PROTOCOL TITLE:

2013-0964 Understanding the brain basis of language and cognitive functions through the study of individuals with brain injury and healthy controls

PRINCIPAL INVESTIGATOR:

Peter Turkeltaub, MD PhD
Neurology
202-784-1764
turkeltp@georgetown.edu

VERSION DATE:

April 15, 2020

Table of Contents

GHUCCTS Questions

GHUCCTS is the Georgetown-Howard Universities Center for Clinical and Translational Science.

Is this study a GHUCCTS Study? ____Yes __X__No

Is the project being sponsored or funded by GHUCCTS? ____Yes _X___No

Does the project utilize GHUCCTS services or facilities? ____Yes __X__No
(e.g., is the study conducted on the Clinical Research Unit (CRU), is the study supported by a GHUCCTS biostatistician, etc.)

1.0 Study Summary

Study Title	Understanding the brain basis of language and cognitive functions through the study of individuals with brain injury and healthy controls
Study Design	Hypotheses regarding the psychological and brain bases of language and cognitive functions will be tested by examining individuals with brain injury and control participants using behavioral tests and structural and functional MRI scans.
Primary Objective	To improve our understanding of the psychological and brain organization of language and cognitive functions through the study of individuals with brain injury.
Secondary Objective(s)	To improve our understanding of how the brain adapts in response to brain injury causing cognitive or language deficits.
Research Intervention(s)/ Investigational Agent(s)	Behavioral Tests of Language and Cognition MRI
IND/IDE #	N/A
Study Population	**Inclusion Criteria:** **Patients:** • Age >=18 • Brain injury resulting from stroke, trauma, infection (i.e. encephalitis), primary progressive aphasia, posterior cortical atrophy, or tumor • Learned English at 8 years or younger **Controls:** • Age >=18 • No history of brain injury resulting from stroke, trauma, infection (i.e. encephalitis), or tumor • Learned English at 8 years or younger **Exclusion criteria:** • History of other brain conditions that could impact interpretation of results (such as MS, premorbid dementia) • Severe psychiatric condition that would interfere with participation in the study **Additional Exclusion Criteria for MRIs:** • Presence metal in the body that is incompatible with MRI • Pregnancy • Claustrophobia
Sample Size	400
Study Duration for individual participants	In this study, participants will complete a battery of behavioral tests. Additionally, most subjects will complete an MRI. Sessions will be completed across approximately 2-

	6 weeks, but may be extended depending on participants' schedules and availability. Some participants will be invited to repeat these procedures again at a later date to monitor for behavioral and MRI changes over time.
Study Specific Abbreviations/ Definitions	Aphasia is an acquired language disorder that negatively impacts one's ability to speak, comprehend spoken language, read, and write. It also impacts understanding of other symbols sets, such as numbers and money.

2.0 Objectives*

2.1 **Objective:** This study aims to improve our understanding of the psychological and brain organization of language and cognitive functions through examination of individuals with brain injury.

2.2 **Hypotheses:** Behavioral outcomes from stroke vary across individuals, and relate to features of the stroke and features of the spared brain tissue.

3.0 Background*

3.1-3.3 Most of our understanding regarding the psychological and brain basis of language and other cognitive capacities has come from the study of individuals with brain injury. These studies provide two main kinds of information: (1) dissociations between psychologically separable processes, and (2) associations between psychological functions and the brain structures responsible for them.

Behavioral dissociations are critical to delineating the functional architecture underlying cognitive processes. For instance, one can demonstrate through the study of brain injured individuals that certain individuals with reading impairment (alexia) have great difficulty reading words that do not follow the ordinary rules of spelling to sound correspondences (e.g. yacht), but are easily able to read novel words that do follow these rules (e.g flig). In contrast, some other patients are easily able to read exception words, but fail completely at novel words. This illustrates one type of behavioral dissociation, which strongly suggests that exception word and regular word reading are performed through (at least partly) independent psychological operations.

The study of individuals with brain injury has also provided a great deal of information regarding the brain structures underlying cognitive operations. This work dates to the 1800s, when such work relied on post mortem examination. Since the advent of modern neuroimaging methods, like MRI, this method of investigation has grown dramatically.

From the 1970s to the 1990s, investigators began reporting detailed case series demonstrating behavioral deficits in individuals with brain injury, along with images of the damage, first as CTs, and later as MRIs. Then, in the 1990s, the Damasios and others began collating lesion locations on standard brain templates, in order to associate lesion location with behavioral deficits at the group level. Eventually, this led to a new technique first published in 2002, voxel-based lesion symptom mapping (VLSM), which borrows statistical methods from functional neuroimaging to quantify the degree to which damage at various locations in the brain contribute to observed behavioral deficits.

Beginning in the late 2000s, investigators began combining functional and structural imaging data along with detailed behavioral data on people with brain injury in order to explain both the deficits caused by brain injury AND the adaptations the brain makes after the injury to functionally compensate for the damage. Thus, by combining detailed behavioral examination with multimodal imaging data in groups of individuals with brain injury, we can learn both about how the normal brain performs cognitive operations (by examining how lesion patterns impacts behavior), but also how people recover from these

injuries (by examining the alterations in functional brain activity).

The PI of this study (Dr. Turkeltaub) is a Cognitive Neurologist, and has several years of clinical experience examining patients with cognitive and language deficits due to various kinds of brain injury. He is the Director of the MedStar National Rehabilitation Hospital Aphasia Clinic, which focuses on language deficits caused by brain injury. His laboratory has been conducting behavioral and imaging research on individuals with language deficits due to brain injury since 2012.

4.0 Study Endpoints*

4.1 **Study Endpoint:** The primary dependent variables of interest will include scores on behavioral tests and various imaging measures of brain structure, function, and connectivity.

4.2 **Safety Endpoints:** Not Applicable

5.0 Study Intervention/Investigational Agent

5.1 Not applicable. This is not a treatment study.

6.0 Procedures Involved*

6.1 **Study Design:**

Behavioral Tests of Language and Cognition: Participants will be examined using a combination of standardized tests and in-house tests of language and cognition. Typically, participants with brain injury will undergo a general assessment using elements of the Western Aphasia Battery-Revised (WAB-R), the Boston Diagnostic Aphasia Examination, and other standard language tests. The assessment will also include tests of other functions (e.g. line bisection test for visuospatial neglect), and questionnaires to be filled out by the patient and his/her family (e.g. the Communicative Effectiveness Index, Beck's Depression Inventory-II). Additional in-house tests of language and cognitive functions (e.g. pseudoword repetition, executive function, auditory perception, audiovisual integration) may be used.

MRI: MRI will be collected to obtain information regarding structural and functional brain data that may be related to performance on the behavioral tasks. Scanning may occur either the CFMI at Georgetown or the 3T research scanner at WHC (which is connected to NRH via a pedestrian bridge). Subjects will be taken to the scanner facility and placed on the bed of the scanning device after having been carefully screened. CFMI operates a Siemens 3T Prisma MRI scanner, whereas WHC operates a Phillips 3T Achieva scanner. Subjects with the following will not be allowed into the MRI scanner: cardiac pacemakers, neural pacemakers, surgical clips in the brain or blood vessels, surgically implanted metal plates, screws or pins, cochlear implants or other metal objects in their body determined to be unsafe for MRI, especially in the mouth or eyes. After the subjects' head is properly positioned in the head-holder, the patient is moved into the scanner. While the scan is being done, the subject is unable to see the experimenter or the technicians, but voice contact is maintained throughout, and the technician can see the subject. A T1-weighted sequence with 1mm cubic voxels

(MPRAGE) will be used for structural scans. Diffusion tensor imaging (DTI), fluid attenuated inversion recovery (FLAIR), High resolution T2-weighted, non-contrast perfusion (arterial spin labeling), and susceptibility-weighted imaging will use standard sequences. Functional MRI will be acquired using standard resting state, block design or event-related EPI BOLD sequences. MRI sessions will not last longer than 90 minutes.

Relationship to Protocol Pro00000315: Some participants in this study will have previously participated in a study on the use of transcranial direct current stimulation for language deficits caused by stroke or brain injury. Data collected under that protocol will be included in analyses conducted in the current study. Participants who were consented for Pro0000315 prior to approval of this protocol will be asked to provide consent for this protocol as well, if possible.

Study Partner: If a participant is unable to transport themselves safely to appointments and/or needs assistance with some aspects of the study, then that participant will need to select someone with whom they have regular contact (at least 1 day a week) as a study partner. The study partner's duties are to attend lab sessions or assist in transporting the participant to sessions, to help the participant with questionnaires and to answer questions about the subject's health.

6.2 Research Procedures

Experiment 1: Case studies of individuals with cognitive and language deficits due to brain injury. This study tests hypotheses on the psychological and brain bases of language and cognitive functions through the detailed examination of individual subjects with brain injury. Typically, the purpose of case study research is to identify dissociations between performance of different tasks that demonstrate the independence of different psychological or brain processes. Individuals with language or cognitive deficits resulting from brain injury will be identified and tested with a series of behavioral and MRI assessments as described above, aimed at dissecting the specific psychological and brain operations disrupted and spared by the injury. Because the specific hypotheses to be addressed in this experiment depend critically on the characteristics of the individual participants (i.e. we cannot know which specific hypothesis will be testable until we encounter a specific patient), and the testing is often time-critical (a dissociation may be observable at one time after the brain injury, but then resolve shortly thereafter either due to spontaneous recovery or therapy), it is not feasible to submit a new amendment describing the specific hypothesis to be addressed in each subject.

Experiment 2: Obtaining control MRI data for protocol Pro00000315. We are conducting a study investigating the use of transcranial direct current stimulation for aphasia or alexia due to stroke or traumatic brain injury. In order to interpret MRI data obtained in this study, we will require similar MRI data from a group of age-matched control subjects. Subjects will be screened for history or stroke or traumatic brain injury, and will be evaluated using a brief behavioral battery to confirm normal language and cognition. They will then complete an MRI session to obtain T1 and T2-weighted images, diffusion tensor imaging, perfusion images, resting BOLD images, and functional MRI data testing naming, reading, or speech comprehension matching that performed in Pro00000315.

Experiment 3: Group study investigating speech production. This study examines the brain basis of deficits in speech production caused by brain injury. Participants with brain injury will be tested using a general battery to characterize their language and cognitive deficits, as well as specific behavioral tests of speech production (e.g. picture description, story-telling, naming, repetition, reading, tests of inner speech), related functions relevant to specific models of speech production (e.g. procedural memory) and control tasks (e.g. written picture description, written naming, declarative memory). Performance on these tasks will be related to MRI measurements of lesion location and distribution, local cerebral perfusion, white matter connectivity, cortical thickness in preserved brain areas, and functional activity during speech production tasks (e.g. naming). Age-matched control subjects without history of brain injury will be used to determine a normal distribution of performance on behavioral tasks, and normal patterns of brain structure, connectivity and function.

Experiment 4: Group study investigating speech perception/processing. This study examines the brain basis of deficits in speech perception and processing caused by brain injury. Participants with brain injury will be tested using a general battery to characterize their language and cognitive deficits, as well as specific behavioral tests of speech perception/processing (e.g. word-to-picture matching, auditory lexical decision, Englishness judgement on pseudowords, statistical learning of novel speech, audiovisual speech perception) and control tasks (e.g. sound-to-picture matching, statistical learning of motor sequences, audiovisual non-speech perception). Performance on these tasks will be related to MRI measurements of lesion location and distribution, local cerebral perfusion, white matter connectivity, cortical thickness in preserved brain areas, and functional activity during speech perception/processing tasks (e.g. listening to speech). Age-matched control subjects without history of brain injury will be used to determine a normal distribution of performance on behavioral tasks, and normal patterns of brain structure, connectivity and function.

Experiment 5: Group study investigating reading and writing. This study examines the brain basis of deficits in reading and writing caused by brain injury (i.e. alexia and agraphia). Participants with brain injury will be tested using a general battery to characterize their language and cognitive deficits, as well as specific behavioral tests of reading and writing (e.g. reading of various kinds of words, pseudoword reading, letter identification, letter case matching, written word recognition, paragraph reading, reading comprehension, writing to dictation, oral spelling, written picture description, written naming), and control tasks (e.g. naming, drawing simple shapes, pseudoword repetition). Performance on these tasks will be related to MRI measurements of lesion location and distribution, local cerebral perfusion, white matter connectivity, cortical thickness in preserved brain areas, and functional activity during reading/writing tasks (e.g. single word reading). Age-matched control subjects without history of brain injury will be used to determine a normal distribution of performance on behavioral tasks, and normal patterns of brain structure, connectivity and function.

Experiment 6: Group study investigating cognition and subjective symptom reports. This study examines cognitive deficits and subjective reports of symptoms, disability, and independence related to brain injury. Participants with brain injury will be tested using a general battery to characterize their language and cognitive deficits, as well as questionnaires about their subjective experience of having brain injury (e.g, depression symptoms, subjective disability, functional independence, and quality of life). Subjective reports will be related to objective measures of cognitive and language deficits. Subjective reports and performance on cognitive tasks will be related to MRI measurements of lesion location and distribution, local cerebral perfusion, white matter connectivity, cortical thickness in preserved brain areas, and functional activity during cognitive tasks. Age-matched control subjects without history of brain injury will be used to determine a normal distribution of performance on behavioral tasks, and normal patterns of brain structure, connectivity and function.

6.3 Risks:

- **Behavioral measures:**
- Risk of discomfort or fatigue with testing- If subjects find the behavioral tasks too onerous, they will be told that they can stop the study at any time.
- If specific questions make them uncomfortable, they will be told that they may omit responses to these questions.
- **MRI:**
- To reduce this risk of flying object injury during MRI scans, subjects are screened using the standard MRI screening form provided by the CFMI. We require that all people involved with the study remove all metal from their clothing and all metal objects from their pockets. No metal objects are allowed in the magnet room at any time. In addition, once a volunteer is in the magnet, the door to the room will be closed so that no one inadvertently walks into the magnet.
- The risk of discomfort during scans will be managed by informing volunteers that they may stop the experiment at any time if these effects are not tolerable.
- If an incidental abnormal finding is noted in a subject's MRI scan, they will be notified of it by the PI and given a written report describing it. It will then be up to the subject to pursue it with their physician.
- Although study personnel may be able to provide some advice, the decision of whether and how to pursue an incidental finding can only be made by the subject's physician who has knowledge of their full medical history.

6.4 Screening Process

We will use a screening form to determine inclusion/exclusion eligibility, an information sheet to collect information regarding past medical history and demographic information, and several questionnaires to gain information about psychosocial state, socieoeconomic status, quality of life, communication effectiveness, etc. All forms are attached.

6.5 Data Collected

Data will be collected via behavioral tasks, MRI, and questionnaires (see above section). De-identified information will be kept indefinitely. Identifiable information will be retained for the duration of the study.

6.6 Long-term follow-up: Not applicable

6.7 Humanitarian Use Device (HUD): Not applicable.

7.0 Data and Specimen Banking

7.1 Not applicable.

8.0 Sharing of Results with Subjects*

8.1 Information Sharing with Subjects

If the study elicits an unexpected finding (e.g., stroke in an enrolled control subject), the information will first be confirmed with the PI, Peter Turkeltaub, who is a licensed physician. The information will then be shared with the subject by study personnel verbally and in writing if requested. Follow-up with their primary care physician or another appropriate healthcare professional will be recommended as appropriate.

Subjects with a history of stroke may receive a written/electronic document outlining a portion of their study results, including both behavioral data and brain images.

9.0 Study Timelines*

9.1 Study Timeline:

Sessions will be completed across a timeframe of approximately 2-6 weeks, but may be extended depending on participants' schedules and availability. Some participants will be invited to repeat the study procedures again at a later date to monitor for behavioral and MRI changes over time.

This study will be open for enrollment of subjects for 9 years. The timeline for study completion is 12 years.

10.0 Inclusion and Exclusion Criteria*

10.1 Screening for Eligibility

When potential participants express interest in the study, either in the PI's clinic, over the phone after a referral, or by contacting the lab, they will complete a screening that covers inclusion/exclusion criteria with a study personnel using a telephone screening script (see attachments). If unable to complete over the phone, interested participants can elect to receive and return the screening via mail or a Box upload. In this instance, if any questions arise about inclusion eligibility, the researcher will contact the person for further information. At times, subjects may be screened in-person as well (e.g., when visiting the lab for participation in another study and they express interest in this study). A partial HIPAA waiver is in place to allow screening prior to consent.

10.2 Inclusion and Exclusion

Inclusion criteria:

Patients:

- Age >=18
- Brain injury resulting from stroke, trauma, infection (i.e. encephalitis), primary progressive aphasia, posterior cortical atrophy, or tumor
- Learned English at 8 years or younger

Controls:

- Age >=18
- No history of brain injury resulting from stroke, trauma, infection (i.e. encephalitis), or tumor
- Learned English at 8 years or younger

Exclusion criteria:

- History of other brain conditions that could impact interpretation of results (such as MS, premorbid dementia)
- Severe psychiatric condition that would interfere with participation in the study
- History of a learning disability that could impact interpretation of results
- Unable to understand basic instructions with visual supports (i.e., due to profound language impairment)

Additional Exclusion Criteria for MRIs:

- Presence of a pacemaker or other metal that is incompatible with MRI
- Pregnancy
- Claustrophobia

10.3 Pregnant women can participate in behavior testing, but will be excluded from the MRI. Pregnancy will be determined by self-report.

This study may include some adults who are unable to consent for themselves. Inability to give consent would result from brain injury and loss of comprehension abilities. Safeguards for these participant's protection are outlined below in section 11.0.

11.0 Vulnerable Populations*

11.1 If the research involves individuals who are vulnerable to coercion or undue influence, describe additional safeguards included to protect their rights and welfare.

In general, individuals who participate in this sort of research have capacity to provide consent because comprehension deficits sufficient to limit capacity can impact the ability to understand task instructions or comply with study procedures (e.g., staying still inside the scanner). At the first session, the consent form will

be reviewed and explained by an experimenter. Consent will be obtained from both the participant and a, LAR, family member, or caregiver (termed, the "study partner") when appropriate.

Some subjects may have alexia (i.e., reading impairment) due to their brain injury. For these individuals, we will read the informed consent and HIPAA documents to them aloud.

Study personnel will closely monitor the subject's well-being during the behavioral and MRI session, providing breaks when necessary. If a participant becomes unduly stressed, the session will be terminated and options for continuation in the study or termination in the study will be discussed.

12.0 Local Number of Subjects

12.1 Total Number of Subjects to be accrued locally: 400

12.2 Not applicable.

13.0 Recruitment Methods

13.1 **Recruitment Methods:** Informal recruitment through social networks, Advertisements/media (e.g., email, advertisements, flyers, letters, text for verbal presentations, etc.), PI/collaborators will recruit participants from his/her/their own patient population, IRB approved subject pool, Online social networks, Online classifieds

13.2 **Sources of Subjects:**

- The primary source of subjects is the PI's clinic and consultation service at the MedStar National Rehabilitation Hospital (NRH). Additional patients will be identified from the speech therapy service at NRH, and from MGUH and MNRH, or may be referred by other clinicians who are familiar with our research (e.g. the Stroke Comeback Center in Vienna, VA; Towson University Speech-Language Pathology Graduate Clinic). Other subjects may be identified through our other approved studies (Pro00000315), IRB-approved database of patients with cognitive and language problems (#2011-463) or the Stroke Recovery Database and Advanced Recovery Registry of stroke patients at NRH (MHRI #2009-171) who have agreed to be contacted for research projects. Finally, subjects will be recruited through flyers and advertisements placed around GUH, NRH, and the DC area. Of note, although the studies allow patients at any age over 18, control subjects will need to be recruited to match the patients for age and health status. Therefore, different versions of advertising flyers for controls have been produced in advance with different age ranges.
- We have included a partial HIPAA waiver request to allow access to limited PHI prior to the formal informed consent process in the context of database searches and provider referrals.
- We will also recruit through ResearchMatch- ResearchMatch is a free and secure registry that has been developed by major academic institutions across the country who want to involve you in the mission of helping today's studies make a real

difference for everyone's health in the future. ResearchMatch has a simple goal – to bring together two groups of people who are looking for one another: (1) people who are trying to find research studies, and (2) researchers who are looking for people to participate in their studies. ResearchMatch is funded in part by the National Institutes of Health (NIH) Clinical and Translational Science Award (CTSA) program, grants UL1TR000445 and 1U54RR032646-01 .The CTSA program is led by the NIH's National Center for Advancing Translational Sciences (NCATS). https://www.researchmatch.org/volunteers/

Below are subject pools and their IRB reference # used in our recruitment for this study:

- Georgetown University: Language and cognitive disorders patient database-- IRB# 2011-463
- National Rehabilitation Hospital: Advanced Recovery Registry-- MHRI IRB# 2009-171
- Stroke National Capital Areal Network for Research (SCANR) Participant Database--MHRI IRB# 2014-112, GUH IRB# 2015-0485

13.3 Subjects will be identified through the aforementioned subject pools, provider referrals, and advertisements (as listed below).

13.4 **Recruitment materials:** Advertisements include Electronic mail, physical placement (e.g., bulletin board, hallway, doorway, kiosk, etc.), Hard copy (e.g., US Mail, inter-departmental, etc.), Online advertisements.

All advertisements are attached.

13.5 Participants will receive $50 for each behavioral session and $50 for MRI session. We expect patients will typically participate in 4 sessions ($200). If they participate in an additional MRI session, the expected total will be $250. We expect control subjects will typically participate in 2 behavioral sessions ($100). If they participate in an additional MRI session, the expected total will be $150. For any additional sessions that are conducted virtually and are not full-length testing sessions, participants will receive $25.

In some instances, a participant may complete the sessions in fewer sessions or may require more sessions based on their abilities. Thus, total payment amount will be determined by each participant's total number of sessions completed.

14.0 Withdrawal of Subjects*

14.1 Participants will be withdrawn from the study if they undergo any new neurological changes, such as a new cerebral vascular accident, that alter their eligibility for the study. These participants may be eligible to re-enroll at a later time if they continue to meet the inclusion criteria. They may also be withdrawn if they are unable to comply with study procedures.

14.2 De-identified data obtained prior to withdrawal will be maintained. Identifiable participant information will be destroyed at their request via shredding.

14. 3 Participants may choose to withdraw from the study if they find any procedures to be uncomfortable. There are no safety implications from partial withdrawal.

Subjects are screened for exclusion criteria. The study personnel will monitor participants during sessions, and will be available to discuss concerns with participants at any time. Participants will be able to discontinue participation at any time. Peter Turkeltaub, the Principal Investigator, will serve as the Study Monitor. He will talk to each person who withdraws to ascertain the reason for the withdrawal. If there are a significant number of withdrawals, we will re-evaluate our protocol to see whether the participants are unduly burdened.

15.0 Risks to Subjects*

15.1 **Foreseeable Risks:**

- **Behavioral Tests**
  - Some subjects may become bored, uncomfortable, or frustrated during performance of the tests.
  - Some questions on questionnaires (e.g. questions about depression symptoms) may make the subject uncomfortable.
- **MRI**
  - The known risks associated with MRI are minimal. The greatest risk is a metallic object flying through the air and hitting the subject. Some volunteers experience transient discomfort from lying in the scanner for prolonged periods. MRI carries theoretical risks if the subject has implanted metal medical devices (e.g., cardiac pacemakers), but such subjects will be excluded from participation.

15.2 Not applicable.

16.0 Potential Benefits to Subjects*

16. 1 **Potential Benefits:** In general, subjects will not receive direct clinical benefit from their participation in the study. However, individuals with brain injury have a tendency to withdraw socially, which can have adverse impact on their functioning and well-being. Participating in this study may provide a way to engage in the community and provide a sense of contributing to society, which could be beneficial for them. They may also learn about their own deficits and strengths by completing the behavioral testing battery.

16.2 Please see section 16.1

17.0 Data Management* and Confidentiality

17.1 Analyses:

Case studies:

Statistical analyses of individual cases will examine differences between scores on different behavioral measures using standard parametric and non-parametric statistics as appropriate. For example, differences in accuracy of exception word and pseudoword reading can be examined using a Fisher's Exact test. In addition, behavioral scores of individual cases will be compared to normative control groups using the single case statistical methods of Profs. John Crawford, Paul Garthwaite, and David Howell (see http://homepages.abdn.ac.uk/j.crawford/pages/dept/SingleCaseMethodology.htm). These methods are essentially adaptations of between-group t-tests in which one group has a sample size of 1. The sample size for the patient group in these experiments is obviously 1, and the sample size of the control group is typically 10 or more for the purposes of confirming behavioral deficits which are usually fairly dramatic (i.e. the effect size is large).

Group Studies:
Analysis of behavioral data from group studies will be conducted using between-group parametric and non-parametric statistics to compare scores with that of a normative control group. In addition, comparisons between different behavioral scores will be conducted within the group of patients. The sample size for comparisons of behavioral scores in group studies of brain injury patients is typically 10 or more, with approximately 20 control subjects.

MRI analyses:
MRI results will be compared with behavioral results using several methods, for example: Lesion-symptom mapping-- this method uses the presence or absence of brain damage at each location in the brain to sort patients into test and control groups, and statistical tests are then performed to identify locations at which the behavior differs depending on the presence or absence of damage. fMRI analysis-- analysis of fMRI data proceeds using fairly standard pre-processing (slice time correction, realignment, spatial and temporal smoothing), and typically uses a generalized linear modeling approach to identify areas activated by various task conditions. Connectivity analyses will also be conducted examining the temporal relationships between activity at various locations in the brain. In addition, behavioral data obtained outside the scanner will be correlated with functional data, and between-group comparisons may be conducted to compare patients and controls, or subgroups of patients (e.g., patients with discrete lesion distributions, or patients with different patterns of behavioral deficits).

17.2 Data Security:

Upon initiation of the study, each participant will sign a HIPAA waiver, providing study personnel to collect, access, and maintain records. Subject name, date of birth, social security number, phone number, email address, and medical history relevant to inclusion/exclusion must be collected for participation and compensation. A unique subject ID will be assigned to each participant and will be used as the sole identifier on all physical or electronic records that do not require identifying information (e.g. informed consent form, HIPAA authorization, payment forms). A computer file linking

the identity of subjects to their subject ID will be stored on a password protected data server in a locked room only accessible to lab staff. In certain tasks video of subjects may be recorded in a digital fashion for later analysis. The subjects will only be identified using their subject ID in these recordings but their voices and images will be unaltered. All computers or servers containing identifiable subject information will be stored in locked rooms and will be password protected. Transfer of PHI and communication of PHI among study personnel will utilize GU Box. All physical files containing personal information and data will be kept in a locked filing cabinet within a locked room accessible only to lab staff.

In addition to the subject's information, we will collect contact information (i.e., phone number, email address) of a family member or caregiver. Communication with individuals with brain injury typically involves their spouse, a close family member, or caregiver. These individuals' names and contact information will be kept on file for communication purposes and will stored with the same safeguards as described above. No other information on these individuals in needed.

Study personnel will complete appropriate CITI training courses prior to receiving authorization to access subject research records. Only study personnel will be granted access to research data containing identifying information. We may require advice from other researchers regarding interpretation of data, in which case deidentified data will be used.

17.3 Quality Control:

Procedures for testing sessions (e.g., general ordering of testing, testing instructions) will be established across all study personnel administering behavioral tests. Interrater reliability will be performed on a given number of tests, and consensus meetings will be held to ensure accuracy in scoring on tests not undergoing inter-rater reliability scoring.

17.4 Data Handling

After a research session is held, data will be transferred to the secure server and/or the data repository (i.e., GU Box). Video images will be deleted from the memory card once successful transfer is confirmed.

17.5 Type of Data being Collected

Protected health information may be collected during this study, including:

- Hospital/medical records
- Lab, pathology and/or radiology records
- Interviews/questionnaires
- Mental Health records
- Data previously collected for research purposes under another approved GU or MedStar IRB study (i.e., Pro315 under GU IRB)
- Database or repository, including: The cognitive and language patient database – GU IRB# 2011-463; The Advanced Recovery Registry- MHRI IRB# 2009-171;

and Stroke National Capitol Area Network for Research (SCANR) Patient Database- MHRI IRB# 2014-112, GU IRB# 2015-0485)

Identifying information that may be collected, includes:

- Names
- Initials
- Residential/mailing addresses
- Dates directly related ot the individual (birth date, admission date, discharge date, etc)
- Phone numbers
- Email addresses
- Social security numbers
- Medical record numbers
- Videos/images with subjects' faces and voices
- Any other unique identifying number, characteristic, or code

Medical records with identifying information will be kept separately and stored securely. Names of subjects will not be used in publications. No digital, video, or photographic recordings of the subjects will be made public.

After the retention period, electronic files will be deleted and paper files will be shredded.

17.6 Data Sharing

Deidentified data used for publications may be posted publicly in supplemental materials of publications or posted on our lab website.

De-identified data (i.e., structural MRI scans, lesion tracing images) will be transferred to the University of Pittsburgh via a secure Box folder. This data will be used to develop automated lesion analysis methods. Collaborating researchers will receive approval from the IRB at the University of Pittsburgh and store data securely per their IRB guidelines.

Video and voice recordings with no further identifiable information will be transferred to the University of North Carolina (UNC) via a secure Box folder. This data will be used to contribute to research investigating diagnosis and treatment of motor speech disorders. Collaborating researchers have received approval from the IRB at the University of North Carolina for reception of this data. They will store data securely per their IRB's guidelines (i.e., on a secured server). UNC will send motor speech behavioral scores and electronic brain scan files back to Georgetown University.

A section in the Confidentiality section of the Informed Consent Form was added for sharing of deidentified data. Consent for sharing identifiable data will be obtained via an addendum on the Informed Consent Form for new participants from this point forward (protocol dated 4/15/20). Past participants will be contacted for provision of verbal or email consent using the attached script. If consent is not granted by the participant, data will not be shared. Consent will be waived when it is impracticable to gain consent (e.g.,

the participant is deceased, participant is unable to be contacted). All attempts at contact and provision/declination of consent will be documented.

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

18.1 N/A. This study has minimal risk. The PI will monitor the safety of the study. Any adverse events will be reported to the IRB promptly.

19.0 Provisions to Protect the Privacy Interests of Subjects

19.1 Privacy of Data Stored

Electronic research information will be kept on a password protected server and RedCap accessed through a secure network only. Subjects will be assigned a code that will separate their research results from their identifying information. A computer file linking the identity of subjects to their subject ID will be stored on on GU Box and on a password protected data server in a locked room only accessible to lab staff. The master list linking codes to the subjects' names will be kept on a secure repository (i.e., GU Box). Hard copies of research information (questionnaires, test forms), ICF, etc. will be kept in a locked filing cabinet in a locked office which can only be accessed by research personnel. Research data will be shared without any identifying information (e.g., with assigned random code).

If medical records are needed, subjects will sign a Medical Release form for study personnel to collect necessary records from other medical facilities.

19.2 Steps for Keeping Participants "at ease"

Subjects will be given rationale as to why information is being collected, however, subject can decline to answer any items on questionnaires or tests that make them feel uncomfortable. We will contact patients by phone or email during the periods between sessions to encourage subject retention. We will also arrange transportation to the study site for subjects who have difficulty with transport, or travel to the subject's home if necessary. Subjects will be allowed breaks during testing sessions to limit fatigue. They will be encouraged to participate in all experimental sessions, but they may voluntarily withdraw at any time.

19.3 Access to Subject Information

Study personnel will be authorized to access subject information after completing CITI training and receiving training on privacy procedures within the protocol. Only study team members who have duties/functions pertaining to documents containing identifying information will be given access to these records. Other study personnel will only access de-identified research data.

20.0 Compensation for Research-Related Injury

20.1 Not applicable. This study has minimal risk.

21.0 Economic Burden to Subjects

21.1 Participant Costs

Subjects may pay for transportation to and from study sessions (e.g., gas to drive to GU, handicap accessible taxi, metro/bus fare). All subjects will be reimbursed for any parking expenses during study sessions. If subjects are unable to pay for transportation to the study site, reimbursement may be arranged or a study personnel may travel to the subject's home to complete testing.

22.0 Consent Process

22.1 Obtaining Informed Consent

The informed consent process will follow HRP-090. When possible, study personnel will provide a copy of the informed consent document at least one day prior to the first study visit. The first study visit will begin with the formal informed consent process at a study site. Study personnel will go through the consent documents with the participant and provide sufficient time for them to review the documents and ask questions.

If there is any question regarding whether the participant's comprehension abilities allow the participant to consent to participate for him/herself, a second signature will be obtained from the participant's spouse, adult son/daughter, parent, or adult sibling. The second signature will document that the spouse/relative has observed and participated in the consent process with the participant, that the spouse/relative and participant understand what was explained to them, and that all of their questions were answered. The spouse/relative of a participant whom study staff determines to have no more than mild comprehension deficits will not be asked to sign. (This procedure for handling questions regarding comprehension ability has previously been approved by the GU IRB for similar study populations under 1996-311 and other protocols from Dr. Rhonda Friedman's group).

Study Partner Consent:
If a participant requires help to answer health-related questions or travel to appointments, a caregiver/study partner will sign a separate caregiver/study partner consent to confirm their willingness to provide contact information and help the participant in the ways described.

There is a separate informed consent form for use of audio or visual recordings.

Non-English Speaking Subjects

- N/A. English proficiency is an inclusion criterion for this study.

Cognitively Impaired Adults

- Auditory comprehension is inquired about on the screening form for individuals who have history of a stroke. When participants indicate they have more than mild deficits, further

assessment will be made to determine if they will need a family member or caregiver to sign the informed consent. Order of priority for signature is listed below.

Adults Unable to Consent

- Informed consent will be obtained in the following priority:
    - Legally Authorized Representative (if not local, consent may be reviewed over the phone and consent documents may be obtained via fax, email, or mail).
    - Spouse/Partner
    - Adult Child
    - Sibling
- All subjects, whether signing the consent form themselves or having a relative/caregiver sign the consent, will be asked for their verbal assent for participation in the study.

23.0 Process to Document Consent in Writing

23.1 We will follow HRP-091.

24.0 Setting

24.1 Research Sites

- Potential subjects will be recruited form the databases listed in section 13.0. They will also be recruited from MedStar NRH, GUH, Towson University, through advertisements online and in the regional community, through healthcare provider referrals, and through word-of-mouth from former participants.
- Behavioral assessment and MRI sessions will be performed at Georgetown University Medical Center, MedStar National Rehabilitation Hospital, and Towson University Department of Speech-Language Pathology. Behavioral assessment may be conducted in a participant's home or other mutually agreed upon private setting for their convenience.
- Of note, Georgetown-MedStar IRB will be the IRB of record for MedStar NRH, but will not be the IRB of record for Towson University at this time as Towson University will be conducting their own IRB review.

25.0 Resources Available

25.1 Describe the resources available to conduct the research: For example, as appropriate:

- Our current cohort of stroke survivors includes approximately 100 people who have completed or express interest in previous research within our lab. In our experience conducting this research over the past several years we are able to recruit 20-50 new stroke survivors per year, and 50-100 control participants per year from the sources listed above.

- Several study personnel will work full time on this project, and several others will work part time. The PI and other members of the study team will be available for weekly meetings to discuss progress, troubleshoot, and make scoring decisions.

- We have access to two separate behavioral testing rooms on the GUMC campus, and an additional testing room at MedStar NRH. These facilities allow for testing of up to 3 participants at one time. The CFMI houses a state-of-the-art MRI facility. We have adequate office space for all study personnel at GUMC, and each has a computer to work on.

- The PI and project manager assigned to this study will ensure the protocol and research procedures are followed by closely monitoring recruitment, research data, and data scoring/storage. Checklists outlining the procedures have been created and are used by all study personnel administering testing. The study team meets on a weekly basis, as well as often in smaller groups, to discuss study procedures and scoring of behavioral tests. A report is given to the team after each MRI session. All these systems will provide continuity between team members, allow for team members to ask questions about their duties/functions, and monitor for any procedures that need adjusted within the protocol.

26.0 Multi-Site Research*

N/A. This is not a multicenter study.