Prism Adaptation in Left Brain Stroke

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PROTOCOL TITLE: Prism Adaptation and Left Brain Stroke Rehabilitation.

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REVISION HISTORY

Revision #	Version Date	Summary of Changes
1	08/28/20	Virtual consent and assessment
2	03/14/21	Option to enroll in Registry
3	06/15/21	Time post-onset ≥ 1 month
4	10/5/21	Recording- VA-approved devices, VA-approved servers
5	10/25/21	Transfer from VA approved devices to VA-approved servers using VA-issued USB device.
6	02/04/22	Data sharing with other Rodriguez study
7	07/05/22	Updated distribution of recruitment materials
8	10/20/22	Permission to use text messaging to communicate with consenting participants

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1.0 Study Summary

Study Title	Prism Adaptation in Left Brain Stroke Rehabilitation
Study Design	Multiple baseline, delayed treatment approach
Primary Objective	To demonstrate the feasibility of adapted methods for assessing and treating spatial and motor function and pain in patients with aphasia and memory impairment.
Secondary Objective(s)	To demonstrate the feasibility of using information about lesion location from the radiology report to classify frontal vs. nonfrontal lesions
Research Intervention(s)/Interactions	Prism Adaptation Treatment (PAT) for spatial neglect in patients with aphasia and memory impairment
Study Population	Left brain stroke patients with aphasia and memory impairment
Sample Size	30
Study Duration for individual participants	7 weeks
Study Specific Abbreviations/ Definitions	DVPRS: Defense and Veterans Pain Rating Scale KF-NAP: Kessler Foundation- Neglect Assessment Protocol PAT: Prism Adaptation Treatment WMFT: Wolf Motor Function Test
Funding Source (if any)	Department of Veterans Affairs

2.0 Objectives

2.1 Specific Aim 1: To demonstrate the feasibility of adapted PAT procedures in patients with aphasia and memory impairment. Hypothesis: Adapted methods for PAT administration in patients with aphasia are feasible. Even in the presence of memory disorder detecting a treatment signal is possible.

Specific Aim 2: To demonstrate the feasibility of adapted methods for assessing spatial and motor function and pain in patients with aphasia and memory impairment. Hypothesis: Adapted methods for assessing spatial and motor function and pain in patients with aphasia and memory impairment are feasible.

Specific Aim 3: To demonstrate the feasibility of using information about lesion location from the radiology report to classify frontal vs. nonfrontal lesions. Hypothesis: Lesion classification results from radiology reports and brain mapping methods are consistent, confirming this adaptation provides a clinically

accessible, reliable way to identify brain-based predictors of optimal PAT response in future studies.

2.2 Specific Aim 1: Adapted methods for PAT administration in patients with aphasia are feasible. Even in the presence of memory disorder detecting a treatment signal is possible.

Specific Aim 2: Adapted methods for assessing spatial and motor function and pain in patients with aphasia and memory impairment are feasible.

Specific Aim 3: Lesion classification results from radiology reports and brain mapping methods are consistent, confirming this adaptation provides a clinically accessible, reliable way to identify brain-based predictors of optimal PAT response in future studies.

3.0 Background

3.1 Every year about 15,000 Veterans are hospitalized for stroke (Cowper, 2004). Given the expected rapid and significant increase in Veterans above age 65 over the next decade (NCVAS, 2011) and the reality that the risk of stroke more than doubles each decade after age 55 (CDC, 2010), our aging Veterans are at an ever-increasing risk of joining the 80,000 Veterans who are already suffering from stroke-related long-term disability (Jia et al., 2006). Stroke and its complications represent the most frequent cause of adult-onset disability in the US, and post-acute stroke care is among the fastest-growing federal expense categories (CDC, 2003; Buntin et al., 2010). Currently, there are separate and modality-specific treatment pathways for cognitive and motor impairments, and pain, in stroke survivors. Clinicians can access guidelines for evidence-based practice from the American Heart Association (Winstein et al. 2016), Veterans Administration/Department of Defense (Management of Stroke Rehabilitation Working Group 2010) and individual professional organizations such as the American Occupational Therapy Association (Wolf and Nilsen 2015). However, current guidelines and care pathways still match single conditions to single methods of rehabilitation.

Because of the limited rehabilitation resources available to address Veteran functional disability after stroke, we need to identify feasible treatments acting on more than one recovery target. Multi-target therapies could also improve rates of diagnosis for hidden disabilities, such as spatial neglect and pain, which are under-identified, and under-treated (Edwards et al. 2006; Chen et al. 2013; Widar and Ahlstrom 2002). Because the care system does not yet emphasize multi-target treatments, stroke survivors can experience a fragmented interprofessional care process, in which treatment of some disabling conditions, but not others, leads to incomplete recovery and reductions in quality of life (Haynes et al. 2015). Lack of care efficiency can also increase care costs, prolong hospital stays, and increase utilization of other healthcare services

(Olson et al. 2013). Combining interventions for cognitive and motor impairments, and pain, and systematically tracking treatment effects would help streamline the process for >50% of Veteran stroke survivors who have both visible and hidden disabilities (Mahon et al. 2017; Yelnik et al. 2011; Management of Stroke Rehabilitation Working Group 2010), and help ensure that they receive optimal services during the post-acute period. By establishing the feasibility of applying standardized methods for assessment, treatment and prediction of treatment response in patients with left brain stroke, we contribute to two broad goals of this line of research.

GOAL 1: To develop clinically translatable, multi-target treatments for broad application in stroke.

Prism adaptation treatment (PAT; Barrett, Goedert, and Basso 2012) is a 10-day spatial retraining treatment regimen developed to treat the disabling post-stroke visual-cognitive disorder, spatial neglect (Barrett and Houston 2019; Heilman, Watson, and Valenstein 2012; Corbetta and Shulman 2011; Hillis, Mordkoff, and Caramazza 1999). Although many studies demonstrated the benefit of using PAT to treat spatial neglect (see Yang et al., 2013 for review), studies have also demonstrated positive effects on motor function (see Champod et al., 2016) and on pain. Direct measurement of functional movements in the laboratory supported a beneficial effect of PAT on arm movements, center of gravity, and posture (Fortis et al. 2011; Shiraishi et al. 2008; Nijboer et al. 2014). In addition, case series data indicate that PAT can be used as a non-pharmacologic treatment to reduce post-stroke pain (Sumitani et al. 2007; Christophe et al. 2016), which occurs in about half of stroke survivors, (Naess, Lunde, and Brogger 2012; Lundstrom et al. 2009; Hansen et al. 2012) adversely affecting cognitive and functional independence, and quality of life (Harrison and Field 2015). As we note above, PAT was developed for spatial retraining. Because spatial function and other cognitive processes are potentially distributed and highly interactive with other functional domains, spatial retraining may provide a “back door” to improve motor recovery and somatic experience through pain relief. Given the high rates at which stroke patients experience spatial-motor-sensory impairments, and in the absence of integrated treatment plans that encompass the three domains depicted in Figure 1, a multi-target treatment such as PAT is highly desirable. Although available controlled trials of PAT and other spatial neglect treatments indicated that these therapies can restore adaptive movements and functional abilities, studies have been conducted exclusively in people with right brain stroke (Yang et al. 2013). Clinicians are unlikely to administer PAT routinely for stroke survivors when there is no evidence that doing so will yield therapeutic benefit in left brain stroke. Additionally, clinicians may hesitate to apply PAT in patients with aphasia and memory impairments, which are common after left brain stroke (Pedersen et al., 1995; Eskes & Barrett 2009). Thus, we identified the potential for a high-risk, high-reward study that demonstrates feasibility of standardized assessment and treatment methods in

left brain stroke patients, to open a path for broad application of PAT in both left and right brain stroke survivors.

GOAL 2: To develop clinically translatable assessment methods for diagnosis and identification of subgroups who will benefit from multi-target treatments.

Patient-centered, precision medicine is tailored to brain-based factors relevant to recovery in an individual stroke survivor. Genetic risk factors are often considered in predictors of stroke recovery (Cramer, 2008). Cognitive deficits also predict response to rehabilitation (Dignam et al., 2017), possibly because they interact with motor brain systems (Barrett, Boukrina, and Saleh 2019) or alter the applicability of global outcome measures (Bosetti et al., 2017; Cramer, 2007). The potential impact of cognitive deficits on rehabilitation outcomes highlights the need for comprehensive and accurate diagnosis to guide clinical decision-making.

In addition, brain physiology and anatomy may also define patient subgroups with better response to specific rehabilitation methods (e.g. non-invasive brain stimulation; Plow et al., 2016; Nouri & Cramer, 2011). Although patients across a range of brain lesion locations may experience treatment benefit from PAT (see Yang et al., 2013 for a review), we and others reported that the presence of frontal lobe cortical lesions predicts optimal response to treatment, and subsequent recovery of functional performance in stroke-induced spatial neglect (Chen et al., 2014; Goedert et al., 2018; Gutierrez-Herrera et al., 2018). These experiments were carried out exclusively in right brain stroke-- no data about brain-behavior relationships in recovery from neglect after left brain stroke, with or without treatment, is available. To develop PAT in future large-scale studies as a multi-target treatment for use in patients with both left brain stroke and right brain stroke, first requires determining whether stratifying patients by frontal lobe lesions reveals differences in treatment benefit. The presence of large differences in PAT response related to lesion location would affect the design and evaluation of PAT for stroke rehabilitation as well as eventual clinical decision-making for assigning PAT to eligible stroke survivors. However, clinicians in rehabilitation settings typically obtain information about lesion location from a patient's medical record. Before guidelines for PAT patient selection can be broadly implemented, we must establish that obtaining information about lesion location from the radiology report, as compared to research-based brain mapping methods, is a feasible and reliable method of categorizing lesions.

3.2 Preliminary Study 1: Members of our team have demonstrated that administration of PAT using standardized methods is feasible and yields therapeutic benefits in right brain stroke (Barrett et al. 2012). Purpose: Expert clinicians who assess and treat invisible disabilities like spatial neglect use a variety of rehabilitation techniques (Chen et al. 2017) depending on barriers present, recovery stage, and characteristics of the deficit. However, clinicians carrying out routine care find a large number of choices for spatial neglect

treatment confusing and impractical. Methods: Of all of the treatments available, prism adaptation treatment (PAT) was identified as being the most feasible (Barrett, Goedert, & Basso 2012). PAT improved spatial neglect in multiple randomized studies (Yang et al. 2013), and is also time-efficient, requiring only 10, short, daily sessions (20-30 minutes), with no components of treatment that need to be cross-implemented, carried out during other times of day, or co-administered as part of other therapies (Barrett & Houston 2019). PAT was manualized, and in a network of inpatient rehabilitation sites that received training, the time for therapists to learn how to administer PAT is less than a day. Results: PAT improves daily life function (Champod et al. 2016), and improvements are noted in self-care, reading and writing, and even wheelchair navigation and posture. Conclusions: Standardizing the administration of PAT allowed for packaging the care process for training of more than 100 therapists in a nationwide practice-based network to deliver right brain rehabilitation (Barrett, 2019). This study will extend this work by establishing the feasibility of adapted PAT procedures in left brain stroke patients with aphasia and memory impairment (Aim 1).

Preliminary Study 2: Members of our team have standardized methods for assessment of spatial neglect in right brain stroke (Chen et al. 2012; Chen et al. 2015). Purpose: In 60-80% of people with spatial neglect, care professionals do not diagnose or document the disorder during routine inpatient rehabilitation (Chen et al. 2013; Edwards et al. 2006). Because it has an independent, adverse effect on multiple domains of daily life function, assessing spatial neglect via functional performance is the first step to assigning treatment and speeding neurological recovery. Methods: The semi-quantitative, examiner-rated Catherine Bergego Scale (CBS), which is a reliable, validated 10-item questionnaire to detect and evaluate spatial neglect severity (Azouvi 2016; Chen et al. 2015; Azouvi et al. 2003) was adapted. The Kessler Foundation Neglect Assessment Process (KF-NAP®), a manualized process was added which provides detailed instructions and specifies that administration takes place by one examiner during a single assessment session (Chen et al. 2012; Chen, Chen, et al. 2015). Results: Catherine Bergego Scale via the KF-NAP® is an excellent predictor of rehabilitation outcomes (Chen et al. 2015) and its simplicity is appealing to clinicians, who report its adoption in 13 countries, and more than 40 US inpatient and outpatient care settings. Conclusions: The KF-NAP® is a systematic, evidence-based valid method of spatial neglect assessment after right brain stroke. This study will extend this work by establishing the feasibility of adapted KF-NAP® procedures for assessing spatial neglect in left brain stroke patients with aphasia and memory impairment (Aim 2).

Preliminary Study 3: Members of our team have developed standardized methods for assessment of motor function in stroke patients without cognitive impairment (Wolf et al., 2001). Purpose: Greater than 70% of stroke patients suffer motor impairments (Mohr et al., 1993), making assessment and treatment

of motor function a high priority in stroke rehabilitation. The Wolf Motor Function Test (WMFT) is a time-based assessment that quantifies functional ability of upper extremities through a series of tasks ranging in complexity and proximal to distal involvement. WMFT requires few tools and minimal training for administration, making it ideal for clinical use. Methods: Healthy older adults and patients with chronic stroke were administered the WMFT and the upper extremity portion of the Fugl-Meyer Motor Assessment (FMA) at two time points 12-16 days apart. Results: The WMFT and FMA demonstrated agreement between raters at both time points. WMFT scores for upper extremities of healthy older adults were significantly different from than those of the stroke patients. The WMFT and FMA scores for the more affected extremity in stroke patients were related. Conclusions: The WMFT is a valid and reliable assessment of motor function in stroke patients without cognitive impairment. This study will extend this work by establishing the feasibility of adapted WMFT procedures for assessing motor function in left brain stroke patients with aphasia and memory impairment (Aim 2).

Preliminary Study 4: Using brain mapping methods, members of our team have shown that right brain stroke patients with frontal lesions respond optimally to PAT (Chen et al., 2014; Goedert et al., 2018). Purpose: Research with neurologically unimpaired individuals suggests that prism adaptation may stimulate lateralized motor-related spatial systems (Fortis, Goedert, and Barrett 2011) linked to frontal cortical brain networks (Ghacibeh et al. 2007). Thus, the presence or absence of frontal brain lesions may affect PAT response. Methods: We had trained raters categorize patients based on their clinical brain images: as having, or not having, a frontal cortical brain lesion (Chen et al. 2014; Goedert et al. 2018). Results: In both studies, patients with frontal brain lesions experienced a more robust therapeutic response to PAT, based on functional performance testing. Although in the first study, medial temporal structures also appeared to play a role in PAT response, this was not confirmed in the second study. Conclusions: A frontal cortical lesion predicts optimal PAT response after right stroke. However, clinical decision-making based on brain mapping with trained raters is not feasible in the clinical environment. This study will extend this work by determining whether obtaining information about lesion location from the medical record is a feasible, reliable way to identify patients with frontal vs. nonfrontal lesions (Aim 3).

3.3 This study is the first to systematically investigate the feasibility of using adapted PAT treatment procedures and spatial-motor-sensory assessments in left-brain stroke patients with aphasia and memory impairment, as well as clinically-accessible methods for identifying patients with optimal response to PAT. This line of research lays the foundation for a potential paradigm shift in the focus of rehabilitation research to PAT as a multi-target treatment to improve spatial function, adaptive movements, functional independence, and pain-free somatic experience. In addition, this study could change the conventional

structure of stroke rehabilitation trials, most of which have not measured the impact of cognitive treatments on motor function, or vice versa, and do not assess the concurrent effect of either cognitive or motor treatment on pain.

4.0 Study Endpoints *

4.1 We will assess four key aspects of feasibility of our adapted assessment and treatment procedures: acceptability, implementation, adaptation, and limited efficacy testing (Bowen et al., 2009). See Table 1. Acceptability: We will use the Client Satisfaction Questionnaire (CSQ-8; Attkinson & Zwick, 1982; Larsen et al., 1979) to assess satisfaction and perceived value of PAT. We will use the Credibility/Expectancy Questionnaire (CEQ; Devilly & Borkovec, 2000) to assess the degree to which PAT is believable, convincing and logical (credibility) and the expectations for PAT-induced improvement (expectancy). The CSQ-8 and CEQ have been used in patients with subjective cognitive impairment (Foster et al., 2018). Implementation: We will record attendance and completion rates to determine whether KF-NAP®, WMFT and PAT can be carried out as planned. Adaptation: Each session, study staff will complete checklists from the KF-NAP®, the WMFT, and the KF-PAT™ manual (Chen, 2015) to track assessment and treatment fidelity. Notations will be made when modifications to administration methods are required. For the brain mapping, trained raters will map brain lesions using the method from Preliminary Study 4. Then, a blinded neurologist will classify participants as having “frontal” or “nonfrontal” lesions. Using radiology reports, lesions will be classified as “frontal” based on use of that word or “anterior” “premotor” “prefrontal” or “precentral” or as “nonfrontal” if none of those words are present. Limited Efficacy Testing: To detect the acquisition and maintenance of a treatment signal, we will assess spatial-motor-sensory and functional recovery over 7 weeks (Figure 2). We will assess: 1) Functional disability, measured by activities of daily living using the Barthel Index (Mahoney & Barthel 1965) and cognitive and motor function with the FIM or FONE-FIM; 2) Spatial neglect, measured by the Behavioural Inattention Test-conventional subtest (Wilson et al., 1987) and CBS via the KF-NAP® (Chen et al. 2012); 3) Motor function, measured by the WMFT (Lin et al., 2009); and 4) Pain, measured by the Defense and Veterans Pain Rating Scale (Polomano et al. 2016), which includes numbers along with pictures and colors to facilitate nonverbal rating of pain. Assessments will be administered by a trained examiner.

TABLE 1. Study Endpoints.

Key Area	Aim	Question	Analysis on Outcome of Interest
Acceptability	1	• Do left brain stroke patients view PAT as a satisfactory and credible tool for rehabilitation?	• Range of post-PAT satisfaction ratings on CSQ-8 • Range of credibility and expectancy ratings on CEQ (pre and post PAT)
Implementation	1,2	• Can KF-NAP®, WMFT, DVPRS and PAT be implemented as planned in left brain stroke patients?	• Completion rate for KF-NAP®, WMFT, DVPRS and full 10-session PAT
Adaptation	1,2,3	• What modifications are necessary for implementation of KF-NAP®, WMFT and PAT in left brain stroke patients? • Is classification of lesion location from the medical record consistent with classification using brain mapping?	• Number and type of modifications to KF-NAP®, WMFT and PAT protocol • Percent agreement on presence or absence of frontal lesion between radiology report and brain mapping
Limited Efficacy Testing	1,2	• Is there promise for application of PAT in left brain stroke patients?	• Visual inspection of recovery trajectories on spatial-motor-sensory and functional assessments over 7 weeks to detect the acquisition and maintenance of a treatment signal

4.2 N/A

5.0 Study Intervention/Investigational Agent

5.1 PAT will be administered 5 days per week for 2 weeks (10 sessions) using a portable kit with manual (KF-PAT®; Chen 2015) by a trained study clinician. This spatial retraining approach involves repeated arm movements to visual targets while wearing goggles that shift the visual field horizontally. To treat right-sided neglect, yoked, 20-diopter, right-based wedge lenses (in which the right side is thicker) are used. The prismatic distortion causes the visual illusion that objects in the environment are displaced to the left. Thus, reaching movements with the prisms on are shifted to the left of a fixed target. Over repeated attempts to interact manually with the target through visual-motor practice, spatial processing leads to motor adaptation, and the participant correctly reaches for the target. After removing the prisms, visual information returns to normal, but the spatial-motor system has increased its propensity to move rightward (Fortis et al., 2011). Thus, when the goggles are removed, the participant will reach for a fixed target and miss by making a movement that is directed too far rightward. The Nausea Profile, found on page 15 of the treatment manual, will be administered the first three days of treatment per recommendations.

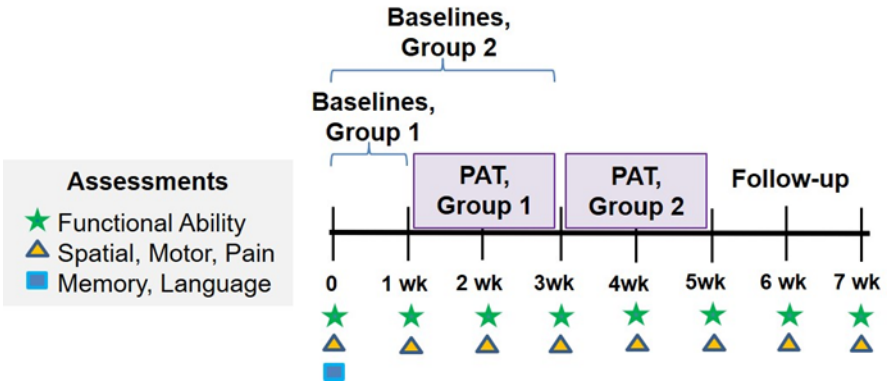
5.2 N/A

5.3 N/A

6.0 Procedures Involved*

6.1 This 7-week prospective study uses a multiple baseline, delayed treatment approach to address four key areas of focus for feasibility studies (Bowen et al., 2009). Participants will be assigned to one of two groups using

computer-generated pre-assignment. Group 1 will begin PAT after two baseline sessions. Group 2 will begin PAT after four baseline sessions.



6.2 Participants will undergo baseline memory and language assessments, along with weekly assessments of functional ability, spatial and motor function, and pain from baseline through 7 weeks. Treatment will be provided 5 days per week for two weeks following a two- or four-week baseline. Assessment and treatment procedures may be conducted face-to-face or by VA-approved audio (phone) or video communication to decrease the amount of face-to-face interaction at the Atlanta VA. Assessment and treatment procedures may be audio and/or video recorded for research purposes. The recordings will be acquired on VA-approved devices. The patients will be informed of the audio or video recording. The recordings will be stored on VA approved servers.

6.3 Risks and procedures to minimize risks are outlined in section 15.0. The source records that will be used to collect data are provided in the IRB smart form and include: Visual Analog Mood Scales (Arruda et al. 1999), the McGill Pain Questionnaire (Melzack 1987), the Michigan Body Map (Brummett et al. 2016), Trail Making Test (Delis, Kaplan & Kramer, 2001), Functional Independence Measure (FIM; Granger et al. 1993) or telephone-administered (FONE-FIM; Chang, Slaughter, et al. 1997; Chang, Chan, et al. 1997), Western Aphasia Battery (Kertesz, 1982), Brief Visuospatial Memory Test- Revised (Benedict et al. 1996), Hopkins Verbal Learning Test- Revised (Benedict et al. 1998), and digit span forward and backward (Lezak et al., 2004), as well as the CSQ-8, CEQ, KF-NAP®, WMFT (described above in section 4.0) and Nausea Profile.

6.4 Data will be obtained through the medical record, assessments of language, memory, spatial, and physical function, pain, and functional ability as described above.

6.5 N/A

6.6 N/A

7.0 Data and Specimen Banking* N/A ☐

N/A

8.0 Sharing of Results with Participants*

8.1 Study-related assessment and treatment results may be shared with participants upon request, without clinical interpretation.

8.2 N/A

8.3 N/A

8.4 N/A

9.0 Study Timelines*

9.1 Participants will complete the study in approximately 7 weeks. We anticipate an active recruitment period of 1.5 years with all study procedures completed by end of 2023.

10.0 Inclusion and Exclusion Criteria*

10.1 Individuals who indicate interest in participating will undergo a brief phone screen to determine if they meet the initial eligibility criteria. Contact will be via telephone to prevent unnecessary burden of traveling to the Atlanta VA if the individual does not qualify for the study. Subjects will be informed of the nature of the study and procedures and their right not to participate.

10.2 Inclusion criteria: Participants will be: 1) 18-89 years of age; 2) ≥1 month post-stroke; 3) proficient English speakers; 4) of moderate functional disability (17-67 scored on Functional Independence Measure, observational (Granger et al. 1993) or telephone-administered (FONE-FIM; Chang, Slaughter, et al. 1997; Chang, Chan, et al. 1997) as indicated by published ranges (Chumney et al. 2010); 5) experiencing aphasia as determined by a Western Aphasia Battery Aphasia Quotient of <93.7 (Kertesz, 1982) and memory impairment as determined by a score that is >1.5 standard deviations below the norm on the Brief Visuospatial Memory Test- Revised (Benedict et al. 1996), the Hopkins Verbal Learning Test- Revised (Benedict et al. 1998) or digit span forward and backward (Lezak et al., 2004); and 6) able to provide informed consent to participate, using aphasia-accessible process, as needed.

Exclusion criteria: History of brain conditions other than left brain stroke, including clinical right brain pathology.

10.3 N/A

10.4 N/A

11.0 Vulnerable Populations* N/A ☐

11.1 N/A

12.0 Local Number of Participants

12.1 30

12.2 Based on attrition rates in our previous studies, we expect ~20% of participants will not complete the study. Thus, we will need to enroll approximately 36 participants to achieve the target sample size of 30. We anticipate needing to screen approximately 100 patients in order to meet our target sample size.

13.0 Recruitment Methods

13.1 This study will target United States Veterans. Non-VA patients maybe enrolled to maximize the number of women in the study as historically difficult to enroll enough women. Our primary recruiting sources will be the VA Clinical Case Registry (CCR) using selected ICD-9 and ICD-10 codes. Potential Veteran participants will be mailed an IRB approved recruitment letter, as well as an opt in/opt out response form to be returned using a postage paid envelope. This will allow for potential subjects to indicate whether they would like to be contacted in the future related to the study. If no response is received within two weeks, we will follow up with a phone call to gauge subject interest. The potential participants that do not meet the screening criteria for this study will be offered the option to enroll in the Atlanta VA Rehab R&D CVNR Participant Registry (IRB00000159), a secure electronic list of people who wish to be told about the research studies at the CVNR. We will also recruit through the CVNR Research Registry (IRB#00000159), referrals from VA healthcare providers, and advertisements in clinics and closed-circuit television at the Atlanta VA Health Care System. As it is estimated that only 20% of Veterans with aphasia receive their healthcare within the VA Health Care System (VAntage Point, 2018), Emory Healthcare is also an important recruitment source for Veterans. Our recruitment network at Emory includes the Emory Stroke Team that includes members of the Emory-Georgia Stroke Network and the Marcus Stroke & Neuroscience Center at Grady Memorial Hospital, which together serve approximately 750 new stroke patients yearly. Recruitment will also be supported by community-based advertisement through online and in person distribution of approved recruitment materials via professional organizations such as the Georgia Speech-Language-Hearing Association (GSHA), the American Speech-Language-Hearing Association (ASHA), and Up Close Marketing, Inc.

13.2 Participants will be recruited from the sources described in 13.1.

13.3 Methods used to identify potential participants include clinical and research registries described in 13.1, referrals from providers, review of medical records and study fliers.

13.4 We will use study fliers to assist with recruitment.

13.5 Participants will receive $15 per session. Payments will be disbursed at completion of the study or at the point of termination or withdrawal.

14.0 Withdrawal of Participants*

14.1 Participants will be withdrawn from the study if they do not follow study procedures or if continuing in the study would be unsafe.

14.2 Terminations will be communicated promptly with the participant and compensation for completed study visits will be processed.

14.3 Data collection will not continue with participants who withdraw from the study, but data already collected may be used.

15.0 Risks to Participants*

15.1 Language and cognitive assessment: Subjects may become worried if they fail to meet cognitive screening criteria. This risk is only occasional, and effects are manageable by study staff who will be administering the tests. Subjects may become frustrated during cognitive and language tests. This risk is only occasional and effects are manageable by study staff who will be administering the tests. Subjects may become fatigued during cognitive and language tests. This risk is only occasional and effects are manageable by study staff who will be administering the tests. Additionally, we will decrease testing burden for participants, when possible. Dr. Rodriguez's study entitled "Intention Treatment for Anomia" (IRB#116056) also investigates stroke and aphasia. While the question for this study is different, the framework is in place to use assessment data collected in Dr. Rodriguez's other study to reduce the number of assessments in this study. Specifically, we may obtain a participant's data on the Western Aphasia Battery-Revised (WAB-R), Hopkins Verbal Learning Test-Revised (HVLT-R), Brief Visuospatial Memory Test-Revised (BVMT-R), and Digit Span.

Nausea due to prism adaptation goggles: Some subjects may experience nausea while wearing the prism adaptation goggles. This risk is minimal and expected to resolve after removal of the goggles. However, per the treatment manual, we will administer the Nausea Profile the first three days of treatment and discontinue if nausea persists. The nausea profile is found on pg 15 of the treatment manual.

Loss of confidentiality: There is a risk that a subject's identifiable information (PHI, PII) will be inadvertently seen by someone other than study personnel who are authorized to access the information. Loss of confidentiality can occur during language and cognitive testing. This risk is minimal and will be managed by adhering to guidelines set forth to maintain confidentiality.

15.2 There may be risks to participants that are currently unforeseeable.

15.3 N/A

15.4 N/A

16.0 Potential Benefits to Participants*

16.1 Participants will receive information about their language, memory, spatial and physical abilities, functional abilities and pain.

16.2 There may be no direct benefit to study participation.

17.0 Data Management* and Confidentiality

17.1 Data on four key areas of feasibility will be analyzed using descriptive statistics, including measures of frequency, central tendency, dispersion and variation. See Table above.

17.2 Study staff will complete and stay current on all training regarding data security and confidentiality. Written and electronic data will be coded by subject number. All written data will be kept in study binders or folders in a locked cabinet in the PI's locked office. Electronic data containing any identifiable information (PHI, PII), including audio and video recordings, will be kept in a VA protected environment (e.g., VA-approved servers). Audio and video recordings obtained on VA-approved devices will be transferred to a VA-approved server using a VA-issued USB device.

17.3 Checklists will be used to ensure that all study procedures are completed. Reliability checks will be completed on data from assessments.

17.4 Describe how data or specimens will be handled study-wide: All data will be stored on the VA trusted server. Data will be stored in closed systems with access only for study team members on VA trusted server. I Identifiable data will only be stored for the length of the study plus any unanticipated delay time. If data is retained after this time it will be de-identified. Study team members will have access to the data. The PI is ultimately responsible for the receipt of the data and storage to the appropriate locations. Data will not be transported as it will be stored to the appropriate online storage from its collection point.

18.0 Provisions to Monitor the Data to Ensure the Safety of Participants*

N/A

19.0 Provisions to Protect the Privacy Interests of Participants

19.1 Confidentiality will be protected throughout the study and following completion of the study. All study participants will receive a Subject ID which will be kept separate from all source documents. As a guard against risk of confidentiality, all information will be stored in locked files in a locked research area that can only be accessed by research personnel. No names or identifying information will be used in publications that result from this research. In cases where data are laptop, no data containing identifiers or PHI will be stored on hard drives—only on removable media, which will be removed from the computer when not in use. All databases will be password protected.

19.2 Study procedures will be explained to the participant during informed consent, and at the beginning of each study visit. Participants will regularly be

asked if they have any questions and reminded that that they can opt out of the study at any time.

19.3 All participant data will be stored on VA Research Server and only approved study team members will have access to this data.

19.4 Study staff will access data through VA approved networks.

20.0 Economic Burden to Participants

20.1 Participants will pay for the cost of traveling to and from study visits. We provide compensation of $15 per visit to help defray these costs.

21.0 Consent Process

The informed consent process may be conducted face-to-face or by VA-approved audio (phone) or video communication to decrease the amount of face-to-face interaction at the Atlanta VA. For face-to-face orientation and consent, the PI/Co-PI or their trained study staff will go over and describe the consent in a quiet room. Prior to providing written consent, potential subjects will be given the chance to ask questions and the PI/Co-PI or study staff will ask questions to ensure the potential subject understands what the study entails. For phone or video consenting, we will mail or email through VA Outlook using Azure encryption two unsigned copies of the ICF/HIPAA. We will ensure the individual has enough time after receiving the document to read it before scheduled phone/video call. Trained staff will perform consenting process including speaking with the individual to discuss the study and highlighting each section of the consent form, allowing the participant an opportunity to ask questions before providing consent, and giving the participant enough time to consider being in the study. Study team will inform the individual that if they would like to take more time to consider the study, another telephone call can be scheduled. If the individual would like to participate, the participant will sign and date the document and return it to study team via mail (phone) or via email to your VA Outlook email address (video). Recordings of the audio or visual communication will not be permitted. Study team will write a “Note to File” that documents everything about the interaction including: 1. When and how the consent form was sent 2. When the video/telephone call was made 3. What was discussed during the call 4. When the signed consent form was received 5. When the signed consent form was signed by the person obtaining consent 6. When a copy of the consent form signed by both subject and study team was given to the participant and 7. A description of why signature dates are different (if applicable). Once the study team receives the signed consent form, the person obtaining consent should sign the form and date it for the day it was signed. Study procedures will begin once the signed copy is received. Text messages may be used by the study team to communicate with subjects who have consented to participate. All text messages will be sent using an encrypted, VA-issued study iPhone. A copy of the fully signed consent form will be given to the participant via mail or in person at next scheduled visit. Prior to any virtual study visits, a

technology questionnaire will be completed to determine if the participant will be able to complete any study procedures virtually. Please describe:

Non-English-Speaking Participants N/A ☐

N/A

Waiver or Alteration of Consent Process (consent will not be obtained, required information will not be disclosed, or the research involves deception)

N/A

Participants who are not yet adults (infants, children, teenagers) N/A ☐

N/A

Cognitively Impaired Adults N/A ☐

N/A

Adults Unable to Consent N/A ☐

N/A

22.0 Process to Document Consent in Writing

22.1 Participants will provide written informed consent.

22.2 N/A

22.3 Document for obtaining written consent available in IRB smart form.

23.0 Setting

23.1 All study visits will take place at Center for Visual and Neurocognitive Rehabilitation (CVNR), Atlanta VA Health Care System. The study staff will identify and recruit potential participants as outlined in section 13.0.

24.0 Resources Available

24.1 Our primary recruiting sources will be the VA Clinical Case Registry (CCR) using selected ICD-9 and ICD-10 codes, CVNR Research Registry (IRB#00000159), referrals from VA healthcare providers, and advertisements in clinics and closed-circuit television at the Atlanta VA Health Care System. As it is estimated that only 20% of Veterans with aphasia receive their healthcare within the VA Health Care System (VAntage Point, 2018), Emory Healthcare is also an important recruitment source for Veterans. Our recruitment network at Emory includes the Emory Stroke Team that includes members of the Emory-Georgia Stroke Network and the Marcus Stroke & Neuroscience Center at Grady Memorial Hospital, which together serve approximately 750 new stroke patients

yearly. Approximately 40% of individuals with left hemisphere stroke present with aphasia, and our recruitment target is 30. We anticipate we will need to screen about 100 people to reach our enrollment target. Screening and enrollment will occur on a rolling basis with PI and staff time dedicated to recruitment. Our facility contains quiet rooms for obtaining informed consent, as well as administering assessments and treatment. Study funds will be used to obtain all necessary materials for completing study procedures. The PI and other study staff are trained in all study-related procedures and will stay current on mandatory trainings related to human subjects research. A signed statement of study roles and responsibilities, along with training certificates, will be kept on file.

25.0 Multi-Site Research when Emory is the Lead Site*N/A ☐

N/A

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Statistical Analysis Plan

Data on four key areas of feasibility will be analyzed using descriptive statistics, including measures of frequency, central tendency, dispersion and variation. **See Table 1**.

Key Area	Question	Analysis on Outcome of Interest
Acceptability	• Do left brain stroke patients view PAT as a satisfactory and credible tool for rehabilitation?	• Range of post-PAT satisfaction ratings on CSQ-8 • Range of credibility and expectancy ratings on CEQ
Implementation	• Can KF-NAP®, WMFT, DVPRS and PAT be implemented as planned in left brain stroke patients?	• Completion rate for KF-NAP®, WMFT, DVPRS and full 10-session PAT
Adaptation	• What modifications are necessary for implementation of KF-NAP®, WMFT and PAT in left brain stroke patients? • Is classification of lesion location from the medical record consistent with classification using brain mapping?	• Number and type of modifications to KF-NAP®, WMFT and PAT protocol • Percent agreement on presence or absence of frontal lesion between radiology report and brain mapping
Limited Efficacy Testing	• Is there promise for application of PAT in left brain stroke patients?	• Spatial-motor-sensory and functional assessments over 7 weeks to detect presence of a treatment signal

Table 1. Key areas of feasibility and related data analysis.

Acceptability: We will use the Client Satisfaction Questionnaire (CSQ-8; Attkinson & Zwick, 1982; Larsen et al., 1979) to assess satisfaction and perceived value of PAT. We will use the Credibility/Expectancy Questionnaire (CEQ; Devilly & Borkovec, 2000) to assess the degree to which PAT is believable, convincing and logical (credibility) and the expectations for PAT-induced improvement (expectancy). The CSQ-8 and CEQ have been used in patients with subjective cognitive impairment (Foster et al., 2018).

Implementation: We will record attendance and completion rates to determine whether KF-NAP®, WMFT and PAT can be carried out as planned.

Adaptation: Each session, study staff will complete checklists from the KF-NAP®, the WMFT, and the KF-PAT™ manual (Chen, 2015) to track assessment and treatment fidelity. Notations will be made when modifications to administration methods are required. For the brain mapping, trained raters will map brain lesions using the method from Preliminary Study 4. Then, a blinded neurologist will classify participants as having “frontal” or “nonfrontal” lesions. Using radiology reports, lesions will be classified as “frontal” based on use of that word or “anterior” “premotor” “prefrontal” or “precentral” or as “nonfrontal” if none of those words are present.

Limited Efficacy Testing: To detect the presence of a treatment signal, we will assess spatial-motor-sensory and functional recovery over 7 weeks. We will assess: 1) Functional disability, measured by activities of daily living using the Barthel Index ((Mahoney and Barthel 1965) and cognitive and motor function with the FIM or FONE-FIM; 2) Spatial neglect, measured by the Behavioural Inattention Test-conventional subtest ((Wilson, Cockburn, and Halligan 1987) and CBS via the KF-NAP® (Chen et al. 2012); 3) Motor function, measured by the WMFT (Lin et al., 2009); and 4) Pain, measured by the Defense and Veterans Pain Rating Scale ((Polomano et al. 2016), which includes numbers along with pictures and colors to facilitate nonverbal rating of pain. Assessments will be administered by a trained examiner.