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Effect of magnetic seizure therapy on regional brain glucose metabolism in major depression

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ABSTRACT

Currently electroconvulsive therapy (ECT) is one of the only available therapies for treatment resistant depression (TRD). While effective, ECT is complicated by side effects, including cognitive impairment. One promising potential alternative is magnetic seizure therapy (MST). To date, no research has explored the effects of 100 Hz MST on brain activity or the brain changes associated with response to treatment. Therefore the aim of this study was to determine the effects of a treatment course of 100 Hz MST on regional brain glucose metabolism. Ten patients with treatment resistant depression underwent positron emission tomography with fluorodeoxyglucose before and after a treatment course of MST. Changes in the relative metabolic rate of *a priori* brain regions were investigated. Areas of increased relative metabolism after treatment were seen in the basal ganglia, orbitofrontal cortex, medial frontal cortex and dorsolateral prefrontal cortex. A secondary analysis showed trend-level differential findings in brain activation between responders and non-responders, namely in the ventral anterior cingulate. These results primarily indicate that MST is affecting regions consistent with the limbic-cortical dysregulation model of depression. Exploratory analysis indicated some differential findings in brain activation between responders and non-responders were also evident; however, the small sample size precludes any firm conclusions.

1. Introduction

Up to 30% of patients with depression suffer from treatment resistant depression (TRD), continuing to experience highly distressing and disabling symptoms despite undergoing standard treatments (Fava, 2003). Currently, electroconvulsive therapy (ECT) is the most effective treatment for TRD (Payne and Prudic, 2009). However, despite considerable research into refining the delivery of ECT, problems with its use persist. ECT is complicated by the production of substantial side effects, especially the development of cognitive impairment and post-treatment confusion that may last for a considerable period of time (Sackeim et al., 2007; Sienaert et al., 2005). In response to these concerns, magnetic seizure therapy (MST) is currently being investigated as a potential alternative. Like ECT, MST also involves the generation of a seizure for therapeutic purposes. However, in MST, the seizure induction occurs through the use of high frequency repetitive transcranial magnetic stimulation (rTMS). In MST, as there is no skull resistance to the passage of the magnetic stimulus, the site and extent of stimulation can be more precisely focused than is possible with ECT (Lisanby et al., 2003). Early MST research used non-human primates, with the first MST seizure induced in 1998 (Lisanby et al., 2001a). This research showed that MST, like ECT, did not produce identifiable histological lesions (Dwork et al., 2004). In addition, this early MST research provided information regarding the optimal stimulation parameters, and indicated that there appeared to be a reduction of cognitive side effects compared with electroconvulsive shock (ECS; the animal form of ECT) (Dwork et al., 2004; Moscrip et al., 2006). Human studies of 50 Hz MST began in 2000, with approximately 40 patients undergoing 50 Hz MST between 2000 and 2006 (Lisanby et al., 2003; , 2001a; Dwork et al., 2004; Kosel et al., 2003; Lisanby et al., 2001b; White et al., 2006). These studies reported a reduced rate of cognitive side effects following MST and that patients recovered orientation much more rapidly than with ECT (for review, see Hoy and Fitzgerald, 2010). However the magnitude of improvement was not as great as that seen with ECT. This was thought to be due to the fact that 50 Hz MST was

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providing a dose only 1.3 times seizure threshold, where ECT response rates are known to be sensitive to dose relative to seizure threshold (White et al., 2006). The technology used to produce MST has since advanced with the development of devices capable of stimulating at high intensity continuously at 100 Hz, and thus at greater degrees above seizure threshold (Spellman et al., 2008). Trials of 100 Hz MST are now underway to establish efficacy and investigate cognitive side effects. Initial results show a more rapid recovery of orientation than traditionally seen with ECT (Kayser et al., 2008; Kirov et al., 2008), and an antidepressant response rate of up to 70% (Kayser et al., 2008). The recently published first direct comparison study of MST to ECT found similar response rates between the 100 Hz MST and right unilateral ECT (Kayser et al., 2011).

To date, limited research has explored the neurobiological changes that occur with MST treatment. Kosel et al., (2003) conducted a [^{99m}Tc]-HMPAO single photon emission computed tomography (SPECT) study in a patient who underwent 50 Hz MST. A baseline scan was recorded 5 days before the start of the MST trial and another 4 days following the successful MST treatment course. This study found increased cerebral blood flow in the frontoparietal region and the basal ganglia, regions that have been implicated in the pathophysiology of depression. However, no studies have explored brain changes in groups of MST treated patients or explored the effects of 100 Hz MST on brain activity. Therefore, the purpose of the current study was to investigate the changes in regional brain glucose metabolism associated with a treatment course of 100 Hz MST in unipolar depressed patients, and to undertake preliminary examination of such changes with respect to treatment response.

2. Methods

2.1. Patients

Ten patients who were taking part in an open label pilot study of 100 Hz MST (two men, eight women; age 44.10 ± 14.36; Montgomery-Åsberg Depression Rating Scale [MADRS; (Montgomery and Åsberg, 1979)] score 40.00 ± 6.75) underwent baseline and end of MST treatment 2-deoxy-2 [F-18] fluoro-D-glucose positron emission tomography [FDG-PET] scans. All patients had a diagnosis of major depressive disorder as confirmed by the study psychiatrist. Patients were required to have a MADRS score of > 20 (moderate–severe depression), and have treatment resistant depression at Stage II of the Thase and Rush classification (Fava, 2003). This requires failure to respond to two adequate courses of antidepressant medication. Exclusion criteria included a medical contraindication to a general anesthetic, the presence of metallic implants in the head, cardiac pacemaker, cochlear implants or other implanted electronic devices, treatment with ECT in the last 3 months, the presence of another DSM-IV Axis I psychiatric disorder (except of an anxiety disorder), the presence of substance abuse or dependence during the last 6 months, diabetes, current pregnancy or a past history of stroke, neurodegenerative disorder or other major neurological illness. Where relevant, patients were required to gradually cease all anticonvulsant medications prior to entering treatment but could remain on antidepressant medication. However, they were not allowed to enter the trial if antidepressant medication had been initiated, or their antidepressant dose increased, in the 4 weeks prior to study enrollment. Three patients were receiving a tricyclic antidepressant, three a serotonin–norepinephrine reuptake inhibitor (SNRI), three agomelatine and one was medication free. The study was conducted as approved by the Alfred Hospital and Monash University Human Research Ethics committees. All patients provided informed consent. See Table 1 for clinical and demographic data.

2.2. Magnetic seizure therapy

Stimulation was provided three times a week on Monday, Wednesday and Friday. Propofol (mean dose 122.13 ± 24.84 mg) and succinylcholine (mean dose 53.61 ± 14.07 mg) were used in all patients for anesthetic induction and muscle relaxation. Each patient's ictal EEG was monitored throughout using MST compatible frontal and mastoid electrodes. The bilateral dual cone MST utilized round coils each 13 cm in diameter, which is the standard MST twin coil that has been used to date in treatment studies (Hoy and Fitzgerald, 2011). Single stimulation trains at 100% machine output were applied at 100 Hz. In the first patient, treatment sessions were provided with a 10 s train duration. For the next nine patients, stimulation was provided using a train 4 s longer than the seizure threshold. This threshold was measured in all patients with an initial dose titration procedure at the first session. Stimulation was provided at progressively escalating train length (commencing at 2 s and increasing each time by 2 s). The first train which induced a tonic-clonic seizure, defined as observable bilateral motor activity of at least 10 s, was regarded as the individual patient's seizure threshold. During the treatment course if patients experienced a seizure of less than 15 s duration, the train length was increased by 2 s for the subsequent sessions (up to the maximum of 10 s). Patients were able to have up to a total of 18 treatments, but were able to cease treatment prior in the instance they had achieved an antidepressant response (as defined by the MADRS rating scale change discussed below).

Table 1
Patient clinical and demographic data.

		Patients	
		Mean/frequency	S.D.
Age		44.10	14.36
Sex (M/F)		2/8	
Diagnosis	MDD—single episode	1	
	MDD—relapse	9	
Number of depressive episodes		3.33	2.52
Length of current depressive episode		1.61	1.59
MADRS		40.00	6.75
Comorbid diagnoses	Panic disorder	1	
	OCD	2	
	Social phobia	2	
	GAD	6	

Clinical measures were performed at baseline, after every 6 treatments and at the end of the MST treatment course by trained raters. The primary clinical outcome variable for response was scores on the MADRS. Patients who experienced a 50% or greater reduction in MADRS scores from baseline were considered responders, those who experienced a reduction of between 20% and 50% were partial responders, and non-responders were defined as those who experienced a less than 20% improvement in MADRS score (Goldapple et al., 2004). All patients also underwent a comprehensive neurocognitive interview which assessed attention and concentration, speed of information processing, anterograde and retrograde memory, perceptual ability and executive functioning. This consisted of the Wechsler test of adult reading (WTAR), autobiographical memory interview (AMI), Rey verbal auditory learning test (word list), brief visual spatial memory test (BVMT), prose passages (story recall), verbal paired associates (Wechsler Memory Scale—Revised), Rey complex figure test, digit span, digit symbol coding, Trail Making Test, Stroop test, and verbal fluency using the Controlled Oral Word Association Test (COWAT). Where participants were unable to complete the entire cognitive assessment, the repeatable battery for the assessment of neuropsychological status (RBANS) was substituted for the memory component of the assessment, with the exception of the AMI, which was completed by all participants. This substitution was required for three participants. Clinical and cognitive outcomes for a larger sample of patients are reported in detail elsewhere [Fitzgerald et al., 2012, submitted].

2.3. Positron emission tomography/computer tomography (PET/CT) procedure

Fluorine-18-labeled deoxyglucose (FDG) PET/CT scans were acquired at the Department of Nuclear Medicine, The Alfred Hospital. The baseline scan was conducted in the week preceding the first MST treatment. A second FDG-PET scan was completed, on average, 3.8 days (S.D. 2.8) following completion of the MST treatment course; this allowed for investigation of both brain changes following MST and any relationship of those changes to clinical response. The images were acquired on a Philips Gemini Dual PET/CT scanner (Cleveland, OH) with PET voxel size of 2 mm. The patient's head was immobilised with a chin and forehead strap. For each scan, a 5 MBq/kg dose of FDG was injected intravenously. After the injection patients remained in a resting state with eyes open in a dimly lit room with low ambient noise for the 60 min uptake period. Image acquisition was then undertaken. Emission data of the brain were acquired with a PET field of view of 256 mm and 20 min per bed position. PET raw images were reconstructed using 3D-Row Action Maximum Likelihood Algorithm (RAMLA). Contemporaneous CT acquisition was performed for attenuation correction using a dual row detector CT and acquisition parameters of 140 kVp, 50 mA s, 2 mm per slice thickness, 1:1 pitch.

2.4. Analysis

2.4.1. Image analysis

After spatial realignment to minimize anatomical variance between the first and second scans, the scans were spatially normalized and Gaussian