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RESEARCH ARTICLE

Task effects on functional connectivity measures after stroke

Kaleb Vinehout[1] · Sheila Schindler-Ivens[2] · Jeffrey R. Binder[3] · Brian D. Schmit[1]

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Abstract

Understanding the effect of task compared to rest on detecting stroke-related network abnormalities will inform efforts to optimize detection of such abnormalities. The goal of this work was to determine whether connectivity measures obtained during an overt task are more effective than connectivity obtained during a "resting" state for detecting stroke-related changes in network function of the brain. This study examined working memory, discrete pedaling, continuous pedaling and language tasks. Functional magnetic resonance imaging was used to examine regional and inter-regional brain network function in 14 stroke and 16 control participants. Independent component analysis was used to identify 149 regions of interest (ROI). Using the inter-regional connectivity measurements, the weighted sum was calculated across only regions associated with a given task. Both inter-regional connectivity and regional connectivity were greater during each of the tasks as compared to the resting state. The working memory and discrete pedaling tasks allowed for detection of stroke-related decreases in inter-regional connectivity, while the continuous pedaling and language tasks allowed for detection of stroke-related enhancements in regional connectivity. These observations illustrate that task-based functional connectivity allows for detection of stroke-related changes not seen during resting states. In addition, this work provides evidence that tasks emphasizing different cognitive domains reveal different aspects of stroke-related reorganization. We also illustrate that within the motor domain, different tasks can reveal inter-regional or regional stroke-related changes, in this case suggesting that discrete pedaling required more central drive than continuous pedaling.

Keywords Stroke · fMRI · Resting state · Task-based · Functional connectivity

Introduction

The relative sensitivity of task-based and resting-state functional magnetic resonance imaging (fMRI) connectivity measures to changes in network function of the brain after stroke has been understudied. Since the discovery that resting-state fMRI identifies functionally correlated regions in the human brain (Biswal et al. 1995), resting-state fMRI has been used to understand network function of the intact, injured, and diseased brain (Barch 2017; Zhang and Raichle 2010). The resting-state approach has been particularly useful for studying participants unable to perform cognitive tasks, including individuals with stroke (Ovadia-Caro et al. 2014). However, emerging evidence suggests that task-based functional connectivity may provide additional insight into brain function that cannot be elucidated at rest (Gonzalez-Castillo and Bandettini 2018). Here, we asked whether task-based methods are more sensitive than resting-state fMRI to changes in working memory, motor, and language networks of the brain after stroke.

Differences in brain connectivity between resting state and task-based approaches have been identified in healthy controls for interregional (defined across spatially distinct regions) and regional (defined within a limited region) networks (Gonzalez-Castillo and Bandettini 2018). These differences include significant increases in connectivity using task-based approaches for areas of the brain involved in that task. During a task, there are increases in regional connectivity within areas engaged in the task (Elton and

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Brian D. Schmit
brian.schmit@marquette.edu

[1] Department of Biomedical Engineering, Marquette University and the Medical College of Wisconsin, P.O. Box 1881, Milwaukee, WI 53201-1881, USA

[2] Department of Physical Therapy, Marquette University, Milwaukee, WI, USA

[3] Department of Neurology, Medical College of Wisconsin, Milwaukee, WI, USA

Gao 2015; Sepulcre et al. 2010a, b) and increases in inter-regional connectivity between areas involved in the task, with corresponding decreases in networks not involved in the task (Gonzalez-Castillo and Bandettini 2018; Cole et al. 2013, 2014). These differences between resting state and task-based connectivity can vary depending on the functional domain and the type of task within a domain. Across cognitive domains, these task-based differences are seen in motor (Hoffstaedter et al. 2014), language (DeSalvo et al. 2014) and working memory (Stanley et al. 2015) networks. In addition, within a specific cognitive domain, there are differences between resting state and task-based connectivity across different cognitive tasks (Cole et al. 2014). For example, in the memory domain, different memory tasks produce unique changes in network connectivity, compared to resting state (Garcea et al. 2018). Additionally, we have found that different motor tasks (pedaling versus foot tapping) produce different connectivity patterns (Vinehout et al. 2019), suggesting that in the motor domain there is a task-specificity to connectivity. This study provided evidence that there are task-specific changes from resting state within the motor domain.

Examining differences between resting states and task-based connectivity in people with stroke might provide valuable information about changes in brain function. In people with stroke, decreases in interhemispheric connectivity between homologous regions are observed in language (Zhu et al. 2014), memory (Yang et al. 2014), and motor (Carter et al. 2010) networks during resting states. Locally, acute stroke-related changes in connectivity are observed in the left superior parietal lobule and precuneus during rest (Zhu et al. 2015). Task-based connectivity might provide additional insight into changes in network function after stroke. Specifically, it is possible that engaging task networks, as measured by brain connectivity, provide brain functional information that better correlates with clinical outcomes. For an upper-limb motor task, task-based functional connectivity reveals more stroke-related deficits in inter-regional connectivity than the intrinsic state, specifically between ipsilesional supplementary motor area (SMA) and contralesional M1 (Grefkes et al. 2008). In addition, task-based functional connectivity is more strongly correlated with clinical motor deficits than resting states functional connectivity (Kalinosky et al. 2019). This work highlights the importance of task-based functional connectivity and the need to understand how connectivity is associated with stroke-related deficits across different functional domains.

Within the motor domain, there are notable differences in connectivity between people with stroke and controls, with different types of tasks. The motor domain might be uniquely sensitive to these within-domain, task-related differences because the motor network is one of the areas of the brain with large task-based increases in functional connectivity (Di et al. 2013; Mennes et al. 2013). It is possible that motor areas show the largest increase in task-based connectivity as compared to other brain areas because they have a lower level of correspondence between resting states and task-evoked coactivation (Mennes et al. 2013). This lower level of correspondence between resting states and task-evoked coactivation in the motor areas suggests that motor area connectivity is highly adaptable by task engagement. This phenomenon makes the motor domain prime for examining task-specific and stroke-related connectivity deficits. Recently, a comparison of task-based functional connectivity of pedaling and foot tapping indicated that stroke has different effects on motor networks, depending on the task (Vinehout et al. 2019). Specifically, interregional functional connectivity is reduced with pedaling but not with paretic foot tapping, and regional connectivity is increased with foot tapping after stroke, but not during a pedaling task. Differences in the tasks, such as the coordination involved, the context of the movement, and the muscle groups activated, likely contribute to differences in brain networks after stroke. Of particular interest is the difference in control of discrete versus continuous tasks; discrete motor tasks require more neural drive than continuous upper-limb motor tasks (Sternad 2008).

In this study, we examined inter-regional and regional brain network function in people with and without stroke during working memory, motor, and language tasks. Comparisons were made to rest. We hypothesized that task-based measures of connectivity would detect stroke-related changes in network function of the brain that are not apparent during rest, and that enhanced detection of altered network function would be specific to brain regions and/or connections involved in each task. Within the motor domain, we further hypothesized that discrete movement would reveal more stroke-related differences in network function than continuous movement. Finally, we hypothesized that task-based functional connectivity would be more strongly associated with clinical measures of stroke-related impairment than resting-state connectivity. Support for these hypotheses would provide evidence that task-based functional connectivity is more sensitive to altered brain function after stroke than resting states connectivity across cognitive (language and working memory tasks) and motor domains (continuous and discrete pedaling tasks).

Methods

Participants

Fourteen individuals with chronic stroke (7 men; mean ± std age 60 ± 11.9 yrs., range 44–81) and 16 age-matched individuals without stroke (6 men; age 58 ± 8.2 yrs., range

42–71) participated. Stroke participants were included if they had a left-sided cortical or subcortical stroke at least 6 months prior and were free of contraindications to magnetic resonance imaging (MRI). We chose stroke onset at least 6 months prior as this time point separates acute from chronic stages of stroke recovery (Bernhardt et al. 2017). Individuals with cortical strokes had lesions affecting cortical gray matter. Subcortical strokes affected white matter tracts, thalamus, and/or cerebellum. All individuals participated voluntarily and provided informed consent in accordance with the Declaration of Helsinki and institutional guidelines. See Fig. 1 and Table 1.

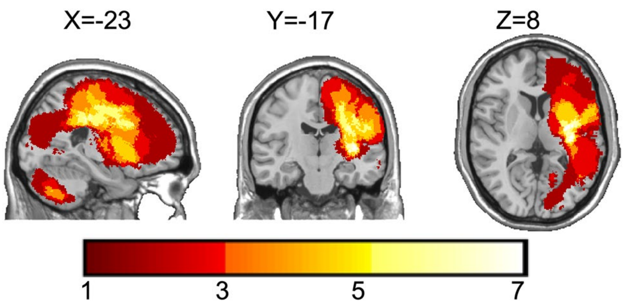

Fig. 1 Lesion location. Visual representation of lesion locations in stroke participants. Colors represent the frequency with which a lesion affected a given voxel. Red represents voxels least frequently affected ($n=1$ participant), and white represents voxels most frequently affected ($n=7$). Lesions are shown in MNI space using radiological convention

Clinical assessment

Participants with stroke underwent clinical testing for cognitive and motor impairment. Cognitive tests included a target cancelation test for hemispatial neglect (Gauthier et al. 1989), Hopkins Verbal Learning Test (Brandt 1991), Short Form Boston Naming Test (Lansing et al. 1999), Counting with Stop Target (Katzman et al. 1983), Repetition and Cookie Theft Picture description from the Boston Diagnostic Aphasia Examination (Goodglass and Edith 1972), Orientation (Katzman et al. 1983), and Category and Letter Fluency (Pendleton et al. 1982) tests. Motor impairments were assessed using the Berg Balance (Berg 1989), 8 m walk (Flansbjer et al. 2005), and lower extremity Fugl-Meyer (Fugl-Meyer et al. 1975) tests. See Table 2.

Experimental paradigm

FMRI was used to examine network function of the brain during the Sternberg Item Recognition Paradigm (Sternberg 1966), lower extremity pedaling (Mehta et al. 2009; Promjunyakul et al. 2015), and Adaptive Language Mapping

Table 1 Demographic and task data

Participant	Age (years)	Sex	Time since Stroke (months)	Lesion size (% of brain)	Affected brain area	Diff. WM (max = 8)	Diff. lang symbol (max = 7)	Diff. lang words (max = 7)	Pedaling rate Hz
S01	81	F	38	7.87	Cort	3	2	4	1.33
S03	59	M	54	7.84	SubCort	6	2	6	1.25
S04	77	M	19	7.04	Cort	5	3	4	0.74
S05	50	F	164	0.46	Cort	5	1	2	1.3
S06	48	M	45	3.72	Cort	6	4	4	1.23
S07	63	M	144	16.40	Cort	4	3	4	0.95
S08	69	F	55	3.39	SubCort	2	3	3	0.97
S10	45	F	56	0.22	SubCort	6	6	4	1.4
S12	48	F	35	5.68	Cort	5	3	5	0.84
S19	58	F	126	4.97	SubCort	6	3	4	…
S20	67	M	7	5.80	Cort	4	1	6	…
S22	44	M	7	0.45	SubCort	8	5	6	1.23
S23	62	F	7	1.06	SubCort	7	4	4	0.22
S24	70	M	93	8.12	Cort	6	6	4	…
Mean(std)	**60.1 (11.9)**		**60.7 (49.9)**			**5.2 (1.5)**	**3.2 (1.5)**	**4.3 (1.13)**	**1.0 (0.3)**
Control mean(std)	**58 (7.9)**					**7.5 (0.5)**	**5.1 (0.8)**	**4.5 (0.6)**	**1.2 (0.3)**

Control participants had a greater mean task difficulty (4.6) than stroke participants (3.4), while stroke participants (1.1) had a greater standard deviation then control participants (0.6). All participants were observed pedaling, non-listed pedaling rates are indicative of technical issues. Bold values represent the mean and standard deviation of the control or stroke group

F female, *M* male, *Cort* stroke affecting cerebral cortex, *Subcort* stroke affecting subcortical white matter, *Diff* Difficulty Level, *WM* Working Memory, *Lang* language

Table 2 Stroke clinical data

Participant (Max)	TC (11)	BNT-s (10)	PMC (10)	HVL (12)	Read (30)	PYNC (6)	CTP (25)	count (2)	BDAE (10)	CF	LF	Orn (6)	MB (12)	Berg (56)	FM_LE total/ motor/sensory (max = 96/34/12)	Walking velocity (m/s)
S01	10	6	4	0	23	2	13	0	10	4	10	2	1	53	94/34/12	0.56
S03	11	9	10	0	29	4	13	2	10	7	3	6	11	45	64/12/6	0.77
S04	7	7	10	0	9	6	5	1	8	3	1	3	0	18	66/13/7	0.12
S05	8	10	10	10	30	6	22	2	10	11	7	6	12	56	90/34/6	0.87
S06	11	10	10	10	30	6	18	2	10	19	14	6	12	56	83/22/12	1.03
S07	10	10	9	4	29	6	6	0	10	6	4	6	7	56	90/28/12	1.28
S08	8	10	10	0	29	4	8	2	10	10	8	6	12	55	89/33/12	0.61
S10	11	10	10	11	30	5	23	2	10	16	19	6	12	56	89/33/6	0.91
S12	10	10	10	6	30	5	16	2	10	10	7	6	12	56	96/34/12	1.07
S19	11	9	10	11	30	6	19	1	10	11	3	6	12	43	89/30/11	0.48
S20	10	8	10	0	27	5	11	1	10	3	2	4	1	54	95/34/12	0.86
S22	11	10	10	7	30	5	16	2	10	15	16	6	12	56	96/34/12	1.19
S23	11	9	10	6	30	6	15	2	9	16	9	6	12	54	92/30/12	0.74
S24	11	8	10	6	29	6	22	2	10	11	6	6	12	51	90/30/12	0.78
Mean (std)	**10 (1)**	**9 (1.3)**	**9.5 (1.6)**	**5.1 (4.4)**	**28 (5.7)**	**5.1 (1.1)**	**14.7 (5.8)**	**1.5 (0.8)**	**9.8 (0.6)**	**10 (5)**	**8 (5)**	**5.4 (1.3)**	**9.1 (4.8)**	**51 (10)**	**87(10)/28(7)/10(3)**	**0.8 (0.3)**

Bold values represent the mean and standard deviation of the stroke group

TC Target Cancelation Task, *BNT-s* Short form Boston Naming Test, *PMC* Progressive Motor Commands, *HVL* Hopkins Verbal Learning Test, *Read* Oral Reading, *PYNC* Progressive Yes/No Comprehension, *CTP* Cookie Theft Picture, *BDAE* Boston Diagnostic Aphasia Examination (Repetition), *CF* Category Fluency, *LF* Letter Fluency, *Orn* orientation task, *Mb* Months backwards, *Berg* Berg balance, *FM LE* lower extremity Fugl-Meyer

(ALM) (Wilson et al. 2018) tasks. These tests probe working memory, motor, and language function, respectively. Comparisons were made to rest. Prior to fMRI, participants were familiarized with each task outside the scanning environment. During familiarization, tasks were adjusted to ability level as described below. MRI scanning was broken into two different sessions to reduce participant fatigue. One session contained the pedaling scans. The other session contained the resting state, memory task, and language task scans. The two sessions were scheduled based on participant availability, which was allowed on the same day or on different days with no more than two weeks between sessions.

Sternberg item recognition

On each trial, participants were shown a list of numbers (i.e., target numbers), asked to maintain them in memory, and then differentiate them from numbers not on the list (i.e., foil numbers). Lists were displayed for 1.5 s. Participants were given 9 s to silently rehearse the list after which one target or foil number was shown. Participants were asked to push a button for target numbers and do nothing for foils. Target and foil numbers were displayed for up to 2.5 s followed by an inter-stimulus interval of up to 0.5 s before a new list was shown. However, when a button press occurred, a new list was presented immediately. Hence, rapid responses resulted in more trials. Target numbers ranged from one to nine, and during familiarization, the length of the list varied from two to eight. A list of only one length was used during fMRI, which was the maximum length for which ≥ 80% success could be achieved. In this way, task difficulty was adjusted for each participant. During fMRI, the Sternberg paradigm lasted for 400 s; it was preceded and succeeded by 18 s of no task for a total of 436 s of data (218 TRs).

Pedaling

Discrete and continuous pedaling were performed. The two conditions were designed to maximize (discrete) and minimize (continuous) the number of start/stop actions performed. Continuous pedaling consisted of four one-minute blocks of pedaling separated by 40 s of no pedaling. Discrete pedaling consisted of forty 10 s blocks. Within these blocks, pedaling duration varied randomly from 4 to 8 s. Conditions were matched for total time spent pedaling (240 s) and no pedaling (160 s). Each condition was preceded and succeeded by 18 s of no task, resulting in 436 s of data (218 TRs). Desired behaviors were cued visually by the words PEDAL and REST presented on a green and red background, respectively. Instructions were to pedal with both legs at a comfortable rate.

Adaptive language mapping

The ALM task (Wilson et al. 2018) comprised a language and control condition. In the language condition, pairs of words were presented. Participants were asked to press a button when the words were related in meaning; e.g., boy–girl, grass–lawnmower, but not walnut–bicycle. Difficulty was manipulated via the salience of the semantic relationship between pairs and by the lexical frequencies of the words. In the control condition, pairs of meaningless symbol strings were presented. A match was defined as identical strings; e.g., ΔΘδЂϟ-ΔΘδЂϟ, but not ΔΘδЂϟ-ϟΔƕϏΔ. Difficulty during the control condition was manipulated by rate of stimulus presentation, length of strings, and degree of mismatch between pairs. Ten blocks of each task were delivered over 400 s (200 TRs). Blocks contained four to ten pairs, depending on the participant's ability. Tasks were continually adapted to maintain a success rate of 80%.

Resting condition

Resting-state data were collected for 400 s (200 TRs) while participants fixed their gaze on a crosshair. The duration of the resting-state trial was selected to approximate the duration of the tasks. Note that resting-state recordings are stable after 300 s (Whitlow et al. 2011). These data were collected to compare the different task states to resting state.

MRI acquisition

During MRI, participants lay supine with the head secured. Visual cues were displayed with a mirrored projector system. During working memory and language tasks, a button box (Current Design PKG-904-ABCD) was placed in the left hand. During motor tasks, the feet were secured to a custom MRI-compatible device, as described previously (Mehta et al. 2009). Additional padding and securements were used to minimize head motion during pedaling. Head motion was calculated by taking the average of the rotation and translation differences between TR images, using the root mean square of image displacement to quantify movement (Jenkinson 1999). A two-way ANOVA (Dunn and Clark 1974) was used to examine the effect of head motion on group and task.

Images were collected using a 3.0 T scanner (MR Instruments, Inc.; GE Healthcare; frequency: 127.73 MHz; field: 3 T). T1-weighted anatomical images were collected using a fast-spoiled gradient recalled (SPGR) pulse sequence with TE = 3.2 ms, TR = 8.16 ms, FOV = 240 mm, and 156 × 1 mm slices. fMRI data were collected using GE's T2*-weighted gradient echo echoplanar imaging protocol with TE = 25 ms, TR = 2000 ms, FOV = 224 mm, matrix: 64 × 64 mm, and 41 × 3.5 mm sagittal slices. A 48-channel head coil was typically used ($n = 27$). However, technical difficulties necessitated the use of a 32-channel coil on 1 occasion and a 24-channel coil on 2 other occasions.

Image processing

T1-weighted images were skull-stripped with Robust Brain Extraction (*ROBEX*) (Iglesias et al. 2011), and T2*-weighted images were skull-stripped with FSL's Brain Extraction Tool (*BET*) (Smith et al. 2004). Bias field correction for T1- and T2*-weighted images was performed using the Advanced Normalization Tools (ANTs) *N4BiasFieldCorrection* (Avants et al. 2009). The Lesion Identification with Neighborhood Data Analysis (*LINDA*) program was used to create lesion masks from T1-weighted images (Pustina et al. 2016). Lesion masks helped with image normalization to the Montreal Neurological Institute (MNI) standard space using the ANTs software (Avants et al. 2011).

The first 4 TRs of the T2*-weighted images were removed to account for magnetic stabilization (Diedrichsen and Shadmehr 2005). Linear and non-linear transformations from participant to MNI space were obtained from T1-weighted images and applied to T2*-weighted images. Motion-based noise was removed with Automatic Removal of Motion Artifacts (*ICA-AROMA*) and FSL's *Linear Image Registration Tool* (i.e., Motion Correction) (Pruim et al. 2015; Jenkinson et al. 2012). T2*-weighted data were temporally (0.1 Hz high pass) and spatially filtered (5 mm Gauss), and prewhitened with fMRI Expert Analysis Tool (*FEAT*) (Woolrich et al. 2001).

Identification of task ROIs and task network

Below we provide a detailed description of how we defined the regions used for analysis. Briefly, we divided the whole brain into regions that we termed 'regions of interest' (ROIs), which were based on functional networks. These functional networks, obtained from an independent component analysis in controls, gave the spatial extent of a given ROI. Then for each task, we selected a subset of the ROIs, including only the regions involved in a given task. We called these 'task regions of interest'. We further identified the connections between these task regions of interest for a given task and defined this as the 'inter-regional task network'. Similar connections between voxels within a region defined the 'regional task network'. Task networks were then used to detect task-based differences in control and stroke groups. Comparisons of networks rather than individual connections allowed us to identify more generalized changes in connectivity between groups within a functional task framework. The same task networks were used in both the control and stroke groups despite expected stroke-related neuroplasticity in standard task networks.

As shown in Fig. 2, identification of regions of interest (ROIs) began using the functional networks identified by prior work (Smith et al. 2009), in which an independent component analysis (ICA) was used to identify 70 spatially and temporally distinct networks of the brain. Networks were derived from a large, publicly available data set of control participants that included resting-state and task-based data. Hence, these data provide a more accurate representation of underlying networks than can be derived from a single data set. Moreover, the output of the Smith ICA (i.e., 70 components) is freely available online. The 70 independent components derived from Smith (Fig. 2.1) were divided into sub-components by splitting each into a left and right half along the midline of the brain (Fig. 2.2). For each of these 140 sub-components, a cluster formation algorithm was used to identify spatially distinct regions. The cluster formation algorithm was applied to the threshold P values associated with the relationship between the individual voxel time series and the mixing matrix from the ICA. This clustering algorithm allowed us to identify spatially distinct regions within the left or right hemisphere of each component. The minimum cluster size was heuristically set to 1.1 cm with a P value threshold of 0.05. This approach was selected to encompass all observable clusters, which were typically 1 or 2 per sub-component. These processes produced 149 ROIs (Fig. 2.2). Gray matter regions of each of the 149 ROIs, as determined by FMRIB's Automated Segmentation Tool (FAST), were used to identify ROI masks (Zhang et al. 2001). The 149 ROI masks, defined from the Smith et al. data, were used for the rest and task fMRI images collected for this study.

Task ROIs were then defined as ROIs that had a correlation of $r > 0.17$ between a modeled hemodynamic response and the mean time series of each sub-component (Fig. 2.3). These task ROIs were based on the mean correlation value across stroke and control groups. Thus, separate task ROIs were defined for each task and used to make comparisons to rest. Across all stroke participants, lesions did not exceed more than 8 percent of any given task ROI, see Table S1.

For the task-based fMRI data, the hemodynamic response directly associated with the task was then removed from T2*-weighted images with a general linear model (GLM) and we used the residual from the GLM for the functional connectivity analysis. This was done to minimize the effect of task design on the correlation analyses while still retaining low-frequency signals associated with functional connectivity (Cole et al. 2014). For all tasks, the task design was convolved with a model hemodynamic response (HDR) consisting of a gamma function with a 6 s delay and 3 s sigma. For working memory and continuous pedaling conditions, the task design was modeled based on a block design representing whether participants were engaged in the task or no task. A block design was also used for the language

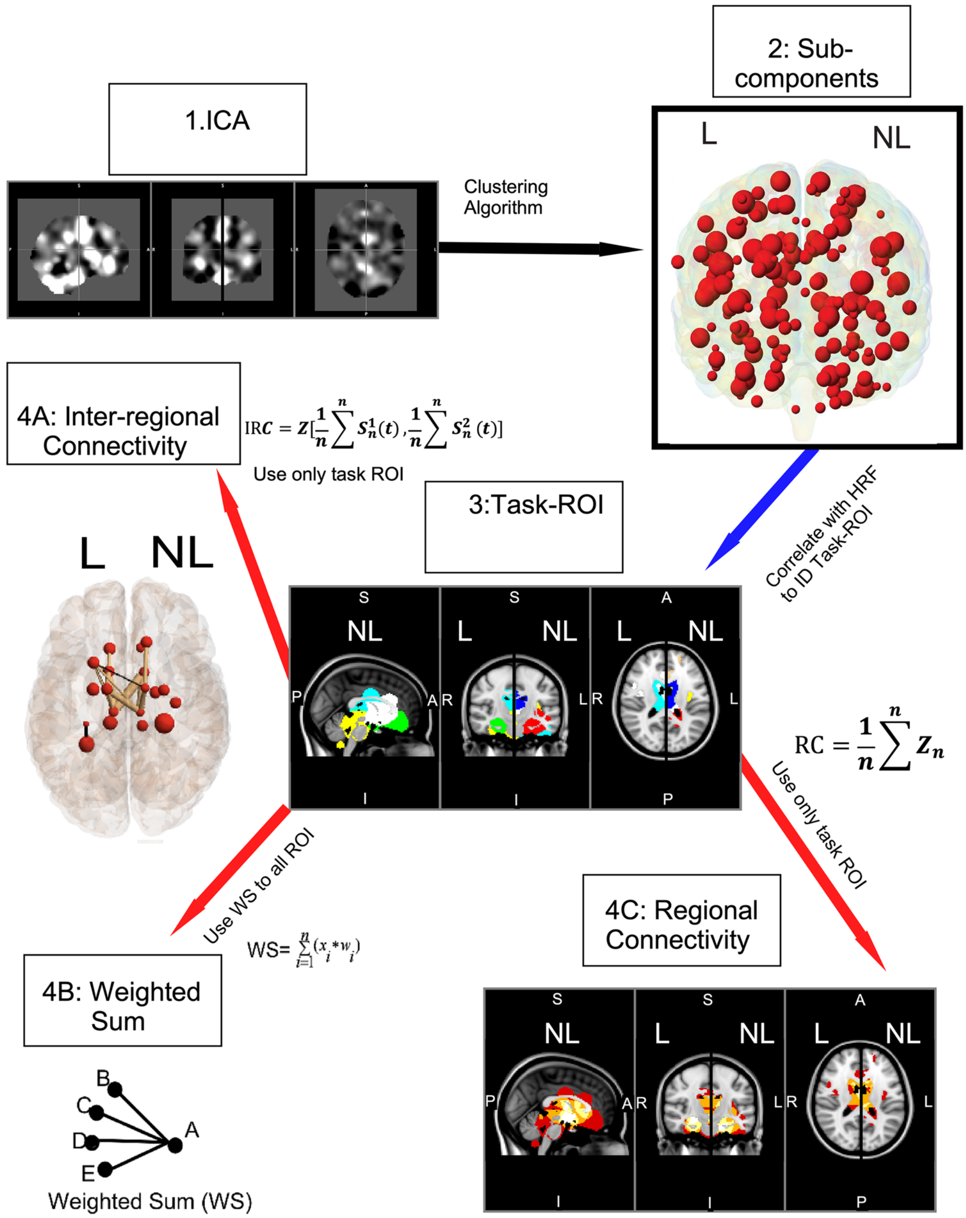

Fig. 2 Methods. Functional network regions were defined from 70 components of an ICA conducted on publicly available data (**1**). A clustering algorithm was applied to these components to get 149 sub-components, defined by the spatial and temporal similarity of the voxels (**2**). The timeseries of each of the 149 sub-components was correlated with the modeled task HDR to identify task ROIs (**3**). The HDR was regressed out of the timeseries for each task ROI, and the inter-regional connectivity (**4A**), regional connectivity (**4B**), and the weighted sum (**4C**) variables were calculated

protocol tasks. Here, language and symbol matching conditions were contrasted. An event-related design based on task engagement was used to model the task-design for discrete pedaling.

For inter-regional connectivity, the inter-regional task network was defined as the task ROI connections between two ROIs that were significantly different during the task compared to the resting state. For regional connectivity, the regional task network was defined as the average connections between voxels within each task-specific ROI that were significantly different during the task compared to the resting state. For both inter-regional and regional connectivity, the task network analysis compared all data collected during each task to the data collected during the resting-state scan. This procedure was done for the control and stroke groups separately. If either group had a connection (between ROIs for inter-regional task networks and between voxels for regional task networks) that was significantly different from resting state, it was considered part of the task network. See Fig. S3 for depiction of the inter-regional task network for each task. Group breakdown of the task networks is included in Fig. S4 and Tables S4–S7. This approach allowed us to limit the connections we examined to task-specific connections.

Measures of inter-regional and whole brain connectivity

For each participant and condition, a mean fMRI time series was computed for each of the task ROIs, as defined above for both the task-based and resting-state fMRI data. Pearson's correlation coefficients were computed on all pairwise combinations of these data, and Fischer-Z transformations were applied. We then limited our analysis of inter-regional connectivity to only the connections that were comprised of the inter-regional task network (that is, connections significantly different from rest). These values provided a measure of inter-regional connectivity that represented the strength of functional connections in the inter-regional task networks (Fig. 2.4A). In Eq. 1, IRC represents inter-regional connectivity, $S_n^1(t)$ is the time series of the nth voxel in ROI 1; Z is the Fisher Z-transformed correlation coefficient.

$$IRC = Z\left[\frac{1}{n}\sum^{n} S_n^1(t), \frac{1}{n}\sum^{n} S_n^2(t)\right] \tag{1}$$

We then calculated the weighted sum (*WS*) among all task ROI connections (Fig. 2.4B) (Rubinov and Sporns 2010). See Eq. 2.

$$WS_j = \sum_{i=1}^{n}\left(w_{ij}\right) \tag{2}$$

where WS_j is the weighted sum of the jth network connections, representing the interregional connectivity of the *j*th ROI; w_{ij} is the individual weighted connection (*z* score) between the *i*th and *j*th ROI. Note that the weighted sum includes all connections for the task ROI for the task under consideration, not just the inter-regional task network. These measures provided insight into the strength of the all of the functional connections between task-related brain regions.

Measures of regional connectivity

For each participant and condition (including rest), Pearson's correlation coefficients were computed for all pairwise combinations of voxel time series within each task ROI. Fisher-Z transformations were applied. For an ROI with n voxels, this process resulted in a correlation matrix of size n by n. Regional connectivity was defined as the mean of all Fischer-Z transformed correlation coefficients of the correlation matrix for each task ROI, yielding one value for each ROI, for each participant and condition. (Fig. 2.4C). In Eq. 3, RC represents regional connectivity, Z represents the Fisher Z-transformed correlation coefficient; n is the number of voxels in a region.

$$RC = \frac{1}{n}\sum\nolimits^{n} Z_n \tag{3}$$

We limited our analysis to only the regional connectivity that comprised each regional task network, i.e., regional connectivity significantly different from rest.

Statistics

A non-parametric permutation (NPP) test was performed on the task ROIs to identify the connections significantly different from rest, or the task network with FSL's *randomize* function (Winkler et al. 2014). This involved a GLM with both rest and task conditions. Bonferroni correction was performed for multiple comparisons. Values were considered significant with corrected alpha = 0.01.

A modified Non-Parametric Combination (NPC) test (Winkler et al. 2016) was used to examine the between-group differences of the task network connectivity values. For this NPC test, we used the FSL *PALM* software (Winkler et al. 2014). This involved a GLM with group (control, stroke). Values were considered significant with corrected alpha = 0.05. Separate statistical tests were done for regional, inter-regional, and weighted sum connectivity. The Fisher combining function was used and a false detection rate (FDR) was applied to correct for multiple comparisons (Winkler et al. 2016).

Between-groups comparisons of task difficulty levels were made with a two sample T test. Between-groups comparisons of variances were made with a two sample F test. Values were considered significant with alpha = 0.05.

Clinical correlations

Associations between task-based connectivity measures and clinical measures were assessed with correlation analysis. Because between-groups statistics were performed with an NPC test across the task network, clinical correlations were performed with the mean connectivity of the task network. Pearson's correlation coefficient was used to correlate all inter-regional and regional connectivity measurements to each of the clinical measurements from the working memory, motor, and language domains. Motor task-network connections were correlated with the motor clinical assessment and language and memory task-networks connections were correlated with the cognitive clinical assessments. Significant correlations were defined using a False Discovery Rate (FDR) applied to correct for multiple comparisons. Values were considered significant with corrected alpha = 0.05.

Results

Participants

Stroke participants underwent clinical testing for cognitive and motor impairment. Overall, participants were high functioning in the motor (lower extremity Fugl-Meyer motor score = 28/34) and language domain (e.g., BNT-s = 9/10), and lower functioning in the memory domain (e.g., HVL = 5.1/12) (see Table 2). Stroke participants had decreased task performance compared to controls for the working memory (5.2 vs 7.5) language (4.5 vs 4.3) and pedaling (1.2 vs 1.0) tasks (see Table 1). Task accuracy and performance levels for all participants are shown in supplementary Table S2.

Task regions of interest

For each task, task ROIs were identified by correlation with a modeled hemodynamic response. These task ROIs, represented with red spheres, are shown in Fig. 3 for each task (see also Fig. S2 for anatomical boundaries of ROIs). For the continuous pedaling condition, 7 task ROIs were identified, predominantly in the bilateral primary motor area, premotor area, posterior cerebellum, and Brodmann area 7. For the discrete pedaling condition, 42 task ROIs were found, predominantly in the bilateral primary motor area, premotor area, anterior and posterior cerebellum, thalamus, anterior cingulate cortex, insular cortex, and the supra-marginal gyrus. For the working memory condition, 19 task ROIs were found, predominantly in the bilateral thalamus, parahippocampal, posterior cerebellum regions, and parts of the inferior frontal gyrus. For the language condition, 7 task ROIs were found, predominantly in the left middle temporal gyrus, left inferior frontal gyrus (IFG), insular cortex, premotor area, and middle frontal gyrus.

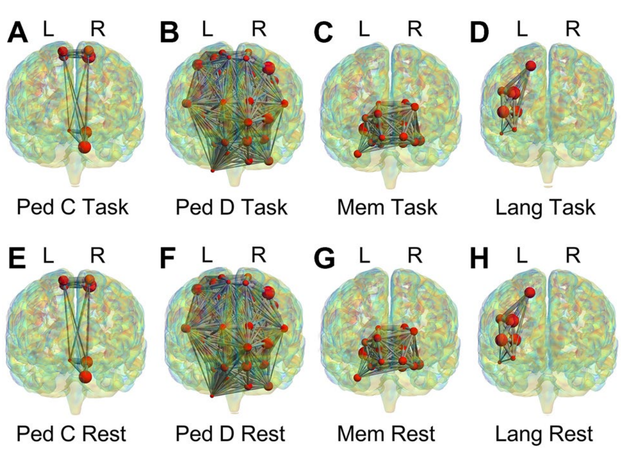

Fig. 3 Task ROIs and Networks. Task ROI inter-regional connectivity (lines) across all task ROIs is depicted. The centers of the task ROIs are depicted by red spheres. The size of the spheres is representative of the size of the task ROI. See Fig. S2 for precise ROI definitions. The task-based connectivity is depicted in A-D for continuous pedaling (**A**), discrete pedaling (**B**), working memory (**C**), and language (**D**) conditions. The resting states connectivity is depicted in E–H for continuous pedaling (**E**), discrete pedaling (**F**), working memory (**G**), and language (**H**) networks. The thickness of the lines represents the average control and stroke connectivity. Images were made with BrainNet Viewer (Xia et al. 2013). *R* Right hemisphere, *L* Left hemisphere. *Ped C* Continuous Pedaling, *Ped D* Discrete Pedaling, *Mem* working Memory, *Lang* Language

Task ROI-weighted sum

A task ROI-weighted sum was calculated by summing all inter-regional connections within the task ROI. Note this means each weighted sum calculation represents the connections of a given task ROI to all other task ROIs. For this task, ROI-weighted sum measurement, we tested for between-groups differences between stroke participants and controls and for differences between task and rest in each group. Between-groups differences (stroke vs. control) in task ROI-weighted sum were observed during continuous pedaling ($P < 0.01$, NPC test). No significant group effects were observed during the other tasks or the rest condition. Within the control group, significant differences between task and rest were found for all conditions ($P < 0.015$, NPC test). In the stroke group, significant differences between task and rest were found for the discrete pedaling and language tasks ($P < 0.012$) (see Fig. 4).

Inter-regional connectivity

Inter-regional task networks were defined as the connections between task ROIs that were significantly different from resting-state connections. For the continuous pedaling task ($P < 0.0004$, NPP test), 3 connections comprised the task network. All were intra-hemispheric connections: between the right anterior and posterior cerebellum, the left premotor and motor areas, and the right premotor and motor areas. All three connections of this task-network were found in both controls and stroke participants. For the discrete pedaling task ($P < 0.0095$, NPP test), 67 connections comprised the task network. On each side of the brain, intra-hemispheric connections were predominantly between the thalamus and premotor areas, thalamus and primary motor areas, thalamus and cerebellum, anterior and posterior cerebellum, and premotor area and primary motor area connections. Also, for discrete pedaling, there were four interhemispheric connections: between the left thalamus and right insula, left thalamus and right premotor areas, right thalamus and left premotor areas, and left thalamus and right thalamus. Of these connections, all were identified in controls, but only 14 of these connections were found in the stroke group. For the working memory task ($P < 0.0064$, NPP test), 16 connections comprised the task network, predominantly between the right hippocampus and right cerebellum, left and right thalamus, left and right thalamus to ipsilateral inferior frontal gyrus, and left and right thalamus to ipsilateral inferior frontal gyrus. Fifteen of these connections were found in the control group and 3 of these connections were identified in the stroke group. For the language task ($P < 0.0013$, NPP test), 3 left hemisphere connections comprised the task network: between the dorsolateral prefrontal cortex (Brodmann areas 46 and 9), the insula cortex and IFG pars orbitalis, and

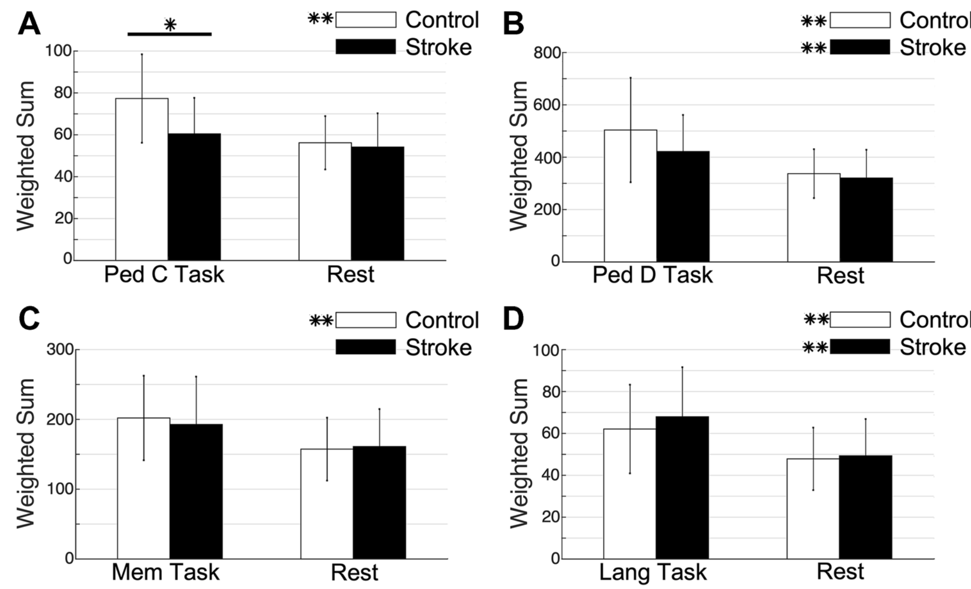

Fig. 4 Task ROI Weighted Sum. The mean weighted sum connectivity across all task ROI connections is depicted. Group means (SD) are shown for control (white), and stroke (black) groups. One asterisk and a line (*) indicates a significant group difference for a given condition. Two asterisks (**) indicates a significant task enhancement for that group. The continuous pedaling (**A**), discrete pedaling (**B**), working memory (**C**), and language (**D**) conditions are depicted. Values on the *y*-axis are weighted sums of Fischer-Z transformed correlation coefficients. *Ped C* Continuous Pedaling, *Ped D* Discrete Pedaling, *Mem* working Memory, *Lang* Language

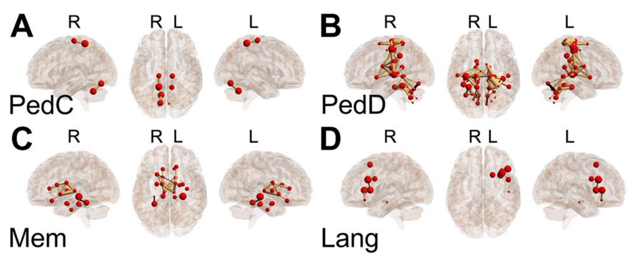

Fig. 5 Inter-regional Task Network. Task ROIs (circles) for continuous pedaling (**A**), discrete pedaling (**B**), working memory (**C**), and language (**D**) are shown on a standard brain. The size of the circles is representative of the size of the task ROI. Lines represent the inter-regional connectivity network for each task. The thickness of the lines represents the absolute difference between control and stroke groups during the task. Images were made with BrainNet Viewer (Xia et al. 2013). *R* Right hemisphere, *L* Left hemisphere. *Ped C* Continuous Pedaling, *Ped D* Discrete Pedaling, *Mem* working Memory, *Lang* Language

the premotor cortex and dorsolateral prefrontal cortex. All 3 of these connections were found in the control group and 2 of these connections were found in the stroke group. These task networks are depicted in Fig. 5.

We then tested the between-group differences in inter-regional connectivity (IRC) of task networks for stroke participants and controls. Between-group differences in inter-regional connectivity were identified during pedaling and working memory tasks but not during the resting states or the language task. During continuous pedaling ($P = 0.0438$, NPC test) a significant stroke-related enhancement in inter-regional connectivity was detected in the task network. During discrete pedaling ($P = 0.0001$, NPC test) and working memory ($P = 0.0020$, NPC test) tasks, there was a significant stroke-related decrease in inter-regional connectivity detected in the task network. See Fig. 6. While between-groups differences here could be attributed to differences in the control and stroke task networks, we saw similar trends in both weighted sum and inter-regional connectivity, suggesting that the network composition did not appreciably impact the results. There were no differences in between-group variances ($P > 0.24$). See supplemental Table S3 for between-groups comparisons of variances.

Regional connectivity

First, regional task networks were identified as the connections significantly different from resting-state data. For all ROIs within each task network, local task networks were identified as a task ROI in which regional connectivity measures (the mean of all pair-wise connectivity values between voxels comprising the ROI) were significantly different from rest. For the continuous pedaling task ($P < 0.0001$, NPP test), all 7 task ROIs were included. For discrete pedaling ($P < 0.0002$, NPP test), all 42 task ROIs were included. For the working memory task ($P < 0.0002$, NPP test), all 19 task ROIs were included. For the language task ($P < 0.0001$, NPP test), all 7 task ROIs were included. These task networks for regional connectivity were found in both the control and stroke groups.

Second, for these regional task networks, we found between-groups differences for stroke participants and controls. The stroke group, as compared to controls, exhibited increased regional connectivity during continuous pedaling ($P = 0.0143$, NPC test) and language tasks ($P = 0.0002$, NPC test). In contrast, during the resting states, the stroke group exhibited decreased regional connectivity in these same regions (continuous pedaling regions: $P = 0.0043$, NPC test; discrete pedaling regions: $P = 0.0001$, NPC test), compared to controls. No significant between-groups

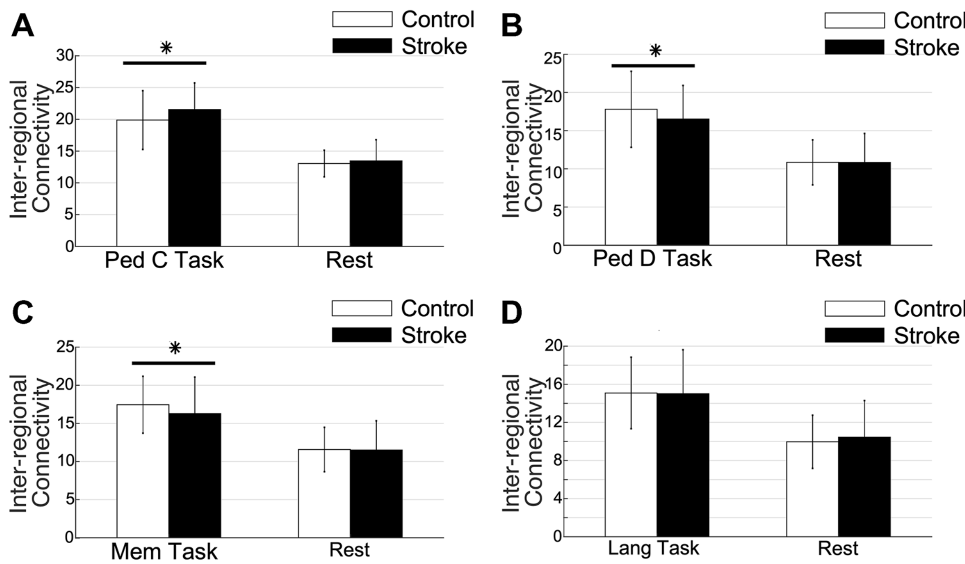

Fig. 6 Inter-regional Connectivity for All Tasks. The mean inter-regional connectivity across all task ROI connections (correlation *Z*-scores) are depicted for continuous pedaling (**A**), discrete pedaling (**B**), working memory (**C**), and language (**D**) conditions. Both the resting state and task conditions use the same task network connections. Group means (SD) are shown for control (white) and stroke (black) groups. One asterisk (*) indicates a significant group difference. *Ped C* Continuous Pedaling, *Ped D* Discrete Pedaling, *Mem* working Memory, *Lang* Language

differences in regional connectivity were found during the working memory task (see Fig. 7). There was no difference in between-group variances ($P > 0.24$). Between-groups differences in variances were only detected during discrete pedaling ($P = 0.0224$) and the language ($P = 0.0147$) tasks. See supplemental Table S3 for between-groups comparisons of variances.

Clinical correlations

No significant clinical correlations were detected between the mean task network connectivity values and corresponding clinical measurements during any of the tasks ($P > 0.05$). We noted that there were no significant correlations between Fugl-Meyer tests and pedaling rate in the MRI scanner ($P > 0.05$). Further, we did not find significant clinical correlations between clinical outcomes and time since stroke ($P > 0.05$).

Task difficulty

For the memory and control language tasks, we found that control participants had significantly greater ($P < 0.0002$) capacity and thus greater task difficulty levels than stroke survivors. While the pedaling and language tasks tended toward control participants having higher difficulty levels than stroke participants, they did not have significantly different difficulty levels ($P < 0.3917$). The stroke participants had a larger variance in task difficulty levels than controls ($P < 0.02$) for all tasks except pedaling. See supplemental

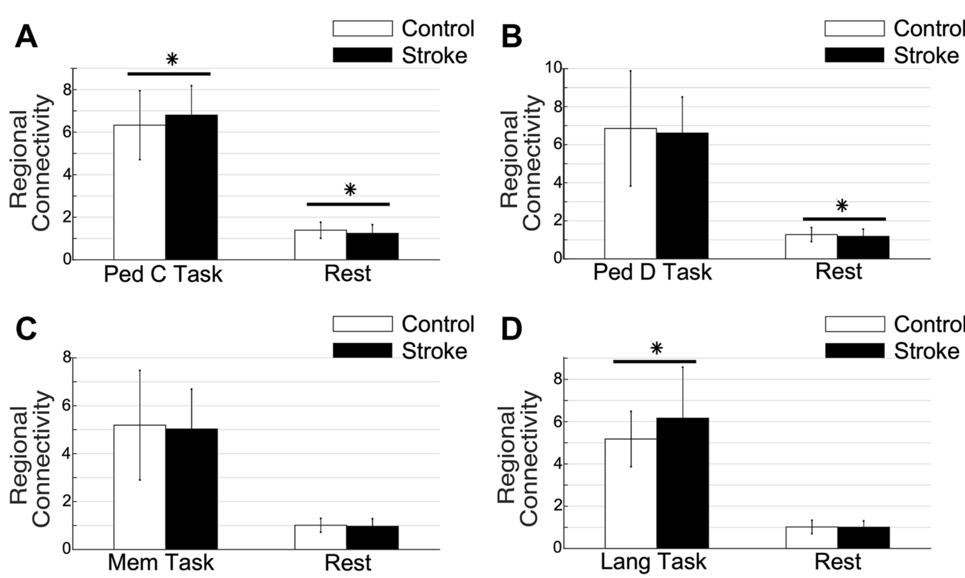

Fig. 7 Regional Connectivity for All Tasks. The mean regional connectivity across all regional task ROIs are depicted for continuous pedaling (**A**), discrete pedaling (**B**), working memory (**C**), and language (**D**) conditions. Group means (SD) are shown for control (white), and stroke (black) groups. One asterisk (*) indicates a significant group difference. *Ped C* Continuous Pedaling, *Ped D* Discrete Pedaling, *Mem* working Memory, *Lang* Language

Table S3 for between-groups comparisons of task difficulty levels and variances.

Discussion

This study provides several novel findings that advance our understanding of network function of the brain after stroke. Consistent with our hypothesis, we found that each task engaged specific areas of the brain and connectivity between those areas. Also consistent with our hypothesis, we found that the ability to detect inter-regional and regional stroke-related changes was enhanced by task-based connectivity in comparison to data collected during rest. The ability to detect stroke-related changes in connectivity depended on the specific task. Whereas stroke-related decreases in inter-regional connectivity were revealed during the discrete pedaling and working memory tasks, stroke-related increases in regional connectivity were detected during the continuous pedaling and language tasks. Overall, our results suggest that task-based connectivity allows for detection of stroke-related changes that are not detected during resting states, but these differences might not predict functional outcomes.

Effects of tasks with varied difficulty

For each of the tasks performed in this study, we sought to match participant effort by having varied difficulty levels for each task. This was done to ensure that all stroke survivors could complete each task. In addition, tasks with adjusted difficulty (matched effort) are useful in minimizing the inter-subject variability found with activity analysis (Berman et al. 2012; Jansma et al. 2007) and functional connectivity analysis (Cole et al. 2013). For our study, all participants were able to complete each of the tasks, even stroke participants who had language, memory or motor deficits. We did not collect data on matched task difficulty to evaluate the effects on our results. Even though we had a wide range of function among our stroke participants, we did not find significant differences in global functional connectivity variances for the stroke group as compared to the control group. Yet, we did find the language task and discrete pedaling task had significant between-groups differences in variances. This could indicate that by having similar efforts for each participant we are seeing less variance in functional connectivity measurements.

For the memory and language tasks we found that control participants had significantly greater ($P < 0.0002$) difficulty levels then controls. While the pedaling and language tasks tended toward control participants having higher difficulty levels then stroke participants, they did not have significantly different difficulty levels ($P < 0.3917$). The stroke participants had a larger variance in task difficulty levels then the control participants ($P < 0.02$) for all tasks except pedaling. This means that while all participants were able to complete each task, the stroke group required an easier task to have a similar performance as the control group. This reflects the stroke-related impairments within each of these cognitive domains. In addition, the higher variance in task difficulty is representative of the wide range of ability we had in stroke survivors.

Importance of task network

The focus on the task ROIs and task networks allowed for the examination of the connections most involved with a given task. This approach yielded differences between the stroke participants and controls that were not detected in resting state connectivity measures. The task ROIs used in this study were based on functional imaging data and were independent of preconceived notions of anatomical regions associated with a task type. Interestingly, the task-specific networks identified through fMRI were located in anatomical brain regions typically associated with the functional domain of the task. For comparison sake, we repeated the analysis using preselected ROIs based on anatomical regions typically associated with the functional domains for each of the tasks (see Supplemental Information on A Priori Task ROI Weighted Sum and Fig. S3 for additional details). The connectivity of these a priori ROIs, shown in Fig. S4, was generally similar to our results based on fMRI classification of ROIs. The working memory task involved connections between the thalamus, hippocampus and frontal cortex areas, consistent with magnetoencephalography localization with the Sternberg test (Brookes et al. 2011). The connections to frontal cortex illustrate the distributed nature of this task. The continuous pedaling condition produced an increase in ipsilateral connectivity between premotor and motor areas, indicative of the motor planning associated with this task. In addition, there was no increase in connectivity between hemispheres during the continuous pedaling task; this might be due to reliance on central pattern generators, once pedaling is initiated (Guertin 2013). The discrete pedaling task produced more thalamus and insula connections than continuous pedaling, indicative of increased cognitive load (Sternad 2008). The involvement of the insula and thalamus regions in discrete pedaling also indicated a higher level of central command in this task (Jansen et al. 1995). The language task highlighted connections between prefrontal areas, motor areas, and areas involved in language processing (Wilson et al. 2018). The laterality of the language network has been reported by others (Tran et al. 2018) and might be indicative of the more localized brain function associated with this task.

We found increased task-based regional connectivity in pedaling and language task ROIs in people with stroke, consistent with the concept that regional connectivity is increased, and inter-regional connectivity reduced in stroke survivors. In healthy young adults, there is a task-based increase in regional connectivity in active regions as compared to data collected during rest (Sepulcre et al. 2010a, b) consistent with our observations, although exact comparisons are difficult due to differences in how regional connectivity is defined and measured across studies. The observed increase in regional connectivity could be due to suppression of endogenous inter-regional communication that occurs during "rest", allowing for enhanced local communication (Lynch et al. 2018). In people with stroke, the prominent increase in local connectivity during tasks may indicate less disruption of local communication than global communication in stroke survivors (Falcon et al. 2015).

Tasks enhance detection of changes in inter-regional connectivity after stroke

Task-based functional connectivity analyses revealed stroke-related changes in inter-regional connectivity that were not seen during the resting states. Specifically, working memory and pedaling tasks demonstrated stroke-related changes in inter-regional connectivity within the inter-regional task network that were not seen during rest. This suggests that both working memory and pedaling require communication between distant brain regions, and that detection of changes in these networks is enhanced using a task-based approach. The language protocol did not demonstrate a similar task-based effect, possibly due to the more localized networks associated with language and specifically within Broca's area (Tomasi and Volkow 2012).

For inter-regional connections, both the continuous pedaling and the discrete pedaling tasks provided evidence of stroke-related changes in connectivity that were not detected during rest; however, opposite effects on connectivity associated with continuous and discrete pedaling were observed in the stroke group. Inter-regional connectivity was greater in people with stroke during continuous pedaling but decreased during discrete pedaling. The differences can be attributed to the structural properties of the inter-regional task network for each task. For continuous pedaling, the inter-regional task network comprised only intra-hemispheric connections, while the network for the discrete pedaling condition included both intra-hemispheric and inter-hemispheric connections. Thus, continuous pedaling detected only the stroke-related increase in intra-hemispheric connectivity, while the discrete pedaling included the effects of stroke on decreased interhemispheric connectivity (Fig. 6). Note that when the weighted sum of all connections in the task ROI was considered, continuous pedaling showed a stroke-related decrease in inter-regional connectivity (Fig. 4), likely due to a strong reduction in the interhemispheric connections in the broader network. These results agree with studies showing stroke-related intra-hemispheric increases and interhemispheric decreases in brain connectivity (Carter et al. 2010; Frías et al. 2018; Lee et al. 2018).

A task-based approach enhances detection of stroke-related changes in regional connectivity for targeted tasks

We identified stroke-related increases in regional connectivity during continuous pedaling and language tasks that were not found during rest. In contrast, stroke-related changes in regional connectivity were not identified with discrete pedaling and working memory tasks. It appears that the ability to detect increases in regional connectivity is task-dependent. Continuous pedaling and language encompassed smaller inter-regional networks than discrete pedaling and working memory tasks, which might be an important underlying factor in the results.

Interestingly, we observed stroke-related decreases in regional connectivity of the pedaling networks during the resting states. These regional connectivity differences detected during rest might be reflective of stroke-related structural connectivity deficits. A previous study showed that resting-state connectivity and structural connectivity have a strong correlation with each other throughout the brain (Ansari et al. 2011). A study in rats showed a strong correlation between structural connectivity and resting-state data for motor areas (Van Meer et al. 2010). The detection of these resting-state differences might have only been detected in motor networks and not other networks because of the unique flexibility of motor networks. When engaging in tasks, the motor network has been shown to undergo more changes from the resting state than most other networks (Di et al. 2013; Mennes et al. 2013). Therefore, the resting-state motor network might be less representative of task states then other areas in the brain and more representative of structural connectivity, and it is these changes in structural connectivity that we might be detecting.

Clinical measurements reveal correlations with pedaling task network during rest

Inconsistent with our hypothesis, we did not find any clinical correlations with task-based functional connectivity. The examination of task networks and not individual connections might have contributed to the lack of clinical correlations. Furthermore, other studies have shown clinical correlations based upon individual connections, not task networks as we describe in our study. In addition, there might not have been enough variation in clinical measurements to detect clinical changes relative to functional connectivity. It is also possible that the clinical tests chosen here were insufficient representations of the chosen tasks. The lack of significant correlations between pedaling speed and Fugl-Meyer scores suggests this is possible.

While these task networks were allowed to be defined as task-based differences from the resting states in control or stroke groups, we found that the control group alone contained most of these task networks. For the regional connectivity, both control and stroke group identified the same task-network regions. For the inter-regional connectivity, we did see some connections only identified in the control group and a few only identified in the stroke group. While this could influence our control and stroke differences for the inter-regional connectivity, we saw similar trends between the weighted sum and interregional connectivity measurements. Because the weighted sum included all connections and not a task-network and showed similar trends as the inter-regional connectivity, it is unlikely the definition of task-network affected the direction of the results.

The prominence of the control group in defining the task network could be due to the stroke group's higher variability in areas engaged in a given task due to lesion size and location. This may mean that each stroke participant has some reliance on other non-task ROI and task network areas to complete the tasks. Task engagement of other areas and/or connections may be why we do not detect clinical correlation with these connectivity measurements. It is also possible that outside of the task network that resting-state functional connectivity had correlations with clinical measurements.

Study limitations

The different task difficulty across participants to match effort for the tasks may have influenced the results of this study. To ensure that all stroke participants could complete the task, and to normalize effort, task difficulty was adjusted (e.g., see (Wilson et al. 2018). While this approach allowed for matched effort, the more difficult version of the task for control participants and high functioning stroke participants may have made it more difficult to detect differences between groups. The lack of a standard task difficulty also makes comparisons to other studies more challenging. Head motion and image processing techniques also lead to sources of error. See supplemental material for additional details on these limitations. Finally, these results can only be interpreted within the context of the included stroke participants, i.e., left-sided lesion, chronic stroke, and able to perform these tasks.

Conclusion

This study showed increases in functional connectivity during a task in specific brain regions, compared to resting states. Working memory and discrete pedaling tasks allowed detection of stroke-related deficits in inter-regional connectivity, and continuous pedaling and language tasks allowed detection of stroke-related enhancements in regional connectivity. These observations illustrate that task-based approaches allow for detection of stroke-related changes in functional connectivity that are not seen during the resting states. This work also provides evidence that different tasks reveal different aspects of stroke-related reorganization.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00221-021-06261-y.

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Code availability Pipeline to process these data is available at: https://github.com/kvinehout/Functional_connectivity_pipeline.

Declarations

Conflict of interest Authors have no conflicts of interest to report.

Ethical approval "All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee (Medical College of Wisconsin: PRO00027569) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards."

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