Session IV Discussion

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This session and its subsequent discussion focused on issues in treatment study design for rehabilitation studies. Topics addressed included: treatment theories and how to turn them into rehabilitative treatments; treatment theory and electrical stimulation techniques; and issues related to study treatment design and how to optimize designs. Three main topics emerged during the discussion: 1) Infrastructure and funding issues; 2) Research coordination; and 3) Specific issues related to electrical stimulation techniques and/or rehabilitation within specific domains.

Treatment Theories

Treatment theory specifies the proposed mechanism of action by which a treatment alters its proximal treatment target. The development of rehabilitation treatments can be thought of as similar to the phases in pharmaceutical development but with rehabilitation specific modifications. The phases progress from basic science issues, early translation, single site studies and designs, to multicenter, very formal designs. The initial phase, **Phase I**, is developed to determine safety of the drug (or in this case electrical stimulation device), doses (parameters of the device to be used in exploratory research or interventional treatment research) and scheduling of treatment/intervention. **Phase II** helps to establish efficacy, often in a small, single center, laboratory setting. It may involve testing smaller populations, patient groups or subgroups within a larger population. A rehabilitative model may include establishing a treatment protocol that is repeatable and generalizable, and should identify and develop outcome measures that capture both change (the proximal results of treatment) and impact (on broader realms of function). **Phase III**, establishes and tests the effectiveness in a larger, multicenter setting. Although the subject pool and research sites are likely to be larger and more heterogeneous, inclusion criteria and quality control are typically still very rigorous, so many would not yet view Phase III as addressing real world "effectiveness." **Phase IV**, involves surveillance of actual use and benefit of the drug or device. In a rehabilitative model, it becomes important to investigate 'reality constraints' and determine the feasibility, effectiveness and cost/benefit of the treatment in a 'real-world' healthcare system. Additionally, it becomes important to follow the impact of a rehabilitative treatment outside the laboratory setting.

Treatment Theory and Electrical Stimulation Techniques

Treatment theory for electrical stimulation techniques is not yet fully articulated. Do these techniques have uniform mechanisms of action across different neural networks or are there network-specific factors to incorporate into theory? To what degree to stimulation techniques directly enhance or dampen the operation of specific neural networks, and to what degree to they simply prepare a more optimal "substrate" for experience-based learning? Do the effects of electrical stimulation vary according to the underlying stage of neural recovery after injury? All of these issues will help shape the treatment theories that direct future research, and, depending on the answers to these theoretical claims, treatment studies would be designed very differently.

Treatment Theories and Issues of Study Design

Treatment theories may be useful in addressing the following issues: subject selection, outcome measures, optimization of an experimental design and other more general study design issues. Subject selection issues that often need to be established and appropriately addressed include, who is likely to show functional benefit, how to address co-existing impairments or other disrupted functions in patient populations, what stage of recovery to enroll participants (acute versus chronic), and what population and/or subgroups to include. Treatment theories may help frame the inclusion criteria of participants. Should only those with 'pure' impairments participate?

Other questions that arose regarding study design include whether or not parallel groups or crossover designs should be utlilized and the impact the choice of study design makes on establishing the appropriate population to examine. Are parallel groups or full crossover designs feasible for a specific population? Should there be an exploratory or preliminary phase to show evidence of treatment impact without an untreated control group? When does a control group become necessary in the establishment of a treatment effect?

Issues regarding outcome measures can also be addressed within a treatment theory. These may include establishing which outcome measurement tools should be used to establish treatment effects or capture change and impact within a study population, whether a multiple baseline design in a long-term treatment study may be necessary. It may be useful when selecting what outcome measures may be appropriate for determining generalization of a treatment effect, when and whether generalization occurs outside of a laboratory setting. Selection of an appropriate outcome measure is important to establish the permanent effect of the intervention. This may include determining when that measurement should occur, whether immediately after treatment or months or years post-recovery. Other issues regarding outcome measures include whether or not the measure is appropriate to test repeatability. Is the measurement capturing only a physiological effect (evidence of the proposed mechanism), or is it a good measure of the actual treatment effect? Is it a good choice to show clinical meaning or ecological validity? When choosing an outcome measure it may also be important to consider which covariates should be accounted for and measured.

Discussion

The discussion surrounded study design and additional issues that may need to be confronted within particular domains and with the use of electrical stimulation techniques (TMS and tDCS).

The first main topic was infrastructure and funding. The need for multicenter sites versus local sites was discussed extensively. Single site studies may be useful for establishing proof of principle, but multicenter sites will likely ultimately be required to address different factors that may be of interest but too large in scope for a single site. However, such large-scale studies require significant funding either from industry or government, e.g., NIH. It was noted that NIH funding is particularly difficult in the “middle stages” of research – that is between proof of principle and an ambitious and formal multicenter RCT, when the focus is on refining the treatment protocol, identifying the types of patients most appropriate for treatment, etc. – since these are viewed as less “innovative” but absolutely crucial stages.

Additional issues regarding infrastructure might include whether or not to engage clinical sites into research or stick to research environments for treatments. Differences between the two may require differing treatment parameters (shorter sessions and fewer visits) and adjustments in the approach or choosing a different approach that may be easier and safer to apply in a clinical setting.

The second topic was research coordination. There was a suggestion and discussion of creating a large database (within a certain topic or domain) for data sharing, but particularly to encourage patient sharing and research collaboration as well. Such a database and potential collaboration is particularly beneficial for pilot, exploratory studies. Drawbacks of multicenter database research include feasibility issues such as IRB approvals, coordination issues, travel and transportation issues for subject populations, and data sharing and confidentiality issues. In addition, it was noted there might be difficulty creating a universally accessible database. However, there was general encouragement for such a database, particularly for instances of rare diseases with small population samples. One current example of the difficulties with multicenter research was the difficulty of coordination of a multicenter traumatic brain injury research across funding agencies where differences in study samples and measures used are obstacles to comparative research. Cross-agency discussions of common research data elements are currently actively underway.

Safety in electrical stimulation studies was discussed, but it applies to behavioral treatments as well. It was agreed that drug studies, studies utilizing devices, and behavioral treatment studies may have vastly different safety issues, and really have the need for completely different designs due to differing safety issues. One model does not fit all.

Timeframe and dosing schedule of the treatment, as well as outcome testing schedules must be considered and established. Should the study be exploratory and examine immediate effects or is the domain ready for longer-term clinical impact studies?
Confounding variables must be controlled as well as possible. Modeling of variables in natural history research may be a useful first step, and studying the natural rate of recovery, for instance in stroke patients, may be necessary to examine impact and aid intervention of any treatment including electrical stimulation.

Subject homogeneity/heterogeneity was discussed, with varying opinions on whether a heterogeneous population offers an advantage. Such a sample allows the investigator to examine differing responses to treatment and to

generalize to a broader population. However, small studies that examine well-defined sub-populations may be important to select patients who are ‘responders’ to confirm the effect of treatment. This could then lead to larger studies to get a more powerful effect or larger studies which can then help establish a contrasting effect. It may be necessary to find the optimal treatment protocol first, before moving on to larger-scale trials. The issues of how to deal with multiple medications arose in discussion, since these may represent a confounding influence and little is known about how certain medications affect physiological treatments and their efficacy.

Subject heterogeneity may obscure varying treatment effects in group studies. For example, the general finding in electrical stimulation studies of motor recovery of a 10-20% improvement in motor function may not apply to the entire population. Some individuals may have a 40-50% effect, whereas others may have little (or a negative?) effect. It isn’t clear whether the variation in effect is bimodal, related to other variables, or “random”.