Available online at www.sciencedirect.com

SciVerse ScienceDirect

www.elsevier.com/locate/brainres

BRAIN RESEARCH

Research Report

# Neural correlates supporting sensory discrimination after left hemisphere stroke

*Alexandra Borstad*[a], *Petra Schmalbrock*[b], *Seongjin Choi*[b], *Deborah S. Nichols-Larsen*[a,*]

[a]*School of Health and Rehabilitation Sciences, The Ohio State University, USA*
[b]*Radiology, The Ohio State University, USA*

ARTICLE INFO

*Article history:*
Accepted 27 March 2012
Available online 2 April 2012

*Keywords:*
Stroke
Sensory discrimination
fMRI
Diffusion tractography
Hand function

ABSTRACT

*Background:* Nearly half of stroke patients have impaired sensory discrimination, however, the neural structures that support post-stroke sensory function have not been described. *Objectives:* 1) To evaluate the role of the primary somatosensory (S1) cortex in post-stroke sensory discrimination and 2) To determine the relationship between post-stroke sensory discrimination and structural integrity of the sensory component of the superior thalamic radiation (sSTR). *Methods:* 10 healthy adults and 10 individuals with left hemisphere stroke participated. Stroke participants completed sensory discrimination testing. An fMRI was conducted during right, impaired hand sensory discrimination. Fractional anisotropy and volume of the sSTR were quantified using diffusion tensor tractography. *Results:* Sensory discrimination was impaired in 60% of participants with left stroke. Peak activation in the left (S1) did not correlate with sensory discrimination ability, rather a more distributed pattern of activation was evident in post-stroke subjects with a positive correlation between peak activation in the parietal cortex and discrimination ability ($r=.70$, $p=.023$). The only brain region in which stroke participants had significantly different cortical activation than control participants was the precuneus. Region of interest analysis of the precuneus across stroke participants revealed a positive correlation between peak activation and sensory discrimination ability ($r=.77$, $p=.008$). The L/R ratio of sSTR fractional anisotropy also correlated with right hand sensory discrimination ($r=.69$, $p=.027$). *Conclusions:* Precuneus cortex, distributed parietal lobe activity, and microstructure of the sSTR support sensory discrimination after left hemisphere stroke.



## 1. Introduction

During tactile sensory discrimination, the human hand differentiates salient object properties such as shape, texture, size, weight and stimulus location (Bodegord et al., 2001; Klatzky et al., 1985). Sensory discrimination impairment in the contralesional hand is found in approximately one-half of stroke patients in rehabilitation (Carey and Matyas, 2011). Because impaired hand function is associated with a decreased quality-of-life post-stroke, (Nichols-Larsen et al., 2005) there is a pressing need for effective hand rehabilitation. Extensive literature documents the relationship between the brain's structure and function in the post-stroke motor system; however, there is a paucity of literature on post-stroke sensory systems. One report of sensory discrimination recovery post-stroke found no activation within primary (S1)

* *Corresponding author at:* 106 Atwell Hall, 453 W. 10th Ave., Columbus, OH 43210-1234, USA. Fax: +1 614 292 0210.
E-mail address: Deborah.larsen@osumc.edu (D.S. Nichols-Larsen).

0006-8993/$ – see front matter © 2012 Elsevier B.V. All rights reserved.
doi:10.1016/j.brainres.2012.03.060

and secondary (S2) somatosensory cortex early post-stroke, with re-emergence of S1 and S2 activation as function returned to near normal levels in participants with mild residual impairment (Carey et al., 2002). Another reported increased activation within the post-central gyrus in association with a trend toward better motor function (Schaechter et al., 2006). Interestingly, an fMRI study of sensory-impaired participants with ventroposterior thalamic stroke found reduced activation of the affected sensory cortex, suggesting the need to examine axonal integrity in thalamocortical sensory projections (Taskin et al., 2006).

Functional imaging studies of healthy participants identified a bilateral network of structures activated during sensory discrimination that link S1 and S2 cortices with higher level sensory processing areas (posterior parietal, intraparietal cortices), attention (paracingulate (Hartmann et al., 2008), frontal operculum (Stoesz et al., 2003)), working memory (S2, frontal cortex (Hartmann et al., 2008)), and language centers in the temporal lobe (Kuroki et al., 2006). While there is some variability in this network, dependent on the object characteristics, a dominant role for the right hemisphere is consistently demonstrated, regardless of hand stimulated (Harada et al., 2004; Reed et al., 2004; Van Boven et al., 2005). A right hemispheric lateralization of proprioceptive spatial tasks has also been suggested, with right stroke participants demonstrating significantly more variability in spatial tasks (Dukelow et al., 2010).

Connectivity refers to the physical connections (axons, dendrites, synapses) linking brain regions (Johansen-Berg and Behrens, 2009). After stroke, a loss of connectivity occurs from direct damage to the axons or secondary degeneration of axons proximal or distal to the infarct site. Diffusion tensor tractography (DTT) is a method of modeling white matter pathways in the human brain in vivo. DTT allows quantification of white matter microstructural integrity (Johansen-Berg and Behrens, 2009) with fractional anisotropy (FA) being the most common metric. It is important to note that in vivo metrics of brain structure are indirect, and therefore, a direct relationship to axon structure should not be assumed. DTT has been used to study the relationship between infarct location and sensorimotor pathways, (Yamada et al., 2006) to quantify damage to the corticospinal tract (CST), (Schaechter et al., 2008) and to monitor recovery of motor function (Yang et al., 2008). A strong correlation between structural integrity of the CST and post-stroke motor function has been found. (Cho et al., 2007; Nelles et al., 2008; Schaechter et al., 2008; Yamada et al., 2003; Yang et al., 2008). The sensory component of the superior thalamic radiation (sSTR) includes all afferent connections to the somatosensory cortex, and thus, is the functional analogue of the CST; (Wakana et al., 2004) stroke-related structural changes to the sSTR may have relevance to post-stroke sensory function.

Particularly for the hand, motor and sensory function is inextricably linked, since the hand functions as a haptically-based sensory organ. An improved understanding of the neural substrates that support post-stroke sensory function in the hand is vital to the development of rehabilitation methods to maximize sensorimotor function. This report is an initial look at this understudied system and represents the first analysis of the relationship between functional activation within the sensory discrimination network, the micro- and macro-structural integrity of the sSTR, and post-stroke sensory function. Our hypotheses were straightforward: 1) in participants with left hemisphere stroke, we expected a positive relationship between sensory discrimination ability in the right hand and contralateral S1 activation, during sensory discrimination fMRI; 2) we also expected a positive relationship between sensory discrimination ability in the right hand and the structural integrity of the left sSTR.

## 2. Results

### 2.1. *Sensory function*

Sensory discrimination (HASTe) accuracy scores for stroke participants for the right (contralesional) hand ranged from 4 to 14/18 (mean = 10.5) and for left hand ranged from 8 to 16/18 (mean = 11.4). For the right hand, four participants scored in the normal range (>12), 5 participants scored between 8 and 11 indicating mild to moderate impairment, and 1 participant scored ≤6 (equivalent to chance), suggesting severe impairment (see Table 1). All participants who were impaired in their contralesional right hand were also impaired in their left hand.

### 2.2. *Functional magnetic resonance imaging*

The mean group effect (one-sample *t*-test) of brush discrimination for the right index finger indicated that control participants on average had significant activation in left S1, bilateral S2, right and left precentral gyrus, and right and left cerebellum. For the stroke group, the mean group effect was one cluster that peaked in the right superior temporal gyrus and extended to S2 and another peaking in the right cerebellum (Fig. 1a). A direct statistical comparison between stroke and control groups was conducted to look for mean group differences. This analysis used the whole-brain statistical maps and was unmasked, and therefore, not confined to a specific region(s) of interest (ROI). Stroke participants were significantly different in a cluster that peaked in the left precuneus (z = 3.78) compared to controls (Fig. 1b). ROI analysis of stroke and control group maps was completed by masking each group map with the left precuneus cluster to determine whether voxels in the ROI were activated or deactivated (positive or negative BOLD response). Mean Z-statistic in this ROI was −3.54 for the control group and −0.94 for the stroke group, indicating that stroke participants are significantly less deactivated in this area compared to control participants. To further explore the extent of precuneus activation, participant's individual statistical parametric maps (SPM) were masked with the precuneus cluster. Z-statistic values for this ROI ranged from 0.8 to 3.5.

### 2.3. *Diffusion tractography*

The left and right sSTR's were reconstructed from diffusion imaging data for all 10 left stroke participants. Individual participant FA and bundle volume values are listed in Table 1. Mean FA (with standard deviation) of the left sSTR = .414(.04),

**Table 1 – Descriptor data of participants with left hemisphere stroke.**

| ID | Age (years) | Gender | Dominant hand | Chronicity (months) | HASTe (right/left) | Lesion location | Lesion volume | sSTR FA R/L | sSTR vol R/L (voxels) |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 62 | F | R | 9 | 14/15 | IC,CR | 2.1 $cm^3$ | .46/.50 | 605/365 |
| 2 | 48 | F | R | 11 | 13/16 | PLIC, CR | 4.1 $cm^3$ | .51/.41 | 558/62 |
| 3 | 84 | F | R | 11 | 13/8 | CR, PLIC | 0.6 $cm^3$ | .55/.55 | 334/401 |
| 4 | 61 | F | R | 24 | 13/13 | P, T, IC, C, CR | 4.9 $cm^3$ | .48/.50 | 140/95 |
| 5 | 71 | M | R | 10 | 11/11 | IC, T | 1.9 $cm^3$ | .50/.40 | 468/189 |
| 6 | 64 | M | R | 20 | 10/11 | PLIC, T, CR | 1.4 $cm^3$ | .53/.46 | 658/73 |
| 7 | 69 | M | R | 9 | 10/10 | FC, PC, CR | 54.3 $cm^3$ | .42/.2[a] | 308/0 |
| 8 | 77 | F | R | 8 | 9/8 | PLIC, CR, PC | 1.9 $cm^3$ | .45/.48 | 348/387 |
| 9 | 39 | F | L | 4 | 8/12 | PLIC | 1.3 $cm^3$ | .53/.43 | 299/81 |
| 10 | 46 | F | R | 96 | 4/10 | IC, T, GP, P, CR | 9.9 $cm^3$ | .48/.2 [a] | 325/0 |
| | 62.1 (14) | | | 20.4(27) | 10.5(3.0)/11.5(2.6) | | 11.7 (20.6) | .496(.12)/ .406(.03) | 404(161)/165(161) |

HASTe = Hand active sensation test, sSTR = sensory superior thalamic radiation, FA = fractional anisotropy, vol = bundle volume, IC = internal capsule, PLIC = posterior limb, C = caudate, P = putamen, GP = globus pallidus, T = thalamus, CR = corona radiata, PC = parietal cortex, FC = frontal cortex, [a] sSTR non-detected, threshold level assigned.

right sSTR = .481(.12). Bundle volume (vol) left sSTR = 165 voxels (51), right STR = 404 voxels (51). An unpaired *t*-test was used to look for laterality effects on the sSTR FA and bundle volume. Mean FA values of the left and right STR were not statistically different (p = .13), while mean bundle volume was (p = .004). Fig. 2 illustrates, in three participants, the relationships between connectivity, fMRI activation and sensory function. Participant 1 had normal sensory discrimination ability, parietal cortex activation very similar to control participants, and microstructure of the sSTR that was symmetrical, as reflected by an FA ratio close to 1.0. In Participant 2, FA of the left sSTR was diminished, sensory discrimination was normal, and cortex activation was primarily ipsilateral to the stimulus. Finally, in Participant 10, no sSTR was reconstructed, low parietal cortex activation occurred, and sensory discrimination ability is absent.

### 2.4. *Correlation analysis*

To test our first hypothesis, the relationship between ipsilesional left S1 activation and sensory discrimination ability, we calculated the correlation between fMRI signal intensity (peak Z statistic) in the S1 cortex ROI, during texture discrimination, and HASTe scores; it was not significant (r = .36, p = .29)

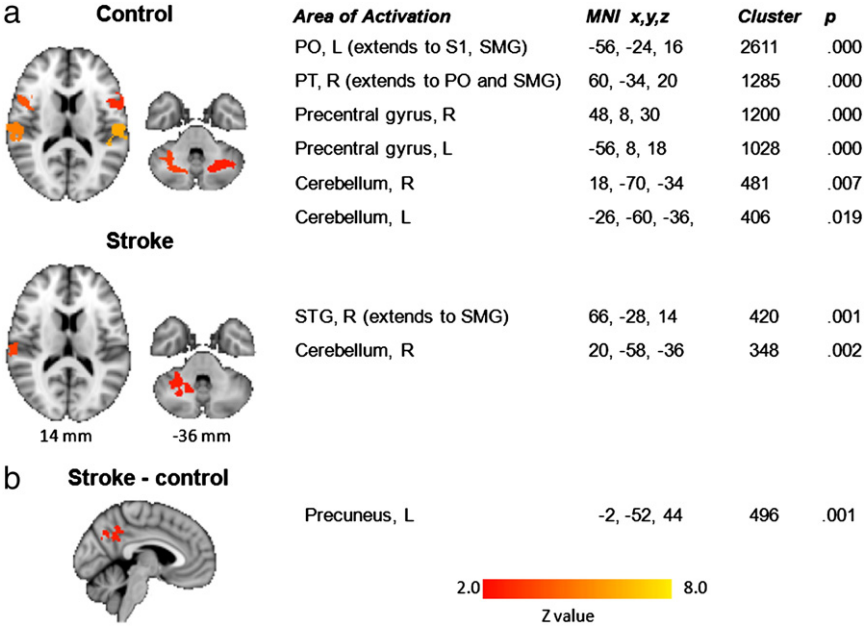


**Fig. 1 – (a) Illustration of group average (one-sample *t*-test) statistic parametric maps for right index brush discrimination task > rest activation (n = 10 control, n = 10 left stroke) (b) A two-sample unpaired *t*-Test of stroke vs. control group. Stroke participants had statistically greater activation in a cluster with the peak (Z = 3.8) in left precuneus cortex. Statistic images were thresholded using clusters determined by Z > 2.3 and a corrected cluster significance threshold of p = .05 and are overlaid on the 2 mm T1 MNI 152 template.**

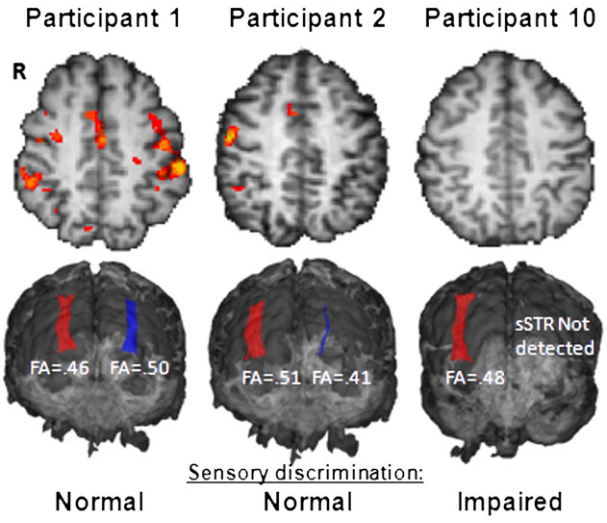


**Fig. 2 – Illustrates, in three participants, the relationships between connectivity, fMRI activation and sensory function. Participant one had normal sensory discrimination ability, parietal cortex activation mirrored that of control participants and microstructure of the sSTR was symmetrical, reflected by an FA ratio close to 1.0 (peak Z = 12.1 in left S1, bundle volume = 615/365) In Participant 2, sensory discrimination was also normal, FA of the left sSTR was diminished, cortex activation was primarily ipsilateral to stimulus. (peak Z = 7.9 in right S2, bundle volume = 558/62) In Participant 10, sensory discrimination ability is severely impaired, the sSTR was not reconstructed, low parietal cortex activation occurred, and (peak Z = 4.7, right S2, inferior to slice shown, bundle volume 325/0). Top row: Axial slices at parietal cortex of individual statistical parametric maps during right brush discrimination task > rest activation (Z > 3.0, p = .01) overlaid on individual participants high-resolution brain images (z ~ 40 mm). Bottom row: Coronal view of bilateral DTT reconstructions of sSTR shown in the 3D brain.**

(Fig. 3a). We noted a more diffuse pattern of parietal activation in stroke participants during this task (including 3 participants whose peak was in the right hemisphere) and conducted a post hoc correlation of peak parietal (S1 and S2) cortex activation (independent of hemisphere) by HASTe score, which was significant (r = .70, p = .023) (Fig. 3b). In testing our second hypothesis, the relationship between sensory discrimination ability and the microstructure of the sSTR; we identified a positive correlation between HASTe scores and L/R ratio of sSTR FA values (r = .69, p = .027) (Fig. 3c). Finally, because left hemisphere stroke participants were significantly less deactivated in the precuneus, we tested the correlation between activation in the precuneus and sensory discrimination ability and found a significant positive correlation (r = .77, p = .008) (Fig. 3d).

## 3. Discussion

The neural correlates of post-stroke sensory discrimination are poorly described. This study was designed to examine functional and structural neural correlates of texture discrimination in the right hand in individuals with left hemisphere stroke. It has been suggested that the re-emergence of activation in ipsilesional S1 and S2 is associated with the recovery of sensory function after stroke. (Carey et al., 2002) In a longitudinal study of motor function after stroke, an increase in activation in ipsilesional primary sensory cortex correlated with motor recovery. (Ward et al., 2006) We hypothesized that in our group of participants with chronic left hemisphere stroke there would be a positive correlation between the intensity of activation in ipsilesional left S1 and right hand sensory discrimination scores on the HASTe. We did not find a significant correlation between the intensity of activation in the left S1 cortex, during sensory discrimination fMRI, and sensory discrimination ability measured by the HASTe. We did find that the peak intensity of activation in the parietal cortex significantly correlated with sensory function; for three individuals this peak was in the right secondary somatosensory cortex ipsilateral/contralesional to the hand stimulated during the task. This finding is in line with other literature describing post-stroke patterns of activation as more diffuse and in some cases dominated by ipsilateral functional activation (Cramer et al., 1997). It is also in line with Carey's recent work, which found a negative correlation between touch discrimination and activation in ipsilesional S1 cortex after sub-cortical stroke possibly due to functionally effective inhibition (Carey et al., 2011).

Researchers consider the CST a natural measure for motor function. A DTT reproducibility study of healthy subjects found the CST symmetrical across hemispheres for FA and tract volume (Wakana et al., 2007). Because we observed diminished FA and tract volume in sSTR in left stroke participants, and the sSTR includes relevant thalamocortical connections, our second hypothesis examined the relationship between sensory discrimination ability and the structural integrity of the sSTR. We expected a positive relationship between structural integrity of the sSTR and sensory discrimination ability, and we indeed found a strong positive correlation between the L/R FA ratio of the sSTR and sensory discrimination ability (Fig. 3c). Importantly, these data agree with recently published work by Rose et. al., who in a study of children with congenital hemiplegia, found that sensorimotor thalamic projections were more significantly correlated with paretic hand function than were corticospinal tract connections. (Rose et al., 2011) While both peak parietal cortex activation and left sSTR integrity related to sensory discrimination ability, in our data set, there was not a statistically significant correlation between them (r = .26, p = .45).

The fMRI brush discrimination paradigm produced robust activation in areas consistent with other discrimination protocols. On average control participants, had activation in left S1, and bilateral S2, precentral gyrus and cerebellum (Fig. 1). Bilateral S2 activation has been associated with texture discrimination, appearing to play a role in tactile learning of shape and texture through a link with structures in the temporal lobe. (Murray and Mishkin, 1984) The "parietal–prefrontal–premotor network"(Harada et al., 2004) appears to link sensory processing areas in the parietal lobe with frontal lobe areas associated with spatial attention (Gitelman et al., 1999) and working memory (Jonides et al., 1993; Stoesz et al.,

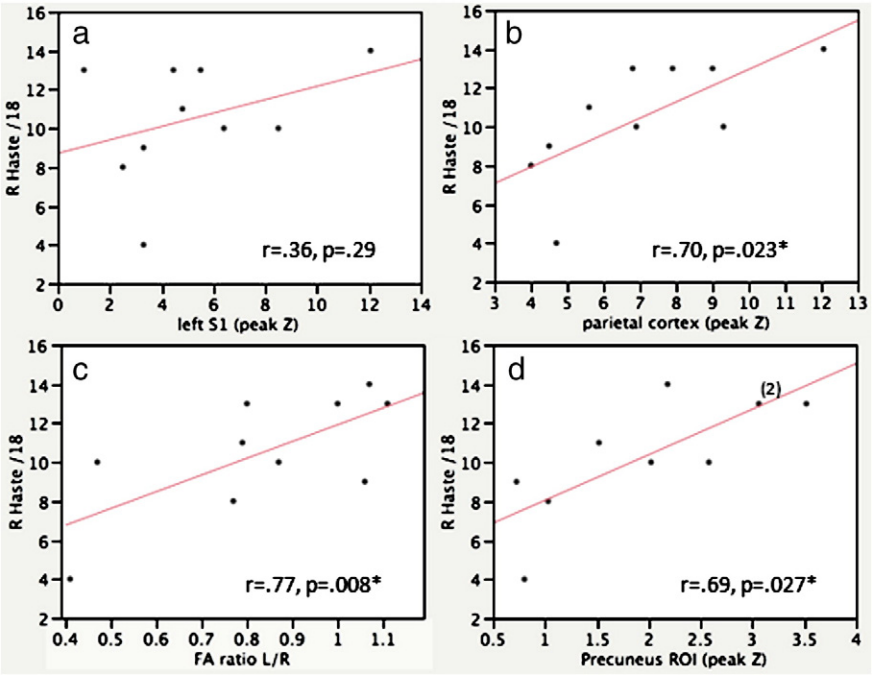


**Fig. 3 – Pearson-product moment correlations for Stroke participants (n = 10), (2) indicates 2 overlapping data points. ROI = region of interest, FA = fractional anisotropy. Haste = Hand Active Sensation Test, S1 = primary sensory cortex, peak Z = highest Z statistic during sensory discrimination fMRI. Multiple comparison correction was applied using the Holm procedure, adjusted alpha levels for our 3 comparisons were p = .016, p = .025 and p = .05. *indicates correlation met statistical significance.**

2003). Activity within the primary motor cortex, during sensory discrimination has been observed previously, with a role in general cognitive function, or preparation for manual interaction with the perceived object postulated (Deiber et al., 1996). Others have found a distinction between hemispheric activity and type of task. For example, a left dominance for form discrimination (grating distance) but right dominance for location (area stimulated) were identified (Van Boven et al., 2005). Thus, there may be some difference between right and left hemisphere activity, dependent on the type of object characteristic analyzed. On average, left stroke participants only shared two common areas of activation during the brush texture discrimination; activity peaked in a cluster centered in the supramarginal gyrus and in the right cerebellum. This reflects the more distributed locations of both parietal and frontal cortex activation during the task in the left stroke participants.

In a direct statistical contrast of right brush discrimination, stroke participants were significantly different from control participants in a cluster that peaked in the left precuneus, the medial aspect of the posterior parietal lobe. The precuneus is known to have a high level of activity during rest, the default mode of brain function (Raichle et al., 2001), which decreases during goal-directed cognitive processing or perceptual tasks (Cavanna and Trimble, 2006). Behavioral functions associated with increased precuneus activity in healthy humans include episodic memory retrieval (Tulving, 1984), visuo-spatial imagery (Goldman-Rakic, 1988), and self-processing (Andreasen et al., 1995). In a study of stroke patients with optic ataxia, the precuneus was found important to the control of visually guided reaching. (Karnath and Perenin, 2005) A post-stroke upper extremity training study that used resting state functional MRI to evaluate functional connectivity changes with training found the precuneus among the areas who's functional connectivity can be used to predict recovery of upper extremity function. (Varkuti et al., 2011) Afferent and efferent connections of the precuneus have been studied in non-human primates, using tracer techniques. Cortico-cortical connections within the posterior-medial parietal cortex as well as bridging connections between hemispheres provide the anatomical basis for functional coupling (Leichnetz, 2001). No direct connections from precuneus to primary sensory regions have been identified; however, connections to the caudal parietal operculum and inferior and superior parietal lobules are present, supporting the precuneus' role in integration and association of information verses processing of external stimuli. Functional connectivity mapping of the precuneus also identified connections to sensory processing areas, including posterior parietal cortices, somatomotor cortex, insula, supramarginal gyrus and middle frontal gyrus. (Zhang and Li, 2011).

The precuneus is the only brain region in which stroke participants had significantly different cortical activation than control participants during sensory discrimination. Control participants were deactivated during this task, which is consistent with the current understanding of precuneus activity decreasing during goal directed cognitive or perceptual tasks. Stroke participants had significantly higher activation during sensory discrimination than control participants on average in the precuneus ROI. This could suggest, as a group, that they were less engaged in the task; however, when we explored precuneus activation in individual stroke participant's, higher

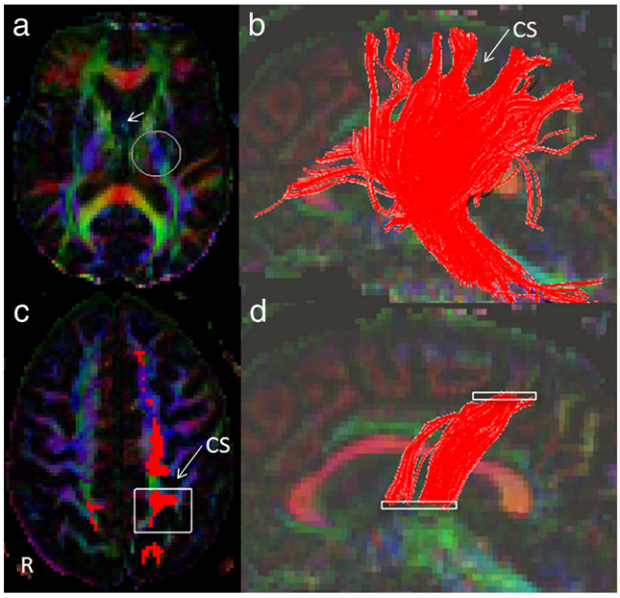


**Fig. 4 – Locations of the regions of interest on two axial slices (a and c) and on the sagital slice d. The first ROI, the PLIC, is drawn in the lowest axial level in which the fornix can be identified as a single intense structure (a). From the tracking results (b) the central sulcus (CS) is identified. In the axial slice in which the bifurcation between the motor and sensory cortex is visible (c) the 'fibers' that extend to the sensory cortex are selected. The result is the tractography model of the superior thalamic radiation used for analysis.**

activation in the precuneus was highly correlated with better sensory discrimination scores (Fig. 3c). We suggest that activation in the precuneus may reflect an increase in functional coupling between secondary somatosensory areas in the right and left hemispheres that supports sensory discrimination after left stroke.

Lesioned brain tissue likely affected our DTI metrics of the sSTR as suggested by left to right mean differences in bundle volume. Lesions of 8 participants overlapped with our PLIC ROI and 4 overlapped with our S1 ROI (Fig. 5) While we did not see a significant correlation between lesion volume and any measure, the two participants in which we were unable to find the left sSTR had the largest lesion volumes. The effect of lesion on our fMRI measure is less clear. We did not see a relationship between peak Z statistic in left S1 with lesion volume or location. We expected that the participant with the largest lesion, which involved the parietal cortex, would have subthreshold z-scores for left S1, they did not, there were voxels that met threshold at the perimeter of their lesion within our left S1 ROI.

Our data identifies three possible neural correlates of sensory discrimination after left stroke: 1) intensity of activation in the parietal cortex, 2) structural integrity of the sSTR and, surprisingly, 3) the intensity of activation in the precuneus cortex. In some participants with normal sensory discrimination ability, parietal cortex activation mirrored that of control participants and microstructure of the sSTR was symmetrical, reflected by an FA ratio close to 1.0(Participant 1, Fig. 2). Conversely, when sSTR structure was diminished, discrimination function was supported by ipsilateral parietal cortex activation and precuneus activation (Participant 2, Fig. 2). Finally, in one participant, sSTR could not be modeled, low parietal cortex and precuneus activation occurred, and sensory discrimination ability appears to be absent (Participant 10, Fig. 2).

There are several limitations to our study. First, both cortical and subcortical left stroke participants with varying degrees of sensory impairment were included. Second, we used different sensory discrimination tasks for fMRI and behavioral testing. Due to incompatibility with the MRI, HASTe scores were not obtained during functional scanning; instead, we used brush texture discrimination, which reliably identifies sensory discrimination dysfunction in stroke survivors. (Dannenbaum et al., 2002) Third, the chronicity of our participants varied from 4 to 96 months. Although the degree of recovery, not time since stroke, is considered the main determinant of brain activation patterns, (Calautti et al., 2007) we completed post hoc analysis for correlation between our outcome measures and chronicity (Ward et al., 2006). We found a strong negative correlation between chronicity and HASTe scores ($r=-.78$, $p=.031$), indicating that the longer the time since their stroke the poorer their sensory function. No other outcome measure had a significant correlation with

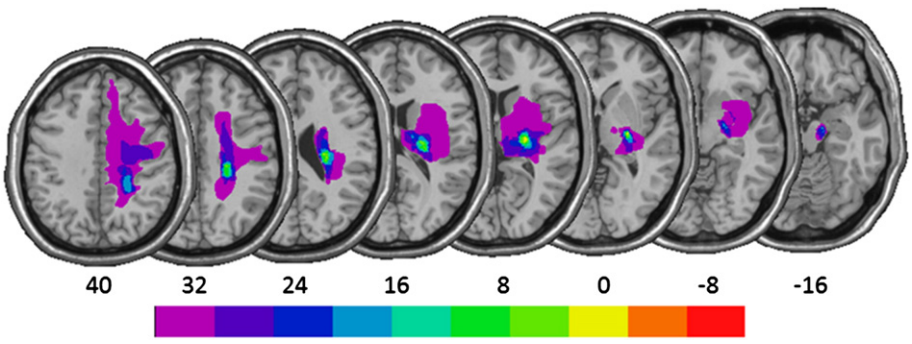


**Fig. 5 – Overlay lesion plots of 10 left hemisphere lesions on the T1 MNI Template. Lesion overlap is illustrated by colors coding increasing frequencies from violet (n=1) to yellow (n=8). Talairach z-coordinates of each transverse section are indicated. The center of overlap is in the posterior limb of the internal capsule and extends superiorly into the corona radiata.**

chronicity. Finally, we did not gather behavioral or diffusion data on control participants, limiting our ability to extend our correlations to controls or make comparisons between groups on those measures.

In summary, 60% of our sample with left stroke had impaired sensory discrimination bilaterally. This study suggests that in addition to primary and secondary somatosensory cortices, the precuneus cortex and thalamo-cortical connectivity have a role in post-stroke sensory discrimination. Future longitudinal studies of the recovery of sensory function and post-stroke sensory rehabilitation regimens should explore the progression of sensory dysfunction from onset to chronicity as well as the impact of rehabilitation on recovery of sensory and related motor function. In addition, longitudinal studies could combine functional localization, using fMRI, and connectivity analysis beyond the large sSTR to smaller axon pathways, with methods such as probabilistic tractography that may yield more reliable representations of cortical connectivity (Behrens et al., 2007) to further elucidate the function–structure relationship observed here.

## 4. Experimental procedures

### 4.1. Participants

A consecutive sample of 10 healthy adults was recruited from the community and screened to verify normal sensation, 5 men and 5 women (39–82 years; mean=56.0). One was left handed. Ten chronic left stroke survivors were recruited from area clinics and stroke groups (Table 1), 3 men and 7 women (39–84 years; mean=62.1). Inclusion criteria: 1) single left stroke more than 4 months prior to enrollment and 2) ability to grasp and release HASTe test objects. Exclusion criteria: 1) Mini Mental State Exam (Folstein et al., 1975) score <24, 2) aphasia or neglect inconsistent with testing requirements; and 3) more than one documented stroke. Participants from both groups were excluded for any medical condition associated with sensory deficits, claustrophobia or metal implants incompatible with the 3 T MRI. This research was approved by the Institutional Review Board. All participants provided written informed consent.

### 4.2. Magnetic resonance imaging

#### 4.2.1. Magnetic resonance image acquisition

A 3 T MR scanner (Philips, Achieva, The Netherlands) with a body transmit and 8 channel receiver coil was used for structural and functional MRI scans. High resolution 3D T1-weighted Magnetization Prepared Rapid Acquired Gradient Echo (MPRAGE) anatomical images were acquired for spatial normalization to a standard atlas. Blood oxygen level-dependant (BOLD) T2* weighted functional MRIs in the transverse plane were obtained using Gradient Echo-Echo Planar Imaging with parallel imaging and a sensitivity encoding reduction factor of 2. (TR/TE=3000/35 ms, flip angle=90°, FOV=23×23 $cm^2$, matrix=80×80 interpolated to 128×128). Functional scans had an interpolated axial in-plane resolution of 1.8×1.8 $mm^2$ and slice thickness of 4 mm. One volume was collected every 3 s during each 204 second scan (67 volumes). Thus, 7 images were collected during each 21 s alternating task and rest periods in a boxcar design. The signal-to-noise ratio of fMRI data for the stroke participantst ranged from 95 to 180 and from 120 to 226 for the control group. Diffusion tensor images were acquired in the axial plane with parameters: TR/TE=9750/92 ms, FOV=25.6×25.6 $cm^2$, Matrix=128×128, Slice thickness/gap=2.0/0.0 mm, two b-values 0 and 1000 s/$mm^2$, diffusion weighting gradient directions=32, SENSE reduction factor of 2.2, scan time of 6 min.

#### 4.2.2. Lesion analysis

Lesion location and volume were determined from T2 Fluid Attenuated Inversion Recovery (FLAIR) images. Lesion volume was calculated after manually outlining signal abnormality slice-by slice in the axial plane (Bazin et al., 2007). Lesion location was determined by visualization of anatomical structures in the T2 image and comparison to a structural brain atlas. (Orrison, 2008) An overlay lesion plot (Fig. 5) was created by manually drawing lesions on a T1-weighted Montreal Neurological Institute template available in MRIcro (Rorden and Brett, 2000). Lesions were mapped onto slices corresponding to 40, 32, 24, 16, 8, 0, −8, −16 in Talairach space in the identical or closest matching slice of each individual (Karnath et al., 2004).

#### 4.2.3. Functional magnetic resonance imaging paradigm

Block-design fMRI, with 21 second stimulation epochs alternating with rest, was obtained brush discrimination. Brushing has previously been used for analysis of sensory perception with fMRI (Staines et al., 2002). Brush discrimination scans of the right index finger were performed in a pseudo-random and balanced order. Participants' hands were passively positioned in supination to expose the palmer surface. Manual brushing was applied to the distal phalanx of the index finger at 1 Hz timed with an auditory metronome heard only by the examiner. Two artist-quality paint brushes (1 cm wide), one soft (Isabey 6236 No. 4) and one firm (Heinz-Jordan 950B No. 6) were used. In previous testing, mean force at bristle deflection with the handle held at 30° is 50.4 (±5.5) grams for the firm brush and 12.8 (±3.1) grams for the soft brush. During each stimulation epoch, the examiner applied 10 s of brushing, paused for 1 s, and applied the same or a different brush for 10 s. Participants were instructed to "think whether the brushes were the same or different." Same/different pairings were randomly applied.

#### 4.2.4. Functional magnetic resonance imaging analysis

We used tools from the Oxford Centre for Functional MRI of the Brain (Smith et al., 2004). Standard pre-statistic processing was applied to individual participants data: motion correction, (Jenkinson et al., 2002) non-brain removal, (Smith, 2002) spatial smoothing using a Gaussian kernel of full width between half maximum =5 mm, and mean based intensity normalization of all volumes by the same factor. High pass temporal filtering and time-series statistical analysis was carried out using a linear model with local autocorrelation correction (Woolrich et al., 2001). Functional images from each participant were co-registered with their high resolution image and standard (MNI 152, 2 mm) images using FLIRT linear image registration (Jenkinson and Smith, 2001).

Registration from high resolution to standard space was further refined using FNIRT non-linear registration (Andersson et al., 2007). First level analysis of functional scans, relative to rest, were carried out with Z>3.0, and a (corrected) cluster significance threshold of p=.01. Mixed effect group analyses were performed, and group Z-statistic images were thresholded by Z>2.3, and a (corrected) cluster significance threshold of P=0.05 (Worsley, 2001). Since one control participant was left-handed, data were analyzed with that participant removed to determine if clusters meeting significance changed; no differences were noted, so that participant is included. Region of interest (ROI) analysis of the left S1 hand area and precuneus was calculated using FSL's Featquery. Individual stroke participant brush discrimination statistical parametric maps were masked with a 10 millimeter spherical ROI centered over the hand area of left S1. Signal intensity (peak Z statistic) was considered to best represent the underlying neural activity (Arthurs and Boniface, 2003; Ward et al., 2006). An unpaired two-group *t*-test was used for direct comparison between stroke and control group activation during the discrimination task. To determine whether groups were activated or deactivated in the area in which we found a significance difference, ROI analysis of stroke and control group maps was completed by masking each group map with the significant precuneus cluster in Featquery. Anatomical areas were defined based on the Harvard Oxford Structural Atlas (implemented in FSLView version 3.1.2) (Desikan et al., 2006). All images are shown in radiological convention.

#### 4.2.5. *Diffusion tractography reconstruction*

We define the sensory portion of the superior thalamic radiation (sSTR) as the white matter bundle between the posterior limb of the internal capsule and the primary sensory cortex. Consistent with published methods, tractography of the sSTR, was completed using a multi-ROI approach (Wakana et al., 2007). ROI's were located on the FA color map, according to the brain anatomy of each participant. The first ROI included the entire posterior limb of the internal capsule at the axial level in which the fornix can be identified as a single intense structure (Fig. 4a). From the reconstruction result of this ROI (Fig. 2b) the bundle that reaches the post-central gyrus was isolated at the level of cleavage of the central sulcus. (Fig. 4c) In this method, only the "fibers" between both ROI's are selected using the 'cut' and 'cut+' functions in DTI Studio (Fig. 4d). Fiber tracking was based on the Fiber Assignment Continuous Tracking (FACT) algorithm carried out in DTI Studio (2010). Tracking was started and stopped in voxels with a fractional anisotropy (FA) of 0.2, and a tract turning angle of ≥40°. To quantify sSTR structural integrity, we used mean fractional anisotropy (FA) and bundle volume (vol). FA, a quantitative measure of the directional dependence of water diffusion in each voxel, reflects microstructural features of white matter (axon caliber, axon density and myelination) (Johansen-Berg and Behrens, 2009). For statistical analysis of the sSTR we used the left/right ratio of FA to eliminate between participant variability. Bundle volume refers to number of voxels in the bundle. We consider bundle volume to represent STR macrostructure yet, a direct relationship to tract structure cannot be assumed.

### 4.3. *Behavioral testing*

Stroke survivors were tested to evaluate the sensory function bilaterally, using the Hand Active Sensation Test (HASTe), a match to sample test of weight and texture discrimination, found to be valid and reliable for documenting sensory discrimination post-stroke. In each trial, participants matched a test object for either weight or texture of one of three sample objects. The accuracy score was recorded. Greater than 12/18 is considered normal function (Williams et al., 2006).

### 4.4. *Statistical analysis*

Pearson product–moment correlation was used. Multiple comparison correction was applied using the Holm procedure (Holm, 1979). Adjusted alpha levels for our 3 comparisons were p=.016, p=.025 and p=.05. Thresholding resulted in non-detection of the left sSTR in two participant's diffusion data (Table 1). For statistical analysis we assigned the detection threshold of 0.2 for the non-detected FA values, (The United States EPA, 2006) 0 was assigned for bundle volume. Laterality effects of left lesions on sSTR were tested using a two-sample *t*-test. Statistics were completed in JMP 9.0.0.

## REFERENCES


Andersson, J.L.R., Jenkinson, M., Smith, S., 2007. Non-linear registration aka spatial normalisation FMRIB technial report TR07JA2. FMRIB Analysis Group Technical Reports TR07JA02.

Andreasen, N.C., O'Leary, D.S., Cizadlo, T., Arndt, S., 1995. Remembering the past: two facets of episodic memory explored with positron emission tomography. Am. J. Psychiatry 152 (11), 1576–1585.

Arthurs, O.J., Boniface, S.J., 2003. What aspect of the fMRI BOLD signal best reflects the underlying electrophysiology in human somatosensory cortex? Clin. Neurophysiol. 114, 1203–1209.

Bazin, P.L., Cuzzocreo, J.L., Yassa, M.A., Gandler, W., McAuliffe, M.J., Bassett, S.S., et al., 2007. Volumetric neuroimage analysis extensions for the MIPAV software package. J. Neurosci. Methods 165, 111–121.

Behrens, T.E.J., Berg, H.J., Jbabdi, S., Rushworth, M.F.S., Woolrich, M.W., 2007. Probabilistic diffusion tractography with multiple fibre orientations: what can we gain? Neuroimage 34, 144–155.

Bodegord, A., Geyer, S., Grefkes, C., Zilles, K., Roland, P.E., 2001. Hierarchical processing of tactile shape in the human brain. Neuron 31, 317–328.

Calautti, C., Naccarato, M., Jones, P.S., Sharma, N., Day, D.D., Carpenter, A.T., et al., 2007. The relationship between motor deficit and hemisphere activation balance after stroke: a 3T fMRI study. Neuroimage 34, 322–331.

Carey, L.M., Matyas, T.A., 2011. Frequency of discriminative sensory loss in the hand after stroke in a rehabilitation setting. J. Rehabil. Med. 43, 257–263.

Carey, L.M., Abbott, D.F., Puce, A., Jackson, G.D., Syngeniotis, A., Donnan, G.A., 2002. Reemergence of activation with poststroke somatosensory recovery: a serial fMRI case study. Neurology 59, 749–752.

Carey, L.M., Abbott, D.F., Harvey, M.R., Puce, A., Seitz, R.J., Donnan, G.A., 2011. Relationship between touch impairment and brain activation after lesions of subcortical and cortical somatosensory regions. Neurorehabil. Neural Repair 25, 443–457.

Cavanna, A.E., Trimble, M.R., 2006. The precuneus: a review of its functional anatomy and behavioural correlates. Brain 129, 564.
Cho, S.H., Kim, D.G., Kim, D.S., Kim, Y.H., Lee, C.H., Jang, S.H., 2007. Motor outcome according to the integrity of the corticospinal tract determined by diffusion tensor tractography in the early stage of corona radiata infarct. Neurosci. Lett. 426, 123–127.
Cramer, S.C., Nelles, G., Benson, R.R., Kaplan, J.D., Parker, R.A., Kwong, K.K., et al., 1997. A functional MRI study of subjects recovered from hemiparetic stroke. Stroke 28, 2518–2527.
Dannenbaum, R.M., Michaelsen, S.M., Desrosiers, J., Levin, M.F., 2002. Development and validation of two new sensory tests of the hand for patients with stroke. Clin. Rehabil. 16, 630–639.
Deiber, M.P., Ibanez, V., Sadato, N., Hallett, M., 1996. Cerebral structures participating in motor preparation in humans: a positron emission tomography study. J. Neurophysiol. 75, 233.
Desikan, R.S., Sθgonne, F., Fischl, B., Quinn, B.T., Dickerson, B.C., Blacker, D., et al., 2006. An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. Neuroimage 31, 968–980.
DTI Studio, 2010. https://www.mristudio.org/wiki/installation. 20105-31-2010 BC. Ref Type: Internet Communication.
Dukelow, S.P., Herter, T.M., Moore, K.D., Demers, M.J., Glasgow, J.I., Bagg, S.D., et al., 2010. Quantitative assessment of limb position sense following stroke. Neurorehabil. Neural Repair 24, 178.
Folstein, M.F., Folstein, S.E., McHugh, P.R., 1975. Mini-mental state: a practical method for grading the cognitive state of patients for the clinician. J. Psychiatr. Res. 12, 189–198.
Gitelman, D.R., Nobre, A.C., Parrish, T.B., Labar, K.S., Kim, Y.H., Meyer, J.R., et al., 1999. A large-scale distributed network for covert spatial attention: further anatomical delineation based on stringent behavioural and cognitive controls. Brain 122, 1093.
Goldman-Rakic, P.S., 1988. Topography of cognition: parallel distributed networks in primate association cortex. Annu. Rev. Neurosci. 11, 137–156.
Harada, T., Saito, D.N., Kashikura, K.I., Sato, T., Yonekura, Y., Honda, M., et al., 2004. Asymmetrical neural substrates of tactile discrimination in humans: a functional magnetic resonance imaging study. J. Neurosci. 24, 7524.
Hartmann, S., Missimer, J.H., Stoeckel, C., Abela, E., Shah, J., Seitz, R.J., 2008. Functional connectivity in tactile object discriminationùa principal component analysis of an event related fMRI-study. PLoS One 3.
Holm, S., 1979. A simple sequentially rejective multiple test procedure. Scand. J. Stat. 65–70.
Jenkinson, M., Smith, S., 2001. A global optimisation method for robust affine registration of brain images. Med. Image Anal. 5, 143–156.
Jenkinson, M., Bannister, P., Brady, M., Smith, S., 2002. Improved optimization for the robust and accurate linear registration and motion correction of brain images. Neuroimage 17, 825–841.
Johansen-Berg, H., Behrens, T.E.J., 2009. Diffusion MRI: From Quantitative Measurement to In Vivo Neuroanatomy. Academic Press, London. Ref Type: Generic.
Jonides, J., Smith, E.E., Koeppe, R.A., Awh, E., Minoshima, S., Mintun, M.A., 1993. Spatial working-memory in humans as revealed by PET. Nature 363, 623–625.
Karnath, H.O., Perenin, M.T., 2005. Cortical control of visually guided reaching: evidence from patients with optic ataxia. Cereb. Cortex 15, 1561–1569.
Karnath, H.O., Fruhmann Berger, M., Knker, W., Rorden, C., 2004. The anatomy of spatial neglect based on voxelwise statistical analysis: a study of 140 patients. Cereb. Cortex 14, 1164.
Klatzky, R.L., Lederman, S.J., Metzger, V.A., 1985. Identifying objects by touch: an ôexpert systemö. Percept. Psychophys. 37, 299–302.
Kuroki, N., Shenton, M.E., Salisbury, D.F., Hirayasu, Y., Onitsuka, T., Ersner, H., et al., 2006. Middle and inferior temporal gyrus gray matter volume abnormalities in first-episode schizophrenia: an MRI study. Am. J. Psychiatry 163, 2103.
Leichnetz, G.R., 2001. Connections of the medial posterior parietal cortex (area 7 m) in the monkey. Anat. Rec. 263, 215–236.
Murray, E.A., Mishkin, M., 1984. Relative contributions of SII and area 5 to tactile discrimination in monkeys. Behav. Brain Res. 11, 67–83.
Nelles, M., Gieseke, J., Flacke, S., Lachenmayer, L., Schild, H.H., Urbach, H., 2008. Diffusion tensor pyramidal tractography in patients with anterior choroidal artery infarcts. Am. J. Neuroradiol. 29, 488.
Nichols-Larsen, D.S., Clark, P.C., Zeringue, A., Greenspan, A., Blanton, S., 2005. Factors influencing stroke survivors' quality of life during subacute recovery. Stroke 36, 1480–1484.
Orrison, W.W., 2008. Atlas of Brain Function. Thieme Medical Pub.
Raichle, M.E., MacLeod, A.M., Snyder, A.Z., Powers, W.J., Gusnard, D.A., Shulman, G.L., 2001. A default mode of brain function. Proc. Natl. Acad. Sci. 98, 676.
Reed, C.L., Shoham, S., Halgren, E., 2004. Neural substrates of tactile object recognition: an fMRI study. Hum. Brain Mapp. 21, 236–246.
Rorden, C., Brett, M., 2000. Stereotaxic display of brain lesions. Behav. Neurol. 12, 191–200.
Rose, S., Guzzetta, A., Pannek, K., Boyd, R., 2011. MRI structural connectivity, disruption of primary sensorimotor pathways, and hand function in cerebral palsy. Brain Connect. 1 (4), 309–316.
Schaechter, J.D., Moore, C.I., Connell, B.D., Rosen, B.R., Dijkhuizen, R.M., 2006. Structural and functional plasticity in the somatosensory cortex of chronic stroke patients. Brain 129, 2722–2733.
Schaechter, J.D., Perdue, K.L., Wang, R., 2008. Structural damage to the corticospinal tract correlates with bilateral sensorimotor cortex reorganization in stroke patients. Neuroimage 39, 1370–1382.
Smith, S.M., 2002. Fast robust automated brain extraction. Hum. Brain Mapp. 17, 143–155.
Smith, S.M., Jenkinson, M., Woolrich, M.W., Beckmann, C.F., Behrens, T.E., Johansen-Berg, H., et al., 2004. Advances in functional and structural MR image analysis and implementation as FSL. Neuroimage 23 (Suppl. 1), S208–S219.
Staines, W.R., Black, S.E., Graham, S.J., McIlroy, W.E., 2002. Somatosensory gating and recovery from stroke involving the thalamus. Stroke 33, 2642–2651.
Stoesz, M.R., Zhang, M., Weisser, V.D., Prather, S.C., Mao, H., Sathian, K., 2003. Neural networks active during tactile form perception: common and differential activity during macrospatial and microspatial tasks. Int. J. Psychophysiol. 50, 41–49.
Taskin, B., Jungehulsing, G.J., Ruben, J., Brunecker, P., Krause, T., Blankenburg, F., et al., 2006. Preserved responsiveness of secondary somatosensory cortex in patients with thalamic stroke. Cereb. Cortex 16, 1431.
The United States EPA, 2006. Data Quality Assessment: A Reviewers Guide.
Tulving, E., 1984. Precis of elements of episodic memory. Behav. Brain Sci. 7, 223–268.
Van Boven, R.W., Ingeholm, J.E., Beauchamp, M.S., Bikle, P.C., Ungerleider, L.G., 2005. Tactile form and location processing in the human brain. Proc. Natl. Acad. Sci. 102, 12601.
Varkuti, B., Guan, C., Pan, Y., Phua, K.S., Ang, K.K., Kuah, C.W.K., 2011. Rs-connectivity Changes Predict Movement Recovery Due to Robot Assisted BCI Training. In .
Wakana, S., Jiang, H., Nagae-Poetscher, L.M., van Zijl, P., Mori, S., 2004. Fiber Tractûbased atlas of human white matter anatomy1. Radiology 230, 77.
Wakana, S., Caprihan, A., Panzenboeck, M.M., Fallon, J.H., Perry, M., Gollub, R.L., et al., 2007. Reproducibility of quantitative

tractography methods applied to cerebral white matter. Neuroimage 36, 630–644.
Ward, N.S., Brown, M.M., Thompson, A.J., Frackowiak, R.S.J., 2006. Longitudinal changes in cerebral response to proprioceptive input in individual patients after stroke: an FMRI study. Neurorehabil. Neural Repair 20, 398–405.
Williams, P.S., Basso, D.M., Case-Smith, J., Nichols-Larsen, D.S., 2006. Development of the hand active sensation test: reliability and validity. Arch. Phys. Med. Rehabil. 87, 1471–1477.
Woolrich, M.W., Ripley, B.D., Brady, M., Smith, S.M., 2001. Temporal autocorrelation in univariate linear modeling of FMRI data. Neuroimage 14, 1370–1386.
Worsley, K.J., 2001. Statistical analysis of activation images. Ch 14 In: Jezzard, P., Matthews, P.M., Smith, S.M. (Eds.), Functional MRI: An Introduction to Methods. OUP. Ref Type: Serial (Book, Monograph).
Yamada, K., Mori, S., Nakamura, H., Ito, H., Kizu, O., Shiga, K., et al., 2003. Fiber-tracking method reveals sensorimotor pathway involvement in stroke patients. Stroke 34, e159.
Yamada, K., Kizu, O., Nishimura, T., 2006. MR Tractography for Stroke. Elsevier, pp. 67–72.
Yang, D.S., Kim, D.S., Kim, Y.H., Jang, S.H., 2008. Demonstration of recovery of a severely damaged corticospinal tract: a diffusion tensor tractography and transcranial magnetic stimulation follow-up study. J. Comput. Assist. Tomogr. 32, 418.
Zhang, S., Li, C.-S.R., 2011. Functional Connectivity Mapping of the Human Precuneus by resting State fMRI. In .