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Study Title	Determining the Implicit and Rule-based Learning Ability of Individuals With Aphasia to Better Align Learning Ability and Intervention
NCT Number	05119023
Document Description	IRB approved protocol
Document Date	Document version date = 8/30/22

PARTNERS HUMAN RESEARCH COMMITTEE
PROTOCOL SUMMARY

Answer all questions accurately and completely in order to provide the PHRC with the relevant information to assess the risk-benefit ratio for the study. Do not leave sections blank.

PRINCIPAL/OVERALL INVESTIGATOR

Sofia Vallila Rohter

PROTOCOL TITLE

Determining the implicit and rule-based learning ability of individuals with aphasia to better align learning ability and intervention

FUNDING

NIH NIDCD R21 DC019203-01

VERSION DATE

Version 7: 8/30/22

SPECIFIC AIMS

Concisely state the objectives of the study and the hypothesis being tested.

The objective of this study is to examine learning in individuals with post-stroke aphasia (acquired language impairment). We aim to determine a behavioral phenotype of learning for people with aphasia (PWA), examining how cognitive-linguistic variables and stroke characteristics (lesion size and location) relate to learning.

To this end, the aims are as follows:

Aim 1. Determine the presence of selective deficits in observational (implicit) and rule-based learning in individuals with aphasia. Participants in our study will be stratified in to one of four learning profiles: learning under (a) both conditions, (b) rule-based conditions only, (c) observational conditions only, and (d) no condition. Pilot work conducted in eighteen individuals with aphasia has identified equal percentages of learners of type a, c and d (20% of pilot participants in each stratification) with 40% showing learning under rule-based conditions only, supporting the hypothesis that differences in learning profile arise among PWA.

Aim 2. Determine the predictors of observational and rule-based learning, incorporating subject-specific measures of structural brain damage, aphasia severity, attention, verbal working memory and executive function. We will use regression models to determine predictors of observational learning and rule-based learning, evaluating findings against theoretical frameworks. We predict that preservation of the striatum and selective attention will contribute to observational learning ability. Preservation of the prefrontal cortex, verbal working memory and executive function are expected to contribute to rule-based learning ability.

BACKGROUND AND SIGNIFICANCE

Provide a brief paragraph summarizing prior experience important for understanding the proposed study and procedures.

Aphasia is an impairment in the expression or comprehension of language that results from stroke, traumatic brain injury or progressive neurological disease. Research has shown that speech-language therapy, the treatment for aphasia, can significantly improve people's ability to communicate. However, A major challenge facing the field of aphasia rehabilitation is the variable response to intervention; while some patients respond to therapy, others show limited progress.

One relatively unexplored possibility is that response to intervention is, in part, due to differences among how patients best learn, which we refer to as learning phenotype. Although learning phenotypes have been used to inform rehabilitation treatments in other domains, treatments for aphasia are currently selected almost exclusively based on language abilities with little to no attention to underlying learning abilities. Our overarching hypothesis is that poor alignment of learning ability and language therapy limits progress and contributes to the variability in outcomes.

During aphasia rehabilitation, patients are guided to relearn language, reaccess language or regain functional use of language via therapies that involve stimuli, tasks, cues and feedback (see Horton, 2006). Consequently, the process of therapy implicitly engages many mechanisms of learning that need to be systematically considered in aphasia. Evidence is emerging to suggest that nonlinguistic learning is impaired in individuals with aphasia (Schuchard & Thompson, 2014; Vallila-Rohter & Kiran, 2013a; Vallila-Rohter & Kiran, 2013b); and furthermore, that PWA develop strategies less consistently and less effectively than non brain-damaged controls (Vallila-Rohter & Kiran, 2015). We suggest that the contribution of underlying cognitive systems is essential to relearning in aphasia and that understanding the behaviors associated with learning are critical for our understanding of the mechanisms of therapy and ways to better tailor treatment to individuals.

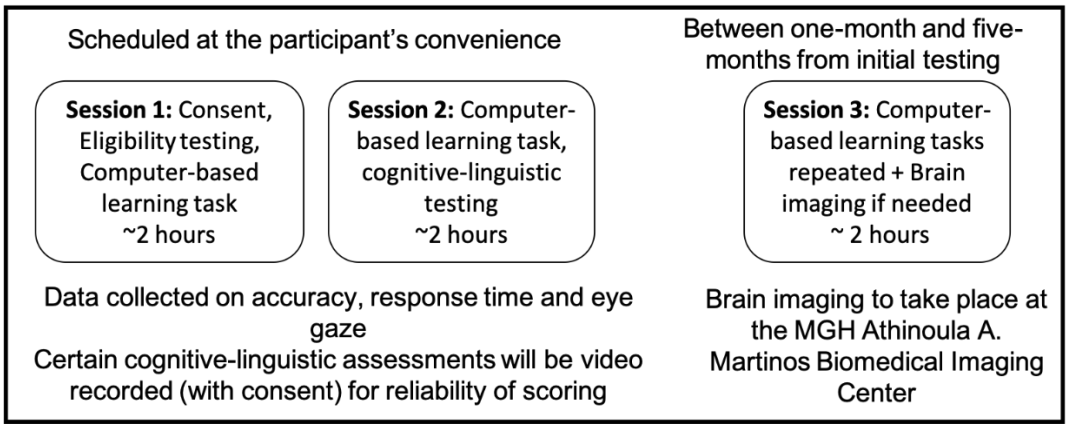
In aphasia, little is understood about how task and treatment manipulations impact patient behaviors and progress with therapy. We propose to thoroughly examine the behaviors of learning and the cognitive-linguistic and lesion characteristics that relate to learning, to characterize a phenotype of learning for individuals with aphasia, setting the foundations for intervention studies aimed at individually tailoring treatment and improving the predictability of outcomes.

RESEARCH DESIGN AND METHODS

Briefly describe study design and anticipated enrollment, i.e., number of subjects to be enrolled by researchers study-wide and by Partners researchers. Provide a brief summary of the eligibility criteria (for example, age range, gender, medical condition). Include any local site restrictions, for example, "Enrollment at Partners will be limited to adults although the sponsor's protocol is open to both children and adults."

Study Design

In this cross-sectional study, 75 participants will complete language and cognitive assessments and behavioral tests of learning. A subset of participants will also complete a structural magnetic resonance imaging (MRI) scan to obtain structural brain images.



Sessions 1 & 2 described above, may take 3 sessions. If an additional session is needed, participants may complete this session in person or over Zoom based on preference. Session 3 described above, may be broken into 2 sessions based on participant scheduling preference.

Participants will be tested over three to five sessions during which they will complete: (a) behavioral testing, (b) structural scanning. We anticipate that behavioral sessions (a) and (b) will take around 6 to 7 hours to complete.

(a) Behavioral testing: Participants will be asked to come to research facilities at the MGH-Institute of Health Professions for behavioral testing. During these sessions, participants will complete standardized cognitive-linguistic assessments and computer-based observational and rule-based tasks, that allow for collection of accuracy, response time and eye gaze data. Most participants are expected to complete behavioral tasks in two to three, two-hour sessions. Some participants may prefer to schedule shorter, and more frequent test sessions and this will be accommodated, and tasks that can be administered over Zoom without affecting data quality (such as those that do not collect response times) can be collected over Zoom if preferred by participants.

(b) Structural scanning: The majority of participants will also complete a structural magnetic resonance imaging (MRI) scan in a 3Tesla scanner at the MGH Athinoula A. Martinos Biomedical Imaging Center to obtain structural images of their brain.

In order to participate in brain scans, participants must:

- be safe to participate as determined by the MR eligibility criteria outlined under eligibility, and
- produce scores of learning on at least one behavior learning task that are above chance. Since brain scan data are being utilized to evaluate and predict learning profile, individuals must show learning on at least one task.

  High resolution clinical MRI scans from hospitalizations may be available for some participants. These scans will be requested, and if judged to be of high quality (e.g. no evidence of motion artifact, whole brain coverage, axial slices with voxels smaller than 3mm) participants may not need to participate in the structural scan at the MGH Athinoula A. Martinos Center for Biomedical Imaging. Scanning will occur on a separate day or on one of the behavioral testing days.

Eligibility criteria are as follows:

- Be between the ages of 18 and 80 years of age
- Have aphasia due to left hemisphere stroke per report and need for speech language therapy
- Be in the chronic stages of aphasia, at least 6 months post onset of stroke
- Report pre-morbid native-speaker level fluency in American English
- Due to the visual nature of stimuli, have near to normal uncorrected or corrected vision per self-report without the presence of visual field cuts or visual neglect as determined by a score within the range of +/-2.5 Comprehensive Aphasia Test (CAT; Hove, 2004)
- Pass a hearing screening (thresholds of <40dB at 1, 2 and 4kHz in at least one ear)

Exclusion criteria are as follows:

- history of significant mental illness, psychiatric disorder, drug/alcohol abuse or neurological condition such as Parkinson's Disease, Alzheimer's Disease, Huntington's Disease or Cerebral Palsy that could influence cognitive, learning and memory systems.
- Participants who must wear bifocals or gas-permeable contact lenses to view pictures on a computer screen are not eligible to participate, as the eye tracking system is not compatible with this type of eyewear.

Participants may have concomitant medical problems such as heart disease or diabetes; however, at the time of their participation they will be medically and neurologically stable and at least wheelchair ambulatory.

At least 80% of the research sample should score 93.8 or below on the Western Aphasia Battery (WAB). The WAB is a diagnostic test of aphasia that reports 93.8 is a possible cutoff for the determination of aphasia. Despite this cutoff, research studies and the WAB manual itself (Kertesz, 2007) have identified the presence of language impairments in individuals producing scores above this cutoff and include participants in this score range within the aphasia group (e.g. Cruice, Pritchard, & Dipper, 2014; Papanicolaou, Moore, Deutsch, Levin, & Eisenberg, 1988; Ross & Wertz, 2003; Sekine & Rose, 2013; Ulatowska et al., 2001; Ulatowska, Reyes, Santos, & Worle, 2011; Wilson et al., 2012). Differences in language behaviors have been measured between people experiencing left hemisphere stroke with scores above a 93.8 and age/education-matched control participants not having experienced a stroke (e.g. Fromm et al., 2017). It has been reported that this subgroup of individuals warrant treatment and should also be attended to in research. Fromm et al. (2017) examined data from people with aphasia included in the Aphasia Bank database, a large NIH-funded database. In their analyses, they examined data from people with aphasia with scores below a 93.8 and those above a 93.8 compared to control data. In their report, 30% of the individuals with aphasia scored above 93.8. Including 20% of the study sample within this range, therefore is in line with the representation within the AphasiaBank.

Conditions that rule out participation in scans:

- Cardiac pacemaker
- Surgical aneurysm clips
- Neurostimulator
- Implanted pumps
- Metal fragments in body/eyes
- Pregnancy
- Weight greater than 350 pounds

To participate in structural scans, participants must be MRI safe with no implanted metal devices or metal fragments that are contraindicated for the scanner. The exclusionary criterion list detailed above is determined by the Martinos Center. All consented participants will complete an MRI screening form to screen for exposure to metal/surgical implants. Medical records will be obtained to ensure MRI safety if needed.

Participants will be asked about the following conditions, outlined by the Martinos Center as these can render one ineligible or must be removed prior to participation in an MR scan:

- Ear implants (certain cochlear implants are not MR safe)
- Metal rods, plates or screws in body or mouth
- Injury to eyes involving metal
- Previous surgery (if metal left in body)
- IUD (most are MR safe, except Copper-7)
- Hearing aid (should be removed before scanning)
- Dentures (should be removed before scanning)
- History of vestibular or inner ear abnormality such as Meniere's Disease
- Prosthetic heart valve (most are MR safe, but this must be verified prior to participation)
- Hair extensions (most are connected with wire and cause artifacts in data)
- Tattoos or permanent eyeliner (if ink contains metallic specks)

- Tattoos obtained outside of the U.S. (must be approved for scanning by the Martinos Operations Manager prior to the day of the scan.
- Nicotine patches (those with foil backing must be removed prior to scanning)

Additional screening considerations

- Claustrophobia
- Physical discomfort lying flat (back or neck pain etc)
- Movement disorders (i.e. ticks, restless legs etc. that might cause movement artifact)

Data to be collected

1) For learning tasks (see below), data will be collected on accuracy, reaction time, and eye gaze position. Accuracy and reaction time data will automatically be collected by the computer program, E-Prime. Information about eye gaze will be collected using a near-infrared eye tracker (the Eyelink 1000 Plus) that is physically unobtrusive and conforms to 62471 standards of conformity established by the International Electrotechnical Commission (IEC) for photobiological safety of lamps and lamp systems.
2) Measures obtained during cognitive-linguistic assessments are standardized and include accuracy of responses, as well as transcription of verbal responses to prompts. Most data will be collected in real-time as assessments are administered. Assessments will be video recorded to perform reliability on assessments and additional scoring/transcription of responses as needed. Many of these assessments can be administered in person or remotely without altering data quality.

The following assessments will be administered:

Test administered	Purpose
Western Aphasia Battery (WAB; Kertesz, 2006)	To determine the presence and type of aphasia
Cognitive Linguistic Quick Test (CLQT; Helm-Estabrooks, 2017)	Symbol cancellation subtest: screener for visual neglect. Visual neglect present if no shapes selected in at least one quadrant Other subtests used to evaluate executive function (self monitoring, flexibility, attention, shifting)
Test of Every Day Attention (TEA; Robertson et al., 2001)	Evaluates auditory sustained attention, visual and verbal working memory
Temple Assessment of Language and (Verbal) Short-term Memory in Aphasia (TALSA; Martin et al., 2018) listening span, synonymy triplet and lexical comprehension subtests	Evaluates lexical-semantic short-term memory and working memory
Berg Card Sorting Test (http://pebl.sourceforge.net/)	Evaluates executive function (self monitoring, flexibility, attention, shifting)
Northwestern Assessment of Verbs and Sentences (NAVS; Thompson, 2012) sentence production priming and sentence comprehension subtests	Evaluates grammatical abilities/syntax. Higher scores on canonical > noncanonical sentences indicate the presence of agrammatism
Villard Sustained Attention Task (Villard & Kiran, 2015)	Evaluates visual sustained attention

Tompkins Listening span task (Tompkins et al., 1994)	Evaluates auditory-verbal working memory

Brief overview of statistical methods

Aim 1. Determine the presence of selective deficits in observational (implicit) and rule-based learning in individuals with aphasia.

Observational learning tasks: Participants will complete two observational learning tasks: Serial Response Time (SRT) Observational learning and Artificial Grammar Learning (AGL) Observational learning.

For the SRT observational learning task (described below), responses are made via eye gaze into a visual area of interest (AOI). Reaction times (RTs) are recorded as the time between target onset and gaze fixation within the target AOI. A trial is considered incorrect if an eye fixation was made that does not correspond to the target AOI. RTs for correct trials are examined. Outlier RTs three standard deviations above the mean RT of each block will be removed. A score of learning will be computed by comparing RTs on the last (7^{th}) sequenced block of trials with RTs on the following (8^{th}) pseudorandomized block (Schwarb & Schumacher, 2012). A Cohen's *d* effect size (ES) of observational learning will be calculated for each individual participant that compares mean RTs on the final sequenced block (S7) and the pseudorandom block (PS8) using pooled standard deviations. Any participant producing a small ES of 0.2 or above (Cohen, 1988) will be classified as a learner in the observational learning condition.

For the AGL Observational learning task (described below), data are collected on the accuracy of match, non-match responses during training computed as a percent correct. Data are also collected as a percent correct score in the testing phase. Each stimulus will be presented two times in testing and accuracy will be coded as 1 (correct) if on both presentations the participant made a correct response. If the item is classified incorrectly on 1 presentation or both presentations, the response for that item will be coded as 0 (incorrect). A threshold probability of 25% will be utilized to characterize performance as above chance and classify a participant as a learner under AGL Observational conditions.

Rule based learning task: For the rule-based task (described below), data are collected on the number of rules learned within the instruction period. Data are also collected on accuracy in testing. An accuracy score is computed for the test phase and is the dependent measure of rule learning. We will compute binomial chance probability. A threshold probability of 50% will be utilized to characterize performance as above chance and classify a participant as a learner under rule-based methods. Any participant whose score does not meet criterion, will be stratified as demonstrating selective weakness in rule-based learning.

Aim 2. Determine the predictors of observational and rule-based learning, incorporating subject-specific measures of structural brain damage, aphasia severity, attention, verbal working memory and executive function.

Calculations of lesion volume and spared tissue. Implicit and rule-based learning are thought to engage partially overlapping brain networks that include the striatum, dorsolateral prefrontal cortex, medial prefrontal cortex, anterior cingulate, thalamus, medial temporal lobe, superior and inferior parietal cortex, occipital gyrus and cerebellum (e.g.,Destrebecqz et al., 2005; Paniukov & Davis, 2018; Peigneux et al., 2000; Reber, 2013; Schneyer et al., 2009; Squire, 1992; Willingham et al., 2002). The amount of spared tissue within regions of this network will be calculated based on previously established methods (Kiran et al., 2015; Meier et al., 2016; Sims et al., 2016). For each PWA a lesion map, in which the lesioned voxels are

assigned a binary value (1 or 0), are normalized from native to MNI space (a standard brain space utilized in imaging studies). The individualized lesion map is subtracted from each brain region of interest (ROI) to yield the volume of spared tissue per ROI. The percentage of spared tissue in each region is calculated by dividing the volume of spared tissue by the total volume of the MNI atlas ROI. We will use MATLAB to identify the union of lesion maps and anatomical ROIs from the MNI template to compute lesion volume and percent spared tissue for each ROI. Percent spared tissue in ROIs will be entered into regression models evaluating predictors of learning.

Cognitive Linguistic Assessments: Language and cognitive assessments will be scored based on norms and methods of administration and scoring provided in testing manuals and publications.

Composite scores of sustained attention, executive function, and auditory-verbal working memory will be computed for entry into regression models.

***Data Analyses*:** Linear regression models will be run to determine the predictors of learning. Separate models will be examined for SRT observational, AGL observational and rule-based and learning. The dependent variable for SRT observational learning will be Cohen's d effect size for the first round of learning computed in Aim 1. The dependent variable for AGL observational learning will be percent correct in testing computed in Aim 1. The dependent variable for rule-based learning is percent accuracy obtained in Aim 1. We anticipate that accuracy rates will fall between .2 and .8 which is recommended if accuracy rates are to be used as a dependent variable for a linear regression. If scores fall outside of this range, we will switch to a logistic regression model where number of successes and the total number of trials are incorporated into the analysis.

Extensive, partially-overlapping neural networks have been identified to support implicit and rule-based learning. In proposed regression models, we first propose to include percent spared tissue in those ROIs that have shown differential activation in observational versus rule-based learning. Thus, for observational learning, the striatum, which shows enhanced engagement in implicit over rule based learning will be included (e.g. Destrebecqz et al., 2005; Peigneux et al., 2000; Schendan et al., 2003) along with composite scores of visual attention, as attention has been found to be important for implicit learning (e.g. Franklin et al., 2016; Seger 1994). We will evaluate the statistical significance of a regression model with two predictors: percent spared tissue in the striatum and cognitive scores of attention, evaluating the statistical significance of the model and variability accounted for.

For rule-based learning, studies have identified the prefrontal cortex as an important neural substrate that shows increased engagement in rule-based relative to observational learning (e.g. Byrne et al., 2016; Milton et al. 2009; Panuikov & Davis, 2018; Tracey et al., 2003). Verbal working memory and executive functions also play a rule in rule management and shifting (e.g. Carpenter et al., 2016). Thus, we will evaluate the statistical significance of a regression model with three predictors: percent spared tissue in the prefrontal cortex and cognitive scores of working memory and executive function, evaluating the statistical significance of the model and variability accounted for.

Power estimations and justification of sample size. Power analysis for a multiple regression with two predictors was conducted in G*Power to determine a sufficient sample size using an alpha of 0.05. Using an effect size $f^2 = 0.25$, based on correlations of .38 between striatal activation and implicit learning (Peigneux et al., 2000) and on correlation values of .32 between attention and implicit learning from pilot data, with a sample size of 50 we will have power greater than .90 to detect significant effects.

For rule-based learning, a power analysis was conducted in G*Power including 3 predictors. An effect size f^2 of .28 was estimated based on correlations between prefrontal

cortex activation and rule-based learning of 0.34 (Paniukov et al., 2018) and correlations between executive functions, attention and learning that range from .25 to.72 (based on Schnyer et al. 2009 and our pilot work). To achieve 85% power with an alpha of .05 a sample size of 49 is necessary.

Additional participants are included in this IRB to account for potential attrition and the possibility that some participants do not learn tasks limiting the interpretability of results.

Briefly describe study procedures. Include any local site restrictions, for example, "Subjects enrolled at Partners will not participate in the pharmacokinetic portion of the study." Describe study endpoints.

Participants who agree to participate and who provide informed consent will perform 3 to 5, sessions up to 2 hours long. Some participants may prefer to schedule testing over a series of several sessions, which will be accommodated. During these sessions, they will complete:

- SRT Observational (implicit) learning task
- AGL Observational (implicit) learning task
- Rule-based learning task
- Cognitive-linguistic assessments
- Brain Scan

Learning tasks are computer based. Tasks involve looking at pictures, shapes. listening to audio instructions and making button presses. Participants will receive audio and visual instructions. They will complete short practice blocks and have the opportunity to ask questions prior to completing tasks.

Observational (implicit) learning tasks (~ 45 mins):

Observational learning will be evaluated using two tasks: SRT observational learning and AGL observational learning.

The SRT Observational learning task is a classic paradigm, which has been integral to the understanding of implicit learning (see Schwarb & Schumacher, 2012). The SRT that we propose to use to characterize observational learning is a replication of classic SRT tasks first described by Nissen and Bullemer (1987), adapted for eye-tracking by Kinder et al. (2008) and piloted by our team in PWA, young adult and older adult controls. During this task:

- Participants will be seated at least 50 cm from a computer screen with their chin resting on a chin rest.
- The chin rest and chair level will be adjusted for comfort
- The eyetracking camera will be focused on one of the participant's eyes (right eye or dominant eye).
- Four geometric shapes will appear on screen
- A target dot will move from shape to shape
- Participants will be instructed to look at the dot as it moves from shape to shape via audio and visual instructions
- For some study blocks, dot movement follows a pattern (sequenced blocks)
- For other study blocks, dot movement is pseudorandomized

The AGL Observational learning task is another classic test of implicit learning involving learning of ordered items through exposure (Schuchard & Thompson, 2017). Artificial grammars contain hierarchal dependencies, similar to the rules that govern word-order and syntax in natural language. Therefore, the artificial grammars may more evidently reveal learning deficits among

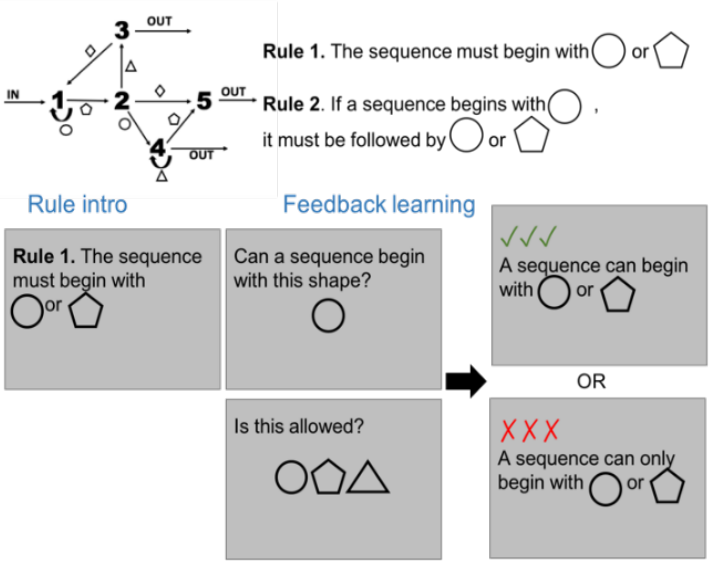
PWA compared to the relatively simple serial reaction time (SRT) task (Schuchard & Thompson, 2017). During the AGL task:

- Participants will be seated a comfortable distance from a computer screen
- In an exposure phase, participants will look at pictures of two to six geometric shapes on a screen
- Participants will judge if two pictures presented in sequence match or do not match
- Responses are made via button press
- After training, participants complete a testing phase
- In testing, participants are informed that geometric sequences followed a pattern. Participants will be shown sequences and must judge if sequences adhere to the pattern or not via button press

Rule-based learning task (~30 mins):

To evaluate rule-based learning, participants will learn rules underlying an artificial grammar that contains hierarchical dependencies similar to the rules that govern word-order and syntax in natural language (Saffran, 2001) but are expressed in non-linguistic form (e.g. with shapes). In the rule-based task:

- Participants will be seated a comfortable distance from a computer screen
- Two to six geometric shapes will appear on screen
- Through visuals and audio instructions, participants will be taught rules of the grammar
- Once a rule is taught, participants answer yes/no questions related to the rule (see figure for examples).
- At the end of training, participants will be shown sequences and must judge if sequences adhere to the rules or not via button press



Cognitive-linguistic assessments

Participants will complete cognitive-linguistic assessments that evaluate their ability to produce and understand language and evaluate cognitive skills of attention, executive function and working memory important for learning. Tests involve paper and pencil, looking at pictures, listening to words, indicating responses on a keyboard and talking. Participants will be asked to do things such as:

- answer questions
- follow directions
- repeat words and phrases
- look at pictures and talk about them
- read and write short sentences
- complete mazes or find symbols
- remember images and recognize them after a short delay
- identify missing elements that complete a pattern

Brain Scan

For the brain scan, participants will be screened to ensure that there is no metal on their body or in their pockets. They will then lie on a table that is slid into the MRI scanner. Participant will be given earplugs and headphones to reduce the noise made by the MRI scanner. Foam pads will be placed around their head to help it keep still during the MRI scan. Participants will be given a panic button that allows them to contact the researcher or MRI technician. Scan sessions are expected to take up to 30 minutes.

For studies involving treatment or diagnosis, provide information about standard of care at Partners (e.g., BWH, MGH) and indicate how the study procedures differ from standard care. Provide information on available alternative treatments, procedures, or methods of diagnosis.

N/A. This is not a treatment or diagnostic study

Describe how risks to subjects are minimized, for example, by using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk or by using procedures already being performed on the subject for diagnostic or treatment purposes.

Minimizing risk during learning tasks and cognitive linguistic assessments: Participants may experience some frustration during the course of the study, however, this frustration is not expected not be more than that what would be faced in situations requiring focused, sustained attention for learning. A researcher will be present to answer any questions or concerns participants might experience and tasks will be tailored to a level that is appropriate for participants. Participants will be offered the opportunity for breaks.

Minimizing risk to confidentiality: To minimize confidentiality risks posed by videotaping (cognitive linguistic assessments), attempts will be made to position participants such that their faces are not captured in the videos. Since it is possible that faces may appear in videos, all video material will be stored on a password protected network to which only IRB approved researchers have access.

Minimizing risks of eye-tracking: The potential for eye-damage due to the use of an infra-red eye-tracking sensor is extremely unlikely, due to the limited power and wavelength of the sensor, the short duration of the study, its distance from the participant, and the natural protective abilities of the eye. The Eyelink 1000 Plus has been tested and approved by certified labs according to the standards of conformity established by the International Electrotechnical Commission (IEC) 62471 standards for photobiological safety of lamps and lamp systems. Light emission that meets the standard of photobiological safety of lamps and lamp systems is safe under any conditions, including using optical viewing devices and lenses.

There are minimal risks, eyestrain/slight discomfort being the most serious if eye safety instructions are not followed. We will ensure that the following precautions are followed:

- Participants will be seated a minimum of 500mm (50cm) distance from the illuminator as recommended by manufacturers for best data quality to ensure that the eye tracker can track participants over a maximum viewing angle.
    - Per manufacturer specifications, distances of under 100mm (4 inches) from the illuminator for an extended period of time, are those that may result in discomfort and unnecessary exposure to heat and levels of infrared (IR) light.
- The illuminator will be mounted on a manufacturer-provided desk mount to avoid unnecessary skin contact that can cause minimal discomfort due to heat from the illuminator.

Minimizing risks of magnetic resonance imaging (MRI): There are no known physical, social, or legal risks or side effects associated with MRI scanning in this study. The magnetic fields used in this study are considered to be harmless and the proposed MRI scanning procedures fall within the FDA guidelines for radiofrequency electromagnetic field exposure. Electrically, magnetically or mechanically activated implants (e.g., cardiac pacemakers), clips on blood vessels in the brain, or other metallic objects in the body such as shrapnel, bullets, buckshot, or metal fragments pose a risk to participants entering an MRI scanner. Therefore, participants will be carefully screened as described below to ensure absence of these items. Although there are no known risks of an MRI scan to the unborn fetus, we will not permit participation by anyone who is or suspects they may be pregnant.

Some participants may experience claustrophobia while in the bore of an MRI scanner. Participants will be asked to notify the PI or MRI technician if they are prone to claustrophobia prior to entering the scanner. The MRI scanner makes loud knocking or beeping sounds during imaging, which are adequately reduced to a safe and comfortable level with earplugs and

headphones. The rapid rate of change of the magnetic gradients during imaging may cause peripheral nerve stimulation, causing participants to feel a creeping or tingling sensation along their arms or lower back. Movement of the head in the bore of the magnet may cause dizziness and nausea. The radio frequency coils, cables to the coils, and response and physiological monitoring devices may produce heat, but the machine is calibrated so that this heating will be no more than one degree of body temperature. Participants will be given a panic button and instructed to notify the PI or the MRI technician immediately if, at any time, they feel uncomfortable, no matter what the reason.

Describe explicitly the methods for ensuring the safety of subjects. Provide objective criteria for removing a subject from the study, for example, objective criteria for worsening disease/lack of improvement and/or unacceptable adverse events. The inclusion of objective drop criteria is especially important in studies designed with placebo control groups.

As described above, multiple measures will be taken to minimize risk including measures to limit the amount of identifiable data collected and/or visible on videotapes and clips. Study codes will be utilized to maintain the privacy of files on a password protected network.

If patient privacy and confidentiality is compromised (if unapproved parties, for example access identifiable video clips), the IRB will be immediately notified.

As there are no known significant risks or side effects associated with procedures, objective criteria for removal are not necessary. Participants may indicate at any point that they wish to discontinue their participation.

FORESEEABLE RISKS AND DISCOMFORTS

Provide a brief description of any foreseeable risks and discomforts to subjects. Include those related to drugs/devices/procedures being studied and/or administered/performed solely for research purposes. In addition, include psychosocial risks, and risks related to privacy and confidentiality. When applicable, describe risks to a developing fetus or nursing infant.

Forseeable risks/discomforts of cognitive linguistic assessment: Videotaping collected for reliability purposes, for coding and transcription of data poses a risk to participant privacy and confidentiality. Measures (described above) will be taken to limit the amount of identifiable data contained in videos, and data will be stored on a password protected network. In addition Zoom enterprise will be used which has additional restrictions on cloud storage etc. For individuals with aphasia, some tasks may be difficult and therefore frustrating. This frustration is not to be more than that what would be faced in situations requiring focused, sustained attention for learning. The participants will be asked to notify the researcher if at any time they feel uncomfortable or wish to stop participating, no matter what the reason.

Forseeable risks/discomforts of eye tracking: As indicated above, there are minimal risks associated with the eye-tracking device, the most serious being eye strain. Participants will be informed of this risk during the consent process. They will be able to withdraw from the study at any time should they experience discomfort.

Forseeable risks/discomforts of magnetic resonance imaging: All participants be screened prior to entry into the magnet room to ensure the absence of electrically, magnetically or mechanically activated implants (e.g., cardiac pacemakers), clips on blood vessels in the brain, or other metallic objects in the body such as shrapnel, bullets, buckshot, or metal fragments which pose a risk to participants entering an MRI scanner. Additionally, all participants will be asked to remove all metallic and magnetic objects in their possession (e.g., keys, jewelry, credit cards)

from their person before entering the magnet room. Participation by anyone who is or suspects they may be pregnant will not be permitted.

As noted above, participants will be asked to notify the PI or MRI technician if they are prone to claustrophobia prior to entering the scanner. Participants with claustrophobia will be allowed to continue the study, if desired, and will receive instructions of how to contact the researchers while inside the scanner to request removal in case of claustrophobic discomfort. Participants' hearing will be protected from the loud knocking or beeping sounds during imaging with earplugs and headphones, which will reduce the noise to a safe and comfortable level.

EXPECTED BENEFITS

Describe both the expected benefits to individual subjects participating in the research and the importance of the knowledge that may reasonably be expected to result from the study. Provide a brief, realistic summary of potential benefits to subjects, for example, "It is hoped that the treatment will result in a partial reduction in tumor size in at least 25% of the enrolled subjects." Indicate how the results of the study will benefit future patients with the disease/condition being studied and/or society, e.g., through increased knowledge of human physiology or behavior, improved safety, or technological advances.

No direct benefits are expected for participants. The current study is designed to address the important issue of learning after aphasia-inducing stroke. Speech-language therapy is the treatment for aphasia and relies heavily on behavioral therapies that engage distinct neural and behavioral systems, but are not currently evaluated. In order to better tailor treatment to individuals and more effectively predict outcomes, we must equip clinicians with ways to characterize learning in individual patients, further identifying stimulus or task manipulations that lead to the development of effective strategies for patients.

EQUITABLE SELECTION OF SUBJECTS

The risks and benefits of the research must be fairly distributed among the populations that stand to benefit from it. No group of persons, for example, men, women, pregnant women, children, and minorities, should be categorically excluded from the research without a good scientific or ethical reason to do so. Please provide the basis for concluding that the study population is representative of the population that stands to potentially benefit from this research.

There are no exclusionary subject criteria with respect to gender, race or ethnicity. Minors will not be studied, as the incidence of stroke in younger individuals is low, and furthermore, the mechanisms of neural plasticity in adults and children are different, resulting in different impacts of stroke in children.

When people who do not speak English are excluded from participation in the research, provide the scientific rationale for doing so. Individuals who do not speak English should not be denied participation in research simply because it is inconvenient to translate the consent form in different languages and to have an interpreter present.

One aspect of this research is to examine learning in the context of language deficits. We are excluding non-English speakers because we are testing speech and language ability in the individuals with aphasia.

For guidance, refer to the following Partners policy:

Obtaining and Documenting Informed Consent of Subjects who do not Speak English **https://www.partners.org/Assets/Documents/Medical-Research/Clinical-Research/Non-English-Speaking-Subjects.pdf**

RECRUITMENT PROCEDURES

Explain in detail the specific methodology that will be used to recruit subjects. Specifically address how, when, where and by whom subjects will be identified and approached about participation. Include any specific recruitment methods used to enhance recruitment of women and minorities.

Individuals with aphasia will be recruited by referral from physicians, speech-language pathologists, neuropsychologists. We will mail and email recruitment letters to neurologists and speech pathologists in the greater Boston area. Interested professionals will describe the study to the potential participants and ask them to contact the researcher if they are interested in participating in the study. Individuals who have participated in lab for previous studies and have indicated that they agree to be contacted for future studies may be contacted. A member of the research team will contact these participants via phone call.

Individuals with aphasia will also be recruited from the MGH-Institute of Health Professions Aphasia Center. Speech language pathologist will share study flyers with individuals with aphasia and ask if individuals are interested in meeting a member of the research team to learn more about the study. If they express interest, a member of the research team will be invited to come to the end of an upcoming scheduled therapy session to talk more about the study. It will be clearly communicated that the treating Speech language pathologist has no affiliation to the research study and that expressing or not expressing an interest to speak to research staff, in no way impacts the therapy services they receive in the MGH-IHP Aphasia Center.

In addition, participants will be recruited via word of mouth, flyers/presentations, and email posts on listservs. We will also recruit via RSVP for health. Information about research studies will be posted on the Institute's website.

Provide details of remuneration, when applicable. Even when subjects may derive medical benefit from participation, it is often the case that extra hospital visits, meals at the hospital, parking fees or other inconveniences will result in additional out-of-pocket expenses related to study participation. Investigators may wish to consider providing reimbursement for such expenses when funding is available

Participants will be compensated for their time and participation in the study. They will be compensated $10/hour of participation in behavioral sessions (anticipate ~ $70/participant to complete all behavioral tasks and assessments). Participants will be compensated more than $50 and therefore will be compensated via check. We will notify participants that a social security number and valid US address will be collected and reported in the MGB eCheck submission.

Participants who complete a structural scan will be compensated an additional $50.

Participants driving to the research site may park in the Building 199 parking garage in the Charlestown Navy Yard. Participants will be given a parking voucher on each day of study participation that they can use in Parking garage buildings upon exit without incurring any personal costs.

For guidance, refer to the following Partners policies:
Recruitment of Research Subjects

https://www.partners.org/Assets/Documents/Medical-Research/Clinical-Research/Recruitment-Of-Research-Subjects.pdf

Guidelines for Advertisements for Recruiting Subjects
https://www.partners.org/Assets/Documents/Medical-Research/Clinical-Research/Guidelines-for-Advertisements.pdf

Remuneration for Research Subjects
https://www.partners.org/Assets/Documents/Medical-Research/Clinical-Research/Remuneration-for-Research-Subjects.pdf

CONSENT PROCEDURES

Explain in detail how, when, where, and by whom consent is obtained, and the timing of consent (i.e., how long subjects will be given to consider participation). For most studies involving more than minimal risk and all studies involving investigational drugs/devices, a licensed physician investigator must obtain informed consent. When subjects are to be enrolled from among the investigators' own patients, describe how the potential for coercion will be avoided.

Once interest in participating in the study is expressed, one of the research staff involved in this study will establish contact with potential participants over the phone or via email. The research project will be explained and screening questions will be asked. ~~and~~ Interested persons will be invited to the research site to discuss the study.

The patient and his/her spouse/next of kin will be invited to the laboratory to discuss the study with a member of the research staff with speech-language pathology training and experience working with individuals with aphasia. In this meeting, research staff will explain the study using simple language. She/he/they will also have sample materials from the study, such as pictures of stimuli to help explain study paradigms. Extra care will be taken to ensure that subjects understand the nature of the study. We will offer to read the consent form to these individuals as reading can be difficult, and information will be reiterated verbally. Individuals and family members will be encouraged to interrupt, ask questions and seek clarifications. They will be given time to assess presented information and formulate questions. Individuals with aphasia are considered capable of making informed decisions and provide consent as indicated in the National Aphasia Association Bill of Rights (2005). Therefore, family members may be present when study procedures are explained, but individuals with aphasia will be giving or declining to give informed consent. The purpose, procedures, possible benefits and risks of the study will be explained. Potential participants will also be instructed that they can withdraw from the study at any time.

NOTE: When subjects are unable to give consent due to age (minors) or impaired decision-making capacity, complete the forms for Research Involving Children as Subjects of Research and/or Research Involving Individuals with Impaired Decision-making Capacity, available on the New Submissions page on the PHRC website:
https://partnershealthcare.sharepoint.com/sites/phrmApply/aieipa/irb

For guidance, refer to the following Partners policy:
Informed Consent of Research Subjects:
https://www.partners.org/Assets/Documents/Medical-Research/Clinical-Research/Informed-Consent-of-Research-Subjects.pdf

DATA AND SAFETY MONITORING

Describe the plan for monitoring the data to ensure the safety of subjects. The plan should include a brief description of (1) the safety and/or efficacy data that will be reviewed; (2) the planned frequency of review; and (3) who will be responsible for this review and for determining whether the research should be altered or stopped. Include a brief description of any stopping rules for the study, when appropriate. Depending upon the risk, size and complexity of the study, the investigator, an expert group, an independent Data and Safety Monitoring Board (DSMB) or others might be assigned primary responsibility for this monitoring activity.

NOTE: Regardless of data and safety monitoring plans by the sponsor or others, the principal investigator is ultimately responsible for protecting the rights, safety, and welfare of subjects under his/her care.

Forms containing personally identifying information such as contact information and questions related to eligibility, are programmed in RedCap with responses directly entered into RedCap. Cognitive-linguistic assessment data is collected on paper forms that will be kept in a locked filing cabinet at the MGH-IHP to which only the PI and approved study staff have access. Information will be transferred into a secure HIPAA compliant web-based application: RedCap to which only approved researchers have access.

Digital data (such as study reaction time, accuracy files, certain cognitive-linguistic assessments such as the TALSA and eye tracking data) will initially be collected on an encrypted, password protected laptop (accessed by the PI and study staff) or desktop computer. Data will be transferred to Dropbox, a secure network or web-based electronic lab notebook, LabArchives, maintained by MGB, which can only be accessed by the PI and approved study staff via electronic ID. These digital files will be coded with identification codes and will not contain personally identifiable information. Deidentified standardized assessment scores will be transferred from paper forms to digital forms in RedCap. Video data will be recorded and kept on MGB Dropbox and accessed only by approved researchers. Deidentified video clips will be kept for education purposes.

MRI imaging data obtained at the Martinos Center are stored and analyzed on an MGB-hosted secure cluster to which only approved research staff have access.

De-identified data are kept for possible future analyses, which will be submitted for approval. If we re-analyze data in the future, we will notify and submit an application for approval from the IRB.

Describe the plan to be followed by the Principal Investigator/study staff for review of adverse events experienced by subjects under his/her care, and when applicable, for review of sponsor safety reports and DSMB reports. Describe the plan for reporting adverse events to the sponsor and the Partners' IRB and, when applicable, for submitting sponsor safety reports and DSMB reports to the Partners' IRBs. When the investigator is also the sponsor of the IND/IDE, include the plan for reporting of adverse events to the FDA and, when applicable, to investigators at other sites.

NOTE: In addition to the adverse event reporting requirements of the sponsor, the principal investigator must follow the Partners Human Research Committee guidelines for Adverse Event Reporting

Since the risks associated with participation in this study are low, we do not anticipate serious adverse events. In the event of internal, external adverse events, of unanticipated adverse device effects, deviations, or breaches of confidentiality; the event will immediately be assessed and the IRB office will be contacted. A detailed description of the event will be provided to the IRB. Furthermore, if it is ever deemed that the risks associated with participation places subjects at increased harm, the IRB will be notified.

MONITORING AND QUALITY ASSURANCE

Describe the plan to be followed by the principal investigator/study staff to monitor and assure the validity and integrity of the data and adherence to the IRB-approved protocol. Specify who will be responsible for monitoring, and the planned frequency of monitoring. For example, specify who will review the accuracy and completeness of case report form entries, source documents, and informed consent.

NOTE: Regardless of monitoring plans by the sponsor or others, the principal investigator is ultimately responsible for ensuring that the study is conducted at his/her investigative site in accordance with the IRB-approved protocol, and applicable regulations and requirements of the IRB.

The PI or study staff will conduct ongoing review of data to ensure completeness, accuracy and compliance with protocols. Quarterly review will ensure that participant inclusion is in adherence with enrollment criteria, that records of subject enrollment are up to date, and that procedures and study visits are being completed as proposed. Review will be completed by the PI or study staff. In the event of an adverse event, the event will be immediately reviewed. Continuing reviews will be submitted in accordance with the IRB.

For guidance, refer to the following Partners policies:

Data and Safety Monitoring Plans and Quality Assurance
https://www.partners.org/Assets/Documents/Medical-Research/Clinical-Research/DSMP-in-Human-Subjects-Research.pdf

Reporting Unanticipated Problems (including Adverse Events)
https://www.partners.org/Assets/Documents/Medical-Research/Clinical-Research/Reporting-Unanticipated-Problems-including-Adverse-Events.pdf

PRIVACY AND CONFIDENTIALITY

Describe methods used to protect the privacy of subjects and maintain confidentiality of data collected. This typically includes such practices as substituting codes for names and/or medical record numbers; removing face sheets or other identifiers from completed surveys/questionnaires; proper disposal of printed computer data; limited access to study data; use of password-protected computer databases; training for research staff on the importance of confidentiality of data, and storing research records in a secure location.

NOTE: Additional measures, such as obtaining a Certificate of Confidentiality, should be considered and are strongly encouraged when the research involves the collection of sensitive data, such as sexual, criminal or illegal behaviors.

All materials (history forms, data obtained during behavioral tasks) are for research purposes only and will be kept in confidence. History forms containing personally identifying information are maintained in RedCap, a secure database to which only study staff have access. Cognitive-linguistic assessments) collected on paper will be kept in a locked filing cabinet at the MGH-IHP to which only the PI and approved study staff have access.

During analysis, de-identified data will be pulled from RedCap coded with identification codes and will not contain personally identifiable information. The RedCap database to which only study staff have access will be the only location that stores the link between study codes and subject identifying information.

Once participants have been paid for their participation, any records containing social security numbers will be destroyed and permanently removed from their research record.

SENDING SPECIMENS/DATA TO RESEARCH COLLABORATORS OUTSIDE PARTNERS

Specimens or data collected by Partners investigators will be sent to research collaborators outside Partners, indicate to whom specimens/data will be sent, what information will be sent, and whether the specimens/data will contain identifiers that could be used by the outside collaborators to link the specimens/data to individual subjects.

N/A. Data will not be sent to research collaborators outside of Partners.

Specifically address whether specimens/data will be stored at collaborating sites outside Partners for future use not described in the protocol. Include whether subjects can withdraw their specimens/data, and how they would do so. When appropriate, submit documentation of IRB approval from the recipient institution.

N/A. No data will be stored outside of MassGeneralBrigham.

RECEIVING SPECIMENS/DATA FROM RESEARCH COLLABORATORS OUTSIDE PARTNERS

When specimens or data collected by research collaborators outside Partners will be sent to Partners investigators, indicate from where the specimens/data will be obtained and whether the specimens/data will contain identifiers that could be used by Partners investigators to link the specimens/data to individual subjects. When appropriate, submit documentation of IRB approval and a copy of the IRB-approved consent form from the institution where the specimens/data were collected.

N/A. No data will be received from outside of MassGeneralBrigham.