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Original article

Computational models of Bitemporal, Bifrontal and Right Unilateral ECT predict differential stimulation of brain regions associated with efficacy and cognitive side effects

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ABSTRACT

Background: Extensive clinical research has shown that the efficacy and cognitive outcomes of electroconvulsive therapy (ECT) are determined, in part, by the type of electrode placement used. Bitemporal ECT (BT, stimulating electrodes placed bilaterally in the frontotemporal region) is the form of ECT with relatively potent clinical and cognitive side effects. However, the reasons for this are poorly understood.
Objective: This study used computational modelling to examine regional differences in brain excitation between BT, Bifrontal (BF) and Right Unilateral (RUL) ECT, currently the most clinically-used ECT placements. Specifically, by comparing similarities and differences in current distribution patterns between BT ECT and the other two placements, the study aimed to create an explanatory model of critical brain sites that mediate antidepressant efficacy and sites associated with cognitive, particularly memory, adverse effects.
Methods: High resolution finite element human head models were generated from MRI scans of three subjects. The models were used to compare differences in activation between the three ECT placements, using subtraction maps.
Results and conclusion: In this exploratory study on three realistic head models, Bitemporal ECT resulted in greater direct stimulation of deep midline structures and also left temporal and inferior frontal regions. Interpreted in light of existing knowledge on depressive pathophysiology and cognitive neuroanatomy, it is suggested that the former sites are related to efficacy and the latter to cognitive deficits. We hereby propose an approach using binarised subtraction models that can be used to optimise, and even individualise, ECT therapies.

1. Introduction

Electroconvulsive therapy (ECT) is a highly effective treatment for depression and other severe psychiatric disorders [1]. However, it carries a risk of cognitive, especially memory, side effects. The risk and severity of cognitive impairment have been clearly shown to be related to ECT treatment technique [2–8]. Moreover, antidepressant efficacy and cognitive impairment related to ECT can be dissociated depending on the ECT treatment approach, a key aspect of which is the location or placement of the electrodes between which the stimulating current is passed. Randomised controlled trials and large effectiveness studies of ECT have established that electrode placement is a major determinant of efficacy and cognitive outcomes.

Efficacy has been demonstrated for Bitemporal (BT), Bifrontal (BF) and Right Unilateral (RUL) ECT in depression and these three electrode placements are commonly used in current clinical

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practice [9]. In some guidelines, BT ECT has been recommended as the placement of choice for severely depressed patients [1]. Several lines of evidence suggest that the BT electrode placement may be associated with unique characteristics in terms of efficacy. BT ECT results in a faster speed of response than BF and RUL ECT [2]. In contrast to RUL ECT, BT ECT is effective at barely suprathreshold doses [4,5], and its efficacy does not seem compromised by the concomitant use of benzodiazepines [10]. BT ECT has also been shown to be effective when there has been no response to RUL ECT [7]; thus in clinical practice, it is not infrequent to switch to BT electrode placement when there has been insufficient improvement after six sessions of RUL ECT [1]. However, BT ECT also produces more pronounced and persistent cognitive side effects than RUL [4–6] or BF ECT [11–14]. The most pronounced differences have been shown for recovery of orientation immediately following ECT treatment [5,7,15], and anterograde verbal memory [5–7,16–18] as well as retrograde amnesia [5–7,17,18] following the ECT course. Differences in acute retrograde memory changes between BT and RUL ECT examined immediately following ECT treatment have further been shown, with BT associated with significantly poorer word recall and word and shape recognition [5]. These findings therefore together suggest that BT ECT is associated with relatively greater verbal memory side-effects, including learning (i.e., anterograde memory), recall and recognition (i.e., reorientation and retrograde autobiographical memory).

Recent computer modelling studies, in which highly anatomically-accurate head models were derived from MRI scans of human subjects, have demonstrated that the distribution and spatial extent of brain regions directly stimulated by the electrical current differ as ECT placement is varied [19–21]. These simulation results concur with those of neuroimaging studies performed after ECT [22]. Together, these lines of evidence indicate that the differences in clinical and cognitive outcomes associated with different electrode placements, are a result of changes in the topographical distribution of the ECT current as the position of the two stimulating electrodes is altered. Other evidence also supports the importance of the direct effects of the ECT stimulus itself, rather than the subsequent induced seizure, for the efficacy of ECT. For example, it is possible to give forms of ECT (e.g. low dose RUL ECT) which involve a seizure but have relatively low efficacy [4,7,8]. Recently, a proof of concept study showed that the ECT treatment technique, given at a subconvulsive level, had antidepressant efficacy [23].

Thus, this present study aimed to provide an in-depth examination into regional differences in brain excitation by the ECT current between the three conventional ECT placements. By examining similarities and differences in current distribution patterns between BT ECT and the other two placements, our purpose was to elucidate brain regions which may be critical for efficacy as well as those responsible for cognitive, particularly memory, adverse effects. This knowledge would assist in further refining the ECT treatment approach. Based on the neuropsychological literature, we hypothesised that greater stimulation of temporal lobe structures, specifically the hippocampus as well as the inferior frontal gyrus, were likely to be related to the greater cognitive side effects typically seen with BT ECT, while stimulation of deeper structures such as the subgenual anterior cingulate cortex (sgACC), thalamus and basal ganglia might be responsible for its efficacy profile. This hypothesis was tested using a computational modelling approach to assess the relative stimulation of these proposed key regions, with BT, BF and RUL ECT. Current distribution maps were simulated using head models from three human subjects, in order to reduce the likelihood of findings reflecting idiosyncratic anatomical variations in any single individual.

2. Methods

2.1. Computer model development

Head models of three subjects: a healthy Asian male aged in his mid thirties (SUB1), a depressed Caucasian female aged in her early fifties (SUB2), and a healthy Caucasian male aged in his mid thirties (SUB3), as shown in Fig. 1, were reconstructed from their T1-weighted 3T MRI head scans. Major tissue compartments including the skin, skull, cerebrospinal fluid, grey matter and white matter were segmented from the scans. All tissue compartments in the head models were electrically homogeneous and isotropic. The electric potential φ in the head models was calculated using

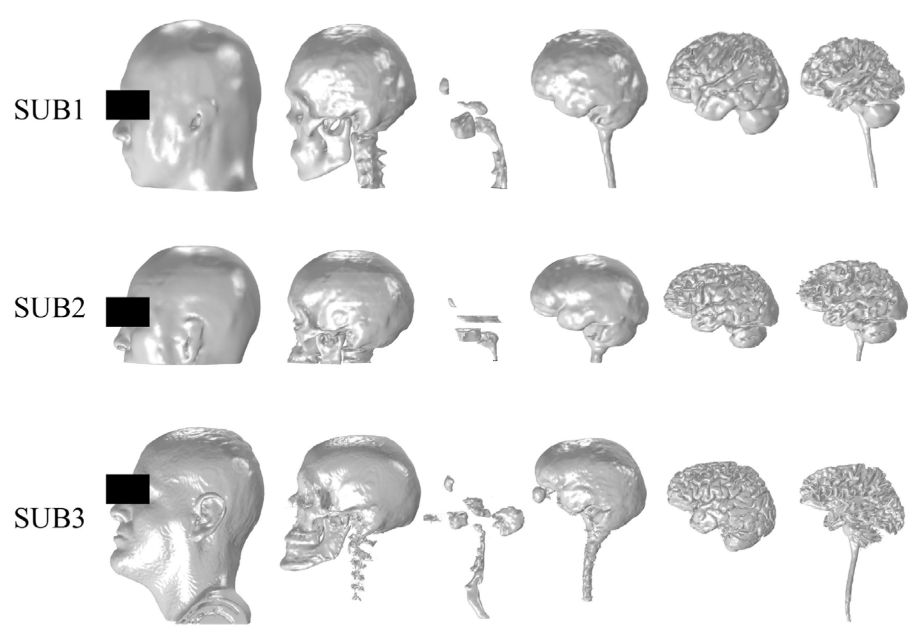

Fig. 1. Geometry of the three head models: SUB1 – an Asian male, SUB2 – a Caucasian female, and SUB3 – a Caucasian male. The various head tissue compartments included (from left to right) the scalp, skull, paranasal sinuses, cerebrospinal fluid, as well as grey and white matter regions of the brain.