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Cognitive and volumetric predictors of response to repetitive transcranial magnetic stimulation (rTMS) — A prospective follow-up study

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ABSTRACT

As the prevalence of treatment resistant depression (TRD) continues to rise, it remains a clinically important issue to identify neurobiological-, patient- and treatment-related factors that could potentially predict response to treatment. Medial temporal lobe (MTL) structures, in particular the hippocampus and amygdala have been implicated in inferior treatment response. The role of related structures such as the entorhinal cortex and the impact of MTL abnormalities on neurocognitive function, however, have not been systematically examined. The current study investigated MTL abnormalities and neurocognitive characteristics of eventual treatment responders and non-responders to a course of repetitive transcranial magnetic stimulation (rTMS) in order to identify potential predictors of treatment outcome. Prior to rTMS treatment all patients underwent magnetic resonance imaging (MRI) and neuropsychological assessment. MRI analysis was conducted using FreeSurfer 5.0. There was a 50% response rate following up to a 6-week course of daily rTMS treatments. Treatment response was defined as 50% reduction in Hamilton Depression Rating Scale and BDI-II scores from baseline. There was no difference in pre-treatment neurocognitive profiles and MTL volumes between eventual treatment responders and non-responders. Smaller pre-treatment left hippocampus volume showed a trend towards predicting eventual subjective improvement in depressive symptomatology. Although preliminary, our findings suggest that structural abnormalities may have some potential for predicting outcome to rTMS.

1. Introduction

Major depressive disorder (MDD) is a common, disabling and difficult-to-treat psychiatric disorder. Although, there is a range of established treatments for MDD, including antidepressant medications, psychotherapy and electroconvulsive therapy (ECT) (Fitzgerald and Daskalakis, 2011), MDD is often resistant to treatment with standard approaches, with approximately 30% of patients meeting standard definitions for treatment resistant depression (TRD) (Fava, 2003). The main treatment option for patients with TRD is ECT (Brakemeier et al., 2007). Despite proven high efficacy of ECT in MDD, its use is often limited due to patient refusal from concerns about marked cognitive side effects, risks from repeated general anaesthetics and stigma (Fitzgerald and Daskalakis, 2011). Repetitive transcranial magnetic stimulation (rTMS) is a relatively new brain stimulation technique that offers a potential alternative for patients with TRD. rTMS involves the production of a magnetic field via an alternating electric current (Barker, 1991). This magnetic field passes into the brain and stimulates electrical activity in neurons; high-frequency rTMS increases brain activity, whereas low-frequency stimulation decreases brain activity (Hoy and Fitzgerald, 2010). Imaging studies have demonstrated that MDD may involve dysregulation of cortical activity and rTMS is thought to act by normalising hypoexcitability over the left prefrontal cortex and normalising hyperexcitability over the right hemisphere (Daskalakis et al., 2008).

Several meta-analyses have provided support for rTMS treatment having significantly more antidepressant efficacy than sham treatment (Burt et al., 2002; Kozel and George, 2002; Martin et al., 2003; Couturier, 2005; Loo and Mitchell, 2005; Fregni et al., 2006; Lam et al., 2008; Schutter, 2009). In particular, both high-frequency left (HFL; usually between 5 and 20 Hz) and low-frequency right (LFR; ≤1Hz) rTMS applied over the dorsolateral prefrontal cortex (DLPFC) have been shown to be effective in the treatment of TRD (Daskalakis et al., 2008; Fitzgerald et al., 2010; Rossini et al., 2010; Fitzgerald and Daskalakis, 2011). Overall, there is overwhelming support for a significant reduction in depressive symptomatology following rTMS; however, the percentage of patients responding to a course of rTMS treatment is less than 50% (Burt et al., 2002; Loo and Mitchell, 2005; Brakemeier et al., 2007; Fitzgerald et al., 2010; Rossini et al., 2010). Therefore, it remains

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a clinically important issue to identify biological-, patient- and treatment-related factors that could potentially predict response to rTMS at baseline and aid in patient selection (Loo and Mitchell, 2005; Brakemeier et al., 2008; Lisanby et al., 2009).

Although a number of studies have explored this question to date, no strong predictors have been identified that would be able to predict response to rTMS with sufficient sensitivity and specificity to be of therapeutic use (Fitzgerald and Daskalakis, 2011). Of the potential predictors that have emerged, degree of treatment resistance and demographic factors have shown significant results. That is, younger age (Fregni et al., 2006) and a lower degree of medication resistance in the current episode (Fregni et al., 2006; Brakemeier et al., 2007; Brakemeier et al., 2008; Lisanby et al., 2009) were found to predict better antidepressant response to rTMS. Furthermore, in one study the likelihood of response to rTMS was four times higher if patients had only received one unsuccessful medication trial before rTMS in comparison with patients having received two or more unsuccessful trials (O'Reardon et al., 2007). Other positive predictors of improvement with rTMS include short duration of the current episode (Brakemeier et al., 2007; Lisanby et al., 2009), a high level of sleep disturbances (Brakemeier et al., 2007), female gender, absence of a co-morbid anxiety disorder and a higher baseline depression severity (Lisanby et al., 2009; Rossini et al., 2010). Conversely, presence of personality disorder (Fitzgerald and Daskalakis, 2011) and psychotic symptoms (Grunhaus et al., 2000) have been linked to inferior rTMS outcome.

Neuropsychological assessments are often included in clinical trials of rTMS efficacy to monitor the safety of the technique. These assessments have frequently demonstrated that rTMS has no detrimental cognitive side-effects after several weeks of daily treatments in clinical samples (Triggs et al., 1999; Little et al., 2000; Loo and Mitchell, 2005; Fitzgerald et al., 2006; Januel et al., 2006; Vanderhasselt, 2009). In fact, some studies have reported improvement in cognitive function following a course of rTMS, namely in the domains of attention, concentration, working memory and processing speed, with probable flow-on effects leading to improvements in learning, memory and aspects of executive functioning (Loo et al., 2008; Vanderhasselt, 2009). These beneficial effects are primarily reported amongst treatment responders and therefore neuropsychological gains are likely secondary to symptomatic remission (Loo et al., 2008). There is some preliminary evidence, however, that suggests that cognitive changes may occur earlier than mood improvement (Vanderhasselt, 2009). These early changes in cognition may provide a useful clinical tool to predict eventual response to rTMS. Further research investigating cognitive characteristics of rTMS responders and non-responders is highly warranted.

Recent studies have also investigated the influence of neurobiological markers on treatment outcome and identified lower concentrations of glutamate in the DLPFC (Luborzewski et al., 2007) and reduced cerebral blood flow in the amygdala at baseline (Nadeau et al., 2002) as positive predictors of rTMS outcome. It has also been demonstrated that rTMS affects underlying regional brain activation and perfusion (Langguth et al., 2007; Lisanby et al., 2009). Left DLPFC stimulation has been shown to induce changes in deeper regions such as the anterior cingulate cortex (ACC), basal ganglia, thalamus and limbic system, areas known to be involved in the pathophysiology of MDD (Albus et al., 1996; Soares and Mann, 1997; Sheline, 2006; Langguth et al., 2007; Price and Drevets, 2010). Accordingly, one might speculate that rTMS exerts its antidepressant effects by modulating this cortico-limbic connectivity (Langguth et al., 2007; Price and Drevets, 2010) with fMRI studies confirming abnormal functioning in frontal (e.g., ACC and DLPFC) and limbic connections (e.g., hippocampus, amygdala) in depression (Lorenzetti et al., 2009; McClintock et al., 2010).

The limbic structures are of particular interest as volumetric reductions especially in the hippocampus have been linked to decreased response to antidepressant medications, poor clinical outcomes, and increased rates of relapse (Frodl et al., 2004, 2008; Kronmüller et al., 2008; MacQueen, 2009; Li et al., 2010). Several studies have shown that patients who achieve remission have larger pre-treatment hippocampal volumes bilaterally than patients who remain depressed (Vakili et al., 2000; Frodl et al., 2004; MacQueen et al., 2008; MacQueen, 2009). Furthermore, in prospective studies, smaller baseline hippocampal volumes were found to be predictive of poorer clinical outcome at 1 and 3 years follow-up (Frodl et al., 2004, 2008). The source of hippocampal volume abnormalities in MDD have been postulated to result from the 'neurotoxic effects of stress' through repeated episodes of hypercortisolemia, glutamate neurotoxicity, decreased neurogenesis, glial cell loss, and decreased expression of brain derived neurotrophic factor (Caetano et al., 2004; Duman and Monteggia, 2006; Czéh and Lucassen, 2007). Given shared glutamatergic transmission between the hippocampus and nearby structures of the medial temporal lobe (MTL), it is not surprising that volumetric reductions have also been found in the amygdala (Drevets, 2003; Hamilton et al., 2008; van Eijndhoven et al., 2009; Lorenzetti et al., 2010) and entorhinal cortex (EC) (Bell-McGinty et al., 2002; Furtado et al., 2008; Gerritsen et al., 2011). Reductions in volumes of the amygdala have also been found to correlate with poor clinical outcomes such as greater number of recurrent MDD episodes and longer illness duration (Caetano et al., 2004; Frodl et al., 2004; Hastings et al., 2004; Lorenzetti et al., 2009). The EC is of additional interest because of its intimate connections with the hippocampus. Early findings from animal models have shown that lesioning the EC could prevent up to 70% of hippocampal damage caused by chronic stress (Sunanda and Raju, 1997) and therefore it is of interest to investigate the role of this structure in chronic treatment resistant MDD illness.

Gender differences in MTL volumes in MDD have not been well explored. Some studies have specifically focussed on female patients and consistently found hippocampal volume reductions compared to female controls (Sheline et al., 1999; McKinnon et al., 2009). The picture of volumetric abnormalities in males is less clear. MacMaster and Kusumakar (2004) found smaller left hippocampal volumes in paediatric MDD males, while Frodl et al. (2002) similarly found smaller left hippocampal volumes in adult male patients compared to healthy controls. Maller et al. (2007) also found smaller hippocampal volumes in males, whilst Kronmüller et al. (2008) found smaller hippocampal volumes in males were predictive of recurrence in MDD. When both sexes are examined together, however, conflicting findings have been reported (Eker and Gonul, 2010), with a meta-analysis failing to find any significant contribution of sex on hippocampal volume (Campbell et al., 2004). It is well known that gender differences exist in brain size and volume. Male brains are on average, about 10% heavier and larger than female brains, however, females have higher percentages of grey matter volume (GMV), even after correcting for brain size (Clarke, 2003; Yan et al., 2011). Therefore, an examination of neuroanatomic abnormalities in the sexes separately would allow for genuine differences to be found.

To date no study has investigated gender differences in the volumes of the EC or hippocampus and amygdala or the role of these volumes in predicting response to rTMS treatment. Therefore, the current study aimed to investigate neuroanatomical (split by sex) and neuropsychological characteristics of rTMS treatment responders and non-responders. To investigate these relationships, we defined response to rTMS as the a priori primary endpoint measure and divided baseline moderators into four domains: 1) demographic features (e.g., age and gender), 2) clinical features (e.g., age at onset of MDD, length of illness, length of current episode, number of previous major depressive episodes, concurrent medical and Axis I psychiatric disorder [e.g., anxiety], symptom severity, resistance to treatment [e.g., number of failed trials of antidepressant medication]), 3) structural biomarkers (volumes of the hippocampus, amygdala and entorhinal cortex) and 4) cognitive markers (e.g., attention, processing speed, memory and executive function). We hypothesised that larger pre-treatment volumes of the hippocampus, amygdala and entorhinal cortex in both sexes would be associated with superior antidepressant efficacy of rTMS.