no modulation of early components following inhibitory paired-pulse technique, whereas Veniero et al. [6,7] found a modulation of P5 and N8 components after applying rTMS over primary motor cortex or premotor area. Namely, the findings by Veniero et al. [7] are hardly explained by a simple peripheral muscular activation as the amplitude modulation of these early components was achieved by applying repetitive TMS over the ipsilateral premotor cortex.

As recently proposed, the contrasting results from different groups could be well explained by a mixed cortico-muscular source generating the earliest response to TMS. It is possible that the contribution of cranial muscles activation may cause highly variable responses across individuals, due to the coil orientation, which is usually chosen to best activate the stimulated area in each

participant, and also to facial muscles anatomy, which can vary across subjects [7].

The debate about the nature of these early TEPs is justified by the important information held about the responsiveness and connectivity of the stimulated area. Indeed, the TMS-induced activity is directly generated by the targeted neural populations and therefore discarding the EEG signals for a long period of time strongly limits the TMS-EEG combination. As an example, some of the TEPs evoked by the stimulation of the primary motor cortex have been linked to the motor evoked potentials amplitude [8,9]. Although significant, these weak correlations have been only found for late latency components, such as N15, P30 and N45, which probably do not reflect the generation of the descending corticospinal volleys evoked by the magnetic pulse, but rather later processes. In the same vein, the direct connections between cortical areas are likely to be activated in the earliest milliseconds after the pulse. Indeed, inter-hemispheric conduction time between homologous motor areas [1] and direct intra-hemispheric connections between the premotor and ipsilateral primary motor area [8] have been found to occur within 10–20 ms.

We therefore suggest that despite P5 and N8 resulting from the co-activation of cortical and extra-cortical sources, they can still carry crucial information about cortical excitability. Moreover, by means of careful study designs keeping the involved muscular activation comparable across conditions, these early TEP components can be informative on the reactivity of the targeted area. As an alternative, PCA and ICA can be applied to isolate and remove the muscular activation [9,10]. However, although these are promising approaches, further studies are needed to establish clear criteria that can be applied when removing PCs or ICs. As the muscular and the cortical activations overlap in time and partially show similar brain topography, the removal of some components can significantly attenuate the signal recorded from the electrodes covering the stimulated area [9]. Moreover, the large muscle artifact can distort ICs topographies, thus affecting the following analysis and preventing a reliable source localization [11]. Encouraging results, however, have been reported by Korhonen et al. [10] with ICA and more recently by Veniero et al. [12]. In this study targeting the left primary motor cortex, the authors applied some of the criteria described by previous studies [5,9,10]. After the removal of the ICs showing a topography congruent with the activation of left temporalis muscle (as described by Ref. [5]), occurring within 15–20 ms from the TMS pulse and exceeding 50 μV amplitude, not only the late latency TEPs component were still present but also a peak around 10 ms survived.

These early latency components reflect direct cortical reactivity of the stimulated area and it seems therefore essential to find an effective method to exploit the information carried by the signal in the first milliseconds after the TMS.

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Low Frequency Repetitive Transcranial Magnetic Stimulation in Children With Attention Deficit/Hyperactivity Disorder. Preliminary Results

Attention Deficit Hyperactivity/Disorder (ADHD) is a common neurobehavioral disorder of childhood with a high prevalence. From meta-analysis of imaging studies it has become obvious that dopaminergic misbalance in the forebrain and basal ganglia is involved in ADHD. The prefrontal cortex, anterior cingulate, insula, amygdala and cerebellum are also probably linked to ADHD pathophysiology [1,2].

Methylphenidate preparations are often the first medication choice for treatment of ADHD and they act by inhibiting the reuptake of dopamine and noradrenaline mainly in the striatum.