Session III Discussion

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The discussion that followed talks by Drs. Naeser and Fregni emphasized crucial questions that have challenged various investigators irrespective of their area of sub-specialization in neurorehabilitation research. These questions included:

- Which brain regions should be stimulated?
- Is the location of cortical stimulation the locus underlying observed behavioral effects?
- How do interhemispheric connections relate to local connections?
- Does electrical stimulation make neural networks function better or differently?
- Can the efficacy of cortical stimulation be enhanced by combining it with other therapies?
- Should therapy be tailored to the individual or the population?
- What is the time course of neuroplastic changes associated with stimulation?

Discussion of these questions is summarized below.

Which brain regions should be stimulated?

The complexity of identifying the most appropriate location to administer brain stimulation was illustrated by Dr. Naeser who indicated that best response site for administration of rTMS to improve naming in aphasia (right BA 45) was not the site identified by functional imaging (right hemisphere M1 for mouth). Furthermore, her finding that stimulation of a region immediately adjacent to the best response area (right BA 44) worsens performance underscores the relevance of local differences in cortical connectivity and responsiveness when choosing a target site. While the use of MRI guided neuronavigation with TMS allows for highly accurate targeting of specific regions, results like those discussed by Dr. Naeser illustrate that the effects of such stimulation can be unpredictable. In the case of patients with aphasia undergoing inhibitory contralesional TMS, this variability of effect necessitates a Phase I study to determine a best response area. More broadly, the strategy for choosing a stimulation site may depend on the type of question being asked. Experiments that test a hypothesis about mechanism will likely be driven by imaging or other physiological data that serves as a foundation for hypothesis testing, while experiments geared toward therapy may be more likely to rely on stimulation sites determined empirically and to leave the elucidation of the exact mechanism to future investigations.

Is the location of cortical stimulation the locus underlying observed behavioral effects?

The answer to this question remains largely unknown. One critical issue raised was that of the downstream effects of cortical stimulation. Given that stimulation at a given cortical site is likely to have secondary and perhaps tertiary effects throughout a more widely distributed network of brain regions, it is important to keep in mind that any therapeutic effect might be related changes at sites remote from the original target of stimulation. For example, Dr. Fregni presented evidence suggesting that in some situations the relevant areas for response to stimulation may be subcortical rather than the cortical sites targeted. The discussion also reinforced another point made earlier in the conference that better characterization of the "map" of current density in the brain during stimulation might be critical in resolving uncertainty regarding the relationship between site of stimulation and area of effect. It would allow for greater understanding of the amount of current lost through shunting, how pathologic processes such as stroke that alter the distribution of CSF space affect current distribution, and the degree to which manipulation of the position of a TMS coil on the scalp corresponds with changes in the region of cortex most affected by stimulation.

How do interhemispheric connections relate to local connections?

The importance of interhemispheric connections was a recurring theme throughout the conference. Convincing evidence was presented that, in the setting of unilateral brain injury, the unaffected hemisphere can exert a suppressive and deleterious effect on the already damaged hemisphere. This model of competitive balance between the hemispheres has lead to studies using inhibitory low frequency rTMS to the unaffected hemisphere. Recent studies using this approach have shown improvement of motor impairment, aphasia and spatial neglect. While these data underscore the importance of interhemispheric interactions, evidence also points to the relevance of local interactions in mediating the therapeutic effects of brain stimulation. Dr. Naeser's talk on the effects of applying TMS to the right inferior frontal gyrus in patients with left hemisphere strokes and nonfluent aphasia illustrates how both interhemispheric and local interactions can be critical. Insofar as Dr. Naeser's approach has involved inhibition of the intact right hemisphere in order to improve left hemisphere function, her data lend strong support to the importance of interhemispheric interactions. However, her finding that the effect of TMS in the right hemisphere is exquisitely sensitive to changes in coil position on the order of millimeters suggests the existence of a system that is very finely tuned locally in addition to its long range effects. This notion is further supported by data suggesting that stimulation of the adjacent right pars opercularis may result in worsening of language performance, implying further effects that depend on local circuitry. The functional architecture of these local interactions remains unknown. One intriguing suggestion explored during the discussion was that brain stimulation acting on local circuits might exhibit properties akin to the center/surround inhibition that has been described in the visual system. Surround inhibition has been described as a method by which a system can improve its spatial resolution and discrimination and has examples at many neural scales from the level of the retina to more recently the level of the parietal cortex. While it seems this has been more often reported in sensory systems, it may also have relevance to other systems like motor control and language. It may thus be the case that the functional architecture of local cortical networks is organized such that stimulation of nearby areas can lead to opposing effects. Such a notion is provocative, both because it highlights the importance of competitive inhibition in short and long range communication, and because it may give some insight into the nature of the computations that are being performed.

Does electrical stimulation make neural networks function better or differently?

One broad conceptualization of how cortical stimulation may affect plasticity after brain injury is that it may modulate one or more nodes in a behaviorally relevant circuit, thereby causing a shift in overall network activity that leads to improved performance. Discussants challenged this model, proposing that TMS, and perhaps cortical stimulation in general, may induce disruption of behaviorally relevant networks or disruption of brain-to-behavior pairings that have been established over time. Rather than causing a modulation of network function that improves performance, disruption of an existing brain-behavior relationship may force the development of a different behavioral strategy associated with a different network of brain activity. For example, patients with nonfluent aphasia who experience improved naming after receiving rTMS may be using new cognitive strategies in order to name, associated with different behaviorally relevant neural networks. This way of conceptualizing the effects of cortical stimulation raised interesting theoretical questions regarding individual variability in network functions and cognitive strategies. For example, it may be the case that individuals with the same type of stroke respond to the computational challenges of recovery in very different ways. Moreover, substantial baseline individual differences in perceptual, motor and cognitive strategies may exist in normal individuals, and may contribute to variability in both behavioral recovery after brain injury and response to stimulation.

Can the efficacy of cortical stimulation be enhanced by combining it with other therapies?

The notion of combining brain stimulation with appropriate behavioral interventions is critical from both research and therapeutic perspectives. At the most superficial level, combined approaches can serve as useful proof of principle experiments to demonstrate that a behavioral effect can be achieved, hence increasing interest in therapeutic applications. However, combined approaches also have theoretical implications for mechanisms of recovery. Therapeutic behavioral interventions for cognitive, perceptual, and motor deficits employ tasks that engage the neural circuits that are involved in the relevant behaviors. As such, combining cortical stimulation with behavioral treatments provides a way to increase the functional resolution of electrical stimulation. For example, tDCS is a technique with limited spatial resolution that presumably changes the threshold for depolarization for large ensembles of neurons in a fairly nonspecific manner. However, behavioral training can provide the specific pattern of activity that targets the neuronal network of interest. The optimal timing between tDCS and activity-based therapy remains to be determined. Similar combined approaches with TMS are possible, although there is a theoretical possibility that in the absence of understanding exactly how TMS is focally modulating a given neural network, combined administration may decouple a behavior from its relevant neural substrate, thus paradoxically degrading performance. Also, applying TMS during another behavioral intervention can be logistically complicated. Consideration must be given to the choice of what stimulation and what activity-based intervention to combine. For example, discussants considered melodic intonation therapy, which putatively relies on right hemisphere mechanisms and activates BA 44 and 45, and contemplated whether the inhibitory rTMS to the right pars triangularis administered to patients with nonfluent aphasia would actually be detrimental if administered in conjunction with this behavioral intervention.

Should treatment studies with brain stimulation be tailored to the individual or the population?

Interindividual variability in neural architecture and response to stimulation presents challenges to therapeutic investigations. In meeting these challenges, individually focused studies and more uniform population studies both have clear advantages and drawbacks and meet different objectives. Studies that investigate improvement on an individual basis can address individual variability more readily, for example using different stimulation sites and different combinations of stimulation and behavioral therapy depending on subject performance. Dr. Naeser’s work with patients with nonfluent aphasia illustrates the challenges of dealing with interindividual variability and the advantage of a more individualized approach. This investigation employs an initial phase of exploratory TMS, in which stimulation of numerous candidate sites reveals a region that is most responsive to stimulation for the purposes of performing naming tasks. This is the site that is targeted in the treatment phase of the investigation. This site differs in location from individual to individual and is difficult to predict on the basis of fMRI. While such “multiple n-of-1” studies are useful for hypothesis generation, it difficult to make clear generalizable inferences about underlying neural mechanisms due to the inability to control for confounding variables. One approach to addressing this problem may be to design an intervention that helps the most people on average rather than pursuing individualized treatment. To that end, improved models of current distribution may eventually be useful for fine-tuning hypotheses regarding optimal sites and stimulation parameters for intervention. Ultimately, the pros and cons of these 2 approaches will depend on the magnitude of individual differences in network architecture and behavioral strategy.

What is the time course of changes associated with the stimulation?

One intriguing element of the results presented by Dr. Naeser on patients with nonfluent aphasia receiving TMS was that these patients appeared to experience more improvement months after receiving TMS than immediately after undergoing stimulation. Speculation as to why this is the case relates to differing models of the effects of cortical stimulation, as discussed above. For example, TMS may result in a suppression of deleterious interhemispheric connections that allows existing language networks of the left hemisphere to operate more efficiently. In that context, improvements in function over time may represent the retraining of an existing but now improved network related to naming tasks. At least one alternative is that TMS disrupts exiting networks in a manner that forces a shift in cognitive strategy, in which case improvement over time may represents the effect of rehearsal of the new cognitive strategy for task performance.

Conclusions

In summary, it remains clear that much needs to be learned about the mechanisms underlying the effects of electrical stimulation. At the same time, the practical successes in rehabilitation using brain stimulation are promising and worth pursuing. A combination of modeling and empirical data from healthy controls and patients can enrich understanding of how stimulation works. While different research programs pursue varied theoretical and therapeutic objectives, there was consensus among discussants that investigators should both optimize their study designs to address their individual questions and also integrate ideas more cooperatively to explore overarching theories of neural architecture, plasticity, and the therapeutic effects of brain stimulation.