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Circuitry Assessment and Reinforcement Training Effects on Recovery

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JHM IRB - eForm A – Protocol

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1. Abstract

Stroke is the most common cause of disability in adults. It commonly results in communication deficits. Left hemisphere stroke causes aphasia, impairment in receptive and/or expressive language. Right hemisphere stroke also causes communication problems, with tangential and digressive speech that often fails to communicate important information.

Primary Progressive Aphasia (PPA) is a debilitating clinical syndrome in which a patient experiences a progressive loss of language skills. At present, there are currently no treatment options for reversal of this disease. PPA patients can be classified into three main variants: semantic PPA (svPPA), nonfluent/agrammatic PPA (nfvPPA), and logopenic PPA (lvPPA). All PPA patients demonstrate deficits in naming skills. There are specific patterns of speech-language deficits within each variant. Treatments that slow the progression of language decline are needed to improve the quality of life and improve functional skill level for those with PPA.

Studies have shown behavioral speech therapy to improve communication skills in those with PPA and post-stroke aphasia. However, many hours of therapy are needed to have an effect. Recently, investigators have sought ways to augment language therapy.

Electroencephalography (EEG) measures the rhythmic synchronous electrical activity in the brain. New advances in technology now allow advanced statistical analyses of live EEG recording, a through a technique entitled Quantitative EEG (qEEG). QEEG brain mapping assessment compares the brainwave activity of a patient with that of a normative database. Using this, clinicians can identify neural electrical activity that is significantly different from that of the patient's same-age peer group. From this, a training protocol can be created to reinforce electrical activity patterns that reach target thresholds using visual or auditory feedback to convey when the thresholds are met that approximate that of their healthy peer group.

Neurofeedback, a form of biofeedback, provides a visual and/or audio representation of an individual's neural electrical activity from live EEG recording. Using operant conditioning

principles, individuals are trained to increase or reduce patterns of brainwave activity to modify behavior and performance (Collura, 2014). Although neurofeedback has not yet been investigated as a treatment for aphasia or other communication deficits due to stroke or neurodegenerative disease, it may be effective. Previous studies have observed improvement in cognitive and behavioral measures in those with conditions such as Attention Deficit Disorder and Attention Deficit Hyperactivity Disorder (Fuchs, Birbaumer, Lutzenberger, Gruzelier, & Kaiser, 2003). Furthermore, it has been associated with reduced anxiety (Nan, et al. 2019; Wang et al., 2019; Banerjee & Argáez, 2017) and sleep disruption (Hetkamp et al., 2019), which both exacerbate language and communication impairments. Research is needed to determine if neurofeedback may be an effective treatment for language disorders such as PPA and post-stroke communication disorders.

It is possible that EEG neurofeedback, which focuses on improving abnormal brainwave patterns, could provide certain therapeutic benefits to individuals with PPA or post-stroke aphasia, either by directly affecting neural networks that underlie language, or more generally by reducing anxiety and inattention through behavioral conditioning. Reduction of anxiety in neurological diseases can be beneficial not only for functional performance but also sleep duration and quality. We will couple EEG neurofeedback with Verb Network Strengthening (VNeST), a behavioral speech therapy program targeting verb naming skills, to examine if EEG neurofeedback can enhance gains made in traditional behavioral speech-language therapy, which is the current gold standard of care for aphasia treatment.

We hypothesize that EEG neurofeedback training will be more beneficial than sham training for improvement of communication, anxiety, and sleep quality. The primary aims of this proposed study are to (1) determine if EEG neurofeedback training coupled with behavioral speech-language therapy results in significantly greater communication skills, compared to sham EEG feedback training coupled with behavioral speech-language therapy in participants with PPA and post-stroke aphasia, and (2) determine if EEG neurofeedback training results in significantly reduced anxiety, better sleep quality and reduced use of sleep aids, compared to sham EEG feedback training in participants with PPA and post-stroke aphasia. This study also aims to investigate characteristics of participants most responsive to neurofeedback training and to examine whether or not neurofeedback improves functional connectivity in language and attention networks in patients with PPA and post-stroke aphasia.

2. **Objectives** (include all primary and secondary objectives)

Primary Objective:
The primary objective of this study is to determine whether 4-channel EEG neurofeedback training can augment traditional speech-language therapy and improve language and cognitive outcomes in individuals with PPA and post-stroke aphasia. A double-blind, sham controlled, within-subject crossover design with randomized order of treatment will be used, to allow each participant to serve as his or her own control. Participants will be randomly assigned to receive

either an active EEG neurofeedback intervention period first followed by a sham intervention period, or a sham intervention period first followed by an active EEG neurofeedback intervention period. Participants will receive 15 training sessions within the active EEG neurofeedback intervention period and 15 sessions within the sham intervention period. Each participant will receive 2-5 sessions per week depending on their preference and availability. All participants will receive traditional behavioral speech-language therapy while simultaneously undergoing active or sham neurofeedback. Speech-language therapy will be performed within the same session as the active/sham neurofeedback training. The EEG neurofeedback and sham intervention periods will be separated by a 1 week "wash out period". Communication will be evaluated before therapy and again in the week immediately following therapy, for each intervention period.

To evaluate the effects of EEG neurofeedback on communication skills in participants with post-stroke aphasia and PPA, we will carry out a randomized double-blind, sham controlled, within-subject crossover trial design. The Object Action Naming Battery (OANB) (Druks, 2000) will be used to evaluate communication skills by testing participants at baseline and in the week immediately following treatment. The primary outcome variable will be the change in number of Content Units (CU) in picture description, because this measure is a sensitive measure of communication impairment in both left and right hemisphere stroke (Agis et al., 2016) and PPA (Berube & Hillis, 2019). Secondary outcome variables will be change in accuracy of naming on the OANB, change in number of words produced on the Controlled Oral Word Association test (COWA, a measure of attention, executive function, and word-retrieval), change in quality of sleep measured with The Pittsburgh Sleep Quality Index (PSQI), change in anxiety measured with State Trait Anxiety Inventory, and change in frequency of use of sleep medications.

Hypothesis 1A. Participants will show greater improvement in correct CU in picture description from baseline to 1-week post treatment, during the EEG neurofeedback condition than during the sham condition.
Hypothesis 1B. Participants will show greater improvement in accuracy of naming on the OANB from baseline to 1-week post treatment, during the EEG neurofeedback condition than during the sham condition.
Hypothesis 1C. Participants will show greater improvement in number of words produced on the COWA from baseline to 1-week post treatment, during the EEG neurofeedback condition than during the sham condition.
Hypothesis 1D. Participants will show greater improvement in sleep quality measured with the PSQI from baseline to 1-week post treatment, during the EEG neurofeedback condition than during the sham condition.
Hypothesis 1E. Participants will show greater improvement in state anxiety (S-anxiety on the State Trait Anxiety Inventory; STAI) from baseline to 1-week post treatment, during the EEG neurofeedback condition than during the sham condition.

Hypothesis 1F. Participants will show greater reduction in the frequency of use in medications used to improve sleep from baseline to 1-week post treatment, during the EEG neurofeedback condition than during the sham condition.

Secondary Objective: The secondary objective of this study is to examine which patient characteristics (stroke hemisphere, PPA variant, baseline severity of communication/sleep deficits or anxiety, baseline QEEG deficiencies) predict the best response to treatment. This will help improve the selection of specific treatments for individual patients in the future. This is an exploratory Aim, as we do not have any preliminary data or literature on which to base hypotheses about the characteristics that will predict change in the primary outcome measure. However, the literature does indicate that neurofeedback can reduce anxiety in stroke patients (Nan, et al. 2019), in people with major depression (Wang et al., 2019), and in people with post-traumatic stress disorder or generalized anxiety disorder (Banerjee & Argáez C, 2019). There is also preliminary evidence that neurofeedback may improve sleep in cancer patients (Hetkamp et al., 2019). Reduction of anxiety with or without improved sleep may be one mechanism of the potential effect of neurofeedback on communication.

Hypothesis 2A: We will be able to identify baseline characteristics (demographics and baseline severity measures, as well as QEEG abnormalities) that influence change in the primary outcome measure (change in CU in picture description from baseline to 1-week post-treatment.

Hypothesis 2B. We will be able to identify changes in secondary outcome measures and changes in qEEG that correlate with the primary outcome measure (change in CU from baseline to post-treatment). These results will allow us to identify variables to explore as interaction variables.

Tertiary Objective: To determine if EEG neurofeedback training is associated with improved physiological measures of neural connectivity via qEEG assessment and fNIRS. This Aim is also exploratory, as we do not have any preliminary data on which to base hypotheses about the effects of EEG neurofeedback on physiological measures of neural connectivity.

Hypothesis 3A: Greater improvement in qEEG normalization (e.g. alpha enhancement) will be observed in the EEG neurofeedback training condition compared to sham training condition.

Hypothesis 3B. Greater connectivity within the attentional network and the language network (and right hemisphere homologues) will be observed in the EEG neurofeedback training condition compared to sham training condition.

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)

There is a need for improved behavioral interventions and objective instrumentation for behavioral syndromes following stroke and in neurodegenerative disease. Sophisticated techniques are needed to provide specific reinforcement to capitalize on principles of neuroplasticity and brain rehabilitation. Z-score neurofeedback training could fill this gap. Neurofeedback training allows conditioning and change to occur on a behavioral level. It is hypothesized that these behavioral changes may correlate with physiological changes that can be identified on qEEG recording and fNIRS.

Limited rigorous research has been done in neural biofeedback, largely in the format of fMRI biofeedback. However, fMRI is often not feasible or able to be generated at a large scale for eventual clinical application due to technical involvement and expense. EEG biofeedback is a non-invasive, significantly more cost-effective modality. If effective in treating behavioral disorders, EEG neurofeedback could be a viable modality for the treatment of these conditions on a broader scale.

It is known that rhythmic synchronous neural activity gives rise to brain oscillations at different frequencies which can be measured by live EEG recording. EEG has been a useful research tool leading to a variety of seminal discoveries in cognitive psychology (Luck, 2014). It is known that the brain produces rhythms that are highly correlated with cognitive activity. However, the underlying mechanisms and the specificity of the rhythm to the activities are still not understood (Cannon et al., 2014). Cannon and colleagues argue that behavioral function reflects the physiological processes underlying multiple mechanisms that generate brain rhythms facilitate and gate the flow of signals within and among brain regions. Temporal and spatial disruptions of neural circuits due to the underlying neural pathologies likely contribute to the behavioral and physiological deficits seen in individuals with PPA and post-stroke aphasia (Cannon et al., 2014).

Recently, Tsai and colleagues (2019) reported that cognitive impairments that occur in neurodegeneration may arise from an accumulation of altered cellular processes that lead to disruptions in neural circuits and network connectivity. The researchers conducted work in mice manipulating the activity of specific neural populations and circuits to investigate the intersection of pathology, network activity and behavior. In their mouse model, increasing gamma frequency in the brain resulted in a significant reduction in amyloid and phospho-tau levels in Alzheimer's disease and neurodegeneration mouse models possibly due to activation and recruitment of microglia in Alzheimer's disease to reduce the production and enhance clearance of amyloid (Iaccarino et al., 2016). The enhancement of gamma frequency also resulted in improved cognitive performance in multiple mouse models in their studies (Martorell et al., 2019).

In the past few decades, analysis of EEG recording has become more sophisticated, with the discovery of "source analysis." EEG signals can instantaneously perceive electrical current variations in the brain. Real-time EEG applications such as neurofeedback and brain-computer interfaces that capitalize on the high-temporal resolution of EEG have become an area of interest for potential clinical applications. The most direct method for using qEEG information to guide

neurofeedback training utilizes training protocols based on z-score deviation for a specific feature. This is called live z-score training (Johnstone & Lunt, 2011).

This study aims to investigate what behavioral and physiological changes can occur in individuals with communication impairments when we reinforce healthier circuitry by reinforcing improved synchronous firing patterns (e.g. enhanced alpha) through EEG biofeedback. There is accumulating literature suggesting that there is value in using EEG information for guiding clinical intervention with medication and neurofeedback (Johnstone & Lunt, 2011).

Since neurofeedback is a learning technique, it has potential for intrinsically lasting effects. Collura (2014) proposed that these "brain exercises" have potential to implement changes that produce the desired feedback and increase self-regulation. Collura hypothesized possible mechanisms of EEG neurofeedback training to include changes in cortical excitability, generation and uptake of neurotransmitters, and cortical and subcortical connectivity. Trainees may benefit from physiological and behavioral changes. Physiological changes may be validated by repeated qEEG assessment, and behavioral changes can be measured through neuropsychological testing.

Since behavioral training is based on principles of neuroplasticity, operant conditioning, and learning principles, it is possible that this type of network-level skill learning could increase recruitment of novel pathways in PPA and in stroke recovery and strengthen current neural network pathways. This modality could also maximize brain regulation to support efficient brain activity for creation of novel pathways during neurorehabilitation. Results of this study could inform future work in behavioral interventions in neurorehabilitation.

It is commonly believed that aphasia recovery involves major reorganization of structure/function relationships, including shifts of language to the right hemisphere following left hemispheric stroke. Changes over time in the intrinsic connectivity networks in the brain, studied with resting state ("task free") fMRI and fNIRS are likely to reveal additional insights regarding aphasia and cognitive recovery. Whether or not normalizing brainwave patterns via EEG neurofeedback training supports and/or enhances increased functional connectivity in the brain is currently not known. To investigate the effects of more normalized brainwave patterns on functional connectivity, we will also collect task-based and task-free ("resting") functional Near-Infrared Spectroscropy (fNIRS) data at the baseline, 1-week post-treatment, and 5-week post-treatment follow-up assessment time points. The fNIRS protocol is expected to take up to 60 minutes and will be completed in the same location in which we administer behavioral assessments. fNIRS is a safe, non-invasive, and flexible modality for brain imaging. It capitalizes on the fact that near-infrared light can propagate several centimeters through tissue because of low optical absorption by hemoglobin and water at specific wavelengths. During an fNIRS experiment, an array of light sources and detectors affixed to a cap is placed on the scalp, and the measures from these different channels allow the reconstruction of an image of the hemodynamic response. fNIRS has emerged as a complementary technology to other brain

imaging and monitoring modalities (e.g., EEG, fMRI). Previous research (Huppert et al., 2006; Strangman et al., 2002) in healthy populations has shown that the hemodynamic response captured in fNIRS is similar to that measured in fMRI. Unlike MR imaging, fNIRS has no contraindications (e.g., implanted ferrous material) and is portable. Similar to task-free fMRI, "resting" fNIRS will allow us to determine intrinsic functional connectivity between regions of the brain at each stage of the study. At each time point, patients will also participate in task-related fNIRS sequences during which they will be asked to perform tasks such as picture naming, sentence comprehension or prosody judgments. The fNIRS data will complement the fMRI sequences and will allow us to determine how changes in brain activity patterns are related to changes in speech-language and cognitive abilities.

Since EEG biofeedback targets the underlying brainwave patterns (e.g., quantity and amplitude of waves in various frequency bands) that ultimately affect and influence an individual's behavior, the resultant behavioral outcomes can vary greatly in response to this intervention. For instance, when targeting an increase of ideal brainwave patterns and a reduction of deviant patterns (e.g., reducing the amount of excess waves in a given frequency band), one could see improvements in a variety of neuropsychological domains such as attention (Egner & Gruzelier, 2004; Fuchs, Birbaumer, Lutzenberger, Gruzelier, & Kaiser, 2003; Yan et al., 2008), memory (Escolano, Aguilar, & Minguez, 2011; Klimesch, 1999), mood (Wang et al., 2019), language skills (Mroczkowska, Bialkowska, & Rakowska, 2014; Nan, Dias, & Rosa, 2019), and anxiety (Banerjee & Argáez, 2018; Moore, 2000). Also, since z-score neurofeedback training targets deviant brainwave activity across multiple frequency bands, behavioral outcomes can vary across individual participants depending on the brainwave patterns that the individual's brain adopts in response to the neurofeedback training. For instance, one individual may experience an increase in alpha wave presence, which is usually associated with a relaxed mental state and report a reduction in anxiety (Evans & Abarbanel, 1999). Whereas another individual may experience more normalization of beta-range brainwaves, which are associated with stronger focused attention (Marzbani, Marateb, & Mansourian, 2016). Since it is not the behavior that is directly targeted, but the underlying brainwave patterns, the resultant behavioral effects of this treatment can vary across individuals.

For this reason and because this intervention can impact general cognitive skills (not necessarily skills specific to speech and language functioning), we would like to add behavioral speech-language therapy to target language skills in a more direct way and examine if EEG biofeedback may augment speech-language therapy for individuals with post-stroke aphasia and Primary Progressive Aphasia (PPA) by improving neural connectivity through reinforcement of ideal brainwave patterns. We hypothesize that individuals who receive active EEG biofeedback in addition to behavioral (traditional) speech-language therapy will make greater gains in language outcomes when compared to individuals with receive sham EEG biofeedback training in addition to traditional speech-language therapy.

We will offer Verb Network Strengthening Treatment (VNeST) in conjunction with EEG biofeedback (i.e., neurofeedback) to test our hypothesis. VNeST has been shown to improve

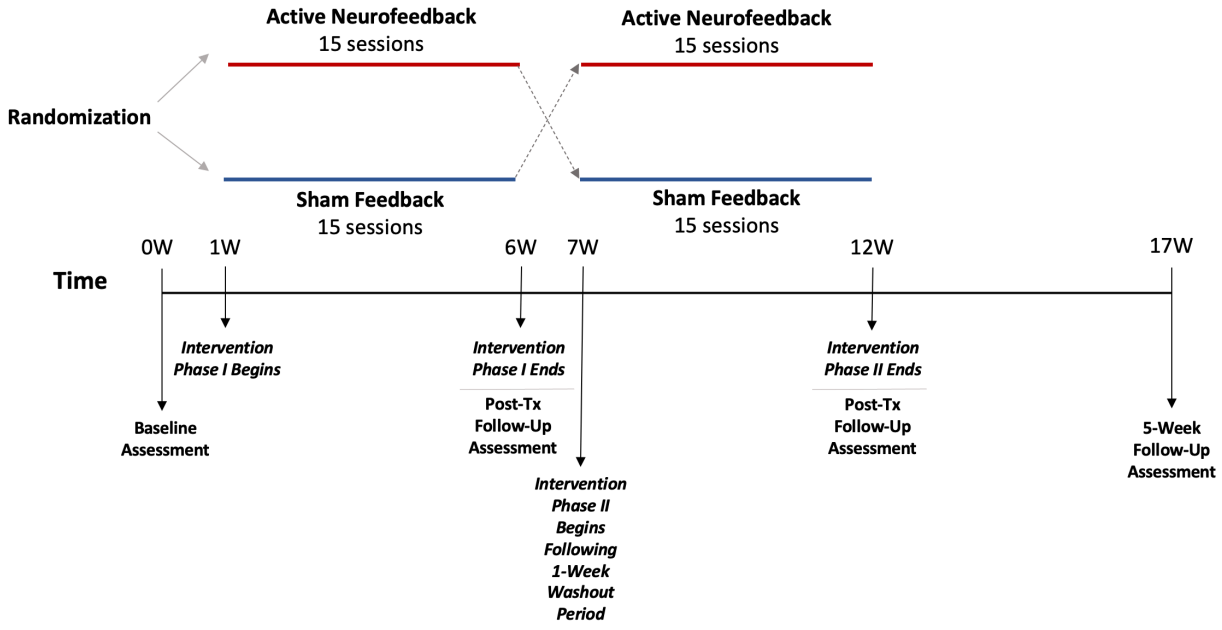
language skills, especially verb naming skills (Edmonds, 2016; Edmonds & Babb, 2011; Edmonds, Mammino, & Ojeda, 2014; Edmonds, Nadeau, & Kiran, 2009; Furnas & Edmonds, 2014). Since VNeST targets verb naming skills, we will also change our language assessment and primary outcome measure from the *Philadelphia Naming Test* (PNT; which assesses noun naming skills) to the *Object and Action Naming Battery* (OANB; (Druks, 2000). The OANB is a validated language measurement tool which assesses both noun and verb naming skills. It will be especially important for us to assess participants' change in verb naming skills pre- and post-intervention since our language intervention targets verb-naming skills.

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).

Study Procedures

Study Design Overview: Participants will take part in two intervention periods of 15 training sessions (2-5 per week), with either neurofeedback training or sham training, separated by a 1-week wash-out period. At each training session, participants will also receive 45 minutes of speech-language therapy (VNeST). Behavioral speech-language testing and physiological testing (qEEG and fNIRS) will be conducted at baseline, at 1-week following each intervention period and at five weeks following the completion of both conditions. See the figure below. In order to effectively analyze and code errors in the participant's speech/language, we will perform audio and/or video recordings of their behavioral language testing. All recordings will be accessed via JHU SAFE Desktop and stored on JHU HIPAA-compliant network drives.



Visit 1: **Screening and Baseline Behavioral Assessment.** These sessions involve language testing with the OANB (first), picture description, and COWA. This will be the baseline language testing for the first intervention period. Participants with an OANB score that exceeds an average of 80% accuracy will be excluded to leave at least a 20% improvement margin. That is, participants who already score close to ceiling may have limited room for naming improvement. During the first visit, participants will undergo screening assessments. This will to determine if they are a candidate for the treatment. If the participant passes the initial screening portion, informed consent will be obtained.

Visit 2: **Baseline qEEG and fNIRS.** Participants will undergo qEEG brain mapping assessment to obtain baseline EEG analysis to assess brainwave patterns and to identify areas of abnormality compared to normative database of same-age healthy peer group to establish appropriate training goals for neurofeedback sessions. Participants will also undergo fNIRS assessments.

Visit 3-17: **Intervention Phase I.** These sessions will include the treatment sessions for the first intervention period. Prior to the start of treatment, participants will be randomly assigned to receive either “neurofeedback then sham” or “sham then neurofeedback.” For example, if a participant is randomly assigned to receive “neurofeedback then sham,” the first intervention period of 15 sessions will be neurofeedback training and the second intervention period will be 15 sessions of sham training. Participants will undergo treatment sessions within each intervention phase at a frequency of 2-5 sessions per week as their schedule allows. At each visit within this intervention phase, participants will also receive speech-language therapy (VNeST).

Visits will take approximately 45-minutes for EEG biofeedback training plus an additional 45-minutes for speech-language therapy.

Visit 18: **1-week Post-Intervention Assessment (following Intervention Phase I)**. This visit will involve post-treatment language testing, qEEG and fNIRS.

Visit 19-33: **Intervention Phase II.** These sessions will include the treatment sessions for the second intervention period. The opposite neurofeedback condition will be implemented here. For example, if a participant is randomly assigned to receive "neurofeedback then sham," the second intervention period will be 15 sessions of sham training. Participants will also receive speech-language therapy (VNeST) during each visit within this intervention phase. Each visit will take approximately 45-minutes for EEG biofeedback training plus an additional 45-minutes for speech-language therapy.

Visit 34: **1-week Post-Intervention Assessment (following Intervention Phase II)**. This visit will involve 1 week post treatment language testing, qEEG and fNIRS.

Visit 35: **Five-Week Post-Intervention Assessment (following Intervention Phase I and II**). This visit with include follow-up language testing, qEEG and fNIRS at 5-weeks post-second intervention period.

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

Participants will receive treatment for 3-6 weeks (2-5 sessions in a week: total 15 sessions) for each intervention period. There will be one active neurofeedback treatment period and one sham treatment period for each participant with a 1-week washout period in between the two treatment phases. Participants will receive speech-language therapy (VNeST) at each treatment visit (during both active and sham intervention phases). We will assess the participants at baseline and at 1-week follow-up appointments after each treatment period. Participants will undergo a 5-week follow-up appointment following the second treatment period. Study duration will be approximately 15-20 weeks, and the number of visits for each participant will be 35.

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

<u>Randomization and Blinding</u>
The study is to be conducted in a double-blind manner. The participants and the clinician performing the behavioral and physiological assessments will not know the treatment assignment. The PI will have access to the unblinded list of randomization codes and treatment assignments. Technicians performing the active and sham neurofeedback sessions will utilize pre-developed scripts for both active and sham conditions to standardize the prompts utilized within each arm of the study. Participants will answer survey questions throughout each

intervention phase regarding their best-guess as to which type of intervention they are receiving (active versus sham) to assist in determining if they are adequately blinded.

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

Participation in this study will not disrupt any current care or therapy. If participants are actively undergoing regular speech therapy while enrolled in this study, we will record the amount of outside speech therapy participants receive during each intervention phase (in terms of number of speech therapy visits and duration of these visits, e.g., 60-minutes) during each intervention phase.

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

All participants will be participants who will undergo active and sham conditions, thus serving as their own control.

f. Definition of treatment failure or participant removal criteria.

Participants will be removed from the study if they are unable to comply with task instructions or tolerate the EEG neurofeedback, measured by self-report or overt signs of discomfort.

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

When the study ends participants will continue to receive management with Dr. Hillis or their own neurologist as usual (generally follow-up visits every about 6 months). If a patient's participation in the study ends prematurely s/he will still receive care as before. In sum, termination of the study or termination of participation in it will not affect regular treatment he or she may be receiving.

5. Inclusion/Exclusion Criteria

Participants in this study will have a diagnosis of Primary Progressive Aphasia or aphasia following stroke. Diagnostic evaluations will be conducted during the participants' initial visit to confirm aphasia diagnosis.

Inclusion Criteria:
1) Diagnosis of PPA or aphasia secondary to stroke and presence of naming deficits with confirmation of diagnosis by neurologist
2) Capable of giving informed consent or indicating another to provide informed consent
3) Age 18 or older.

4) If aphasia is secondary to stroke, the stroke must have occurred between 6 months and 5 years prior to enrollment in the study.

Exclusion Criteria:
1) Lack of English proficiency
2) Not medically stable
3) Picture naming accuracy above 80% on the OANB
5) Prior history of neurologic disease affecting the brain (e.g., brain tumor, multiple sclerosis, traumatic brain injury) other than stroke or PPA and its underlying neurological pathologies: Alzheimer's Disease, Frontotemporal Lobar Degeneration or Dementia with Lewy bodies
6) Prior history of severe psychiatric illness, developmental disorders or intellectual disability (e.g., PTSD, major depression, bipolar disorder, schizophrenia, OCD, autism spectrum disorders)
7) Uncorrected severe visual loss or hearing loss by self-report and medical records

6. Drugs/ Substances/ Devices

a. The rationale for choosing the drug and dose or for choosing the device to be used.

EEG neurofeedback has been established as a safe tool for providing visual or auditory feedback on the brain's electrical activity with minimal risks. Raw EEG will be recorded with no more risk than a clinical EEG. Since neurofeedback does not directly alter a person's neural activity, it merely provides feedback on the trainee's brainwave activity, there are minimal risks for the participants.

The Discovery 24 EEG amplifier developed by Brainmaster Technologies, Inc has been cleared by the FDA to acquire, record, transmit, and display physiological and data for EEG studies of patients of all ages; 510(k): K150498.

The NIRSport2 Functional Near-Infrared Spectroscopy (fNIRS) system has been established as a safe tool for assessing brain activity using optodes attached to a cap placed outside of an individual's scalp.

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

The primary outcome variable will be the change in number of Content Units (CU) in picture description from baseline to 1-week post-treatment. Hypothesis 1A is: Participants will show greater improvement in CU from baseline to 1-week post treatment, during the EEG neurofeedback condition than during the sham condition.
To test Hypothesis 1A, we will subtract baseline CU from 1-week post-treatment CU, for each condition. We will use a paired t-test to determine if, as a group, patients showed greater increase in CU during the neurofeedback condition compared to the sham condition. We will also carry out paired t-tests for post-stroke aphasia and PPA separately, to determine if the effect was greater in one group.

b. Secondary outcome variables

Hypothesis 1B-F take the form of: Participants will show greater improvement in [outcome variable] from baseline to 1-week post treatment, during the EEG neurofeedback condition than during the sham condition.

To test each hypothesis 1B-F, we will subtract baseline score from follow up scores (1-week post-treatment), for each condition. We will use paired t-tests to determine if, as a group, patients showed greater improvement during the neurofeedback condition compared to the sham condition, at each follow-up. We will correct for multiple comparisons using a Bonferroni correction.

Hypothesis 2A is: We will be able to identify baseline characteristics (demographics and baseline severity measures, as well as qEEG abnormalities) that influence change in the primary outcome measure (change in CU in picture description from baseline to 1-week post-treatment).

To test this hypothesis, we will carry out multivariable linear regression, with the dependent variable (change in CU in picture description from baseline to 1-week post-treatment), and independent variables of age, baseline CU, baseline OANB, baseline COWA, baseline sleep quality, baseline S-anxiety (STAI), brainwave activity (absolute power, peak amplitude frequency) in each frequency band (alpha, beta, theta, delta, gamma) on qEEG.

Hypothesis 2B is: We will be able to identify changes in secondary outcome measures and changes in qEEG that correlate with the primary outcome measure (change in CU from baseline to 1-week post-treatment). These results will allow us to identify variables to explore the mechanisms of the effects.

To test this hypothesis, we will carry out Pearson correlations between the dependent variable (change in CU in picture description from baseline to 1-week post-treatment), and change in CU, change in OANB, change in COWA, change in absolute power and peak amplitude frequency within each frequency band (alpha, beta, theta, delta, gamma) on qEEG, change in coherence on qEEG (e.g., coherence between left and right hemispheres).

Hypothesis 3A is: Greater improvement in qEEG normalization toward healthy control group (e.g. alpha enhancement with absolute power and peak amplitude frequency ≤1.5 standard deviations away from healthy group average) will be observed in the EEG neurofeedback training condition compared to sham training condition.

To test this hypothesis, we will compare baseline and follow-up z-scores for absolute power and peak amplitude frequency of each of the frequency bands (alpha, beta, theta, delta, gamma) by subtracting the absolute value baseline z-score from the absolute value follow-up z-scores for each condition. We will use paired t-tests to determine if, as a group, patients showed greater improvement during the neurofeedback condition compared to the sham condition, at each follow-up. We will correct for multiple comparisons using a Bonferroni correction. We will also carry out paired t-tests for post-stroke aphasia and PPA separately, to determine if the effect was greater in one group.

Hypothesis 3B is: Greater connectivity within the attentional network and the language network (and right hemisphere homologues) will be observed in the EEG neurofeedback training condition compared to sham training condition.

To test this hypothesis, we will compare baseline and follow-up z-scores for coherence in each of the frequency bands (alpha, beta, theta, delta, gamma) by subtracting the absolute value baseline z-score from the absolute value follow-up z-scores for coherence in each condition. We will use paired t-tests to determine if, as a group, patients showed greater improvement during the neurofeedback condition compared to the sham condition, at each follow-up. We will correct for multiple comparisons using a Bonferroni correction. We will also carry out paired t-tests for post-stroke aphasia and PPA separately, to determine if the effect was greater in one group.

c. Statistical plan including sample size justification and interim data analysis

Statistical Analyses

Statistical tests to evaluate each hypothesis are described above. No interim data analyses are planned, although we will become unmasked to condition after each participant completes the 5 week follow-up

Sample Size Determination

This study is a novel application of neurofeedback for treatment of aphasia, and we have no preliminary data to guide a power analysis. However, we will use this preliminary cross-over study (with each patient as their own control) to identify effect size (if any), in order to plan a randomized, double-blind, parallel, sham-controlled trial. For this preliminary trial, we plan to study 8 patients per year with post-stroke aphasia, and 8 patients per year with PPA, based on our other ongoing trials of post-stroke aphasia and PPA, in which we have found that it is feasible to recruit and retain 8-10 of each per year. We hope to obtain a total of 40 patients with post-stroke aphasia and 40 with PPA over 5 years, to obtain preliminary data for a multicenter, randomized, double-blind, parallel, sham-controlled trial, if the preliminary results are positive.

Missing Data

We plan to minimize missing data by avoiding prolonged intervals between conditions. Most of the study will take place within 7-11 weeks, with each person scheduled to have a 5 week follow up to determine if any changes are long-lasting. To minimize biases, analyses will be by

intention to treat; any missing data will be addressed with the technique of multiple imputation (Rubin, 2004), generally recognized as best for handling missing data (Little et al., 2012).

d. Early stopping rules.
N/A

8. Risks

a. Medical risks, listing all procedures, their major and minor risks and expected frequency.

Two primary instrumental techniques will be utilized, EEG and fNIRS, neither of which have major risks associated. Since EEG neurofeedback is a passive learning process, there is a limit to the extent of negative reactions that can arise as a result of its use (Collura, 2014). Collura discusses two types of abreactions (expression and consequent release of a previously repressed emotion) that might occur as the brain learns self-regulation and normalizes through neurofeedback training. One type of such reactions could be if neurofeedback training results in normalization of a compensatory mechanism that has helped the client cope with particular stresses or other dysregulations. An example could be if a chronically anxious client exhibits excess alpha as a coping mechanism to reduce anxiety. If through neurofeedback training, alpha levels normalize and reduce this coping mechanism, anxiety levels could increase. The long-term goal of neurofeedback is to allow the client to develop healthier circuitry patterns that do not rely on maladaptive patterns in order to cope. The second type of possible abreaction could be the resurfacing of psychological trauma that had been dealt with through coping mechanisms once these coping mechanisms are lessened through more normalized brainwave activity. Another possible negative response is the development of negative effects from current medication regimens as the trainee's brain learns to self-regulate and normalize.

Near-infrared spectroscopy (NIRS) is a relatively new investigational tool. Although no adverse effects have been reported, it is possible that effects not yet reported may occur. The LED light in the NIRS devices used to make the measurements has low power (within the ANSI limit for long-term exposure to infrared light). Thus far, no hazard to patient, staff or third party has been observed. Should any adverse effects be observed during the study, they will be immediately reported to the IRB. NIRS monitoring requires coupling "optodes" (optical sensors) to the skin on the scalp. This is achieved by fastening the optodes to a cap, placing the cap over the head and holding it in place with a strap placed under the chin or behind the head. The subject's hair may need to be parted in the location of the optodes to provide better coupling to the skin. The procedure does not cause pain or distress. Subjects will be asked to keep their head relatively still for several periods of up to approximately 10-15 minutes each while performing the tasks. However, the NIRS device will be made as insensitive as possible to head motion, and hence strict subject compliance is not essential. Fatigue from performing the tasks is the most likely risks in this study.

There are no known risks to behavioral speech-language therapy. Participants may experience fatigue, frustration, or boredom during the tasks. Participants will be offered breaks, as needed.

In the event of a global pandemic due to an outbreak of a highly contagious viral infection (e.g., COVID-19), participants have some risk of transmission and contraction of the virus upon participating in in-person study tasks due to being in contact with (or in close proximity to) other people who are potentially infected or who are carriers of the virus and by being potentially infected with (or carriers of) the virus themselves. So, in the event of a pandemic of this nature, precautions will be taken as outlined below.

b. Steps taken to minimize the risks.

Participants will be carefully screened prior to being scheduled, to assure that they meet study criteria. EEG neurofeedback sessions will be closely supervised to monitor for any adverse reactions. The participant may stop testing or the intervention at any time. On any given session, if the patient experiences significant frustration, anxiety, or fatigue, that session may be terminated early. Short-term abreactions will be monitored closely. Those with a history of severe psychological trauma and severe psychological conditions will be excluded from the study.

In the event of a global pandemic (such as COVID-19 outbreak), precautions will be taken to reduce the spread of infection related to the viral outbreak. This includes the following:

1. Remote testing will become the primary mode of testing.
2. If remote testing is not feasible, we will perform home visits whenever possible to limit contact of participants with others at the hospital setting.
3. We also have the option of using the STAR Car, a mobile lab space (wheelchair-accessible van) to reduce the number of people on-campus.
4. If remote testing and/or home visits are not possible, participants may be seen at their outpatient appointment scheduled for clinical follow-up.
    a. For outpatient appointments, we will limit session room attendance to the participants only (rather than allowing family members to be present in the testing room) and one staff member to administer the session.
    b. We will also limit lab staff members on-site to essential personnel only, per JHU guidelines.
5. We will screen participants by phone to inquire about recent symptoms and exposure to (e.g., related to COVID-19) before any in-person appointments. Per JHU guidelines, we will defer any appointments (i.e., if any active symptoms are present, we will defer any in-person appointments).
6. Staff will reference JHU policies for self-screening and will defer any in-person or on-campus activities if they suspect that they have any active symptoms (e.g., related to COVID-19).
7. For all in-person visits, we will disinfect test and treatment materials (computers, caps, tablets, pens), devices (EEG amplifier, electrode leads, fNIRS system, optodes) and surfaces (tables, doorknobs) before and after each session.

8. During in-person visits, staff and participants will wear disposable or cloth face masks, eye shields, and disposable gloves per JHU guidelines.
9. Participants will be asked to use hand hygiene at the beginning of in-person test and treatment sessions before handling equipment; this may include washing hands with soap and water or using hand sanitizing gel/foam approved by the university.

c. Plan for reporting unanticipated problems or study deviations.

Adverse events will be monitored during the entire visit by the study team. The families will be given telephone numbers of study team as well. The study physician (Dr. Argye Hillis) will be notified immediately if any adverse events are reported. Adverse events will be monitored until they are resolved or clearly determined to be due to a subject's stable or chronic condition or intercurrent illness. Medical care will be provided, as defined in the informed consent, for any adverse event related to trial participation. All adverse events, regardless of intensity or causality, will be recorded in the study documentation and reported to the JHMI IRB. Any serious adverse events will be reported to the JHMI IRB within 24 hours.

Plan for dealing with incidental findings: qEEG will be reviewed by a neurologist if any concerning abnormal findings are present (e.g., possible seizure activity). If an incidental finding is discovered, the site PI (Dr. Hillis) will call the patient, and arrange to see the patient in clinic on a timely basis to discuss the finding and the plan for medical follow-up (if any). As Dr. Hillis is the neurologist of the PPA and stroke patients, she will provide care for most of the findings seen on behavioral and physiological assessments, but will refer the patient to other physicians as appropriate.

d. Legal risks such as the risks that would be associated with breach of confidentiality.

Participation in this study should not put participants in any legal risk, even in the case of a breach of confidentiality. We will undertake every effort to keep the information in the study confidential. Participants will be assigned a code number for all data in order to keep the information confidential. The computers on which the information will be stored are password protected. Everybody involved in the study will have completed the appropriate HIPAA training and are fully aware of confidentiality issues. No names will be included in any publications resulting from this work.

e. Financial risks to the participants.

No financial risk is involved. There will be no cost for the therapy or any procedures.

9. Benefits

a. Description of the probable benefits for the participant and for society.

We cannot ensure that this research will provide any direct, sustainable benefit to the participants. Participant's language skills may or may not improve from the training.

Completion of this project will result in better understanding whether and how EEG neurofeedback may help individuals with PPA or post-stroke aphasia. This project may provide a way to treat language in individuals with PPA or post-stroke aphasia. If we find that a participant shows more improvement in naming during the active feedback than the sham feedback, he or she will be offered up to 15 more sessions of the active feedback at no cost. He or she may accept or decline the additional feedback sessions.

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.

Participants will not be paid to participate in the study. There is no penalty for not completing an assessment or treatment session.

11. Costs

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

There is no cost to the participants for participating in the study.

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