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Quantifying motor recovery after stroke using independent vector analysis and graph-theoretical analysis☆

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ABSTRACT

The assessment of neuroplasticity after stroke through functional magnetic resonance imaging (fMRI) analysis is a developing field where the objective is to better understand the neural process of recovery and to better target rehabilitation interventions. The challenge in this population stems from the large amount of individual spatial variability and the need to summarize entire brain maps by generating simple, yet discriminating features to highlight differences in functional connectivity. Independent vector analysis (IVA) has been shown to provide superior performance in preserving subject variability when compared with widely used methods such as group independent component analysis. Hence, in this paper, graph-theoretical (GT) analysis is applied to IVA-generated components to effectively exploit the individual subjects' connectivity to produce discriminative features. The analysis is performed on fMRI data collected from individuals with chronic stroke both before and after a 6-week arm and hand rehabilitation intervention. Resulting GT features are shown to capture connectivity changes that are not evident through direct comparison of the group *t*-maps. The GT features revealed increased small worldness across components and greater centrality in key motor networks as a result of the intervention, suggesting improved efficiency in neural communication. Clinically, these results bring forth new possibilities as a means to observe the neural processes underlying improvements in motor function.

1. Introduction

The loss of hand function is often cited as the most devastating consequence following a stroke (Barker and Brauer, 2005). Over the past several decades, many novel rehabilitation approaches for this functional loss have developed in parallel with advances in neuroscience (Cauraugh et al., 2010; French et al., 2007; Langhorne et al., 2011; Thieme et al., 2013; Veerbeek et al., 2014; Waldner et al., 2009). The most effective treatments generally involve high doses of functionally meaningful tasks beginning in the early weeks post stroke. However, while practice guidelines for effective treatment are emerging, the lack of strong evidence regarding the content of these treatment paradigms remains a critical concern. Findings that certain treatments produce beneficial outcomes in some subjects, while are ineffective or even detrimental in others (Cauraugh et al., 2010; Coupar et al., 2010; Langhorne et al., 2009; Winter et al., 2011), underscores a crucial need to characterize individual differences in treatment responsiveness.

Given the extent of brain reorganization due to a stroke lesion (Westlake and Nagarajan, 2011; Westlake et al., 2012), it is essential to consider the marked variability in brain networks as a primary contributor to these differences. However, frequently used neuroimaging analysis tools are unable to adequately capture and efficiently use the statistical variability — within or across subjects with various lesion locations and reorganization patterns due to stroke. Hence, it is very important that the analysis approach is multivariate rather than mostly univariate as in the frequently used general linear model (GLM) and seed-based connectivity approaches. To this end, both data-driven and multivariate independent components analysis (ICA) have surfaced as effective alternatives. The commonly used group ICA (Calhoun et al., 2001) has been successful for the analysis of data from multiple subjects, but its ability to capture individual subject differences — which is especially critical in group comparisons of subjects with stroke — is limited. IVA of multiple datasets is a recent generalization of ICA that has been shown to be superior in capturing subject variability and making full use of the statistical information within and across multiple datasets (Adali et al., 2014; Ma et al., 2013; Michael et al., 2014). Moreover, the addition of graph theoretical (GT) approaches to IVA components creates a unique and powerful metric for interpreting brain states after stroke.

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The aim of this study was to identify changes in intrinsic brain networks as a result of a task-oriented unilateral intervention of the affected upper extremity in subjects with stroke. We applied the GT framework to generate neural connectivity metrics within canonical cognitive and sensorimotor neural networks, as identified using IVA. We hypothesized that following the intervention, subjects would demonstrate increased sensorimotor network communication efficiency (i.e., increased clustering and decreased path lengths) that would correlate with clinical tests of affected upper extremity function. Data related to the behavioral effects as a result of the unilateral intervention in this study are part of a larger study comparing two different interventions, but these data have not yet been published or presented.

2. Methods

2.1. Study population

Ten volunteer subjects with a first ever monohemispheric stroke in the distribution of the middle cerebral artery participated. Additional inclusion criteria were as follows:

1. Score of 25–35/66 on the Upper Extremity Fugl–Meyer Assessment Scale, indicating moderate to moderately severe impairment in arm function.
2. 50–80 years of age.
3. Completion of all conventional rehabilitation.
4. Able to actively perform a range grasp (finger flexion) with at least two fingers and the wrist maintained in a neutral position.

Subjects were excluded from the study for the following reasons:

1. Participation in an arm exercise program more than 20 min 3 times a week (to avoid bias from training).
2. Medical history of (a) recent hospitalization for severe disease or surgery, or (b) significant orthopedic or chronic pain conditions limiting upper extremity exercise.
3. Neurological history of (a) untreated major post-stroke depression, (b) dementia based on Folstein Mini-Mental Status Score or (c) severe receptive or global aphasia that confounded testing and training (unable to follow 2 point commands).
4. A non-stroke neuromuscular disorder restricting exercise (e.g., Parkinson's syndrome).
5. Independent ability to grasp, lift, transport and release a 6 inch diameter foam ball.
6. Indwelling metals, medical implants, or claustrophobia incompatible with MRI.

The study protocol was approved by the Institutional Review Board and was conducted in accordance with the Declaration of Helsinki. All participants gave written informed consent prior to study participation.

2.2. Rehabilitation intervention

The intervention consisted of two 6-week training blocks of three, 1-h training sessions/week for a total of 36 sessions. Because the subjects included in this study demonstrated moderate to moderately severe arm function, the aim of the first 6 weeks was to prime the affected upper extremity to improve voluntary motor control and active range of motion such that functional tasks could be more effectively practiced during the second 6 week session. Therefore, during the first block, training was focused on repetitive, active movement of the affected arm into shoulder flexion and elbow extension. The Tailwind, bilateral arm training with rhythmic auditory cueing (BACTRAC) device was used for all sessions, which was previously shown to improve arm function in subjects with chronic (>6 months) stroke (McCombe Waller et al., 2008). Training at each visit included four 5-minute training bouts with a 10-minute rest period between bouts. Rate was initially set at a preferred speed and then increased as tolerated. Adjusting the height of the BATRAC device added resistance to the training. The device was flat during the first week and the height was increased as tolerated for the remaining weeks of treatment. During the second 6-week session block, the focus was on task-specific training that included use of the affected arm and hand in grasp, reach, and release activities. This study focused on the group before and after the first 6 weeks of training.

2.3. Behavioral measures

A testing battery of clinical assessments was conducted on each subject before and after the intervention and included the following measures:

1. The Upper Extremity Fugl–Meyer Assessment Scale was used to assess motor impairments.
2. The Wolf Motor Function Test was used to assess motor function in terms of movement time and quality.
3. The University of Maryland Arm Questionnaire for Stroke (UMAQS) was selected to measure daily use of the paretic arm.
4. Isometric grip strength was assessed with a hand dynamometer and pinch strength (lateral pinch and 3-jaw pinch) was assessed using the Jamar Pinch Gauge.
5. The Box and Block Test was used to assess hand function.

To determine the combined clinical effects of affected upper extremity training on measures of brain connectivity, a composite measure of the difference in all clinical outcomes was calculated and used as the single primary outcome measure. Intersubject baseline variability was normalized by use of a change score in which the difference between baseline and post-intervention was divided by the baseline score of each outcome measure.

2.4. Neuroimaging acquisition

A 3 T Phillips Archieva MR scanner was used for all magnetic resonance (MR) data acquisition. fMRI data were acquired using an echo-planar imaging (EPI) sequence with the following scanning parameters: TR = 3000, TE = 30, flip angle = 75, voxel size is 2.5/2.5/3, 50 slices/3 mm slice thickness with no gap. Data were collected while participants performed an auditory-cued affected hand grasp and release task. The hand motor task was standardized based on available range of finger flexion achieved with minimal effort. An MRI compatible SAEBO-FLEX exoskeleton (Saebo, Inc., Charlotte, NC) was worn by each participant to assist with finger extension at the completion of each finger flexion task. The task was cued once every 3 s in a block design of 24 s of motor task followed by 30 s of rest. Subjects were instructed to squeeze lightly at each beep, then to relax and wait for the next beep. Eight blocks were completed during each session. Practice blocks outside of the scanner ensured consistency in task performance and the absence of mirror movements of the unaffected hand. In addition to the fMRI data, a high-resolution 3-dimensional T1-weighted, image was acquired for anatomical reference.

2.5. fRMI preprocessing

The SPM8 software package (Friston, 2013) was employed to perform fMRI preprocessing. Slice timing was performed with a shift relative to the acquisition time of the middle slice using sinc-interpolation. All images were spatially realigned to the 1st volume to correct for inter-scan movement. To remove movement-related variance the realigned images were processed using the unwarp SPM8 function. Given the observed variance (after realignment) and the realignment parameters, estimates of how deformations changed with subject movement were made, which subsequently were used to minimize movement-related variance. Data were then spatially normalized to a standard echo-planar imaging template based on the standard Montreal Neurological Institute space (Friston et al., 1995) with an affine