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Characteristics of ictal EEG in Magnetic Seizure Therapy at various stimulation frequencies

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H I G H L I G H T S

- Magnetic Seizure Therapy (MST) stimulation frequency impacts seizure characteristics.
- Seizure qualities predict response differently in MST and ECT which may suggest different mechanisms.
- Lower slow-wave amplitude and shorter polyspike duration may predict response to MST.

A B S T R A C T

Objectives: The first objective of this study aimed to elucidate the relationship between seizure characteristics and Magnetic Seizure Therapy (MST) treatment outcome. The second objective was to determine the effect of stimulation frequency on seizure characteristics.
Methods: Using a between-subjects design, we compared the seizures of patients with unipolar depression receiving MST at three separate stimulation frequencies: 25 Hz ($n = 34$), 50 Hz ($n = 16$) and 100 Hz ($n = 11$). Seizures were rated for overall seizure adequacy on a scale of 0–6, with one point given for each measure that was considered to be adequate according to the ECT literature: (1) seizure EEG duration (2) motor duration, (3) post-ictal suppression, (4) ictal EEG maximum amplitude, (5) Global Seizure Strength, and (6) Symmetry. Mixed-effect models were used to evaluate the effect of frequency on seizure characteristics and the relationships between seizure characteristics and clinical outcome.
Results: (1) 100 Hz induced seizures that were less adequate than seizures induced with 50 Hz and 25 Hz stimulations. Seizures induced by 50 Hz stimulations had longer slow-wave phase durations and total EEG durations than the 100 Hz and 25 Hz groups. Global seizure strength was less robust in seizures induced by 100 Hz MST compared to the other stimulation frequencies. (2) Shorter polyspike durations and smaller slow-wave amplitude predicted reductions in overall symptoms of depression as measured by the 24-item Hamilton Depression Scale.
Conclusion: Analysis of our first objective revealed stimulation frequency significantly influences measures of overall seizure adequacy. However, our results also revealed these descriptions of seizure adequacy based on ECT literature may not be useful for MST-induced seizures, as the characteristics of MST-induced seizure characteristics may predict clinical response in a different manner.
Significance: These results may help to distinguish the biological processes impacted by stimulation frequency and may suggest different mechanisms of action between convulsive therapies and challenge the current understanding of seizure adequacy for MST.

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1. Introduction

1.1. Convulsive brain stimulation therapies

Electroconvulsive therapy (ECT) is the most effective treatment for treatment-resistant and severe forms of major depression, with approximately 50–65% of patients achieving response (Coffey, 1993; Heijnen et al., 2010). Despite the considerable effectiveness of ECT, only a small percentage of individuals who may benefit from the intervention go on to have treatment, often due to concerns regarding adverse cognitive effects (Chakrabarti et al., 2010).

Magnetic Seizure Therapy (MST), a more intense and higher frequency form of repetitive transcranial magnetic stimulation (rTMS), is currently under investigational use as an alternative convulsive therapy to ECT, with a superior cognitive adverse effect profile (Lisanby et al., 2003). MST involves the application of high-intensity repetitive magnetic field pulses that penetrate the cortex unimpeded and create a secondary electric field to induce a seizure (Lee et al., 2016). As such, when positioned over the frontal cortex, MST has the potential to stimulate superficial brain regions involved in depression (ie. dorsal-medial prefrontal cortex) (Downar and Daskalakis, 2013), while sparing deeper structures involved in the cognitive adverse effects of ECT (ie. the hippocampus) (Radman and Lisanby, 2017).

1.2. Optimizing parameters of stimulation

Parameters of an electromagnetic stimulus can be adjusted in many different ways, including altering the shape, length, and frequency of the stimulation, among others (Peterchev et al., 2010), and may have different effects on the biological properties of the intervention. For instance, altering the frequency of ECT pulses in a train affects the physiological characteristics of a seizure (Kotresh et al., 2004), and can be used to minimize the electrical charge required to elicit a seizure (Swartz and Manly, 2000; Girish et al., 2003; Roepke et al., 2011). Altering frequency may therefore be used to optimize ECT, and exploring differences in inter-ictal characteristics of MST seizures induced at different frequencies may also help to elucidate differences in their biological processes.

1.3. Characterizing the effect of frequency on seizures in MST

While some studies have evaluated the effect of treatment frequency in ECT-induced seizures, the impact of frequency on MST-induced seizures remains largely unexplored. Initial reports of human seizure induction with the 40 Hz device suggested MST-induced seizures had less robust EEG amplitudes, poorer post-ictal suppression, and shorter motor durations than ECT-induced seizures (Lisanby et al., 2003). Another published report noted post-ictal suppression and ictal amplitude is not as prominent in 100 Hz MST relative to ECT seizures, and that, while some MST-induced seizures are stereotypical of ECT-induced seizures, others are much less robust with poor suppression (Fitzgerald et al., 2013).

Taken together, these results suggest that MST-induced seizures may correlate with poorer outcome relative to ECT; however, early comparisons between ECT and MST have shown no difference in efficacy (Kayser et al., 2011). It is therefore important to investigate the direct relationship between seizure characteristics and therapeutic outcome in MST, as the relationship between ictal-EEG characteristics and treatment outcome may differ across types of convulsive therapy.

MST seizure characteristics have been described in the literature using MST stimulation frequencies between 25 and 100 Hz (Lisanby et al., 2003; Kayser et al., 2011; Fitzgerald et al., 2013; Kayser et al., 2013). Over the past 2 decades, the maximum frequency of MST devices has increased by 10-fold, and the maximum output intensity of these devices has simultaneously changed. Thus, older literature exploring seizure characteristics in MST, which used lower frequency stimulations, may not reflect the biological changes induced by novel devices at the same frequency, and as such, describing seizure characteristics at different frequencies using the same device is warranted.

1.4. Seizure characteristics predicting treatment response

In addition to informing our understanding of frequency on the biological impact of brain stimulation, seizure characteristics may also help to identify "good" ECT treatments. Aspects of the ictal electroencephalogram (EEG) morphology are used clinically to characterize seizure quality in patients treated with ECT, and may also be used to predict response in patients treated with MST. Little is known about the biological mechanisms of action in MST, and "good" seizure characteristics, as described by ECT literature, may not relate to therapeutic outcome in the same manner as in MST. There is currently a paucity of research exploring the relationship between seizure characteristics and therapeutic outcome in MST, and as such, identifying potential characteristics warrant further investigation.

To our knowledge, only one paper has investigated the relationship between seizure characteristics and treatment outcome in MST, with findings suggesting no characteristics could be used to predict treatment response (Kayser et al., 2015). However, this study grouped individuals into responders and non-responders, which may have diluted the predictive value of differences in symptom severity across the participants. Moreover, a large subset of this patient group underwent both ECT and MST treatments and showed comparable seizure characteristics between ECT- and MST-induced seizures (Kayser et al., 2013).

However, it is important to note this group of patients did not respond to either convulsive therapy, and predictors of response may be harder to identify in patient groups with low response-rates, especially those who are resistant to ECT response. Additionally, this MST study induced seizures at the vertex while obtaining EEG recordings at the prefrontal cortex. As the ictal activity is strongest at the site of stimulation, a distal site of recording may display a dissipated EEG signal that does not adequately reflect EEG activity in the site of stimulation. As such, recording the EEG at the same site of stimulation may help to increase the integrity of the MST-induced seizure recordings. In turn, this may help to identify seizure characteristics related to treatment response.

Additionally, differences in the ictal-EEG have been related to treatment outcome in ECT (Minelli et al., 2015). For instance, post-ictal suppression, an abrupt termination of ictal activity, is one of the strongest predictors of seizure adequacy of ECT-induced seizures (Farzan et al., 2014), and other inter-ictal EEG characteristics, such as polyspike duration, ictal amplitude, global seizure strength (Kimball et al., 2009) and hemispheric-coherence (Minelli et al., 2015), have also been noted as markers of therapeutic efficacy in ECT.

However, due to the vast differences in seizure properties across the two convulsive therapies, it is still unclear whether these EEG properties of MST-induced seizures are also related to therapeutic effectiveness. As such, exploring the relationship between seizure characteristics and the therapeutic outcome may help to determine which parameters are important in altering treatment response.

1.5. Aims

The primary purpose of this study was to (1) characterize the ictal EEG from patients in an open-label trial of MST using three