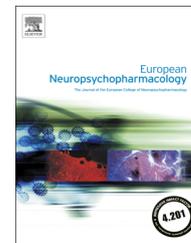




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Comparable seizure characteristics in magnetic seizure therapy and electroconvulsive therapy for major depression



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Abstract

Electroconvulsive therapy (ECT) is highly effective for treatment-resistant depression (TRD); however, its use for less severe forms of depression is somewhat limited by a lack of control over current spreading to medial temporal lobe memory structures, resulting in various cognitive side effects. In contrast, magnetic seizure therapy (MST), which uses high frequency repetitive transcranial magnetic stimulation (rTMS) for local seizure induction, has been associated with reduced cognitive side effects. To assess whether different characteristics of seizures induced by both methods are responsible for the differences in neuropsychological side-effect profile, we studied seven TRD-patients undergoing both MST and ECT in an open-label, within subject, controlled crossover pilot study. Comparison parameters included seizure-related ictal characteristics, including motor activity, electromyogram (EMG), electroencephalogram (EEG), and postictal recovery and reorientation times. Our results showed no differences in motor activity or EMG and EEG characteristics, thus implicating similar electrophysiological processes in seizure induction with MST and ECT. In line with previous studies, we observed shorter postictal recovery and reorientation times following MST. The ictal characteristics of induced seizures were found similar with ECT and MST suggesting that the more focal seizure induction associated with MST may account for the more beneficial neuropsychological side effect profile of MST.

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1. Introduction

Major depressive disorder (MDD) is a very prevalent disorder with a lifetime risk of 7-12% in men and 20-25% in women (Kessler et al., 2005) and its often a highly disabling condition (Holtzheimer and Nemeroff, 2008). Various forms of psychotherapy and pharmacotherapy are currently the most commonly used antidepressant treatments. Though these therapies lead to symptomatic improvement, up to 70% of the treated patients suffering from depression have residual symptoms (Trivedi et al., 2006). Furthermore, the Sequenced Treatment Alternatives to Relieve Depression study (STAR*D) demonstrated that one third of patients do not respond despite completing an algorithm that included four evidence-based treatment steps for depression (Rush et al., 2006). Recurrent episodes of depression are the rule and not the exception (Kessler et al., 1997). Results from the US National Institute of Mental Health's (NIMH) program indicate that the chance of remission decreases significantly if two treatment attempts with adequate dose and duration have already failed. Patients who are unable to respond despite completing two different antidepressant medications of adequate dose and duration are considering having treatment-resistant depression (TRD) (Schlaepfer et al., 2012). Unfortunately TRD frequently results in disability and elevated risk for suicide (Nemeroff, 2007). Electroconvulsive therapy (ECT) is a long-established therapeutic intervention and the most effective treatment for TRD (Sackeim et al., 2008). But its clinical utility is limited to some extent by its burden of neuropsychological adverse effects, including postictal disorientation, as well as transient and long-term cognitive disturbances (UK ECT Review Group, 2003). Up to 79% of the cognitive side effects in ECT (Rose et al., 2003) result from widespread electric current distribution throughout the brain, including temporal lobe structures such as the hippocampus (Lisanby, 2002). Modern developments of ECT techniques have impressively advanced the risk/benefit ratio, although the degree of retrograde amnesia remains a significant risk (Morales et al., 2004). Recent studies have demonstrated that the effectiveness and side effects of ECT are influenced by the site of seizure initiation and dispersion of seizure activity (McCall et al., 2000), which cannot be entirely controlled with current ECT techniques (Sackeim et al., 1994).

New non-convulsive and convulsive brain stimulation techniques with the purpose of less cognitive side effects have therefore been developed with the intention of equaling or topping ECT's efficacy. Better cognitive side effect profiles aimed at improving the quality of life for patients needing non-convulsive or convulsive therapies should increase the endeavor for effective treatments (Morales et al., 2004). A non-convulsive treatment is the repetitive transcranial magnetic stimulation (rTMS), which uses strong, rapidly alternating magnetic fields to non-invasively stimulate the prefrontal cortex (Schlaepfer et al., 2010). More than 35 placebo-controlled rTMS studies have shown moderate antidepressant effects and the cognitive functions were not affected (Janicak et al., 2008). Therefore, rTMS is considered to be a safe treatment method, but without strong antidepressant efficacy in severe depression. Further development of rTMS at higher frequencies (>50 Hz) has demonstrated the ability of using

rTMS to induce seizures (Belmaker et al., 2003). The application of rTMS to induce a seizure is referred to as magnetic seizure therapy (MST). The use of MST has been found to produce a more localized seizure that stimulates the superficial cortex while significantly avoiding the medial temporal lobe structures such as the hippocampi responsible for cognition (Lisanby et al., 2003a). During ECT, electricity is applied directly to the scalp, while during MST, electricity is indirectly induced in the brain by magnetic stimuli (George, 2002). MST results in a more focused point of origin of seizures, whereas the secondary generalization of the convulsions involves the entire brain (Morales et al., 2004). Measurements in non-human primates with intracerebral electrodes have supported the hypothesis that MST-induced seizures are more focally than those elicited with ECT (Lisanby et al., 2003c). Furthermore, the electric field induced by magnetic stimulation is less penetrating and insensitive to tissue conductivity (Lisanby et al., 2003b). MST induces neural depolarization at a depth of 2 cm beneath of the scalp; therefore, direct effects are limited to the superficial cortex (Davey et al., 2003). In contrast, the electrical fields during ECT are impeded by scalp and skull and show limited precision in spatial targeting (Geddes and Baker, 1967). This leads to a non-focal, widespread intracerebral current distribution by ECT (Sackeim et al., 1994). Moreover, ECT and MST use different pulse shapes and widths, resulting in different levels of neural stimulations for the same electric field (Deng et al., 2009a, 2009b). The main advantage of MST over ECT involves an improved side effect profile, which includes reduced postictal disorientation and faster recovery and reorientation (Kayser et al., 2011; Kirov et al., 2008).

The purpose of electrical stimulation in ECT is to therapeutically induce an initial focal and secondary generalized grand mal seizure using serial administration of electrical current through the brain under general anesthesia (Rasimas et al., 2007). Generalized grand mal seizures can be controlled by monitoring both ictal motor responses (convulsions) and ictal electroencephalogram (EEG) activity (electrophysiological activity of the brain during the seizures). The traditional opinion that the therapeutic benefit depends on an adequate ECT-induced seizure lasting at least 25 s (Weiner et al., 1991), although retained in contemporary guidelines of ECT practice, was not necessary (Swartz, 2009). The clinical view changed, and ictal parameters such as ictal EEG seizure amplitude (Krystal et al., 1995), degree of EEG postictal suppression (Nobler et al., 1993, 2000), ictal heart rate (Swartz, 2000), and ictal EEG coherence (Krystal, 1998) were considered to be significant predictors for adequate therapeutically seizures. This fundamental paradigm shift, which has gained support in the past two decades, has potential clinical relevance in guiding ECT treatments (Mayur, 2006).

Previous studies showed differences in electroencephalogram (EEG) during MST induced seizures compared to ECT induced seizures. Specifically, MST treated groups demonstrated ictal activities with lower amplitudes and a relative absence of postictal suppression (White et al., 2006). However, the development of MST devices has progressed; for example, an increase in stimulation amplitude and frequency has changed the EEG semiology of MST (Kayser et al., 2011). Although ECT invoked generalized grand mal seizures, these were not able to shed light on the

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