

TITLE: Efficacy of Web-Based Social-Cognitive Interventions in Right Hemisphere Stroke and Frontotemporal Dementia

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JHM IRB - eForm A – Protocol

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1. Abstract

- a. Provide no more than a one page research abstract briefly stating the problem, the research hypothesis, and the importance of the research.

We have been studying the neural and behavioral correlates of language and other cognitive functions longitudinally in patients with stroke from the acute stage to approximately one year after stroke. fMRI and MRI scans in conjunction with behavioral data have allowed us to gain insight on some of the neural dynamics of recovery and factors that may impact or predict that recovery. We have identified important deficits in social cognitive function in individuals with right hemisphere stroke, including impaired recognition of emotion from tone of voice and facial recognition, and loss of empathy. We have identified very similar impairments in individuals with frontotemporal dementia. While we are currently testing transcranial direct-current stimulation with language therapy as a method for treating language deficits in patients with left hemisphere stroke, we have not previously attempted to treat social cognitive deficits following right hemisphere stroke and frontotemporal dementia (FTD). We now aim to use an web-based social-cognitive training program developed by Posit Science Inc. to treat empathic deficits in patients whose social-emotional functioning has been affected by stroke.

The proposed study utilizes the PI's experience in speech-language pathology and cognitive neuropsychology, clinical training in neurology, and expertise in dementia to test the effectiveness of web-based social-cognitive training organizations in FTD and right hemisphere stroke. The investigation will focus on characterizing each individual patient's deficits and determining whether cognitive training improves their performance on social-cognitive tasks. The training follows a drill-and-practice bottom-up model that uses principles of neuroplasticity to build and strengthen empathic skills such as prosody identification and facial expression recognition. The design is a cross-over trial, with randomized order of conditions; each participant will serve as their own control. Every participant will engage in both a social-cognitive training condition and a non-specific control training condition in a random order. They will be assessed at baseline, after completing one condition, and after completing the second condition. We hope to identify specific social cognition domains that are influenced by treatment and to characterize what types of patients (e.g. based on lesion location or severity of disease progression) who can benefit from these exercises.

The importance of the results is to provide a potentially effective and low cost treatment for social-emotional impairments in patients with FTD and stroke. Currently there are almost no interventions available for these symptoms in these populations, and if this treatment proves to be effective, it could have major clinical implications for the prognosis and functional outcome

of patients with stroke or FTD. The scientific impact of these results could provide greater understanding of the brain's ability to reorganize and repair damaged empathic networks in the context of training. This mode of training has not been attempted in FTD previously and previous studies of training platforms have primarily focused on language or non-social deficits in stroke. This study will be one of the first in this domain and will elucidate the nature and malleability of the social-emotional impairments in stroke and FTD.

2. Objectives (include all primary and secondary objectives)

1. Test the hypothesis that patients with right hemisphere stroke and frontotemporal dementia (FTD) show more improvement on untrained tests of social cognition after web-based social-cognitive training exercises (Posit Science Inc.) than after non-specific cognitive training.
2. Evaluate patients with FTD and stroke in multiple domains of social cognition (such as emotional contagion, affective perspective-taking, and affective prosody identification) as well as mood, attention, and working memory, before and after intervention to identify which functions improve after training.
3. Assess the feasibility and acceptability of web-based interventions in patients with stroke or FTD through examination of usage data and patient feedback.
4. Determine the effects of location of lesion or focal atrophy on improvements in social-cognitive training exercises with intervention.

3. Background (briefly describe pre-clinical and clinical data, current experience with procedures, drug or device, and any other relevant information to justify the research)

Problem: Both patients with stroke or FTD can experience impairments in social-emotional functioning. While the profile of deficits may differ in these two illnesses, there are convergent issues in empathic abilities especially in right hemisphere stroke and behavioral variant FTD. Deficits or deterioration in empathy can impact patients' interpersonal relationships and adversely impact patients' quality of life. However, there are currently very few treatments that specifically target these issues, and many of them are limited in their scope and effectiveness. Recently, web-based training interventions have shown efficacy in treating functional impairments in stroke and social deficits in other disorders such as schizophrenia. It is crucial to test whether this cost-effective and mobile intervention can be effectively utilized to treat social-emotional deficits in patients with stroke or FTD.

4. Study Procedures

- a. Study design, including the sequence and timing of study procedures (distinguish research procedures from those that are part of routine care).

Based on medical chart review, all patients will first be screened for eligibility. Patients will only be enrolled in the study if they meet both inclusion and exclusion criteria. The study will be explained to the patient and informed consent will be obtained before they undergo baseline social and cognitive assessments and receive a laptop to begin either a social-cognitive or control training condition (randomly determined by selecting one of 30 sealed envelopes). Following the completion of the 20-30 hours of training over the course of 4 weeks, the patient will be assessed with the same measurements again. The patient will then complete the second training condition (20-30 hours over 4 weeks) that they were not randomly assigned to initially. The patient will then receive a final assessment, return the laptop, and receive compensation for the study.

Each of the three assessments will include the following tests: 1) Star Cancellation test, an assessment of spatial attention (Friedman, 1992); 2) Interpersonal Reactivity Index (IRI), a subjective evaluation of 4 components of empathy, rated by the caregiver (Davis, 1983); 3) Reading the Mind in the Eyes Test (RMET), an objective evaluation of empathy (Baron-Cohen

et al., 2001); 4) Social Cognitive Tasks from the University of Pennsylvania Computerized Neurocognitive Battery (Penn CNB), a measure of affect perception and facial memory (Gur et al., 2010); 5) Prosody Battery, a well-validated test of expression and production of prosody (Ross and Monnot, 2008; Ross et al., 1997); 6) Forward and Backward Digit Span, a brief assessment of attention and working memory; 7) Faux Pas Test, a test of social awareness (Gregory et al., 2002); and 8) the Patient Health Questionnaire-9, a well-validated screening tool for depression (Kroenke et al., 2001). The IRI must be completed by a caregiver or spouse.

- b. Study duration and number of study visits required of research participants.

The study duration is around 8 weeks for each participant and will require 3 total participant visits for the baseline, 1st post-treatment (1st condition), and 2nd post-treatment (2nd condition) assessments. If there are technical issues with the laptop or online portal, assistance will be provided remotely if possible.

- c. Blinding, including justification for blinding or not blinding the trial, if applicable.

Double-blinding is not possible in this study due to the large difference in the training content between the two training conditions.

- d. Justification of why participants will not receive routine care or will have current therapy stopped.

Participants will receive their routine care, medications, or therapies while enrolling in this study. Cognitive rehabilitation for chronic right hemisphere stroke and behavioral variant FTD is very rare, so we anticipate most patients will be receiving no specific therapy for the deficits being targeted.

- e. Justification for inclusion of a placebo or non-treatment group.

There is no placebo or non-treatment group in this study. There is a control condition (non-specific cognitive exercises) that we expect may improve general attention, but we do not expect such training to affect social cognition.

- f. Definition of treatment failure or participant removal criteria.

N/A.

- g. Description of what happens to participants receiving therapy when study ends or if a participant's participation in the study ends prematurely.

Participating in this current study is independent of their routine medical care. Therefore, if they prematurely end participation in the study or complete the study, patients will still continue their standard care.

5. Inclusion/Exclusion Criteria

Inclusion criteria:

1. Clinical diagnosis of right hemispheric stroke or behavioral variant frontotemporal dementia.
2. Able to give informed consent.
3. Premorbid proficiency in English (by self-report).
4. Age 18 or older.
5. Score of 21 or higher on the mini-mental state examination.

Exclusion criteria:

1. Prior history of neurological disease affecting the brain other than stroke or frontotemporal dementia (e.g., brain tumor, multiple sclerosis, traumatic brain injury)
2. Known uncorrected hearing loss
3. Known uncorrected vision loss
4. Prior history of severe psychiatric illness, developmental disorders, or mental retardation (e.g., schizophrenia, autism spectrum disorders).
5. Score of 20 or lower on the mini-mental state examination.

6. Drugs/ Substances/ Devices

- a. The rationale for choosing the drug and dose or for choosing the device to be used. N/A, no drugs to be used.
- b. Justification and safety information if FDA approved drugs will be administered for non-FDA approved indications or if doses or routes of administration or participant populations are changed. N/A
- c. Justification and safety information if non-FDA approved drugs without an IND will be administered. N/A

7. Study Statistics

- a. Primary outcome variable.
Change in performance from baseline to 1st post treatment on Penn CNB tasks (Total) vs. 1st post-treatment (new baseline) to 2nd post-treatment on Penn CNB tasks (total).
- b. Secondary outcome variables.
Changes in total and subtest scores on IRI, Prosody Battery, RMET, Faux Pas Test, and star cancellation.
- c. Statistical plan including sample size justification and interim data analysis.

We will compare the change in means of outcome measures after social cognition treatment vs. control treatment. The primary outcome variable will be change in performance on the Penn CNB tasks after the end of each treatment. The null hypothesis is $H_0: \mu_1 = \mu_2$, where μ_1 is the mean change in performance on the Penn CNB tasks between pre-treatment and post-treatment with social cognition treatment and μ_2 is the mean performance on the Penn CNB tasks between pre-treatment and post-treatment with control treatment.

Analyses. In a cross-over trial, it is essential to evaluate the effect of condition versus the effect of sequence of the treatment, and to evaluate for carry-over from one treatment to the next. Based on our clinical experience we expect little change in the Penn CNB with the control (non-specific cognitive exercises) in chronic right hemisphere stroke (as we see decline rather than recovery in chronic stroke in these functions), and little change or decline in patients with behavioral variant FTD. But we will evaluate the effect of condition versus sequence independently. The primary analyses will evaluate the change in performance on Penn CNB as the dependent variable, $Y_{ij} = \mu + S_i + \mu_{(j)} + C_{(j)} + e_{ij}$ where i represents a subjects, j represents the sequence (1 or 2). The Y_{ij} is the change in the evaluations. The S_{ik} represents the random effect of the subjects. The $\mu_{(j)}$ represents the means of the two treatments (social cognition or control). The $C_{(j)}$ represents the carryover effects. The test for the treatment effect can be obtained from this model. Firstly, the effect of carryover effects will be tested at $p < 0.1$. If this is significant, then only the first sequence data will be analyzed as this sequence is free of carryover effects. A similar analysis will be done for the change in accuracy of secondary outcome variables.

Power. We expect to enroll up to 50 patients in the study, and expect 20-30 participants will complete the study. Because of the social cognitive deficits in these patients (accompanied by relatively low insight and motivation), there is likely to be high attrition. If the sample size in each treatment group is 13, (a total sample size of 26) a crossover design will have 86% power to detect a difference in means of 6 (the difference between treatment mean change in accuracy, m_1 , of 10 and a control mean change in accuracy, m_2 , of 4) using a two group t -test with a two-sided alpha of 0.05.

- d. Early stopping rules.
Patients will be allowed to stop at any time, but they will not receive compensation if they fail to complete all criteria for compensation. Their data will only be used for Aim 1 if they complete the entire study. We may be able to use data from participants who complete the social-cognition treatment condition only for Aims 2 and 3.

8. Risks

- a. Medical risks, listing all procedures, their major and minor risks and expected frequency. There are no known risks associated with the training software, use of a laptop computer, or the assessments used in this study. Participants could become bored, anxious, or embarrassed during assessment of cognitive function.
- b. Steps taken to minimize the risks.
The participant will be able to stop participation at any time if they experience any issues with the use of the training software or assessments of social abilities.
- c. Plan for reporting unanticipated problems or study deviations. The PI will report unanticipated problems or study deviations to the IRB immediately.
- d. Legal risks such as the risks that would be associated with breach of confidentiality.
Results of cognitive training and assessment measures will be kept strictly confidential and only the investigators participating in this study will have access to these records. If the patient wishes to know the results, or wishes to have them sent to one or more care providers, the results will be made available. If we identify any problems in thinking skills, the patient will be given the option of referral to rehabilitation specialists after the treatment study. If we identify depression (a score of 10 on the PHQ-9 or a score >0 on item 9, regarding suicidal thoughts, we will refer the patient for evaluation and treatment of depression if they are not already receiving treatment for depression. There is a small risk of breach of confidentiality, resulting in information about cognitive deficits or diagnosis being disclosed to individuals who are not care providers. There are no known legal risks, although such a breach in confidentiality might affect the person's employment. The only people who will know the patients are in a research study and will see the information about patients are members of the research team. Patients will be assigned codes for data collection and analysis. Data will be kept in locked file cabinets or secure computers that are password protected. When the study is over and the results are public, no information linked to the patient will be included. We will not collect sensitive information.
- e. Financial risks to the participants.
All costs of study procedure and training modules will be provided to the patient for free at no cost to the patient or his/her insurance company.

9. Benefits

- a. Description of the probable benefits for the participant and for society.
- b. Individual participant. The study might improve a participant's cognitive and social-emotional functioning if the training is effective. The participant will also receive a small financial compensation if they complete the study (see below).
- c. Society. The results of this work may provide a novel treatment option in right hemisphere stroke and behavioral variant frontotemporal dementia and allow for future development of further interventions that target social-emotional deficits in right hemisphere stroke and behavioral variant frontotemporal dementia. Identifying a cost-effective treatment intervention will also contribute to the overall care of stroke patients.

10. Payment and Remuneration

- a. Detail compensation for participants including possible total compensation, proposed bonus, and any proposed reductions or penalties for not completing the protocol.

If the patient satisfactorily completes the following requirements, he or she will receive \$100 total. First, the patient must complete both training modules and all three assessment sessions. Second, this compensation is contingent on the return of the laptop to the lab in working condition without severe damage. If the patient does not return the laptop in reasonable working condition, the patient will not receive compensation for participation in the study.

If the patient completes both training modules within 9 weeks, they will receive a \$25 bonus following their final assessment and return of the laptop.

11. Costs

- a. Detail costs of study procedure(s) or drug (s) or substance(s) to participants and identify who will pay for them.

Each laptop will cost between \$250 to \$300, and each participant's compensation will be between \$100.00 to \$125.00, which will all be paid for by Charlten Long's Woodrow Wilson Research Fellowship fund. There will be no cost to the patient or to the patient's insurance.

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