On assumptions and key issues in electric field modeling for ECT

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August 23, 2023

Recently, Dr. Alexander Sartorius commented on our work [1] on assessing relationships between electric field (E-field) strength, hippocampal volume change, and electroconvulsive therapy (ECT) clinical outcomes [2]. Dr. Sartorius questioned the applicability of E-field modeling for ECT based on 1) temporal waveform dependence; 2) tissue impedance dependence; and 3) tissue anisotropy dependence. We appreciate these considerations and agree that E-field modeling would benefit from further validation and improvement. However, we need to point out misconceptions of E-field modeling assumptions and delineate some key issues involved.

Dr. Sartorius asserted that E-field modeling was done with the assumption of a direct current application that deviates from the alternating current waveform used in ECT, which is affected by tissue inductance and capacitance. In many models of time-dependent bioelectromagnetic phenomena, solutions of low-frequency problems commonly employ the quasi-static approximation [3]. This approximation allows the Maxwell's equations to be simplified by neglecting the wave propagation, inductive, and capacitive effects in biological tissue. The conditions for neglecting the wave propagation and inductive effects are easily satisfied due to the physical dimensions and non-magnetic nature of the tissue [3]. The condition for neglecting capacitive effects is that the displacement current is small compared to the conduction current, i.e., $\mathrm{j}\omega\varepsilon/\sigma \ll 1$, where σ is the tissue conductivity, ε is the dielectric permittivity, and ω is the excitation frequency. For very low frequencies, e.g., 10 Hz, tissue (skin, bone, and brain) permittivity is substantial and the capacitive effects cannot be easily ignored [4]. However, the permittivity is approximately a log-linear, decreasing function with frequency [5, 6]. For certain stimulus waveforms (e.g., monophasic square pulses with pulse width up 1 ms) typically used for deep brain stimulation and ECT, the error between the electric potential calculated under the quasi-static approximation and the exact solution is limited to 5%–13% [7]; the capacitive effects could be ignored.

Since we assumed that the head tissues are purely resistive, the E-field is linearly proportional with input current amplitude. Therefore, we first calculated the E-field based on an input current

of 1 mA, and then multiplied by the individual treatment current (600–800 mA). Dr. Sartorius pointed out that at low current strengths such as 1 mA, the measured head impedance (so-call "static impedance") is much higher than the impedance seen during the pulse (the "dynamic impedance"). The small-signal impedance is affected by conditions at the electrode-skin interface. To model the E-field in both low and high current situations, Unal et al. devised an impedance model of the scalp in which a superficial scalp layer with adaptive conductivity that linearly increases with E-field up to a limit, and a deep scalp layer with a fixed conductivity [8]. In their high current model, the overall scalp conductivity ranges from 0.16–0.5 S/m across four subjects [8]. In our model, we use a scalp conductivity value of 0.465 S/m, which is within the range of appropriate scalp conductivity values to model high current ECT.

Finally, Dr. Sartorius pointed out that strong direction dependent effects from white matter tracts may affect the E-field distribution. Indeed, previous ECT E-field modeling investigations have incorporated white matter anisotropic conductivity [9]. Relevant to an older patient population, white matter hyperintensities may also impact E-fields variability [10]. However, E-field modeling incorporating white matter anisotropy did not improve E-field accuracy in an important validation study with *in vivo* intracranial recordings in humans [11]. In another study examining the relationship between E-field and ECT-induced brain volume expansion, we found that incorporating diffusion tensor imaging derived anisotropy data to improve the E-field model produced similar regression results [12]. Nevertheless, the impact of direction dependent effects on E-field modeling, or generally more accurate representation of the geometry and electrical properties of various brain tissue, is an area of active research.

We acknowledge that E-field modeling is in the nascent stage of development and further validation is necessary. Efforts have been made to verify the accuracy of human head models for transcranial electrical stimulation through *in vivo* intracranial recordings [11, 13] and magnetic resonance current density reconstruction approaches [14]. Furthermore, ECT stimulus modeling of amplitude-determined seizure titration has been validated with non-human primates [15, 16]. E-field models can be further improved with more accurate tissue segmentations [17], additional anatomical details [18], and refined conductivity estimates [8]. Advances in E-field modeling approaches must be balanced with computational costs and complexity to achieve translational impact. The context of these improvements will systematically improve the accuracy of E-field modeling, but these anticipated improvements do not preclude research focused on elucidating the role of ECT E-field strength and clinical outcomes.

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