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The "Quasi-Uniform" Assumption in Animal and Computational Models of Non-Invasive Electrical Stimulation

Transcranial stimulation encompasses all non-invasive brain stimulation techniques where electrical current is generated or induced in the brain for experimental or therapeutic purposes using scalp electrodes or magnetic coils. Each modality (e.g. transcranial current stimulation, cranial electrotherapy stimulation, transcranial magnetic stimulation, electroconvulsive therapy) produces a spatio-temporal pattern of electric current flow in the brain that then determines neurophysiological response. Due to the relatively large separation between electrode/coil and stimulated tissue, the target region is often in the "far-field" of the electric field. Thus, unlike stimulation with implanted electrodes, the gradient of the electric field is limited in the vicinity of the brain target.

Computational models of transcranial stimulation predict brain current flow patterns for dose optimization. Translational animal models aim at elucidating the cellular mechanisms of neuromodulation. Here we identify and define a ubiquitous assumption underlying both computational and animal models, referred to herein as the "quasi-uniform assumption". Though we attempt to rationalize the biophysical plausibility for the quasi-uniform assumption based on the limited electric field gradients generated during stimulation, our goal is neither to justify nor repudiate it, but rather emphasize its implicit use in a majority of modeling and animal studies.

The quasi-uniform assumption states that local polarization in a target region is proportional to the local electric field magnitude (EF): Polarization (target) $\propto$ EF (target). This assumption is not trivial because membrane polarization has long been linked to the change in electric field, via the so-called "activating function". However, it is well known that in a uniform electric field, where by definition the electric field gradient is zero, membrane compartments may polarize linearly with electric field (see below). The term "quasi-uniform" implies that the spatial gradient of electric field is locally negligible (within a brain region) to bring about changes in membrane polarization, and thus local membrane polarization is determined by electric field. The electric field may vary globally across brain regions, thus determining which targets are preferentially polarized. The general quasi-uniform assumption is that polarization is linear with electric field magnitude for each target with comparable sensitivity: compartment polarization distribution across targets is comparable for a given electric field. The general assumption ignores regional differences in morphology, biophysics, and function, but may be a reasonable first approximation when considering cortex.

Because any neuromodulation, and resulting cognitive/behavioral changes, are assumed to follow from membrane polarization, the extent of polarization indicates the probability of a region to be influenced by the stimulation. Certainly, "neuromodulation" encompasses a broad swath of potential acute and plastic changes, and is dependent not only on polarization but also endogenous factors such as ongoing (patho) physiological neuronal activity. Changes may even be non-monotonic with polarization level. Nonetheless, membrane polarization remains the only known biophysical mechanism of action for transcranial stimulation modalities.

In this letter we establish the ubiquity of the quasi-uniform assumption rather than address the more complex issue of its justification and limitation; nevertheless, some explication is useful. During transcranial stimulation, the generated electric field changes incrementally over space (compared to the space constant of the neuronal membrane) such that the resulting membrane polarization of any given neuronal segment is approximated by the local electric field.

For example, if we consider the electric field generation around the initial segment of a cortico-spinal axon, the same segment would respond similarly (e.g. trigger an action potential) to a uniform electric field of comparable magnitude. More generally, the electric field is assumed to change incrementally on the scale of a neuron or cortical column. Thus, on the scale of a neuron, any electric field gradients are not significant in the sense of contributing to neuronal polarization. This assumption of functionally negligible electric field gradient is reasonable for transcranial electrical/magnetic stimulation, which uses macro-scalp electrodes or coils at a distance from the brain [1,2]. To be clear, it is not assumed that the electric field is uniform across the entire brain.

The two key implications of the quasi-uniform assumption are then:

1. The quasi-uniform assumption is required in translational animal studies of transcranial stimulation. During transcranial stimulation, the electric field varies in a complex manner across the brain. It is not technically feasible in animal or brain slice studies to replicate the electric field in all brain regions. The solution is to select a clinical region of interest (e.g. a cortical target), predict the generated electric field in that region of the human brain, and then to replicate that electric field in an analogous region of the animal brain. In selecting one electric field, the quasi-uniform assumption is applied. Whether interpreting classic animal studies or planning meaningful translational studies, the quasi-uniform assumption is inevitable.
   Animal studies are only meaningful if a controlled (known) electric field is generated. It is not prudent to heuristically apply "smaller" stimulation (e.g. a smaller electrode/coil and reduced applied current) because the resulting brain electric field may not be clinically meaningful in humans. The use of large parallel wires in brain slice studies generates a uniform electric field with controlled orientation. In general, it is preferred to avoid invasive micro-electrode stimulation in animal studies precisely because they produce highly non-uniform fields near the electrodes.
2. From classic concentric-sphere approximations [3] to modern MRI-derived Finite Element Method simulations [1,2], forward models represent the influence of stimulation by electric field, or equivalently by current density. By representing electric field/current density, these approaches imply that local electric field/current density provides some approximation of neuromodulation, and so rely on the quasi-uniform assumption. For cortical modulation, the electric field may be decomposed into radial and tangential components.
   In a 'soup' of non-compact, bending, and terminating processes (axons, dendrites), the electric field may indicate maximal polarization [4], while compact neuron polarization will also track electric field [5]. Straight axonal processes extending beyond the quasi-uniform area may be influenced by changing electric fields [6,7], but local terminations and bends will polarize with electric field. Certainly, the quasi-uniform electric field representation is only a first step toward predicting the effects of non-invasive stimulation of the brain, which is a non-linear, non-stationary, and coupled system. When representing the spatial influence of transcranial stimulation by the electric field (current density), the quasi-uniform assumption is implied.

Though computational models and animal studies are not explicitly linked, they inform each other. For example, the cellular mechanisms of stimulation are characterized in brain slice studies using uniform fields [8]. Conversely, the electric fields predicted by forward models are the input for animal studies [9]. Animal and computational studies will continue to inform clinical practice; in interpreting published studies and in ongoing research, the quasi-uniform assumption is ubiquitous.

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Mirror Neuron Disinhibition may be Linked with Catatonic Echo-Phenomena: A Single Case TMS Study

Letter

Dear Editor:

Echo-phenomena are abnormal involuntary automatic imitations of behaviors (echopraxia) or verbal utterances (echolalia) without explicit awareness. Though various subtypes of echo-phenomena have been described, echolalia and echopraxia appear to be more common, and are one of the principal motor signs of catatonia [1]. They are observed in a variety of other conditions ranging from normal early childhood speech (as a conditional reflex that is suppressed when voluntary speech takes over), to disorders like autism, Tourette's syndrome, dementia, frontal lobe epilepsies and trans-cortical aphasias [2]. Factor analytical studies in catatonia suggest that echo-phenomena are seen more commonly in affective disorders like mania [3]. Other than the aphasias and epilepsies, where a definite relationship between focal structural lesions and echo-phenomena can be drawn, the neurophysiological underpinnings of this complex phenomenon in other disorders are not well understood.

The neurophysiology of imitative behaviors has been boosted by the discovery of mirror neurons [4]; a specialized subset of neurons in the inferior frontal, ventral premotor and inferior parietal cortices that fire during both action performance and action observation. Being an integral component of motor cognition, abnormalities in mirror neurons have been implicated in catatonia [5]. Since echo-phenomena involve imitation that persists beyond the point of relevance, it has been proposed that a lack of 'inhibitory' control over the mirror neurons may underlie these behaviors [6]. This hypothesis has not been tested in catatonic patients with echo-phenomena. We report a single case study, to explore mirror neuron activity during echolalia and after recovery, 2 weeks later using transcranial magnetic stimulation (TMS).

Case report

Mrs. X, a 28 year old married lady, with high school education, presented to the emergency psychiatric services with 3 days history of acute onset behavioral problems. She was found to be withdrawn, had sleep disturbances, severe psychomotor retardation and repeated verbatim, whatever was spoken to her. She had to be forced to take oral feeds and attend to her daily routine. On further questioning, it was found that she had been feeling depressed in the last 3 years which had worsened over the last 1 year. She reported anhedonia, easy fatigability, frequent crying spells, low self-esteem, intense anxiety, being irritable, and had two instances of harming herself by trying to slash her wrists. She developed these symptoms in the background of ongoing stressors, learning about her husband's extramarital relationship. On examination, her vital signs and systemic examination revealed no abnormalities. She had staring, passive negativism, catalepsy, echolalia, echopraxia, near mutism and withdrawn behavior. Bush-Francis Catatonia Rating Scale revealed a score of 14. She repeated verbatim whatever was spoken to her. Her metabolic, hematological and brain imaging studies revealed no abnormalities. She was described as a premorbidly well-adjusted personality, and had family history of alcohol dependence in father, with history of migraine for the past three years.

She was diagnosed to have severe depression and was initiated on a trial of lorazepam at 6 mg/day in three divided doses. She showed dramatic improvement in catatonic signs, including echo-phenomena within the next 48 h. Sertraline 150 mg per day and supportive psychotherapy were initiated. Immediately after recovery from catatonia, she was found to be euphoric, overfamiliar, had increased speech output and was mildly disinhibited. A possibility of bipolar disorder was considered as her depression improved dramatically and she showed features of hypomania and sodium valproate was added as a mood stabilizer. She improved and was maintaining well on follow up after one month.

TMS experiment

We conducted a pre-post TMS experiment to assess mirror neuron activity (MNA). This experiment was conducted (a) during