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Methodology and Research Protocols

Defining Trajectories of Linguistic, Cognitive-Communicative, and Quality of Life Outcomes in Aphasia: Longitudinal Observational Study Protocol

Leora R. Cherney, PhD [a,b], Allan J. Kozlowski, PhD [c], Andrea A. Domenighetti, PhD [a,b], Marwan N. Baliki, PhD [a,b], Mary J. Kwasny, ScD [d], Allen W. Heinemann, PhD [a,b]

[a] *Shirley Ryan AbilityLab, Chicago, IL*
[b] *Department of Physical Medicine & Rehabilitation, Feinberg School of Medicine, Northwestern University, Chicago, IL*
[c] *John F. Butzer Center for Research and Innovation, Mary Free Bed Rehabilitation Hospital, Grand Rapids, MI*
[d] *Department of Preventive Medicine, Division of Biostatistics, Feinberg School of Medicine, Northwestern University, Chicago, IL*

KEYWORDS
Aphasia;
Clinical protocols;
Longitudinal studies;
Recovery of function;
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Stroke

Abstract *Objective:* To describe the trajectories of linguistic, cognitive-communicative, and health-related quality of life (HRQOL) outcomes after stroke in persons with aphasia.
Design: Longitudinal observational study from inpatient rehabilitation to 18 months after stroke.
Setting: Four US mid-west inpatient rehabilitation facilities (IRFs).
Participants: We plan to recruit 400 adult (older than 21 years) English speakers who meet the following inclusion criteria: (1) Diagnosis of aphasia after a left-hemisphere infarct confirmed by CT scan or magnetic resonance imaging (MRI); (2) first admission for inpatient rehabilitation due to a neurologic event; and (3) sufficient cognitive capacity to provide informed consent and participate in testing. Exclusion criteria include any neurologic condition other than stroke that could affect language, cognition or speech, such as Parkinson's disease, Alzheimer's disease, traumatic brain injury, or the presence of right-hemisphere lesions.
Interventions: Not applicable.

List of abbreviations: fMRI, functional magnetic resonance imaging; HRQOL, health-related quality of life; IRF, inpatient rehabilitation facility; MRI, magnetic resonance imaging; SLP, speech-language pathology; SNP, single-nucleotide polymorphism; SRAlab, Shirley Ryan AbilityLab.
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Main Outcome Measures: Subjects are administered a test battery of linguistic, cognitive-communicative, and HRQOL measures. Linguistic measures include the Western Aphasia Battery-Revised and the Apraxia of Speech Rating Scale. Cognitive-communicative measures include the Communication Participation Item Bank, Connor's Continuous Performance Test-3, the Communication Confidence Rating Scale for Aphasia, the Communication Effectiveness Index, the Neurological Quality of Life measurement system (Neuro-QoL) Communication short form, and the Neuro-QoL Cognitive Function short form. HRQOL measures include the 39-item Stroke & Aphasia Quality of Life Scale, Neuro-QoL Fatigue, Sleep Disturbance, Depression, Ability to Participate in Social Roles & Activities, and Satisfaction with Social Roles & Activities tests, and the Patient-Reported Outcome Measurement and Information System 10-item Global Health short form. The test battery is administered initially during inpatient rehabilitation, and at 3-, 6-, 12-, and 18-months post-IRF discharge. Biomarker samples are collected via saliva samples at admission and a subgroup of participants also undergo resting state fMRI scans.
Results: Not applicable.
Conclusions: This longitudinal observational study will develop trajectory models for recovery of clinically relevant linguistic, cognitive-communicative, and quality of life outcomes over 18 months after inpatient rehabilitation. Models will identify individual differences in the patterns of recovery based on variations in personal, genetic, imaging, and therapy characteristics. The resulting models will provide an unparalleled representation of recovery from aphasia resulting from stroke. This improved understanding of recovery will enable clinicians to better tailor and plan rehabilitation therapies to individual patient's needs.

Approximately 17 million people worldwide experience a first stroke annually[1] of which 610,000 occur in the United States.[2] Aphasia is 1 of the most devastating consequences of stroke and occurs in about one-third of patients.[3-5] Aphasia impairs, to varying degrees, understanding and expression of spoken and written language which can negatively affect participation in rehabilitation and patient health outcomes. People with aphasia report significantly greater isolation, loneliness, loss of autonomy, restricted activities, role changes, stigmatization, and depression as compared with stroke survivors without aphasia.[6-11] Aphasia is not only an acute event, but has long-term consequences[7,12] on relations with family, friends, and community life.[13-17] As more individuals survive acute stroke, the need for effective rehabilitation strategies to reduce aphasia-related disability becomes urgent.

Approaches to the management and rehabilitation of aphasia continue to evolve. Over the past 2 decades, therapists have moved from medical model-focused interventions that treat impairments and restore language function toward biopsychosocial models that focus on the broad life context of the person.[18-21] Despite research on the importance of participation for persons with aphasia, health care policies and insurance coverage of services have not adapted with this paradigm shift as insurers typically cover therapy of limited duration and intensity that targets impairments.[22-25] Understanding long-term patterns of recovery, and how outcomes of language, communication, cognition, and health-related quality of life (HRQOL) relate to therapy exposure, will enhance the evidence base for the practice of speech-language pathology (SLP). This improved understanding will enable clinicians to tailor and plan rehabilitation therapies to individual patients' needs, and provide value-based interventions that maximize recovery while minimizing the cost of stroke rehabilitation.[26]

The Trajectory of Aphasia Recovery

Language recovery in post-stroke aphasia is variable and difficult to predict even in the first 90 days post-stroke.[27-32] A multitude of variables affect short- and long-term linguistic, cognitive-communicative, and HRQOL outcomes (fig 1). Specific aphasia interventions provided to patients are presumed to contribute substantively to improved outcomes. However, treatment effects are confounded with the natural course of recovery, which may be influenced by patient, stroke, and other characteristics. To understand the effectiveness of any aphasia treatment requires that we also understand factors associated with the magnitude and rate of recovery, while controlling for individual differences on these parameters.

Although language recovery is dependent on many factors, neuroplasticity may be important as well.[33,34] Neuroplasticity may vary by genetic predisposition based on neuroplasticity-associated single-nucleotide polymorphisms (SNPs) and brain inter- and intra-network connectivity. Despite promising advances in identifying SNPs associated with post-stroke motor and cognitive skill recovery,[35-37] SNPs predictive of language recovery in stroke patients remain elusive. As complex human diseases and traits cluster in families and are influenced by the interaction of genetic and environmental factors,[38] there is a need to investigate the genetic association and interactions of SNPs in genes that are linked to neuroplasticity at the cellular and molecular level in post-stroke recovery[39] including growth factors mediating neurogenesis, angiogenesis, synaptic remodeling, and neuroprotection.

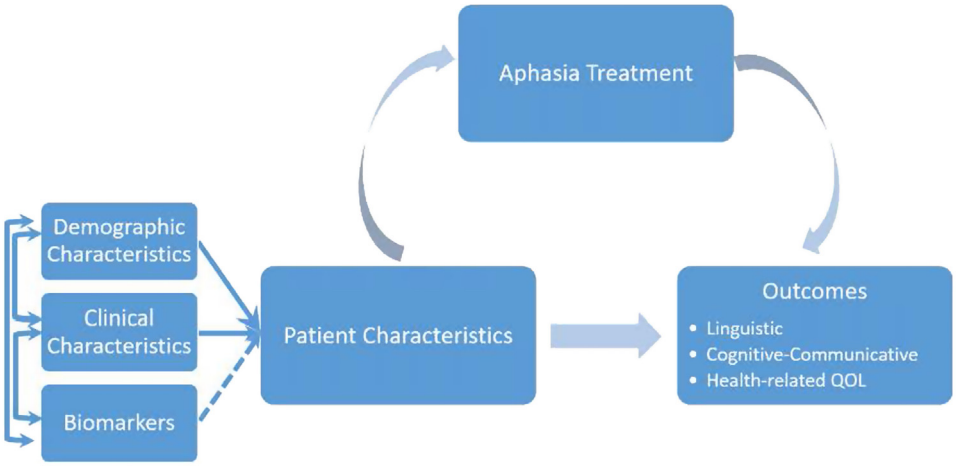

Fig 1 Model of linguistic, cognitive-communicative, and health-related quality of life outcomes.

Brain resting state inter- and intra-network connectivity is another promising candidate biomarker of neuroplasticity and recovery,[40] which can be measured by resting state, functional magnetic resonance imaging (fMRI) scan. The few small-sample studies that have explored resting state fMRI in aphasia[41-44] indicate a relation between aphasia severity and an acute disruption of functional connectivity within the language network.[45] Recent studies from our group and others have used graph theory, a powerful tool that is used to quantify and simplify the relations between different parts of dynamic systems, which in this case, is to investigate the relation between global and local topological properties of brain functioning networks with aphasia symptoms.[46] These studies showed that brain topological properties (eg, clustering and efficiency) are (1) disrupted in aphasia, (2) associated with language abilities, (3) partially recover with time and after treatment, and (4) significantly influence effectiveness of speech therapy. Such observations indicate that brain network properties can be used as a potential indicator of language function recovery trajectories in patients with aphasia.

The objective of this study is to describe the trajectories of linguistic, cognitive-communicative, and HRQOL outcomes after stroke in persons with aphasia during inpatient and outpatient rehabilitation to 18 months after stroke. The study has 3 aims. The first aim is to establish a prospective cohort of stroke patients with aphasia and define their typical patterns (trajectories) of linguistic, cognitive-communicative, and HRQOL recovery. We hypothesize that linguistic outcomes improve and then plateau, whereas cognitive-communicative outcomes and QoL outcomes continue to improve.

The second aim is to identify patient and treatment characteristics, and genetic and neuroimaging biomarkers that are associated with linguistic, cognitive-communicative, and HRQOL outcomes. Specifically, we hypothesize that (a) patients with smaller lesions, fewer comorbidities, and less severe initial aphasia achieve greater gains in all outcomes than other patients; (b) patients who begin speech and language therapy earlier, receive more intense therapy, and therapy that is longer in duration, as well as those who receive more formal and informal aphasia services, achieve better outcomes than other patients; (c) biomarkers including the presence or absence of critical neuroplastic polymorphisms and the degree of resting state connectivity interact with patient characteristics to influence outcomes.

In the third aim, we plan to evaluate the stability of the recovery models. We plan to identify trajectory models that are stable, that is, the variables in the final model appear in most bootstrapped replications, and prediction error (ie, the median difference between an observed and predicted score at any time point) is no greater than the minimally clinical important difference for each outcome.

Methods

Design

The study employs a longitudinal observational design and was approved by the Northwestern University's Institutional Review Board (STU00209555).

Setting

We are enrolling participants after admission to 4 inpatient rehabilitation facilities (IRFs) in the Midwestern US and following them to 18 months post-stroke. Study sites are Shirley Ryan AbilityLab (SRAlab), formerly the Rehabilitation Institute of Chicago in Chicago, IL; AMITA Health Alexian Brothers Rehabilitation Hospital in Elk Grove Village, IL; Marianjoy Rehabilitation Hospital in Wheaton, Illinois; and Mary Free Bed Rehabilitation Hospital in Grand Rapids, MI. Enrollment began in July 2019 and was scheduled to run through March 2022, with 18-month follow-up for all participants. Because of a work stoppage during the Covid-19 pandemic, enrollment continues through March 2024, with the last follow-up scheduled in September 2025.

Participants and sample size considerations

Participants provide informed consent before enrollment. Inclusion criteria are (1) diagnosis of aphasia after a left-hemisphere infarct confirmed by computed tomography (CT) scan or magnetic resonance imaging (MRI); (2) first admission for inpatient rehabilitation due to a neurologic event; (3) age

21 years or older; (4) sufficient cognitive capacity to provide informed consent and participate in testing; and (5) speak and understand English. Exclusion criteria included any neurologic condition other than stroke that could affect cognition or language, such as Parkinson's disease, Alzheimer's disease, traumatic brain injury, or right hemisphere lesions. A subsample of participants from SRAlab also undergo resting state fMRI scans. Additional exclusion criteria for that sample included metallic implants, tattoos on large body parts, claustrophobia, and pregnancy in women of child-bearing age.

As preliminary data were not available at the time of study design, we based sample size on feasible enrolment over 33 months. While sample sizes on the order of 500 are preferable for longitudinal mixed effects regression models,[47] studies have been able to detect up to 4 different recovery trajectories in stroke patients with sample sizes as small as 102 participants.[48] Such longitudinal models permit identification of a best-fit mathematical function to describe a general pattern of change over time as a recovery trajectory. Including random effects on trajectory parameters explains variance in how trajectories for individual participants vary from the general recovery pattern.

To maximize potential for adequate detection of group-based trajectories, we planned for a sample of 300 participants at 18 months which allows confidence in robust trend analyses and sufficient power to develop viable models within the limits of the funding. Assuming a dropout rate of 15% loss to follow-up at 6 months and an additional 10% loss at 18 months, we plan on enrolling 400 participants. Should we observe lower rates of dropout, and time constraints become prohibitive, we will adjust enrolment.

Consent process for persons with aphasia

Patients' physicians, SLP therapists or research staff inform eligible subjects with stroke and aphasia about the project. Research assistants describe the purpose of the project and obtain informed consent from those willing to participate using an approved consent form. Personnel who are trained in the use of supported conversation techniques obtain consent to ensure understanding by the prospective subject. They use pictographic materials to supplement the consent form and to aid comprehension. In cases of severe aphasia, staff also obtain a witness signature.

Speech-language pathology therapy

SLP therapy is provided as standard of care in the IRF and outpatient settings. IRFs report total minutes of individual, group, and co-treatment therapy for SLP each week using Current Procedure Terminology codes. Research staff extract treatment type, frequency, and duration of SLP therapy sessions from medical records. In addition, the SLP therapists record the language modality (auditory comprehension, oral expression, reading comprehension, written expression) and language level (eg, sound, word, sentence, conversation) on which the task focuses and the start and stop times of each treatment task during each therapy session. Research staff derive SLP therapy characteristics and minutes provided from therapist logs and notes to summarize therapy for inpatient and outpatient settings. We provide extensive training on documentation before and during the study to facilitate accurate and reliable reporting. We record 10% of the treatment sessions for reliability checking of treatment logs. SLPs are told that "... the focus of these recordings is on the participant to collect information on the interventions they do. We will not be critiquing the therapist in these recordings." After discharge from the IRF, patients often receive additional SLP services such as hospital-based outpatient therapy, private or university clinics, aphasia conversation groups, and intensive comprehensive aphasia programs. Study participants and caregivers complete a checklist of these formal and informal SLP services. A research assistant contacts participants or their designated family members weekly during the first 3 months post-stroke, and then monthly to review and summarize the therapy and other service information.

Outcome measures

The 3 primary outcome measures are the Western Aphasia Battery-Revised (WAB-R AQ),[49,50] the Communication Participation Item Bank (CPIB),[51,52] and the 39-item Stroke & Aphasia Quality of Life Scale (SAQOL),[53–56] which measure linguistic, cognitive-communicative, and HRQOL outcomes, respectively. They are administered initially during inpatient rehabilitation, and at 4 follow-ups (table 1). Other secondary linguistic and cognitive-communicative measures are the Apraxia of Speech Rating Scale,[57] Connor's Continuous Performance Test-3,[58,59] the spatial span and symbol span subtests of the Wechsler Memory Scale, WMS-III and WMS-IV, respectively,[60,61] the Communication Confidence Rating Scale for Aphasia,[62-64] the Communication Effectiveness Index,[65] and the Neuro-QoL Communication short form and Cognitive Function short form.[66-68]

Secondary HRQOL measures are Neuro-QoL Fatigue, Sleep Disturbance, Depression, Ability to Participate in Social Roles & Activities, and Satisfaction with Social Roles & Activities,[66-68] the UCLA 3-Item Loneliness Scale,[69] and the Patient-Reported Outcome Measurement and Information System (PROMIS) 10-item Global Health short form.[70] We also complete the Modified Rankin Scale[71] and administer a 1-item global rating of change in which participants are asked to indicate the extent to which their ability to speak has changed since admission to the IRF or since their last assessment, using a 5-point multiple choice scale of worse, no change, a little better, much better, and very much better. Caregivers complete the Communicative Effectiveness Index[65] to rate communication skills in everyday situations. These measures have been selected because they represent different constructs. We expect similarities in the natural pattern of recovery across these constructs and are looking for variations in these general patterns and in how individuals vary within each construct. We examine correlations between these instruments to identify those that may serve as better prognostic measures for determining longitudinal outcomes.

Data collection

We collect patient demographic characteristics (age, sex, education, employment, and marital status), stoke

Table 1 Study instrumentation and assessment schedule*

Instrument	Construct	Mode	When
Demographic characteristics			
Sociodemographic Information†	Various	Interview	A
Clinical characteristics			
Stroke characteristics†	Person characteristics	Medical record review	A
CT/MRI review for lesion size and location	Brain structure	Medical record review	A
Charlson Comorbidity Index	Body structure and function	Medical record review	A
Medication review	Various	Medical record review & patient reported	A D 6, 12, 18
Neuro-QoL Fatigue, Sleep Disturbance, Depression†	Fatigue, sleep, mood,	Patient-reported	A D 6, 12, 18
Apraxia of Speech Rating Scale	Motor-speech planning	Performance test	A D 6, 12, 18
National Institutes of Health Stroke Scale†	Sensory, mental, movement-related & communication functions	Interview	A & D
Inpatient Rehabilitation Facility-Patient Assessment Inventory	Movement-related, self-care, mental functions	Medical record review	A W 6, 12, 18
Modified Rankin Scale	Measure of global disability	Clinician Reported	A D 6, 12, 18
Biomarkers			
Resting state brain fMRI (AbilityLab subsample, 100)	Network connectivity	Imaging	A
Genetic samples	DNA polymorphisms	Saliva sample	A
Aphasia treatment			
Inpatient SLP Therapy	Current Procedural Terminology codes, therapy taxonomy	Medical, financial records; patient log	E 6, 12, 18
Outpatient community groups, Private pay therapy	Current Procedural Terminology codes, therapy taxonomy	Medical, financial records; patient log	Weekly/monthly after discharge
Outcomes — Linguistic			
Western Aphasia Battery-Revised	Aphasia severity and classification	Performance test	A D 6, 12, 18
Outcomes — Cognitive-Communicative			
Communication Participation Item Bank	Participation in life situations, control over participation	Patient-reported	A D 6, 12, 18
Connor's Continuous Performance test-3	Attention	Performance test	A D 6, 12, 18
Wechsler Memory Scale-III (Spatial Span) and Weschler Memory Scale-IV (Symbol Span)	Memory	Performance test	A D 6, 12, 18
Communication Confidence Rating Scale for Aphasia	Communication confidence	Patient-reported	A D 6, 12, 18
Communication Effectiveness Index	Communication in everyday environments	Caregiver-reported	A D 6, 12, 18
Neuro-QoL Cognitive Function†	Cognition	Patient-reported	A D 6, 12, 18
Neuro-QoL Communication†	Communication	Patient-reported	A D 6, 12, 18
Outcomes — Health-Related Quality of Life			
Stroke & Aphasia Quality of Life Scale-39	Stroke & aphasia-related HRQOL	Patient-reported	A D 6, 12, 18
Neuro-QoL Satisfaction with Social Roles & Activities, Ability to Participate in Social Roles & Activities†	Community, social, and civic life	Patient-reported	A D 6, 12, 18
Patient-Reported Outcome Measurement and Information System Global Health	Global health	Patient-reported	A D 6, 12, 18
UCLA 3-Item Loneliness Scale	Loneliness	Patient-reported	A D 6, 12, 18
Global Rating of Change	Patients' global perception of improvement	Patient-reported	D 6, 12, 18

Abbreviations: A, admission, D, discharge/3-months post-stroke; DNA, deoxyribonucleic acid; E, every day; W, weekly; 6, 6-months post-stroke; 12, 12 months post-stroke; 18, 18 months post-stroke.

* All assessments are planned to be completed at the above stated schedule as time allows.

† National Institute of Neurodegenerative Diseases and Stroke Common Data Elements, including socio-economic status, education, age, sex, race/ethnicity, handedness, stroke etiology, location, and so on.

characteristics, and genetic material. Data from MRI scans are collected for a subsample of SRAlab participants. Mobility and self-care function are scored on the Quality Reporting Program item sets of the IRF-PAI[72] and derived from medical chart review. Clinical characteristics include stroke type and severity, stroke lesion size and location, National Institutes of Health Stroke Scale score,[73] aphasia type and severity, medical comorbidities scored on the Charlson Comorbidity Index,[74] and medications.

All assessments conducted by research assistants or SLP therapists are video recorded to establish initial reliability. After reliability has been established, approximately 10% of these recordings are reviewed for data collection quality purposes. For patients who provide consent, video

recordings are stored for educational purposes. Otherwise, we will retain video recordings for 7 years after the end of the study and then destroy them. All testing and some therapy sessions including telehealth therapy sessions are video or audio recorded. All virtual assessments are recorded directly through videoconferencing software and saved to a study folder on a secure network.

Participants complete follow-up assessments around 6-, 12-, and 18-months post-stroke with a variety of speech, language, cognitive-communicative, and HRQOL assessments. We are flexible on the timing of research visits to accommodate schedules of participants and families. Assessments require 3-4 hours and may be completed segmentally over several days. We developed a virtual assessment format via videoconferencing software for participants who are unable to complete in-person assessments due to distance or personal factors, but adopted this format as the primary assessment mode due to the coronavirus pandemic. Study data are collected and managed using REDCap electronic data capture tools hosted at Northwestern University, Feinberg School of Medicine.[75,76]

Genetic material is collected by saliva sample with Oragene Discover OGR-600[a] saliva kits, or for patients unable to produce saliva on command, by buccal swab with PurFlock Ultra Tipped Applicator with Transport Tube.[b]

A subset of subjects also undergo brain imaging during their IRF stay. These are subjects who are enrolled at SRAlab, meet the eligibility requirements for MRI without contrast and provide specific consent to undergo a research fMRI scan. These SRAlab participants attend 1 imaging session during which they receive 2 resting state fMRI scans, a high-resolution (T1) anatomic scan, and a 2-shell diffusion tensor image scan. These scans are acquired on a 3 Tesla Siemens Magnetom Prisma whole body scanner and follow Human Connectome Project (HCP) protocols and standards.[77] At other sites, we review participants' clinical MRI scans to define, if possible, the size and anatomic site of lesions.

Analysis

Single-nucleotide polymorphism genotyping: SNP-specific assays

Deoxyribonucleic acid is extracted, purified, and quantified from the saliva sample or buccal swab and tested for expression of specific SNPs in genes that are linked to neuroplasticity at the cellular and molecular level in post-stroke recovery. We use PCR-based TaqMan SNP Genotyping assays, also known as TaqMan Allelic Discrimination assays,[c] to genotype SNPs.[78] Assays are available commercially and optimized. Selected SNPs include brain derived neurotrophic factor (rs6265, rs10835210), apolipoprotein E (rs429358, r7412), glial fibrillary acidic protein (GFAP) (rs2070935), catechol-O-methyltransferase (COMT) (rs4680), insulin growth factor 1 (IGF1) (rs7136446, rs9989002), fibroblast growth factor 2 (FGF2) (rs308379), and vascular endothelial growth factor A (VEGFA) (rs833069).[39,79-83] These SNPs have been selected because studies have shown that they can affect brain structure or modulate neuroplasticity in patients with stroke.

We use canonical correlation analyses to identify and measure the associations between individual SNPs, clinical outcomes and fMRI data. We also analyze epistatic SNP-SNP and gene-gene interactions using multifactor-dimensionality reduction methods.[84]

Neuroimaging analysis

We complete brain-imaging analysis on free-share software including FIMRIB software library,[85] SPM,[86] FreeSurfer,[87] Caret,[88] and ad hoc routines written in MATLAB,[d] C++,[e] Python,[f] and Awk.[g] We perform all anatomic and functional brain imaging data preprocessing and quality control using validated pipelines adapted from the Human Connectome Project.[89] High-resolution T1 images are used to assess global and local structural brain properties including (1) global brain volume, (2) localized based gray matter density, (3) shape and volume of cortical and subcortical regions, and (4) lesion size and location in patients. Resting state fMRI is used to construct and examine brain functional networks using the open-source brain connectivity toolbox.[90,91] Properties include clustering (a measure of information segregation), global efficiency (a measure of information integration), and modularity (a global measure of the near-decomposability of the network into a community structure of sparsely interconnected modules).[90,92] In addition, we use region of interest (ROI) based analysis to examine changes in functional connectivity and spontaneous activity of specific brain regions involved in language and attention processing. Finally, diffusion tensor image is used to examine white matter property changes, specifically fractional anisotropy, using FMRIB's Diffusion Toolbox.[93] We assess local and global fractional anisotropy and compare it across individuals and conditions. We also perform probabilistic tractography using PROBTRACKX[93] to generate and assess the integrity of white matter connectivity of specific ROIs.

Outcome analysis

Longitudinal designs that employ mixed-effects methods allow us to describe individuals' change over time.[47,94-97] These methods include individual growth curve models, also known as random slopes and intercepts models, which have been used to describe recovery for persons with spinal cord injury,[96,98-100] acquired brain injury,[101-104] and stroke.[105] Trend lines, or trajectories, are modeled simultaneously for each person, where the trajectory shape is determined by the best fit to the data Instead of modeling and comparing group differences as means at each time point, the group trend (fixed effects) is modeled as the average of the intercept and slope for the individual trend lines. We also model individual differences in the trajectory parameters (random effects); thus, we can test between-group differences and covariate associations with trajectory parameters. Differences on the intercept indicate individual variability at baseline, and differences on the slope indicate individual variability in rates of change. Additionally, using PROC TRAJ in SAS (v 9.4, Cary, NC), finite mixture models are fit in an application of group-based trajectories, and clusters of individuals who follow similar changes over time are identified. The number of groups and the degree of change (linear or curvilinear) are to be determined using Akaike and Bayesian information criteria to assess the best fit to the data.

Longitudinal data collection is at risk for missing data. While we anticipate some missed visits, interim missing data are often assumed to be missing at random, whereas study drop out is often non-ignorable. To address this, we will create missing data patterns and include them as covariates in trajectory models.[106] Additionally, PROC TRAJ can model drop out when fitting group-based trajectories.

Once individuals are assigned to each trajectory pattern, we can determine if covariates or a set of covariates, such as demographic, impairment, and therapy characteristics, are associated with different outcome trajectories. Additionally, we will fit a longitudinal model to describe recovery and to examine between-group and individual differences related to rehabilitation therapies received during and after inpatient rehabilitation.

Discussion

To understand aphasia recovery better, there is a critical need for large, prospective, methodologically sound studies that examine the multitude of factors that affect linguistic, cognitive-communicative, and quality of life outcomes for persons recovering from stroke. Further, we examine these outcomes as trajectories of change over the 18 months after study enrollment accounting for individual differences from a common pattern of recovery. We have included a comprehensive battery of clinically relevant measures for outcomes of linguistic, cognitive-communicative, and quality of life recovery post-stroke. In addition to personal characteristics, we include a battery of clinical interventions and genetic and imaging biomarkers to test their associations with available trajectory parameters. In combination, resulting models will provide an unparalleled representation of recovery from aphasia resulting from stroke.

Although this study does not test for effects of specific interventions to treat aphasia, we do quantify the types and amounts of inpatient SLP interventions. Data will allow us to integrate genetic biomarkers with neuroimaging biomarkers, and clinical and demographic characteristics in models that provide a detailed understanding of the relations between speech and language therapy and other aphasia-related factors with patients' outcome trajectories.

Genetic variations are genome-wide modifications in DNA sequences among individuals of a population. SNPs can lead to biological variations in molecular and cellular processes that have functional and systemic consequences.[107,108] While current practices may not fully incorporate the assessment of disease-related genetic polymorphisms affecting neuroplasticity in stroke and post-stroke rehabilitation, the outlook suggests that the integration of such genetic biomarkers will become an integral part of patient assessment in the future. This evolving paradigm holds the potential to enhance the personalization and effectiveness of rehabilitation strategies for better patient outcomes.[109,110]

Patients' activity limitations and participation restrictions evolve over time, reflecting residual impairments and environmental factors. Consequently, outcomes reflecting recovery after stroke are more suited to modeling as trajectories of change over time than to point-in-time difference measurements such as admission to discharge. Conversely, longitudinal mixed effects models can explain individual variations on a trajectory of recovery by retaining individual differences on a set of covariate associations, such as demographic, impairment, biometric, and therapy characteristics. Thus, longitudinal models are the most appropriate methods to describe recovery and to examine between-group and individual differences related to rehabilitation therapies received during and after inpatient rehabilitation. Longitudinal designs that employ mixed-effects methods will allow us to describe typical patterns of change over time on linguistic, cognitive-communicative, and HRQOL outcomes, the extent to which individual patients' recoveries vary from the typical pattern, and to identify factors that are associated with the pattern of change.[47,94,95,97]

Study strengths and limitations

Strengths of this study design include modeling of outcomes over time rather than at discrete time points, inclusion of a comprehensive battery of linguistic, cognitive-communicative, and quality of life outcomes and covariates for clinical interventions and genetic and imaging biomarkers. Mixed-effects models can account for missing outcome data assuming it is missing at random.

There are several study limitations in regard to study protocol adherence. First, the observational design does not permit accounting for unmeasured confounders, provide strong evidence for causal relation between SLP intervention and outcomes, and does not control for biases due to confounding, selection, or other sources. Results may not be generalizable beyond samples and settings similar to participants and sites included in the study. The study sample may not be representative of the site populations due to eligibility requirements, recruitment rates, and potential for self-selection bias. Aphasia limitations can complicate the consent process and for many, may require engagement of family members. Patients with more severe linguistic and cognitive-communicative deficits may be less likely to enroll or more likely to drop out in part due to intensity of inpatient and day rehabilitation programs and challenges associated with return to home and community.

Conclusions

This longitudinal observational study will develop trajectory models for recovery of clinically relevant linguistic, cognitive-communicative, and quality of life outcomes over 18 months after inpatient rehabilitation. Models will identify individual differences in the patterns of recovery based on variations in personal, genetic, imaging, and therapy characteristics. The resulting models will provide an unparalleled representation of recovery from aphasia resulting from stroke.

We expect that findings from this large, prospective longitudinal cohort study will provide a more detailed understanding of the effects of speech and language therapy characteristics and other participant and aphasia-related factors on patients' outcome trajectories, which will help inform clinical practice and rehabilitation service delivery during and after inpatient rehabilitation. Findings will provide valuable insights for clinicians in modeling aphasia recovery and support the development of patient-centered therapies. A better

understanding of recovery may assist with prognosis, allowing patients and caregivers to plan, helping clinicians choose appropriate therapies, providing benchmarks against which to measure change, and allowing therapy modifications when patients do not attain benchmarks. Knowing which patient factors and treatment variables are key predictors of aphasia recovery may inform all stakeholders of the linguistic, cognitive-communicative, and health-related QoL outcomes in adults with post-stroke aphasia. Aphasia therapy delivery will potentially benefit from an appreciation of how neurobiological patient factors such as brain and genetic biomarkers influence aphasia recovery. Appreciating which SNPs are associated with functional and QoL outcomes will inform our understanding of the brain mechanisms that influence aphasia recovery. Amelioration of aphasia symptoms after intensive therapy may well reflect pre-stroke brain connectivity properties with improvements across behavioral domains being dependent on global and system-specific connectivity. Further, this study may help clinicians appreciate how social determinants of health may affect aphasia recovery, particularly when funding for rehabilitation services is tied to employment or health insurance access. Discovery of genetic and neuroimaging biomarkers associated with unfavorable aphasia and QoL outcomes should not be used to deny or limit services because of poor prognosis, but instead invigorate efforts to evaluate interventions for patients with these characteristics.

Suppliers

a. Oragene Discover OGR-600, DNA Genotek, Inc
b. PurFlock Ultra Tipped Applicator with Transport Tube, Puritan Medical Products
c. TaqMan Allelic Discrimination assays, ThermoFisher Scientific Inc
d. MATLAB, Optimization Toolbox version: 9.4 (R2022b); the MathWorks Inc
e. C++, International Organization for Standardization (ISO)
f. Python, The Python Software Foundation
g. Awk, free software license.

Corresponding author

Leora R. Cherney, PhD, Shirley Ryan AbilityLab, 355 E Erie St, Chicago, IL 60611. *E-mail address:* lcherney@sralab.org.

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