Session I Discussion

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During the first lecture session, Dr. Pascual-Leone reviewed crucial issues in the technical and physiologic aspects of transcranial magnetic stimulation (TMS) and Dr. Nitsche reviewed technical and physiological issues in transcranial electrical stimulation (TES), chiefly in regard to transcranial direct current stimulation (tDCS). During the discussion session that followed, a number of core questions were raised which were revisited repeatedly during the conference. The discussion is summarized below, organized according to some key themes.

I. Studying Mechanisms versus Studying Efficacy

Both TMS and tDCS are techniques whose mechanisms at the molecular, cellular, and network levels are being investigated simultaneously with their development for therapeutic use in humans. The noninvasive and non-painful nature of these techniques has led to a rapid increase in their use in humans, before many of the basic questions of how these techniques work and how to optimize their effects have been elucidated. These lines of investigation inform each other but ask essentially different questions, and should continue to proceed in parallel. In other words, clinical investigation will continue to ask, *is the technique therapeutically useful as it is currently administered*, which is a separate question from the mechanistic one -- *how is stimulation achieving its effect*.

For example, the modeling of current distribution through the brain is necessary for understanding the effects of brain geometry and tissue characteristics on the dispersion of current density. This line of investigation is likely to offer important information for optimizing stimulation delivery in therapeutic protocols. However, the burden of modeling fiber orientation and current density for each patient in a therapeutic trial would be prohibitive at this point, and is not necessary for producing valid results in a study asking whether a given stimulation paradigm is effective or not in a group of subjects compared to a control population.

The degree to which the result of non-invasive stimulation resembles long term depression (LTD) or long term potentiation (LTP) is also an open question, and further studies on the physiology of task dependent plasticity augmented by stimulation is needed.

II. Focality

There were several questions about the issue of focality of stimulation in TMS and tDCS during this discussion section. In the most basic view, the focality of TMS depends on the shape of the coil being used -- figure of eight coils are more focal than round coils, producing maximal current at the intersection of the two loops. In tDCS, neuronal firing rates in the area below the electrode are altered – rates are increased at the anode and decreased at the cathode. However, the focality of the area being stimulated does not appear to be the only factor in determining the complex effects of TMS or tDCS.

With the increased use of stereotactic navigation techniques, attention to the focality of stimulation has increased. While focality may be crucial in investigations of cognitive function using highly specific tasks, focality may not be desirable in therapeutic trials in the rehabilitation setting.

A key emerging concept is that the specificity of stimulation does not depend solely on the presumed focality of stimulation, or the area of the tissue initially effected. The induced tissue current is not the only parameter of importance. The position and orientation of the coil in TMS relative to the brain may affect the way the induced current interacts with the underlying axons. The current may affect axons at the site of stimulation, downstream of this site, and in post-synaptic fibers. Shunting of current through CSF may affect current density and distribution. Additionally, the effect of stimulation may be state dependent. Discussants agreed that coupling non-specific stimulation with highly specific task performance may be a method to markedly increase the magnitude and specificity of the effect of stimulation on neural pathways.

With tDCS, the problem of reference electrode placement was raised. Dr. Walsh offered a specific example in which the presumably active electrode was placed over the motor cortex and the so-called reference electrode was placed over the frontal pole. On stimulation, the patient complained of an irresistible urge to move, suggesting that the midline supplementary motor area may have been activated and implicating the

reference electrode as exerting an active effect. Flow of current through CSF may also be an important component affecting the specificity of stimulation in tDCS, as it is appears to be in TMS.

III. Interindividual Variability

Variability between subjects also arose as a significant potential obstacle for making observations about the mechanisms of noninvasive stimulation and for finding stimulation paradigms that make a therapeutic impact. In clinical investigations, the degree of baseline interindividual variability is complicated further by the heteroegeneity of disease or acquired insult, and the hetereogeneity of individual responses to the recovery process. Study design and statistical methods which take into account both individual subject level data and group level data may improve the validity of clinical investigations.

IV. Outcome Measures

Brian stimulation studies in the laboratory setting often report effects on a very small scale, for example, increases in MEP amplitudes of a few microvolts. The practical benefit to patients of such modest effects is unclear. Translating these experimental findings into meaningful therapeutic strategies for patients presents a larger challenge. Outcome measures which are specific, valid, reliable, and clinically meaningful are needed to carry out future trials of non-invasive stimulation for therapy in the rehabilitation setting.