Forecasting Patterns of Delirium and Early Recovery After Acute Stroke

Abstract

Delirium is common after acute stroke, and likely represents an impediment to recovery. However, the concrete manifestations of delirium comprise a spectrum, and it is unclear whether various patterns of symptoms may have differential effects on outcomes. Many of these symptoms are intimately connected, including arousal, attention, and activity level, and as a result, delirium phenotypes have been traditionally labeled as hyperactive, hypoactive, and mixed. Unfortunately, patients with hypoactive delirium are known to be underdiagnosed using standard screening tools, and the presence of pre-existing neurological symptoms only magnifies this challenge.

We therefore propose an ***innovative approach*** aimed at diagnosing and categorizing delirium using *wearable sensors* capable of measuring activity on a granular scale. Activity data will then be analyzed using *machine learning techniques* to identify delirium phenotypes corresponding to patient activity patterns. We hypothesize that such patterns may also be predictive of early motor recovery after stroke, and we propose to apply similar machine learning techniques to identify activity-based phenotypes corresponding to post-stroke functional outcomes.

We aim to leverage Rhode Island Hospital's strength in clinical stroke care and Brown University's expertise in biomedical informatics to build a collaborative partnership that will allow both institutions to become leaders in the field of translational stroke research. It is anticipated that the co-PIs of the proposed study will continue their collaboration to build a competitive research program based on novel data acquisition and analysis techniques. The insights obtained from this study will be used as crucial preliminary work enabling future NIH R01 funding applications.

Forecasting Patterns of Delirium and Early Recovery After Acute Stroke

Specific Aims:

Delirium is common after acute stroke, and likely represents an impediment to recovery.[1-4] However, the concrete manifestations of delirium comprise a spectrum, and it is unclear whether various patterns of symptoms may have differential effects on outcomes. Many of these symptoms are intimately connected, including arousal, attention, and activity level,[5] and as a result, delirium phenotypes have been traditionally labeled as hyperactive, hypoactive, and mixed. Unfortunately, patients with hypoactive delirium are known to be underdiagnosed using standard screening tools, and the presence of stroke-related symptoms only magnifies this challenge.[6] Activity levels in stroke patients may be of particular importance, as lower levels of early post-stroke activity may also reflect a diminished potential for longer-term recovery.[7]

We therefore propose an ***innovative approach*** using wearable sensors called wrist actigraphs to diagnose and categorize delirium by measuring patient activity in a highly granular fashion. In conjunction with machine learning-based analytic techniques, actigraph data can be utilized to identify patterns of activity in non-paretic limbs (those unaffected by stroke) corresponding to a diagnosis of delirium, and patterns of activity in paretic limbs (those that have stroke-related weakness) corresponding to early motor recovery. Our **central hypotheses** are that these models will be able to a) reliably differentiate delirium phenotypes, and b) predict both early motor recovery and longer-term functional outcomes after stroke.

Specific Aim 1: To develop machine learning models of sensor-based activity measurements that can reliably distinguish among phenotypes of delirium and non-delirium in patients with stroke.

Hypothesis 1: Quantitative measurements of non-paretic limb activity can be used to identify and categorize delirium phenotypes in stroke patients with a high degree of accuracy, as compared with reference-standard expert assessments.

Specific Aim 2: To develop machine learning models that can predict patterns of early motor recovery and longer-term functional outcomes based on phenotypes of delirium and non-delirium in patients with stroke.

Hypothesis 2: Quantitative measurements of paretic limb activity can be used to differentiate patterns of early motor recovery after stroke based on delirium phenotype, and can in turn predict 3-month functional outcomes.

Significance:

Despite advances in acute treatment, stroke remains the leading cause of serious, long-term disability in the United States. The foundation for subsequent functional recovery after stroke is based on acute rehabilitation, but many patients are unable to realize the benefits of rehabilitation due to poor participation, attention, or motivation. In many cases, these symptoms may be a result of persistent delirium, which occurs frequently after stroke and is known to have adverse effects on outcomes.[1-4]

Indeed, many patients represent outliers not conforming to expected patterns of recovery, as previous studies have suggested that post-stroke motor recovery is predicted only moderately by traditional clinical predictors.[8] However, because of proposed underlying mechanisms for delirium and neurorehabilitation which may be shared—for example, alterations in neurotransmitter pathways[9-11] and functional connectivity networks[12,13]—the development of delirium may play a role in some of the variability in post-stroke recovery. Leveraging activity data may therefore serve as a major step to better recognizing and understanding the effects of delirium on motor recovery after stroke, while also potentially representing a biomarker that could help tailor future treatment paradigms based on specific delirium phenotypes.

The proposed study capitalizes on the synergy between the co-PIs and their respective departments, as well as their unique strengths—Dr. Reznik's clinical expertise and experience conducting stroke research, and Dr. Eickhoff's proficiency in data-driven computational methods and skills in developing analytic models based on machine learning techniques. Funding towards this project would help cultivate a long-term collaboration leading to future multi-PI NIH grant proposals, and would position both the departments of Neurology and Biomedical Informatics as pioneers in the field of clinical and translational stroke research.

Innovation:

The proposed project is innovative in three ways, two methodological and one conceptual. First, we seek to validate wrist actigraphy as a novel method of detecting and categorizing delirium in patients with acute stroke. If actigraphy proves reliable in comparison to reference-standard expert assessments, then its use can potentially be extended to other patient populations for whom delirium detection using existing screening tools may be challenging (e.g. patients with other forms of acute brain injury or those with dementia), with larger scale applications to both clinical practice and other research platforms. Additionally, given its high resolution and detailed data on patient limb movement, wrist actigraphy may also represent a novel method of quantifying patterns of early recovery after acute stroke, potentially serving as a biomarker for both clinical and research purposes. Conceptually, we seek to study the interface between delirium and neuro-recovery after stroke, a relationship that has been previously unexplored, and one which may help inform some of the unexplained variability in post-stroke recovery.

Approach:

Study Design: We propose to enroll a prospective observational cohort of 40 patients with moderate-to-severe acute intracerebral hemorrhage (hemorrhagic stroke) and hemiparesis (unilateral weakness) over the course of 12 months. For the duration of their hospitalization, enrollees will have daily delirium assessments performed by expert clinicians using a standardized clinical interview protocol. The results of these assessments will be compared with data obtained from wrist actigraphs worn continuously on patients' non-paretic (unaffected) limbs throughout their hospitalization. Additional actigraph data will be collected from patients' paretic (weak) limbs to determine temporal trends in overall activity level. Patterns of early recovery for patients' paretic limbs will then be stratified based on the presence or absence of delirium, and by specific delirium phenotype.

Month	*Study training*	*Study enrollment*	*Data acquisition*	*Data analysis*	*Manuscript preparation*
September 2018	X	X	X		
October 2018		X	X		
November 2018		X	X		
December 2018		X	X		
January 2019		X	X		
February 2019		X	X		
March 2019		X	X		
April 2019		X	X		
May 2019		X	X	X	
June 2019		X	X	X	
July 2019		X	X	X	
August 2019		X	X	X	X
September 2019				X	X
October 2019	***NIH R01 submission***				

Figure 1. Study timeline.

***Inclusion and Exclusion Criteria*:** All patients age ≥ 18 with moderate-to-severe acute intracerebral hemorrhage (NIH stroke scale ≥ 5) and hemiparesis will be consecutively screened for potential enrollment. Patients with previous limb amputation or significant pre-morbid functional disability requiring assistance with their daily activities (as assessed using the modified Rankin Scale) will be excluded from consideration. Patients with devastating strokes considered to have a high likelihood of mortality will be excluded from consideration.

***Study Recruitment*:** Study recruitment will be facilitated by the high volume of stroke admissions at Rhode Island Hospital (>1000/year, including approximately 250-300 patients with intracerebral hemorrhage per year) and other ongoing clinical stroke studies, for which we have been listed among the highest enrolling sites. However, simultaneous study recruitment will be limited by our number of actigraph devices: with 6 total devices, there can be 3 patients enrolled simultaneously at any given time. After subject screening, patients' healthcare decision-makers will sign informed consent should they agree to participate in the study.

***Delirium Diagnosis*:** Expert clinicians will assess patients for delirium on a daily basis using criteria from the Diagnostic and Statistical Manual of Mental Disorders, 4th and 5th editions (DSM-IV and DSM-5) to help guide their diagnoses.[14] Patient interviews will be supplemented by interviews of the patient's family and care-team, as well as by chart review.[15] There will be quality checks on assessments, with regular meetings to obtain a consensus on delirium diagnoses.

***Measurements & Data Collection*: ** Activity counts (per 30-second epoch) represent the source actigraph measurements. Based on these activity counts, dedicated proprietary software (Action4, Ambulatory Monitoring Inc.) will provide data on duration of time with minimal or no movement, scored as “rest” periods, and duration of time with greater than minimal movement, scored as “active” periods. Based on these estimated durations, the percentage of time spent at rest will be calculated, and an estimation of total movement with area under the curve analysis will also be facilitated by the software’s Proportional Integrating Measure (PIM). The aggregated data from patients’ non-paretic limbs will be used by machine learning-based algorithms to determine actigraph patterns corresponding to clinical delirium diagnoses. Additional machine learning models will be applied to actigraph data collected from patients’ paretic limbs to determine temporal trends in activity level corresponding to clinical recovery of motor movement, and to categorize these patterns based on delirium phenotype.

In addition, we plan to collect data on patient demographics (including age, sex, and race), pre-morbid functional status and 3-month functional outcome (using the modified Rankin Scale), medical comorbidities, and clinical characteristics including stroke location, size, and mechanism, serial neurological examinations, imaging and laboratory findings, and relevant medication administration. Data will be collected with a combination of paper and electronic data capture methods. Research staff will enter study data into a dedicated REDCap database (Vanderbilt University, Nashville, TN), which will be housed on a password-protected server that is backed up daily. Patients’ data will be linked with unique study identifiers, allowing for de-identification of protected health information.

***Analyses*:** We propose to develop machine learning methods to determine patterns of actigraph data corresponding to different clinical delirium diagnoses. First, analyses will be performed using supervised learning techniques on actigraph data obtained from non-paretic limbs with expert assessments serving as the classification reference standard. Neural network algorithms[16] will identify both global and local actigraph features corresponding to reference-standard delirium diagnoses.[17] These algorithms will then be used to develop additional models of specific delirium phenotypes based on activity patterns. Second, we will develop machine learning-based models of early motor recovery using trends in activity data from patients’ paretic limbs as they correspond to 3-month functional outcomes. These recovery patterns will then be further stratified by delirium and non-delirium phenotypes using activity data from each patient’s non-paretic (control) limb, effectively forming a within-patient control.

***Sample Size Considerations*:** It can be conservatively estimated that at least 3-4 patients can be enrolled per month, yielding a cohort of approximately 40 patients over one year. Assuming a mean hospitalization and survey time of 7 days per patient, this would yield a total sample size of approximately 800,000 total activity epochs to be input into our machine learning models. Based on previous data[1-4] it is expected that up to half of the patient cohort may be diagnosed with delirium. With 40 participants, we will be able to estimate population proportions of 50% with a 95% confidence interval of 34-66%. As a feasibility study, our pilot will not be powered with the goal of pre-specified levels of statistical significance, but we anticipate our results will be able to provide reasonable precision for building preliminary models and for the design of future studies. Further, we expect to find a clinically meaningful difference between delirious and non-delirious patient cohorts as part of Aim 2, which would suggest the feasibility of using this approach for future studies.

Collaboration:

We aim to leverage Rhode Island Hospital’s strength in clinical stroke care and Brown University’s expertise in biomedical informatics to build a collaborative partnership that will allow both institutions to become pioneers in the field of translational delirium and stroke research. It is anticipated that the co-PIs of the proposed study will continue their collaboration to build a far-reaching research program based on novel data acquisition and analysis techniques. The insights obtained from this study will be used as crucial preliminary work enabling a competitive NIH R01 application for the October 2019 cycle (see the “Future Funding Strategy” section of this proposal for a detailed strategy for seeking subsequent external funding).

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