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Investigating the neurobiology of schizophrenia and other major psychiatric disorders with Transcranial Magnetic Stimulation

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ABSTRACT

Characterizing the neurobiology of schizophrenia and other major psychiatric disorders is one of the main challenges of the current research in psychiatry. The availability of Transcranial Magnetic Stimulation (TMS) allows to directly probe virtually any cortical areas, thus providing a unique way to assess the neurophysiological properties of cortical neurons. This article presents a review of studies employing TMS in combination with Motor Evoked Potentials (TMS/MEPs) and high density Electroencephalogram (TMS/hd-EEG) in schizophrenia and other major psychiatric disorders. Studies were identified by conducting a PubMed search using the following search item: "transcranial magnetic stimulation and (Schizophrenia or OCD or MDD or ADHD)". Studies that utilized TMS/MEP and/or TMS/hd-EEG measures to characterize cortical excitability, inhibition, oscillatory activity, and/or connectivity in psychiatric patients were selected. Across disorders, patients displayed a pattern of reduced cortical inhibition, and to a lesser extent increased excitability, in the motor cortex, which was most consistently established in Schizophrenia. Furthermore, psychiatric patients showed abnormalities in a number of TMS-evoked EEG oscillations, which was most prominent in the prefrontal cortex of Schizophrenia relative to healthy comparison subjects. Overall, results from this review point to significant impairments in cortical excitability, inhibition, and oscillatory activity, especially in frontal areas, in several major psychiatric disorders. Building on these findings, future studies employing TMS-based experimental paradigms may help elucidating the neurobiology of these psychiatric disorders, and may assess the contribution of TMS-related measures in monitoring and possibly maximizing the effectiveness of treatment interventions in psychiatric populations.

1. Introduction

Transcranial magnetic stimulation (TMS) is a non-invasive brain stimulation technique that alters directly the membrane potential of cortical neurons. TMS was introduced a little over three decades ago (Barker et al., 1985), and single pulse TMS has been initially employed to test the functional integrity of human cortico-spinal pathways in humans. Specifically, TMS can induce motor evoked potentials (MEPs) in peripheral muscles, and MEPs amplitude, which depends on cortical, spinal, and peripheral neurons, is a straightforward measure of corticospinal excitability. Over the years, various TMS/MEPs paradigms have been developed to assess more specifically excitatory and inhibitory neurons within the motor cortex (Hallett, 2007; Rossini et al., 2015). Nonetheless, all these paradigms relied on modulating MEPs amplitude, thus providing only an indirect assessment of cortical neuronal activity. Furthermore, areas outside of the motor cortex could not be investigated with TMS, due to the lack of measurable outputs.

High-density electroencephalography (hd-EEG) provides a large number of electrodes–anywhere from 64 to 256 channels–to record the brain's electrical activity. As with conventional EEG, hd-EEG records with high temporal resolution, and the increased number of channels also improves spatial resolution. Such a dense array of electrodes allows detecting local, developmental and/or learning related changes in EEG activity with greater accuracy (Lustenberger and Huber, 2012), and the recent availability of source modeling analyses has enabled the identification of the cortical sources underlying scalp-recorded hd-EEG signals (Lucka et al., 2012).

Building on these premises, TMS in combination with hd-EEG has been increasingly utilized to investigate the functional properties of neuronal populations in various cortical areas. For example, some studies have employed TMS excitatory and inhibitory paradigms on the motor cortex (M1) of healthy subjects to induce comparable changes in TMS-evoked EEG and MEP amplitude, thus revealing the cortical nature and the neuronal groups underlying such changes (Ferreri et al., 2011; Ferreri et al., 2012). It has also been shown that the amplitude of TMS-evoked EEG components of M1 can be modulated by peripheral stimuli, and that a similar modulation can be obtained in the Prefrontal cortex (PFC), an area that play a critical role in a number of psychiatric

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disorders(Daskalakis et al., 2008b). TMS/hd-EEG can be utilized to assess the oscillatory properties of cortical areas, with TMS evoking alpha oscillations (8–12 Hz) in the occipital cortex, beta oscillations (13–20 Hz) in the parietal cortex and fast beta/gamma oscillations (21–40 Hz) in the frontal cortex (Rosanova et al., 2009), and this variability across brain regions has been confirmed for other TMS-EEG metrics in healthy individuals (Casula et al., 2014; Farzan et al., 2009; Kahkonen et al., 2004). Furthermore, TMS-evoked EEG responses allow assessing with unique spatiotemporal precision connectivity between cortical areas across different behavioral states, including several conditions characterized by loss of consciousness (Ferrarelli et al., 2010; Massimini et al., 2005; Massimini et al., 2010), thus providing the possibility to investigate differences in communication patterns between the healthy and diseased brain. It is therefore not surprising that an increasing number of TMS/hd-EEG studies have been recently conducted in major psychiatric disorders.

In this article, we will first review studies employing TMS/MEPs and TMS/hd-EEGs to investigate the motor cortex of psychiatric patients and control subjects. We will then present TMS/hd-EEG studies showing abnormalities in the neurophysiological properties, including oscillatory activity and connectivity, of other cortical areas, including PFC, in psychiatric populations, and especially Schizophrenia. Finally, we will discuss future directions for the TMS/hd-EEG technique, which include characterizing the longitudinal effects of major psychiatric disorders on TMS-evoked responses as well as utilizing TMS-related measures to monitor the efficacy of treatment interventions in psychiatric patients.

2. Materials and methods

The systematic literature research for this article was conducted via the internet databases PubMed and MEDLINE (1990–2016), using the following search items: "Transcranial magnetic stimulation and (Schizophrenia or OCD or MDD or ADHD)". This search offered a total of 713 publications. Since the present review focused primarily on the role of TMS in identifying neurophysiological abnormalities in major psychiatric disorders, publications concerning the treatment of psychiatric disorders were excluded, including those involving repetitive TMS paradigms. We then reviewed the titles and abstracts of the remaining studies and selected those that utilized TMS/MEP and/or TMS/hd-EEG measures to characterize cortical excitability, inhibition, oscillatory activity, and/or connectivity in psychiatric patients. Next, we read through the full text of the articles to evaluate relevant data. This led to an additional 21 publications, which were not identified with the initial search. Only studies published in English, which clearly described in the method section clinical characteristics of participants and the TMS-based experimental design were included. Studies were then divided in those focusing on the motor cortex, and those involving also other cortical areas. This choice was based on three main reasons. First, to emphasize the initial and original contribution of TMS/MEPs studies in characterizing motor cortex dysfunctions in psychiatric patients relative to healthy controls. Second, to highlight the importance of collecting both TMS/MEP and TMS/hd-EEG measures in the same study participants to better characterize the neuronal mechanisms of motor neurophysiological impairments in psychiatric patients. Third, to underlie the unique potential of TMS-related EEG measures in identifying electrophysiological abnormalities beyond the motor cortex, including brain regions such as PFC, which is known to play a critical role in major psychiatric disorders like Schizophrenia. To improve readability for those less familiar with TMS-related measures, we briefly described those measures and cite the most pertinent articles, where these measures were first or best characterized. Finally, some studies that have started using TMS-related measures to characterize the effectiveness of pharmacological and nonpharmacological treatment intervention in psychiatric populations were quoted in the future direction section of this article as preliminary, corroborating evidence.

3. Results

3.1. TMS-related findings in the motor cortex of psychiatric and healthy populations

3.1.1. Motor cortical excitability

3.1.1.1. TMS/MEP findings. Numerous studies have investigated excitability of the motor cortex in psychiatric populations, including Schizophrenia, major depression (MDD), obsessive compulsive disorder (OCD), and attention-deficit hyperactivity disorder (ADHD). Resting motor threshold (rMT), which is the intensity required to induce a ≥50 μV MEP in 5 of 10 trials, and MEP amplitude were initially the most commonly reported measures. However, since MEPs are affected by the excitability of cortical, spinal as well as peripheral neurons, additional TMS paradigms have been developed to specifically assess cortical excitability within the motor cortex (Hallett, 2007), including intracortical facilitation (ICF) (Nakamura et al., 1997) and I-wave facilitation (Ziemann et al., 1998). ICF is measured by comparing a supra-threshold test stimulus (TS) with a subthreshold conditioning stimulus (CS) delivered at 10–15-ms intervals, whereas I-wave facilitation involves a subthreshold CS following a TS at specific intervals of 1.3, 2.5, and 4.5 ms.

In a recent meta-analysis rMT did not differ between patients with Schizophrenia (SCZ, $N = 500$) and healthy subjects (HC, $N = 617$) across 21 studies (Radhu et al., 2013), although one study not included in the meta-analysis found an elevated rMT in SCZ ($N = 22$) relative to HC ($N = 22$) (Hasan et al., 2011). Similarly, MEP amplitude did not differ between SCZ and HC across eight studies (Table 1). Furthermore, no differences were found in ICF in individuals at risk of schizophrenia (Hasan et al., 2012), first-episode (Eichhammer et al., 2004; Wobrock et al., 2009; Wobrock et al., 2008), and both medicated and unmedicated chronic SCZ (Daskalakis et al., 2002; Daskalakis et al., 2008a; Fitzgerald et al., 2002a, 2002b; Hasan et al., 2011; Liu et al., 2009; Pascual-Leone et al., 2002) relative to HC, whereas I-wave facilitation was increased in both medicated ($N = 9$) and unmedicated ($N = 9$) SCZ compared with HC ($N = 9$), although data are from a single study on a small group of patients (Fitzgerald et al., 2003).

In a meta-analysis of excitability measures in patients with MDD and healthy controls, no group differences were found in rMT (MDD: $N = 176$; healthy controls: $N = 188$) or ICF (MDD: $N = 115$; healthy controls: $N = 130$) (Radhu et al., 2013). While only three of these studies measured MEP amplitude, no differences were found between MDD ($N = 34$) and HC ($N = 37$) (Radhu et al., 2013) (Table 1). In OCD, two studies investigated motor cortical excitability and found that these patients ($N = 50$) did not differ from HC ($N = 45$) in rMT values, whereas they had higher ICF (Greenberg et al., 2000; Richter et al., 2012). Similarly, MEP amplitude was not different between the two groups (Richter et al., 2012).

Alterations in rMT, MEP amplitude, and IFC have been inconsistently found in children with ADHD relative to HC, with the majority of studies reporting negative findings (Buchmann et al., 2003; Garvey et al., 2005; Gilbert et al., 2011; Gilbert et al., 2007; Hoegl et al., 2012; Wu et al., 2012). Similarly, in adults with ADHD, no changes in rMT have been reported (Hasan et al., 2013; Hoeppner et al., 2008a; Hoeppner et al., 2008b; Richter et al., 2007; Schneider et al., 2007), and enhanced ICF was found only in one study (Hasan et al., 2013).

3.1.1.2. TMS/EEG findings. Only a handful of studies have examined cortical excitability in healthy and psychiatric patients using TMS/hd-EEGs (Table 2). Casarotto et al. investigated the effects of ECT on eight patients with severe, treatment resistant MDD and found an increase in cortical excitability, measured by the subtended area encompassing the early consecutive positive and negative EEG waves triggered by TMS, in sensorimotor areas compared to baseline recordings, which was significant in every patient (Casarotto et al., 2013). Furthermore, Ferrarelli et al. reported decreased frontal cortical excitability, assessed

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