European Psychiatry 41 (2017) 21–29

Contents lists available at ScienceDirect

European Psychiatry

journal homepage: http://www.europsy-journal.com

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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ARTICLE INFO

Article history:
Received 15 July 2016
Received in revised form 21 September 2016
Accepted 24 September 2016
Available online 3 February 2017

Keywords:
Depression
Electroconvulsive therapy (ECT)
Brain stimulation
Computational model
Efficacy
Cognition

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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http://dx.doi.org/10.1016/j.eurpsy.2016.09.005
0924-9338/

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

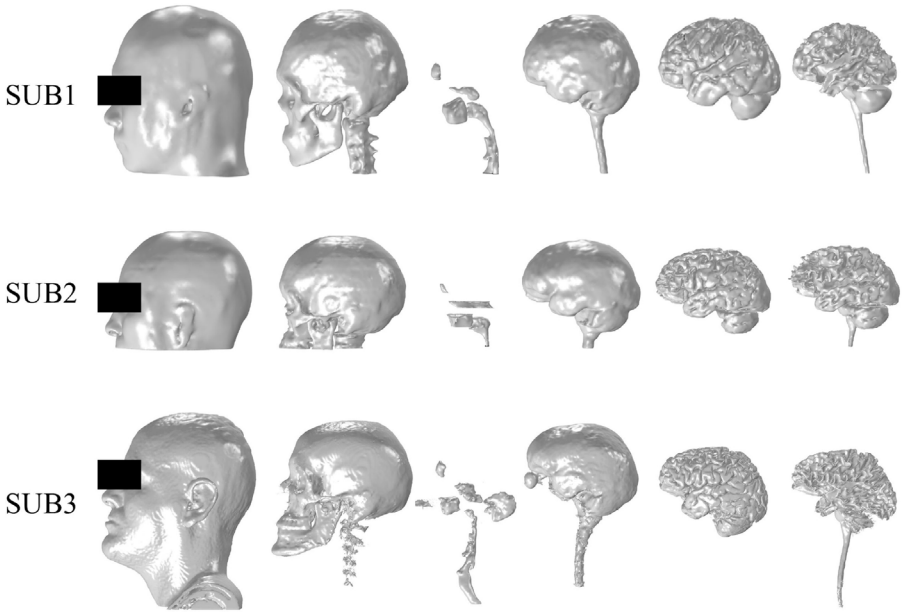

Fig. 1. Geometry of the three head models: SUB1 – an Asian male, SUB2 – a Caucasian female, and SUB3 – a Caucasian male. The various head tissue compartments included (from left to right) the scalp, skull, paranasal sinuses, cerebrospinal fluid, as well as grey and white matter regions of the brain.

Laplace's equation: $\nabla \cdot (-\sigma \nabla \varphi) = 0$, where σ is the electric conductivity, and ∇ is the nabla partial differentiation operator given by $\nabla \equiv (\partial/\partial x, \partial/\partial y, \partial/\partial z)$. The electric field (E-field) vector **E** was calculated from the negative gradient of electric potential according to $\mathbf{E} = -\nabla\varphi$. It should also be noted that in a purely resistive volume conductor, current density **J** is proportional to the E-field vector according to $\mathbf{J} = \sigma\mathbf{E}$. Detailed methods on model development can be found in our previous studies [24,25].

2.2. Electrode placements

Three conventional ECT placements were simulated, as shown in Fig. 2. In each placement, the anode delivered a total current of 800 mA through the scalp over a circular electrode of radius 2.5 cm, whilst the cathode, having the same size as the anode, delivered a total current of −800 mA. These current amplitudes represent typical levels of clinical ECT currents utilised. Remaining boundaries of the scalp were set as electrically insulating, whilst the lower boundary at the bottom of the neck was set to a distributed impedance condition with conductivity 0.001 S/m and thickness 50 cm. This setting resulted in a near insulating boundary, with total outward current across the neck boundary being less than 0.001% of total delivered current, and equal current flowing in due to balanced stimulus currents (±800 mA being applied at the scalp electrodes). The three electrode placements were defined as follows:

- BF: the centre of each electrode was placed 5 cm superior to the lateral canthus of each eye;
- BT: the centre of each electrode was placed on each side of the scalp 3 cm superior to the midpoint of a line connecting the external ear canal with the lateral canthus of the eye;
- RUL: the cathode was placed on the temporal scalp position (described in BT placement) on the right side of the scalp, and the anode was placed just right of the vertex of the head.

2.3. Data analysis

All simulations were carried out using the COMSOL Multiphysics v5.0 (COMSOL AB, Sweden) finite-element software package running on a Windows 64-bit Precision workstation (Dell, TX) with 24 GB RAM. To solve the stationary equations, a direct linear solver was utilised with an absolute error tolerance set to 10^{-5}. It took ~30 min to solve for each simulation, having approximately 5×10^6 degrees of freedom.

Simulation results were analysed in MATLAB R2014b (MathWorks, MA) by comparing the difference among the various electrode placements in the distribution of E-field strength in terms of E-field magnitude across the brain. Specifically, in order to investigate the reason for the superiority of BT over the other two placements, an integrated difference was expressed as a binary map that satisfied:

$$f(E_{BT}, E_{BF}, E_{RUL}) = \begin{cases} 1 & \text{if } A \text{ is true,} \\ 0 & \text{if } B \text{ is false,} \end{cases} \quad (1)$$

where E_P was the E-field magnitude with P placement (P = BT, BF, RUL), and A denotes a Boolean quantity equal to true (or 1) if E-field magnitude is higher for BT than the other two placements at a given point in the brain, and false (or 0) otherwise, namely: $A = (E_{BT} > E_{BF})$ AND $(E_{BT} > E_{RUL})$. The resulted brain map is thus called the integrated binary (subtraction) map, which comprises only 0s and 1s. The analysis of the results was based on the "quasi-uniform" assumption, namely that the degree of activation in a target region is proportional to the local E-field magnitude [26].

3. Computational results

Fig. 3 shows the integrated binary maps over the brain surface for each of the three subjects from three different views. Figs. 4–6 respectively show the E-field magnitude distribution in the brains of the three subjects SUB1, SUB2 and SUB3, for various coronal (C1 & C2), horizontal (H1 & H2) and sagittal (S1 & S2) planes. As opposed to the common notion that BT simply produced more current flow throughout the entire brain, the integrated binary maps revealed a differential stimulation pattern of BT: compared to the other two conventional placements, electric current density under the BT placement had a tendency of being higher around the central and lateral sulci, as well as the ventral parts of the brain. Specifically, BT affected bilaterally the middle and inferior parts of the temporal lobe (including hippocampi, shown in C1, C2, H1 & H2), the thalamus and basal ganglia (shown in C1, C2 & H1), the brainstem and anterior part of cerebellum (shown in S1 & S2), the anterior part of sgACC (shown in S1) a large section of the orbitofrontal cortex (OFC, shown in Fig. 3). In addition, BT also affected a larger area of the left hemisphere, extending its influence to the middle and posterior part of the inferior frontal cortex, the entire left temporal lobe and a large part of the left parietal lobe.

Despite the observation that the integrated maps indicate a large coincidence among the three subjects in terms of the regions where BT had a higher E-field, some variations across subjects were apparent. For instance, as shown in Fig. 3, SUB2 revealed a smaller "affected" area in the parietal lobe, whilst SUB3 exhibited lower effects in the frontal lobe and cerebellum, and SUB1 showed lesser activation in the sgACC. These inter-subject variations are likely reflected by anatomical differences, such as the shape, size and thickness of each head compartment.

The regions with stronger BT E-fields, revealed by the integrated binary maps, did not necessarily share the same E-field magnitude. For instance in Fig. 4, the E-field was over 120 V/m

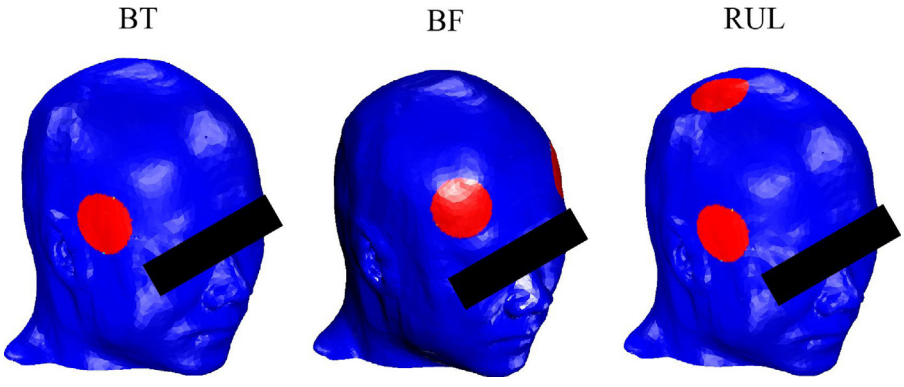

Fig. 2. Three conventional ECT scalp electrode placements, shown by the red circular scalp regions: Bitemporal (BT), Bifrontal (BF) and Right Unilateral (RUL). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of the article.)

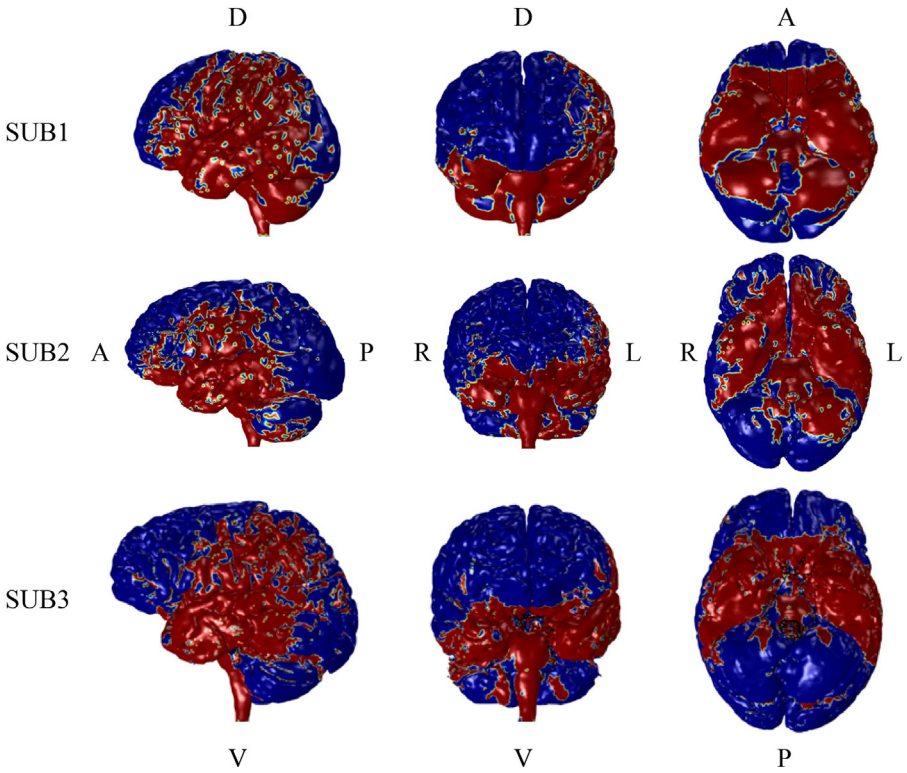

Fig. 3. Integrated binary maps over the brain surface for the three different subjects from the left side (leftmost column), front (middle column) and bottom (rightmost column) views, in which red indicating regions with a higher E-field magnitude under BT compared to the other two placements, whereas blue regions indicated the contrary. "A", "P", "L", "R", "D", "V" respectively represents "anterior", "posterior", "left", "right", "dorsal", "ventral". (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of the article.)

at the inferior temporal lobe (shown in C1), approximately 100 V/m at the pons (shown in S1 & S2), approximately 110 V/m at right superior temporal lobe (shown in H1), and less than 60 V/m at the lateral cerebellum (shown in S1).

4. Discussion

An optimal ECT technique would match the efficacy of BT ECT without its negative effects on cognition. This study is a first step into the understanding of how ECT technique can be tailored to stimulate areas responsible for efficacy while avoiding or minimising the stimulation of areas responsible for cognitive side effects. In this study, we modelled the three most commonly-used electrode placements in clinical practice; however, unlike previous studies in the literature [19,21], more than just one subject was included to investigate the subject variability. In addition, we have used BT ECT as the reference model to construct a subtraction map due to the efficacy profile and greater cognitive impact of BT ECT.

Present results suggested that BT ECT presented a differential stimulation pattern that may account for its characteristic clinical effects. In comparison to RUL and BF placements, BT ECT produced greater stimulation of deep mid-line structures (nucleus accumbens, ventral striatum, anterior part of the subgenual ACC, thalamus), temporal structures (including bilateral hippocampi), and also the posterior orbitofrontal cortex (OFC), the brainstem and the cerebellum. The majority of these structures have been widely implicated in depression pathophysiology, and some of them have been specifically associated with antidepressant response. In particular, volumetric reductions [27,28] and abnormalities in resting metabolism and cerebral blood flow (CBF) [29,30] have been found in the hippocampus, amygdala, insula, basal ganglia, medial orbitofrontal cortex (mOFC), ACC, dorsolateral prefrontal cortex (DLPFC) and the thalamus in depressed subjects. Some studies also suggest that the cerebellum [31,32] and even the brainstem [33,34] – areas specifically stimulated by BT ECT – might present structural alterations that may play a role in the pathophysiology of depression. Interestingly, computational modelling results show that the sgACC was more intensely activated by BT ECT than by the other placements. Alterations in the structure and function of the sgACC appear to be specifically associated with depressive states [35]. The sgACC has multiple afferent and efferent connections to the PFC, OFC, ACC, insular cortex, hypothalamus, amygdala, nucleus-accumbens, locus ceruleus, the ventral tegmental area and the dorsal raphe nucleus [36]. This region has thus been identified as a potential key target for treatment of depression using Deep Brain Stimulation (DBS) [36] and several studies have suggested that changes in its metabolic activity are correlated with response to antidepressant medications [37–40], ECT [41] and DBS [42]. Thus, more intense stimulation of this region with BT ECT compared to RUL and BF ECT may well account for the greater efficacy of BT ECT.

Neuroimaging studies have shown that verbal learning and semantic recall are largely lateralised to the dominant hemisphere (i.e., the left hemisphere in the majority of patients), specifically to regions of the frontal and temporal cortex [43]. The hippocampus is known to subserve several key memory functions, including encoding, retrieval and working memory [44]. For retrograde memory, specifically, memory retrieval processes are critical. Findings from neuroimaging [45], and lesion studies [46], indicate that the hippocampi are functionally important for retrieval processes, irrespective of the stimulus modality (i.e., autobiographical, semantic, verbal or visual). Given the dual functional role of the left medial temporal structures in verbal learning and recall, and especially the role of the hippocampus in memory retrieval processes, greater stimulation of this region with BT relative to BF and RUL ECT, as shown with our computational

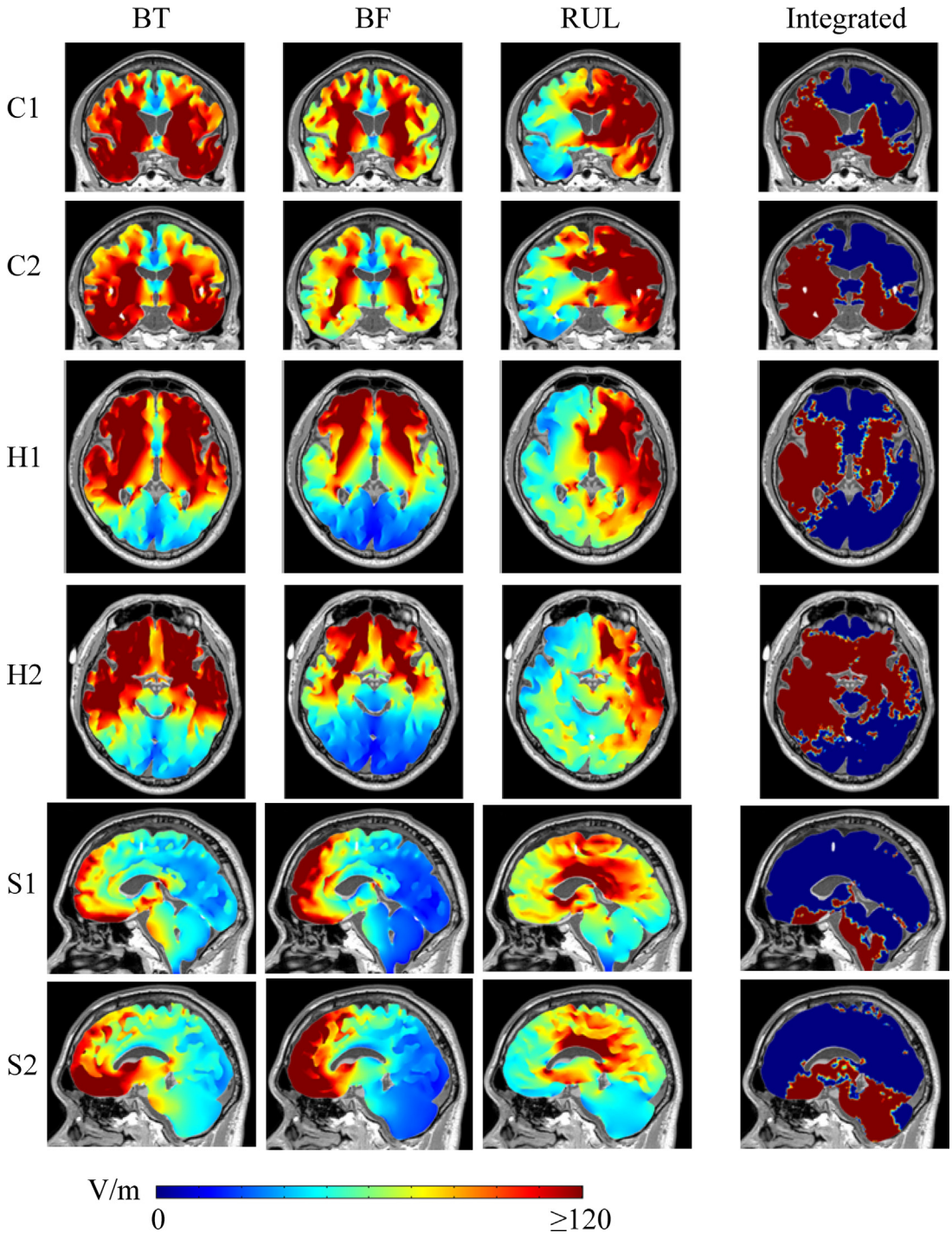

Fig. 4. Brain E-field magnitude distribution in the computer model of SUB1 for various coronal (C1 & C2), horizontal (H1 & H2) and sagittal (S1 & S2) planes. The first three columns from the left respectively show the E-field for BT, BF and RUL placements. The rightmost column shows the integrated maps, in which red indicates regions with a higher E-field magnitude with BT than the other two placements, whereas blue indicates the contrary. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of the article.)

modelling, is therefore consistent with this profile of increased cognitive side effects. Furthermore, regions of the frontal cortex are also identified to underlie memory retrieval processes, specifically the inferior and middle frontal gyri [47,48], which are considered part of a common retrieval network [45]. Greater relative stimulation of left frontal regions with BT ECT as shown with our modelling, particularly Brodmann areas 44, 45, and 47 (i.e., corresponding to the left inferior frontal lobe), is additionally broadly consistent. For reorientation and retrograde memory side-effects specifically, this could be the case as assessment typically involves verbal recall of a mixture of both episodic (e.g., place you are in, last birthday) and semantic information (e.g., date of birth, family member/friends details). As there is evidence that long term episodic memories become "semanticised" over time [49], greater relative left inferior frontal cortex stimulation may also therefore be relevant.

Overall, this study suggests that when compared to RUL or BF ECT, BT electrode placement leads to a particular pattern of brain excitation that might be related to its characteristic efficacy profile and greater cognitive side effects. Interpreted in light of existing

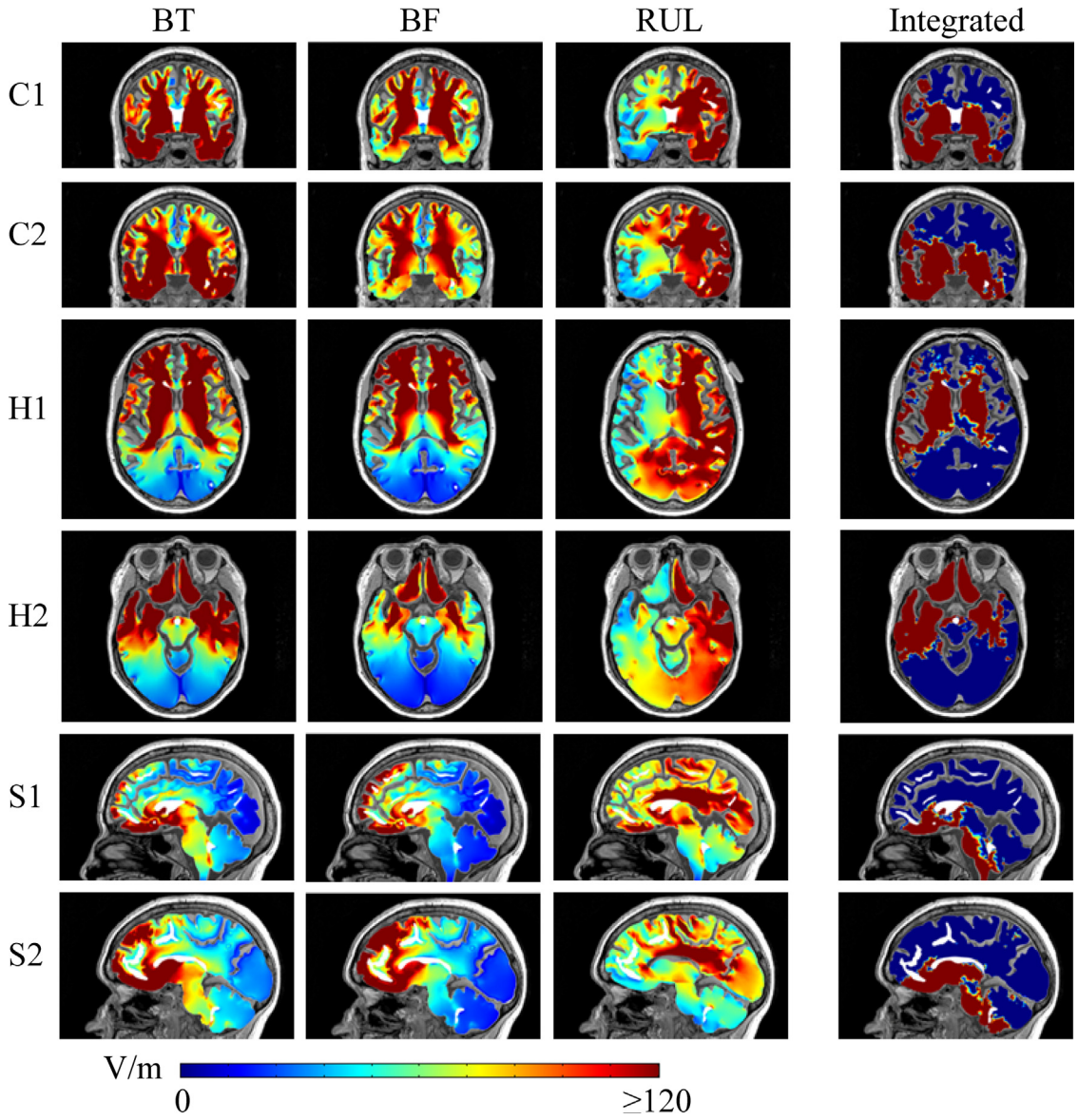

Fig. 5. Brain E-field magnitude distribution in the computer model of SUB2 for various coronal (C1 & C2), horizontal (H1 & H2) and sagittal (S1 & S2) planes. The first three columns from the left respectively show the E-field for BT, BF and RUL placements. The rightmost column shows the integrated maps, in which red indicates regions with a higher E-field magnitude with BT than the other two placements, whereas blue indicates the contrary. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of the article.)

literature on the pathophysiology of depression, results of this study suggest that the efficacy of BT ECT may be related to direct excitation of deep midline structures, such as the sgACC, nucleus accumbens, ventral striatum, thalamus and basal ganglia, despite a weaker stimulation at the superior prefrontal cortex. Conversely, greater direct stimulation of the hippocampus and inferior frontal cortex probably accounts for the greater cognitive deficits observed with BT ECT, though it is unclear to what extent stimulation of these areas may also be important for antidepressant efficacy.

Our general conclusions are based on the integrated binary map findings, which were robust across the three subjects studied. However, individual differences, reflecting subject-specific anatomy, raise the prospect that individual variations in efficacy and side-effects may reflect subject-specific variations in electric current patterns between montages. Therefore, individual electric current model and binary subtraction map may provide a process to predict an individually-optimised therapy.

This study is the first to use subtraction maps to directly compare effects of the ECT stimulus with BT, BF and RUL ECT, as modelled with computational methods. The binary subtraction map is capable of producing a peculiar and nontrivial prediction of prefectural active brain regions. By using these binary maps, as opposed to simple subtraction, region by region ranking is allowed without the need to assume compatible sensitivity of any given region to electric fields.

5. Limitations and future work

Our study relied on the quasi-uniform assumption [26] and on absolute subtraction maps developed here to address the hypothesis about how differential stimulation of brain regions may be associated with efficacy and cognitive side effects using the three common ECT placements. There are numerous ways to further develop our method based on secondary biophysical assumptions: in addition to adding anatomical detail, e.g.

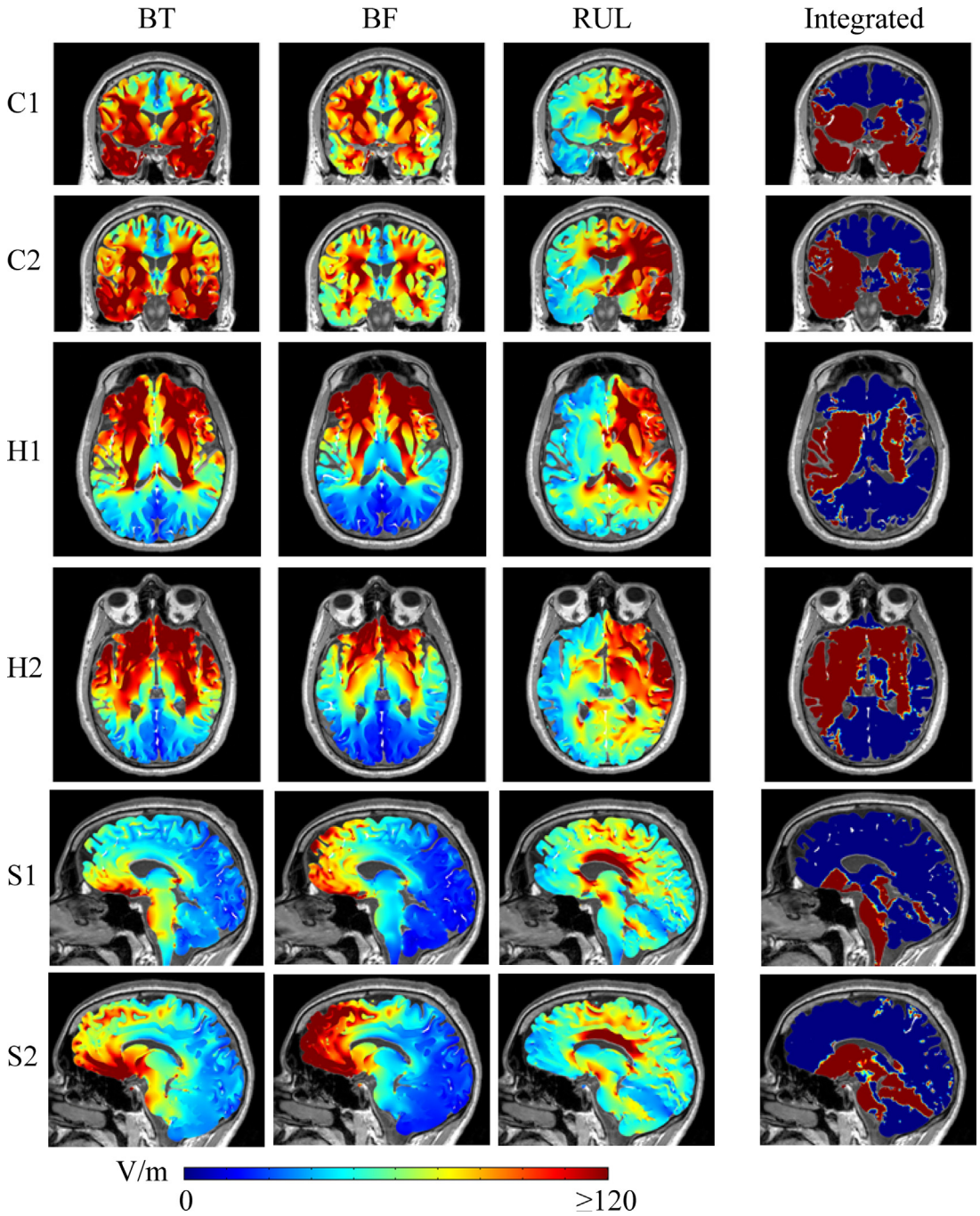

Fig. 6. Brain E-field magnitude distribution in the computer model of SUB3 for various coronal (C1 & C2), horizontal (H1 & H2) and sagittal (S1 & S2) planes. The first three columns from the left respectively show the E-field for BT, BF and RUL placements. The rightmost column shows the integrated maps, in which red indicates regions with a higher E-field magnitude with BT than the other two placements, whereas blue indicates the contrary. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of the article.)

anisotropy [21,24,50,51], the relative susceptibility of each brain region can be modelled by including cellular detail [52,53], or by applying additional post-processing (thresholds, normalisation, spatial filters) to our subtraction maps. However, these secondary steps not only increase the complexity of our models, but also are subject to assumptions that require additional constraints/parameters, which are yet to be validated.

The computational models in this study primarily investigated differences between electrode placements with a current of 800 mA. However, in clinical practice, alteration of other stimulation parameters (e.g. pulse width and duration) has also been shown to affect efficacy and cognition. Modelling of these ECT parameters was beyond the scope of this study. In future, computer models incorporated with excitable tissue property of the brain will be developed, and such models will provide more insights into the effects of ECT by taking other stimulation parameters into consideration. In addition, due to the observation of subject-variability in our simulation results, it would be useful to include more subjects in the simulation, in order to construct a conjunction map that describes the consistency of stimulation across different subjects.

The interpretation of our modelling results are heavily based on prior literature regarding whether regions more strongly stimulated with BT ECT may contribute to efficacy or cognitive

outcomes. Proof of these propositions would require combined clinical – imaging/computational studies, in which clinically measured efficacy and cognitive outcomes in patients undergoing ECT are compared with E-field magnitude in these brain regions in the same patients. The latter would require pre-ECT MRI head scans of these patients, from which anatomically accurate individual head models are constructed, allowing computational modelling of E-field magnitude in the hypothesised regions of interest. Next, studies could examine novel placements which stimulate the above midline structures, while avoiding the medial temporal lobes, to demonstrate that the high efficacy of BT ECT can be maintained while cognitive impairment is reduced, by more focussed stimulation to key brain targets.

Disclosure of interest

Dr. Bai, Dr. Galvez, Assoc. Prof. Dokos, Dr. Martin and Prof. Bikson declare that they have no conflict of interest. Prof./Dr. Loo received an honorarium from Mecta for teaching in an International ECT course.

Acknowledgements

The authors would like to thank Prof. Caroline Rae from Neuroscience Research Australia for providing the structural MRI of SUB1 and SUB2, Dr. Elizabeth Tancred from the University of New South Wales for her expertise in the neuroanatomy, and Mr. Dennis Truong from the City College of New York for their contributions in reconstructing SUB3. Dr. Bai currently holds a Humboldt Research Fellowship for Postdoctoral Researchers from Alexander von Humboldt Foundation.

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