# Altered functional connectivity differs in stroke survivors with impaired touch sensation following left and right hemisphere lesions

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## ABSTRACT

One in two survivors experience impairment in touch sensation after stroke. The nature of this impairment is likely associated with changes associated with the functional somatosensory network of the brain; however few studies have examined this. In particular, the impact of lesioned hemisphere has not been investigated. We examined resting state functional connectivity in 28 stroke survivors, 14 with left hemisphere and 14 with right hemisphere lesion, and 14 healthy controls. Contra-lesional hands showed significantly decreased touch discrimination. Whole brain functional connectivity (FC) data was extracted from four seed regions, i.e. primary (S1) and secondary (S2) somatosensory cortices in both hemispheres. Whole brain FC maps and Laterality Indices (LI) were calculated for subgroups. Inter-hemispheric FC was greater in healthy controls compared to the *combined* stroke cohort from the left S1 seed and bilateral S2 seeds. The left lesion subgroup showed decreased FC, relative to controls, from left ipsi-lesional S1 to contra-lesional S1 and to distributed temporal, occipital and parietal regions. In comparison, the right lesion group showed decreased connectivity from contra-lesional left S1 and bilateral S2 to ipsi-lesional parietal operculum (S2), and to occipital and temporal regions. The right lesion group also showed *increased* intra-hemispheric FC from ipsi-lesional right S1 to inferior parietal regions compared to controls. In comparison to the left lesion group, those with right lesion showed greater intra-hemispheric connectivity from left S1 to left parietal and occipital regions and from right S1 to right angular and parietal regions. Laterality Indices were significantly greater for stroke subgroups relative to matched controls for contra-lesional S1 (left lesion group) and contra-lesional S2 (both groups). We provide evidence of altered functional connectivity within the somatosensory network, across both hemispheres, and to other networks in stroke survivors with impaired touch sensation. Hemisphere of lesion was associated with different patterns of altered functional connectivity within the somatosensory network and with related function was associated with different patterns of altered functional connectivity within the somatosensory network and with related functional networks.

## 1. Introduction

One in two stroke survivors experience clinically significant impairment or loss of touch sensation (Carey et al., 2011; Doyle et al., 2010). Post stroke, damage to the somatosensory system has been associated with increased length of hospital stay, decreased daily activity and mobility (Sommerfeld and von Arbin, 2004) and negatively impacts on recovery outcomes (Kessner et al., 2016). Despite the high prevalence of sensory impairment, the impact of stroke on changes in

neural networks that support processing of tactile information remain virtually unknown.

In healthy participants, inter-hemispheric interaction has been observed during tactile processing (Eickhoff et al., 2008; Kastrup et al., 2008; Klingner et al., 2010; Schäfer et al., 2012). For example, Eickhoff et al. (2008) found sensory stimulation of the hand produced increased probability of activation in the primary somatosensory cortex (S1) contralateral to the hand stimulated and a higher probability of deactivation in ipsi-lateral S1. The secondary somatosensory cortex (S2)

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exhibited high probability of activation in both hemispheres. Kastrup et al. (2008) reported deactivation changes in a spatially extended S1 region in the same hemisphere as the hand stimulated that was correlated with a simultaneous increase in perception thresholds of the unstimulated finger. Schäfer et al. (2012) using electrical stimulation of the median nerve found an increase in contralateral S1 response and ipsi-lateral decrease, while S2 showed bilateral activation. This pattern appears to be similar across tactile stimuli (Lee et al., 2016). Interaction between the two hemispheres is thought to arise from a circuit involving connectivity between the S2 regions via callosal fibres (Chung et al., 2014; Klingner et al., 2010; Wegner et al., 2000). These studies suggest the perception of tactile sensation involves complementary inter-hemispheric activity of S1 and S2 coupled with distinct activation and deactivation patterns.

The analysis of resting state functional connectivity (FC) using functional MRI (fMRI) provides a useful method to examine changes in brain networks post-stroke (Carey et al., 2013; Ovadia-Caro et al., 2014). FC represents stable (Biswal et al., 2010), intrinsic correlations in the haemodynamic signal typically examined at low frequencies (< 0.1 Hz) relating to cortical connections. Connections between regions (networks) are grey matter localised, anatomically distinct (although some overlap does exist; Tomasi and Volkow, 2011), found across neuroimaging modalities (Brookes et al., 2011), and are thought to show neural energy demands of regions that have become connected through Hebbian processes, suggesting a common functional purpose (Cole et al., 2010; Smith et al., 2009). Networks have high correspondence with anatomical regions that are activated during tasks and are thought to underlie a large collection of sensory and cognitive processes (Smith et al., 2013).

Two primary reasons make FC methods attractive to study vulnerable populations, such as stroke survivors. First, FC acquisition and the demands placed on participants are markedly lower than standard task-related fMRI studies as participants are simply required to lie in the scanner during the scan and remember basic instructions. In contrast, the cognitive and physical demands of a task-based study may be difficult after a stroke and in turn can impact performance and subsequent results (Carter et al., 2012). Second, FC allows for the examination of sub network, network and internetwork connectivity in unison and exploration of the impact neurological damage may have on how these regions connect. This is ideal for deficits caused by stroke lesions, which have been suggested to alter brain functioning both local, and remote, to the lesion area (Carey et al., 2013; Grefkes and Fink, 2014).

Changes in FC have been described in motor recovery under resting-state and task conditions (Grefkes and Ward, 2014). Resting-state studies indicate the importance of inter-hemispheric connectivity in motor recovery (Carter et al., 2010) while task based studies highlight the role of disrupted ipsi-lesional connectivity (Rehme and Grefkes, 2013). Despite the potential advantages of using FC for examination of reorganization of the somatosensory system following stroke, few studies have made use of the technique. Dinomais et al. (2013) examined rest period derived FC from a task in two young adult groups of perinatal stroke survivors with middle cerebral artery (MCA) based and periventricular lesions (PL). The study explored FC from cortical regions of interest (seeds) within the ipsi- and contra-lesional S1 areas to ipsi- and contra-lesional S1, S2 and cerebellar areas. Decreased functional connectivity was found for ipsi-lesional seed to ipsi-lesional S2 for the MCA compared to the PL group, but no other seeds/regions showed significant changes. No differences were found between the two groups when controlling for grey matter volume, however group sizes were small (6 and 8 subjects in the MCA and PL groups respectively) and no comparisons to healthy controls were undertaken. Data were flipped so lesions were represented within a single hemisphere within groups.

Bannister et al. (2015) used FC to explore changes in somatosensory network reorganization over a six month period post-stroke. Using bilateral S1, S2 and thalamus as seed regions, they observed significant decreases in FC from the contra-lesional S1 seed to the contra-lesional

occipital lobe at one month post-stroke compared to healthy controls. In addition, there was a re-establishment of connectivity between hemispheres from one month post-stroke to six months post-stroke. Improvement in touch discrimination at 6 months was associated with increased FC between contra-lesional seeds and distributed regions, including cerebellum. The study was limited by a small sample (10 participants) that comprised a mix of single hemisphere lesions (six left, four right). Similar to Dinomais et al. (2013) data were flipped so any differences in FC associated with side of lesion were therefore hidden.

With the prevalence of post stroke somatosensory dysfunction and lack of studies examining possible local and distal affects of lesion damage to the somatosensory system, we sought to examine changes in FC of the somatosensory network in a cohort of stroke survivors with tactile impairments and explore the impact of lesion damage within the left or right hemisphere relative to healthy controls. We hypothesised that within stroke groups, connectivity between the ipsi-lesional seed regions and the contra-lesional hemisphere would be disrupted. Furthermore, we hypothesised that relative to healthy controls, both groups would show changes in FC in regions both local and remote to lesion site.

## 2. Materials and methods

### 2.1. Participants

Participants were recruited as part of the Connecting New Networks for Everyday Contact through Touch (CoNNECT) clinical trial (https://anzctr.org.au/Trial/Registration/TrialReview.aspx?id=364147). Participants were required to be at least three months post-stroke, first episode of stroke (ischaemic or haemorrhagic) and experiencing somatosensory impairment in the upper limb. In addition, they were required to be medically stable, able to give informed consent, comprehend simple instructions, and be right-hand dominant. Stroke participants were excluded if they had a brainstem infarct, previous neurological dysfunction, history of impaired hand function, peripheral neuropathy in upper limbs, evidence of neglect on standard neuropsychological tests, or were not suitable for MRI.

Of 36 participants initially recruited and tested, seven were not included due to excessive head motion that caused noticeable distortions on the unprocessed functional scans and one was removed due to large drop out of signal in the anterior region of the brain caused by an implant. A final cohort of 28 stroke survivors (left lesion = 14, right lesion = 14, aged 27–75 years) were included. A healthy control group consisted of 14 participants (aged 27–81 years) who had no history of neurological dysfunction. They were matched to stroke survivors for age and sex. All participants were safe to undergo MRI scanning, able to give informed consent and right hand dominant. Informed consent was obtained before subjects participated in the study.

### 2.2. Demographic and clinical data

Background demographic data included age, sex and premorbid hand dominance (Oldfield, 1971). Clinical data included stroke type, time since stroke, lesion location and severity of neurological impairment using the National Institutes of Health Stroke Scale (Brott et al., 1989).

Tactile sensation for the fingertip (usually index) was measured within 48 h of the MRI scan using the Tactile Discrimination Test (TDT; Carey et al., 1997). The TDT requires participants to discriminate differences in finely graded plastic texture surfaces using the method of constant stimuli and a three-alternative forced-choice design. It has high retest reliability, age-appropriate normative standards, and good discriminative properties. Touch detection, using the WEST hand monofilaments (WEST; Weinstein, 1993), and a visual analogue scale of ability to feel the touch stimulus during the functional MRI scan were also obtained. Healthy controls were also assessed on measures of

somatosensation within 48 h of the MRI.

### 2.3. Functional MRI acquisition

Imaging data was acquired on a 3 Tesla Siemens Trio MRI scanner. Resting-state functional data was acquired using an echo planar imaging (EPI) sequence over 7 min (TR = 3000 ms, TE = 30 ms, 3 mm isotropic voxels, 72 × 72 matrix, 44 slices, 216 mm FOV). Participants were instructed to "Close your eyes and rest. You do not need to think about anything in particular" and also that they should "stay awake throughout the scan". Following the scan this was confirmed by participant report. Resting state acquisition was consistently conducted after a touch activation task to the fingertips (for a description of the paradigm, please see Carey et al., 2011).

A high resolution MPRAGE scan (TR = 1900 ms, TE = 2.55 ms, 256 × 256 matrix, 160 slices, 216 mm FOV) was collected for co-registration to the functional data, segmentation and normalisation to Montreal Neurological Institute (MNI) space. 2D FLAIR (fluid attenuation inverse recovery sequence; 1 mm isotropic, TR = 6000 ms, TE = 388 ms, 100 mm FOV) acquired axially for delineation of infarcts.

Functional MRI task data for seed construction was collected on the same scanner from 24 healthy controls, also from the CoNNECT study, performing a tactile discrimination task (described in Carey et al., 2002). Of the 24 participants, 14 were also included in this study. Briefly, digits two through four were stimulated on a single hand per run using a texture grid moving from side to side across the fingers at alternating frequencies of 1.5 and 3 Hz for 30 s per frequency. One hundred and thirty volumes were collected for each run (TR = 3000 ms, TE = 30 ms, 3 mm isotropic voxels, 72 × 72 matrix, 44 slices, 100 mm FOV).

### 2.4. Lesion mask creation

Axial FLAIR images were used to identify and draw a region of interest (ROI) mask around the primary infarct hyperintensity using mricron (http://www.mccauslandcenter.sc.edu/mricro/mricron/index.html). Masks were drawn by a trained neuroimaging researcher, quality checked and modified as necessary by a neurologist to ensure they accurately represented the infarct.

### 2.5. Seed construction

To examine FC of the somatosensory network and differences between lesioned hemispheres, four seed regions of interest were identified within the functionally and anatomically defined left and right S1 and S2 cortical regions. Seed regions were defined from the fMRI data of 24 healthy control participants described in section 2.3. Data were preprocessed and analysed using a standard pipeline using SPM8 and iBrain Tools for SPM (https://www.florey.edu.au/iBrain; slice timing correction, realignment, normalisation to MNI space). First level analysis consisted of a standard general linear model with stimulation periods of each hand contrasted with rest. Significant voxels from individual contrasts of left hand stimulation and right hand stimulation compared to baseline were initially thresholded using voxelwise family wise error (FWE) correction ($p < 0.05$). Two sub clusters were identified for S1 and S2 regions. The peak voxel value in each cluster was identified (S1 left = −60, −22, 44; S1 right = 60, −18, 40; S2 left = −58, −16, 16; S2 right = 54, −18, 16) and the seed created by taking voxels with the top 100 highest values within the cluster including the peak. Seeds were checked for contiguousness and none contained disconnected voxels. The 2 mm-sampled seeds were then spatially resampled to 1 mm for registration onto T1 weighted structural scans for visualization purposes and 3 mm for further analysis using SPM12. Overlap of the seed regions with primary and secondary cytoarchitectonic-defined somatosensory areas was checked using the SPM Anatomy toolbox (Eickhoff et al., 2005, 2007). Percentage overlap

**Table 1**
Percentage overlap of seed within anatomically defined somatosensory regions.

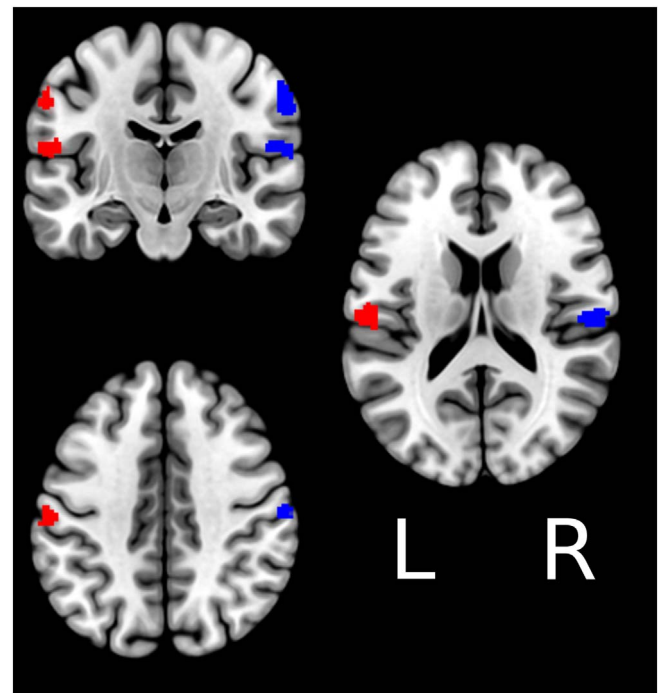| Seed | Total percent overlap | Region | Percent overlap |
|---|---|---|---|
| S1 left | 88.7 | Area 3b | 54.1 |
| | | Area 1 | 34.6 |
| S1 right | 87.7 | Area 1 | 74.6 |
| | | Area 3b | 13.1 |
| S2 left | 85.2 | Area OP4 | 74.8 |
| | | Area OP1 | 10.4 |
| S2 right | 84.1 | Area OP4 | 45.9 |
| | | Area OP1 | 38.2 |



**Fig. 1.** Seed regions for the primary (S1) and secondary (S2) somatosensory cortices in the left (red) and right (blue) hemispheres. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

of seeds within cytoarchitectonic-defined primary and secondary somatosensory regions are presented in Table 1.

From Table 1 it can be seen that the majority of all seeds were within the primary or secondary somatosensory regions. Seed positions can be visualised in Fig. 1.

### 2.6. Analysis of clinical data

Statistical analysis of demographic and clinical data was conducted using R v. 3.3.1. (http://www.r-project.org) and the following packages: *stats* (R Core Team, 2013) for chi-square and *t*-testing, *phia* (https://cran.r-project.org/web/packages/phia/) for extraction of interaction summary statistics, *lme4* (Bates et al., 2015) for analysis of variance (ANOVA) modelling, and *multcomp* (Hothorn et al., 2008) for post-hoc analysis and control of multiple comparisons the using pairwise Tukey's method.

### 2.7. Functional connectivity pre-processing and analysis

Customised data cleaning pipelines were constructed to optimise pre-processing. This included a pipeline tailored for the pre-processing of stroke data. Pipelines were constructed using components of *DCMstack* (https://github.com/moloney/dcmstack), *Analysis of Functional NeuroImages* (AFNI; Cox, 1996), SPM12 v6685 (http://www.
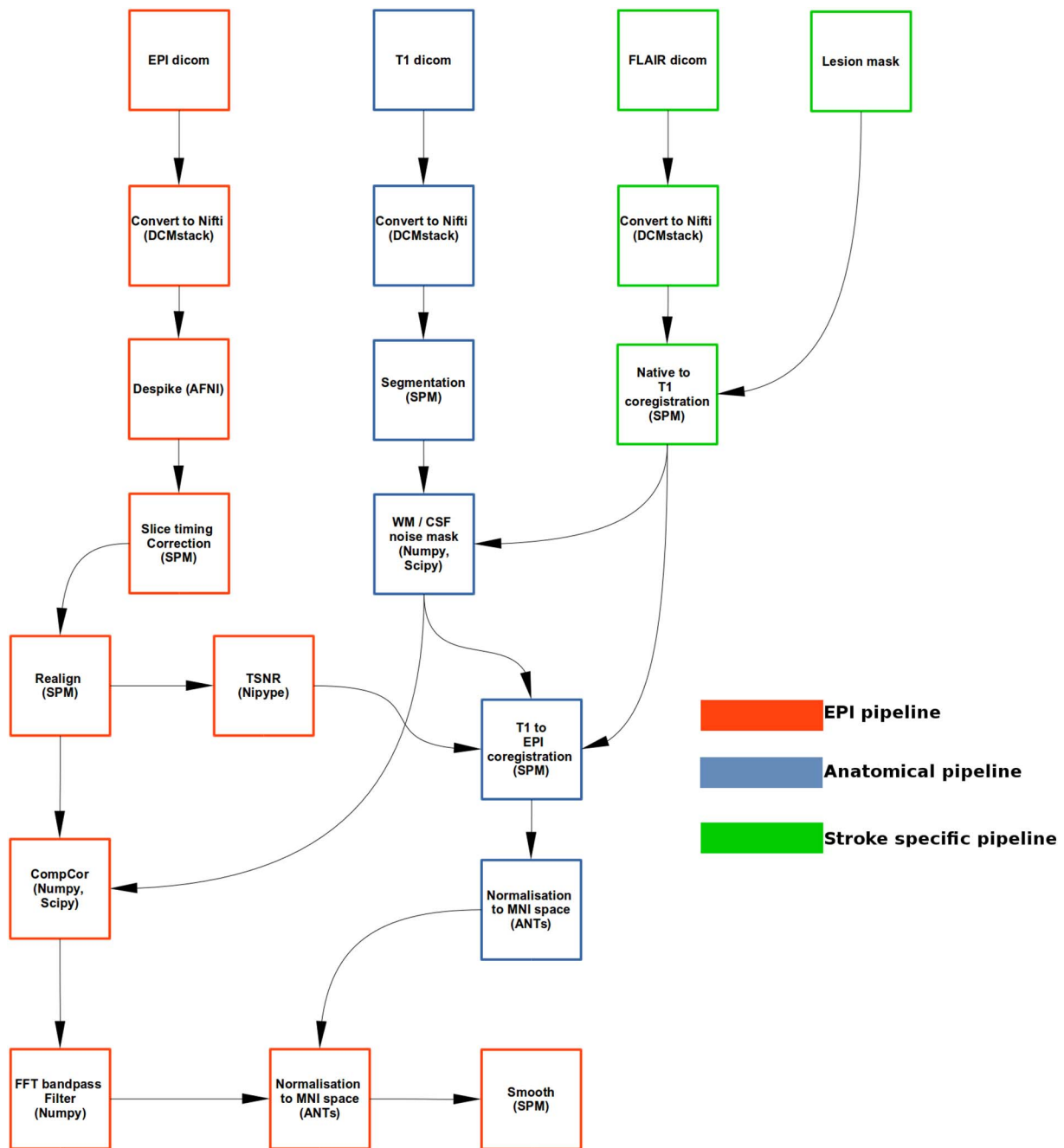
**Fig. 2.** Schematic diagram of the stages used in pre-processing functional connectivity data for both control and stroke participant's functional (red), and anatomical (blue) data. Stroke specific stages are marked in green. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

fil.ion.ucl.ac.uk/spm/software/spm12/), Advanced Normalization Tools (ANTS; Avants et al., 2011), Numpy (van der Walt et al., 2011), Scipy (Oliphant, 2007) and Nibabel (https://github.com/nipy/nibabel), and combined under the NiPype framework (Gorgolewski et al., 2011). See Fig. 2 for a schematic of the processing procedure and software used.

Anatomical image pre-processing consisted of segmentation using the SPM new segmentation method (Ashburner and Friston, 2005) and co-registration to the mean echo-planar imaging (EPI) image. White matter (WM) and cerebro-spinal fluid (CSF) masks were created by thresholding the segmented WM and CSF images at 0.99 and eroding two times using a $3 \times 3 \times 3$ mm structure element. Normalisation to MNI space was performed by transforming an MNI space $3 \times 3 \times 3$ mm template image to subject space then using the inverse transformation matrix to warp the T1 image from subject space to MNI space. Stroke patients had their FLAIR and lesion mask included in the pipeline,

which were co-registered to the T1 image and co-registered to the EPI image. Lesion masks were warped to MNI space and resliced to 1 mm resolution for group summary information.

Pre-processing of EPI data included despiking, slice timing correction to the central slice and realignment to the first volume. Motion and physiological related artifact were regressed from the data using the Friston 24 parameter model (Friston et al., 1996) and aCompCor (Behzadi et al., 2007) taking the top five components each for WM and CSF mask extracted signals. The data were Fourier bandpass filtered (high-pass = 0.01 Hz/100 s, low-pass = 0.08 Hz/12.5 s), normalised to MNI space using the inverse transform matrix computed from the EPI space T1 and smoothing using a 6 mm Gaussian kernel. Global signal regression was not used (Gotts et al., 2013). Data were visually inspected before and after each pre-processing run to ensure data quality and inclusion for further analysis.

Mean time series from each of the seeds were extracted (using a customised script based on nibabel and numpy) and the signal correlated with all voxels within the brain masked pre-processed EPI images using Pearson's correlation coefficient. One correlation map was produced for each seed for each participant (four maps per participant). Connectivity maps for each seed were then Fisher transformed to satisfy the normality assumption of general linear modelling and used in second level full factorial analysis performed with SPM. One and two sample *t*-test contrasts were initially conducted between controls and lesion subgroups and were corrected for multiple comparisons using FWE cluster level correction with the cluster forming threshold set at $p < 0.001$ (Eklund et al., 2016; Woo et al., 2014). Contrasts that showed significant differences in FC between healthy controls and lesion subgroup were subsequently used to examine for differences in FC between the lesion subgroups with the cluster mask used as a region of interest. A small volume correction (SVC) analysis was used to assess for significant differences. Clusters of significant FC from each of the seeds were localised using the Automatic Anatomical Labelling (AAL) atlas (Tzourio-Mazoyer et al., 2002) as found in the WFU PickAtlas v3.0.5 (Maldjian et al., 2004; Maldjian et al., 2003).

### 2.8. Laterality index

A laterality index (LI) was calculated for each MNI space Fisher transformed seed map for each participant using the method outlined by Park et al. (2011). In short, voxels equal to or above the upper 95th percentile of values were considered connected with the seed and used in the formula LI = (seed hemisphere − contra-seed hemisphere)/ (contra-seed hemisphere + seed hemisphere), modified from Seghier (2008). This resulted in LIs that ranged from −1 to 1, with an LI of −1 indicating contra-seed hemisphere connectivity only, 1 indicating ipsi-seed hemisphere connectivity only and 0 symmetrical connectivity. Seed and contra-seed hemispheres were determined by splitting the maps at the mid-point of the x-axis.

## 3. Results

### 3.1. Demographic and clinical information

Demographic and clinical results for left and right lesion groups and healthy controls are presented in Table 2.

#### 3.1.1. Demographics

Pearson's Chi-squared test with simulated *p*-value based on 10,000 replicates found no significant difference between the groups in numbers of each sex ($\chi^2 = 3.41$, $p = 0.28$). No differences were found in ages between the groups ($F(2, 39) = 0.07$, $p = 0.93$).

Both stroke groups contained outlier values for days post-stroke (the left lesion group had one female participant who was 3775 days post-stroke. The right lesion group had two females who were 1553 and 2188 days post-stroke). No differences were found in days post-stroke between the left the right lesion groups with the outliers included ($t$ (21.85) = 0.14, $p = 0.88$) or removed ($t(23.89) = 0.59$, $p = 0.56$). There was no significant difference in lesion size between the two lesion group ($t(19.08) = 0.031$, $p = 0.76$).

#### 3.1.2. Clinical

To test for differences in group scores on the TDT, a 3 (group) × 2 (hand: affected/unaffected) mixed model ANOVA was conducted. The analysis showed significant main effects of group ($F(2,39) = 13.28$, $p < 0.001$), hand ($F(1,39) = 46.61$, $p < 0.001$) and a group × hand interaction ($F(2,39) = 15.47$, $p < 0.001$). Post-hoc pairwise Tukey analyses showed the interaction was due to significantly lower TDT scores for left lesion group compared to healthy controls (left affected vs. healthy left: $z = 6.20$, $p < 0.001$, left affected vs. healthy right: $z = 6.66$, $p < 0.001$) and right lesion groups compared to healthy

**Table 2**

Participant demographic and clinical data.

| Group | L hem lesion | R hem lesion | Healthy |
|---|---|---|---|
| Age mean (SD) years | 49.00 (12.04) | 49.29 (13.55) | 50.93 (16.26) |
| Sex M/F | 13/1 | 10/4 | 9/5 |
| Days post-stroke<br>Mean (SD)/Median (MAD) | 589.14 (937.85)/ 381.00 (286.88) | 545.36 (587.08)/ 331.50 (167.53) | N/A |
| Lesion size in voxels<br>Mean (SD)/Median (MAD) | 4240.86 (2767.61)/ 3272.50 (2510.04) | 4761.14 (5556.74)/ 2749.00 (3633.85) | N/A |
| NIHSS score<br>Mean (SD)/Median (MAD) | 3.32 (1.20)/ 3.25 (1.22) | 3.25 (1.11)/ 2.00 (1.48) | N/A |
| TDT-stroke affected hand<br>Mean (SD)/Median (MAD) | 20.95 (26.19)/ 15.60 (26.02) | 23.82 (25.55)/ 24.12 (31.76) | 73.41 (12.14)/ 77.29 (14.92) |
| TDT- unaffected hand<br>Mean (SD)/Median (MAD) | 69.14 (17.91)/ 76.51 (12.24) | 62.16 (18.0)/ 62.57 (19.13) | 69.03 (18.6)/ 81.87 (8.42) |
| WEST affected hand<br>Mean (SD)/Median (MAD) | 101.10 (110.01)/ 53.00 (77.61) | 112.18 (136.27)/ 52.50 (77.71) | 0.24 (0.37)/ 0.05 (0.04) |
| WEST unaffected<br>Mean (SD)/Median (MAD) | 0.38 (0.47)/ 0.14 (0.12) | 0.31 (0.56)/ 0.14 (0.10) | 0.15 (0.28)/ 0.07 (0.05) |
| VAS touch - affected hand<br>Mean (SD)/Median (MAD) | 4.82 (3.45)/ 4.15 (4.37) | 6.84 (2.58)/ 7.20 (3.34) | 8.32 (1.82)/ 9.10 (1.33) |
| VAS touch – unaffected hand<br>Mean (SD)/Median (MAD) | 8.65 (2.08)/ 9.50 (0.74) | 8.92 (1.68)/ 9.55 (0.67) | 8.58 (1.33)/ 9.00 (0.74) |

Abbreviations: NIHSS = National Institute of Health Stroke Scale (score 0–42; higher score indicates greater impairment; scores below 5 suggest mild impairment). TDT = Tactile Discrimination Test (score is percentage correct area under the curve [AUC], the criterion of normality is 66.1 AUC, with lower scores indicating poorer performance); WEST, Weinstein Enhanced Sensory Test touch detection score for the fingertip used in the TDT (threshold is in grams pressure. Normal performance at the fingertip is 0.07 g and severe impairment 200 g. Due to wide range in the WEST scores, data were log transformed for statistical analysis). VAS touch = Visual Analogue Scale of perceived ability to feel tactile stimulus during functional magnetic resonance imaging (scale 0.0–10.0, with lower scores indicating poorer performance).

Note: Affected hand refers to the hand opposite to the side of lesion. Unaffected hand refers to hand on the same side as the lesion, although it is acknowledged that this limb may also have some impairment. For control participants where no impairment exists, the right hand has been designated "affected" and the left "unaffected" for comparison with clinical scores.

controls (right affected vs. healthy left: $z = 5.76$, $p < 0.001$, right affected vs. healthy right: $z = 6.22$, $p < 0.001$). The 'unaffected' hand of the left lesion group had a significantly higher TDT score compared to the affected ($z = 6.97$, $p < 0.001$). Similarly, the right lesion group showed higher TDT score for the 'unaffected' hand compared to the affected ($z = 5.43$, $p < 0.001$). There were no detected differences in TDT score for: the right and left hands of controls; affected hands between left and right lesion groups; unaffected hands between left and right lesion groups; or unaffected hands of each lesion group and controls (all $z < 1.30$, $p > 0.75$).

WEST log pressure scores were also examined using a 3 × 2 mixed design ANOVA. The analysis showed significant main effects of group ($F(2,78) = 22.96$, $p < 0.001$), hand ($F(1,78) = 67.85$, $p < 0.001$) and a group × hand interaction ($F(2,78) = 13.66$, $p < 0.001$). Post-hoc tests showed a similar pattern of impairment as for the TDT. The interaction was due to lower log WEST scores for healthy controls in both the left and right hands when compared to the left lesion group's affected right hand (left affected vs. healthy left: $z = 8.73$, $p < 0.001$, left affected vs. healthy right $z = 8.13$, $p < 0.001$) and the right lesion group's affected left hand (right affected vs. healthy left: $z = 6.78$, $p < 0.001$, right

affected vs. healthy right: $z = 6.18$, $p < 0.001$). The unaffected hand of the left lesion group had a significantly lower (better) log WEST score compared to the affected ($z = 7.68$, $p < 0.001$). Similarly, the right lesion groups showed lower log WEST score for the unaffected hand compared to the affected ($z = 5.98$, $p < 0.001$). There were no differences in WEST log score detected for: the right and left hands of controls; affected hands between left and right lesion groups; unaffected hands between left and right lesion groups; or unaffected hands for each lesion group and controls (all $z < 1.04$, $p > 0.90$).

Differences between groups for the Visual Analogue Scale (VAS) were also examined using a 3 (group) × 2 (hand: affected/unaffected) mixed model ANOVA and Post-hoc pairwise Tukey analyses. There was a significant effect of group ($F(2, 76) = 3.99$, $p = 0.02$), hand ($F(1, 76) = 16.67$, $p < 0.001$) and group by hand interaction ($F(2, 76) = 4.15$, $p = 0.02$). The interaction was due to decreased perceived stimulus intensity in the left lesion group's affected hand compared to healthy control's left ($z = 3.99$, $p < 0.001$) and right ($z = 4.27$, $p < 0.001$) hands, the right lesion group's non-affected hand ($z = 4.76$, $p < 0.001$) and the left lesion group's unaffected hand ($z = 4.45$, $p < 0.001$). No significant differences between hand or group were found for controls or the right lesion group.

In summary, the affected hands of the left and right hemisphere lesion groups showed significantly poorer touch discrimination and less tactile sensitivity when compared to unaffected hands, or either hands of healthy controls for both the TDT and WEST. The boxplots presented in Fig. 3 display: (A) the means, medians and range of TDT scores; (B) the log mean, median and range of WEST gram pressure scores and (C) Visual Analogue for the three groups.

### 3.2. Lesion location

Both groups showed lesions spread over frontal, parietal and temporal cortical regions. Subcortical lesion damage was present within thalamic and striatum regions. The left lesion group had a larger proportion of participants with damage to the S1 region while the highest overlap for each group was within the insula/operculum (OP) (S2). Two of the left group also showed lesion damage within the superior cerebellum. No individual showed cross hemispheric damage. Lesion overlap images are presented in Fig. 4.

Due to lesion damage within primary and secondary somatosensory areas, the percentage of overlap of a lesion of an individual on a seed for the two stroke sub-groups was calculated for all seeds to determine the residual percentage of the seed region not impacted by a lesion. As summarised in Table 3, the seeds within the lesion damaged hemisphere for both groups had between 44.42 and 65.71% not overlapping with lesions, while non-lesion hemisphere seeds were unaffected.

### 3.3. Functional connectivity

#### 3.3.1. Within group results

Resting state functional connectivity maps from S1 and S2 seeds are presented for healthy controls, left hemisphere lesion and right hemisphere lesion groups. Results of the one sample *t*-tests for each group relative to each seed region are presented in Fig. 5.

Healthy controls showed the expected symmetric FC and inter-hemispheric FC between the seed regions and other regions associated with somatosensory processing. These regions included bilateral postcentral gyri (S1), bilateral insula/operculum (S2), anterior cingulate, bilateral superior and mid occipital gyri, bilateral thalami and bilateral cerebellum. Both left and right lesion groups showed qualitative disruption of FC between the seeds and inter-hemispheric regions including the cerebellum.

#### 3.3.2. Between group results

Regions where significant differences in FC were found between the groups are summarised in Table 4. The region, the peak voxel value and

MNI coordinates of the connected region are reported, together with cluster size and associated statistics. In addition, the SVC analysis between lesion sub groups is presented. Fig. 6a presents the regions in which controls showed increased FC compared to stroke lesion groups and Fig. 6b displays regions of increased FC for the right hemisphere lesion group compared to healthy controls and the left lesion group.

Healthy age-matched controls showed increased FC compared to lesion subgroups for the left S1, left S2 and right S2 seeds. Increased FC was observed from the left S1 seed when compared to both lesion subgroups combined, and when examined individually. Controls showed increased FC to the combined subgroups from the left S1 seed to three regions exclusively in the right hemisphere; the postcentral gyrus (S1), mid temporal gyrus and the operculum (OP) (S2). FC between the left S2 seed was significantly increased for controls when compared to combined lesion subgroups and the right lesion group only. Both contrasts showed increased S2 FC for controls to right insula/OP (S2). The control compared to combined lesion groups showed increased FC between the right S2 seed and three regions within the left hemisphere; the left insula/OP (S2), supramarginal gyrus and mid occipital region.

When contrasted to the left lesion group, the control's left S1 seed showed increased FC to the right postcentral and mid temporal regions. Increased FC was also observed for controls to the left parietal and mid occipital regions. There were no other significant differences from other seeds. When compared to the right lesion group, the control left S1 seed showed increased FC to the right OP. In addition, increased FC was observed for controls from the right S2 seed to the right mid occipital area, the left superior temporal and mid occipital areas.

Only the right lesion subgroup showed significantly increased FC compared to controls and the left lesion group. Increased FC was observed between the right S1 seed and the right inferior parietal area. When contrasted to the left lesion subgroup, three neighbouring clusters showed increased FC for the right lesion group compared to the left, two within the right angular gyrus and one in the right inferior parietal area. No significant increases in FC were detected for the left lesion subgroup when compared to controls or the right lesion subgroup.

#### 3.3.3. Laterality index

Laterality Index (LI) data for each of the three groups and four seed maps (S1 left/right, S2 left/right) are presented in Table 5. Fig. 7 presents the LI for each seed map and group. High inter-individual variance was observed particularly for S1 LIs (see error bars in Fig. 7).

LI analysis was conducted using a 3 (group) × 4 (seed map) mixed model ANOVA. There was a significant main effect of group ($F(2, 39) = 7.93$, $p < 0.001$), seed map ($F(3, 117) = 3.04$, $p = 0.03$) and a group × seed map interaction ($F(6, 117) = 2.83$, $p = 0.01$).

Post-hoc pairwise Tukey analyses revealed that within the left lesion group, there was significantly higher LI values (greater lateralisation toward the seed hemisphere) for the contra-lesional S1 map ($z = 4.34$, $p < 0.001$) and the contra-lesional S2 map ($z = 3.92$, $p < 0.01$) compared to the ipsi-lesional S2 seed. No other within group effects were found.

Between group results showed significantly increased LI for the left lesion group's contra-lesional (right) S1 seed map compared to the healthy control's left S1 map ($z = 3.87$, $p < 0.001$), right S1 map ($z = 3.34$, $p = 0.036$), left S2 map ($z = 3.78$, $p ≤ 0.01$) and right S2 map ($z = 3.38$, $p = 0.03$). The left lesion group also showed significantly increased LI in the contra-lesional (right) S2 seed map compared to healthy control's left S1 map ($z = 3.54$, $p = 0.02$) and left S2 map ($z = 3.46$, $p = 0.02$).

The right lesion group showed significantly increased LI for the contra-lesional S2 seed map compared to healthy control's left S1 seed map ($z = 3.40$, $p = 0.28$) and left S2 seed map ($z = 3.35$, $p = 0.03$). No significant differences in LI were found between left and right lesion groups.

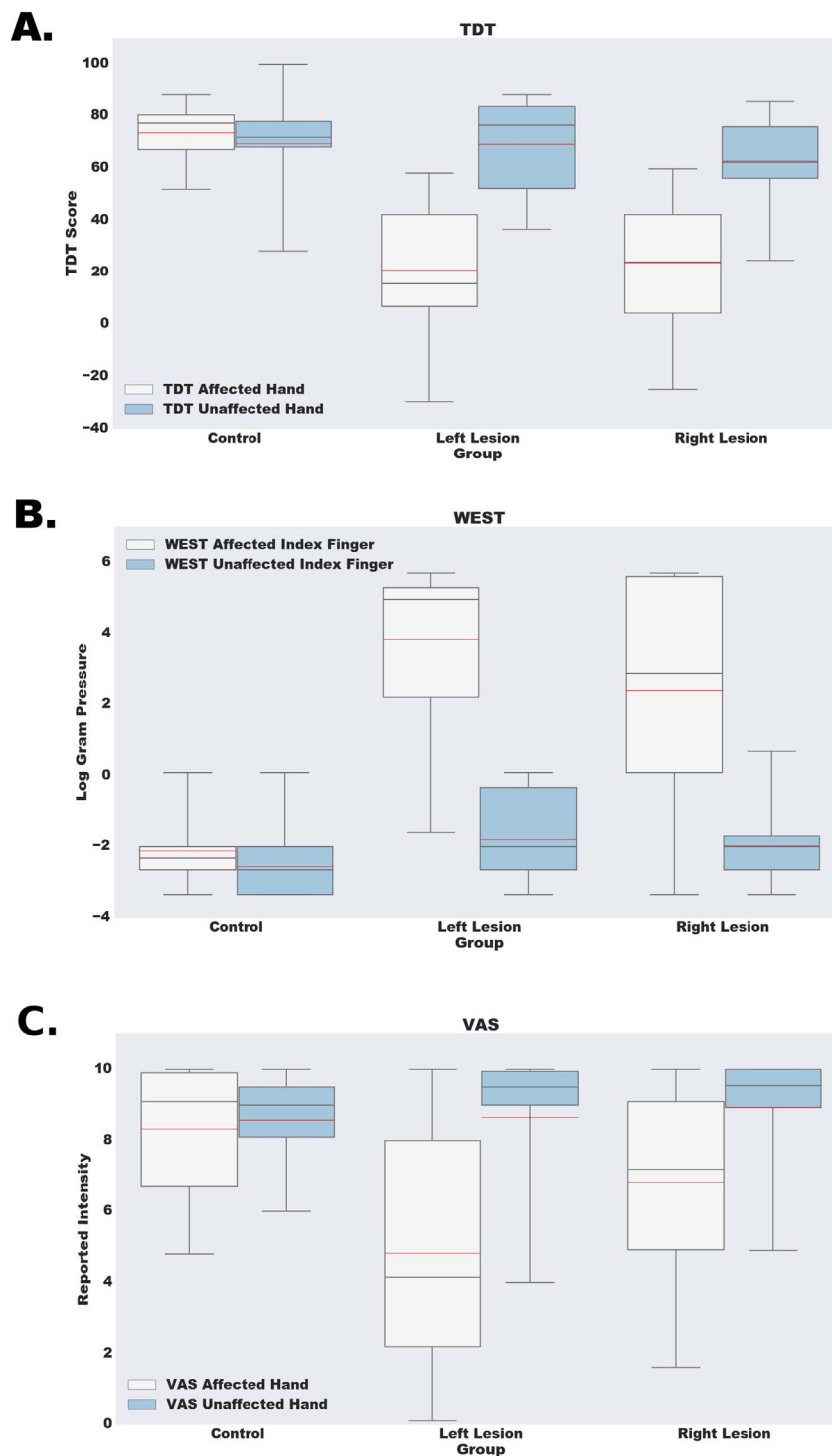In summary, healthy controls showed symmetrical activity across

**Fig. 3.** Mean (red line), median (black line), first and third quartiles (boxes) and data range (whiskers) of (A) TDT score and (B) WEST monofilament gram pressure and (C) Visual Analogue of reported touch intensity for affected (white) and unaffected (blue) hands for control, left lesion and right lesion groups. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

hemispheres. The left lesion group showed a more symmetrical pattern of connectivity from the ipsi-lesional S2 seed map compared to contra-lesional seed maps. Additionally, LI was increased for contra-lesional seed maps compared to controls. The right lesion group showed increased LI in the contra-lesional S2 seed map compared to left seed maps of controls.

## 4. Discussion

Our findings highlight the influence of hemisphere of lesion on differences in location and laterality of functional connectivity (FC) alterations in stroke survivors with impaired touch sensation. Additionally, our findings suggest further investigation into the role attention plays in tactile recovery post-stroke.

We explored differences in FC from primary and secondary somatosensory areas (S1/S2) in chronic stroke survivors with tactile
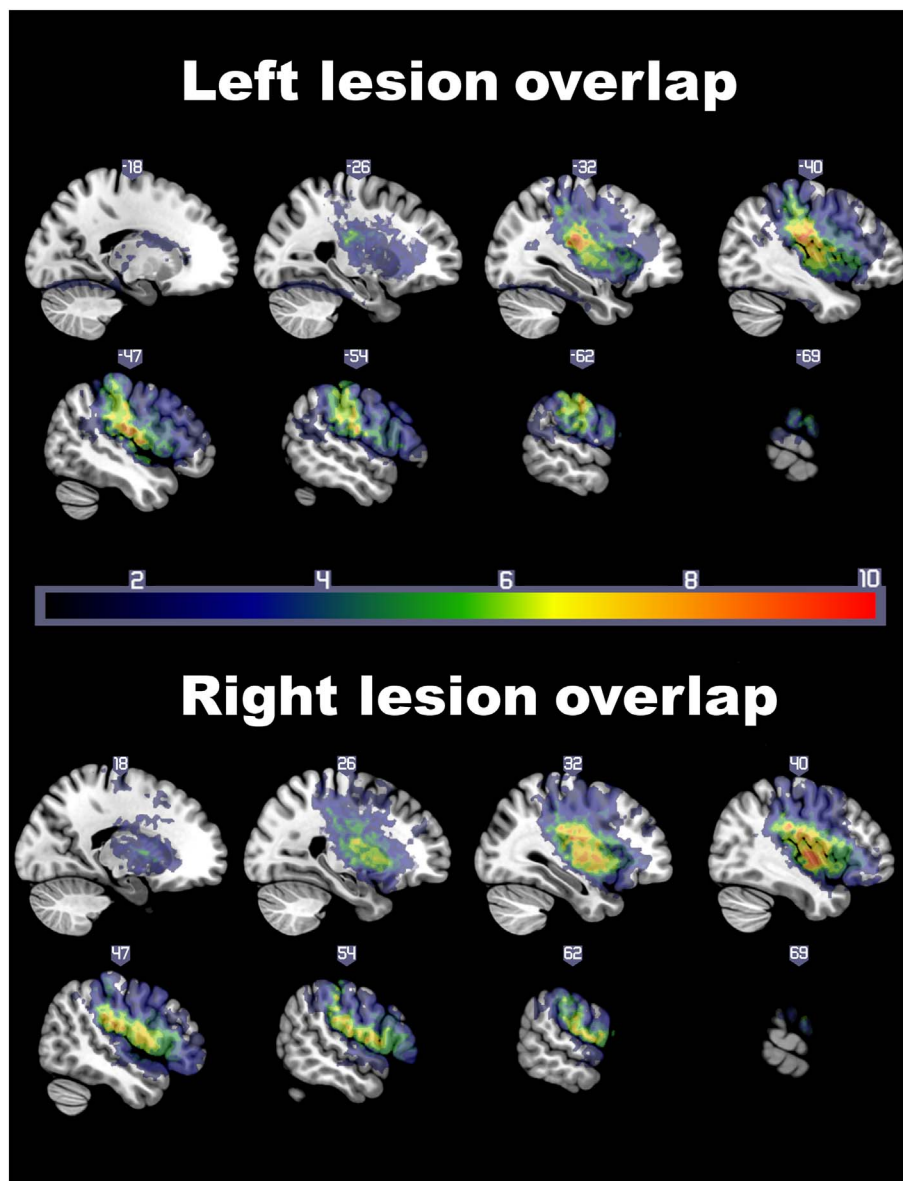
**Fig. 4.** Lesion overlap maps for left lesion (sagittal slices −69 to −18) and right lesion (sagittal slices 18 to 69) groups.

**Table 3**
Percentage of primary and secondary somatosensory seeds not influenced by overlap of lesion (mean and SD), for the left hemisphere lesion and right hemisphere lesion groups.

| | Left hemisphere lesion group | Right hemisphere lesion group |
|---|---|---|
| Seed | % seed with no lesion overlap Mean (SD) | % seed with no lesion overlap Mean (SD) |
| S1 left | 50.48 (51.42) | 100 (0) |
| S1 right | 100 (0) | 65.71 (43.98) |
| S2 left | 46.19 (40.34) | 100 (0) |
| S2 right | 100 (0) | 44.42 (50.00) |

S1 = primary somatosensory; S2 = secondary somatosensory.

dysfunction based on lesioned hemisphere. Clinically, the lesion subgroups displayed somatosensory deficits in contra-lesional but not ipsilesional hands. Anatomically, both left and right lesion stroke groups showed damage localised to their respective hemispheres, with the highest amount of lesion overlap occurring within the insula/S2 region. Healthy controls showed highly symmetrical functional connectivity between hemispheres from left and right S1 and S2 seeds in both FC and LI analyses. FC and LI in left and right lesion groups was noticeably altered between the hemispheres. Disrupted inter-hemispheric functional connectivity was observed for both lesion groups. Between-group analysis of lesion subgroups compared to healthy controls showed decreased FC in areas within the somatosensory network (including right S1, right S2, and bilateral insula) and other functional networks (e.g. visual) for both lesion groups. The right lesion group showed increased FC when compared to the left lesion group in several regions including those associated with visual processing and attention. Differences in laterality were found with a significant interaction between group and seed.

### 4.1. Functional connectivity

#### 4.1.1. Within groups effects

We observed disruption of inter-hemispheric FC from both hemispheres irrespective of hemisphere of lesion. This observation was supported by our LI results for S1 and S2. Changes to inter-hemispheric FC are commonly reported for stroke survivors (Carter et al., 2012; Grefkes and Fink, 2014), with increased FC between the two hemispheres suggesting better recovery outcomes (Carter et al., 2010; van Meer et al., 2010). In the motor system, Ward and Cohen (2004)
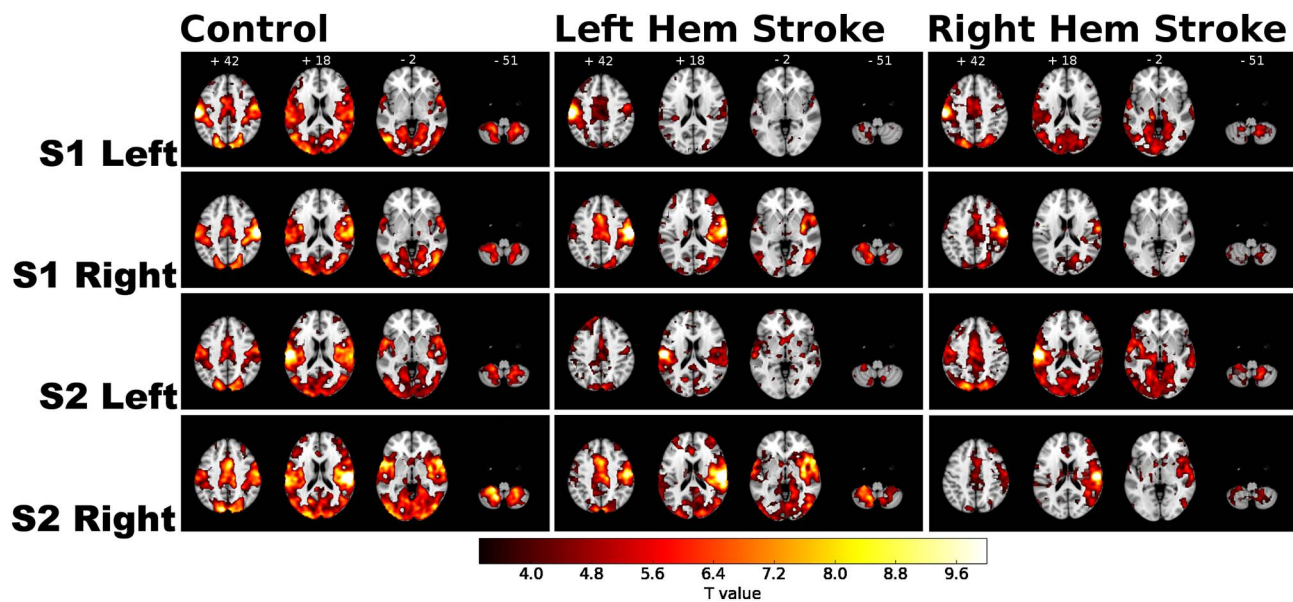
**Fig. 5.** Significant, functionally connected voxels from each seed region for healthy controls (left column), left hemisphere lesion stroke (middle column) and right hemisphere lesion stroke (right column) groups. Functional connectivity for each of the seeds is depicted as follows: from the S1 left (top row), S1 right (second row), S2 left (third row) and S2 right (bottom row) seeds. Axial slices were chosen to show the mid point of seeds for S1 (Z = +42) and S2 (Z = +18), and connectivity to thalamus (Z = −2) and cerebellum (Z = −51) of both hemispheres. Left side of brain is shown on left of image.

proposed that inter-hemispheric FC is due to an inhibitory relationship between the two hemispheres, whose function is to suppress mirrored, simultaneous movements. While these observations are specific to the motor system, the somatosensory system also typically displays a symmetrical FC profile across the hemispheres (Eickhoff et al., 2008; Kastrup et al., 2008; Klingner et al., 2010) and interacts strongly with the motor system (Ackerley et al., 2016). There is some evidence for a cross-hemisphere inhibitory effect in the somatosensory system from healthy participants during tactile stimulation (Kastrup et al., 2008; Klingner et al., 2010). These studies showed greater deactivation from the side ipsi-lateral to stimulation. Furthermore, the deactivation response was associated with decreased regional perfusion and correlated with increased perceptual thresholds (Schaefer et al., 2006). We propose that damage to the somatosensory system in one hemisphere may disrupt inter-hemispheric inhibition and affect tactile thresholds.

*4.1.2. Pooled lesion groups compared to control*

Healthy controls showed greater inter-hemispheric FC from the left S1 seed and bilateral S2 seeds compared to the combined stroke cohort. The left S1 seed showed increased FC to the right S1, S2 and mid temporal regions. In addition, both S2 seeds showed increased connectivity to the opposite insula region, and for the right S2 seed, to left supramarginal gyrus and mid occipital regions.

To our knowledge this is the first time that changes in inter-hemispheric connectivity have been reported for somatosensory function in chronic stroke. A similar study by Bannister et al. (2015) used seed based analysis of major nodes in the somatosensory network to examine FC post-stroke in a cohort with identified tactile impairment. Differences were however noted between the two studies. For example, Bannister et al. observed reduced intra-hemispheric connectivity between S1 regions at 1 and 6 months post-stroke, however no inter-hemispheric effects were found.

Divergent results may be due to sample and methodological differences. The sample used in Bannister et al.'s study were all recruited and scanned at 1 and 6 months post-stroke. In this study we had a sample of chronic stroke survivors at different times post-stroke (median 13 months). It is likely the difference in results between this study and those of Bannister et al. were contributed to by the differences in sample time post-stroke. Stroke participant data were flipped

by Bannister et al. to produce a common lesioned hemisphere. Despite an argument for increasing statistical power, the effects of flipping have not been systematically examined. In our study, significant differences were only observed in the contra-seed hemisphere.

*4.1.3. Left lesion group*
*4.1.3.1. Left lesion group compared to controls.* The left lesion group showed significantly decreased FC between the ipsi-lesional S1 seed and contra-lesional S1 region compared to controls. Studies examining changes in inter-hemispheric activity in the motor system post-stroke (Rehme et al., 2012) have shown ipsi-lesional disruption between the primary motor (M1) area with the contra-lesional M1. Park et al. (2011) examined inter-hemispheric FC between M1 regions in 12 patients and found connectivity between the two regions remained decreased from onset of stroke until at least 6 months post. Bannister et al. (2015) showed a similar disconnection in the somatosensory system from one month post-stroke, but with some return at six months. Our findings add to this with evidence that chronic stroke patients with a left lesion displayed decreased inter-hemispheric FC between primary somatosensory regions at a median of 13 months post-stroke compared to controls.

In addition to decreased FC between primary somatosensory areas, there was also decreased connectivity from ipsi-lesional S1 to the ipsi-lesional parietal and mid occipital, and contra-lesional temporal areas. These areas are part of the dorsal attention network (DAN), which has been associated with selective focussing of attentional resources toward sensory information of importance (Vossel et al., 2014). Tactile sensation has been linked with attention, with animal models showing neuronal synchronous firing is altered based on attentional load (Hyvärinen et al., 1980; Steinmetz et al., 2000). In human studies, electrophysiological responses have shown alterations in amplitude and latency (for event related potential studies) and power (for frequency studies) when tactile stimulation has been coupled with cued attention (Eimer et al., 2003; García-Larrea et al., 1995; Jones and Forster, 2014), as have fMRI studies (Johansen-Berg et al., 2000; Meador et al., 2002). Functional connectivity studies post-stroke have also found potential links between the somatosensory system and attention (Bannister et al., 2015; Carey et al., 2011), suggesting that further examination of the possible connection between the somatosensory system, attention and

**Table 4**
Regions that showed significant between-group functional connectivity differences.

| Seed | Region connected | MNI coords (xyz) | Cluster size | T/Z | p |
|---|---|---|---|---|---|
| Control > L hem + R hem combined lesion groups | | | | | |
| S1 Left | R postcentral | 51–27 60 | 106 | 5.94/4.99 | 0.001 |
| | R mid temporal | 39–63 24 | 82 | 5.33/4.59 | 0.005 |
| | R parietal operculum | 60–21 24 | 132 | 4.60/4.09 | < 0.001 |
| S2 Left | R insula | 33–6 18 | 51 | 4.21/3.80 | 0.048 |
| S2 Right | L insula | −48 3–6 | 94 | 4.84/4.26 | 0.002 |
| | L supramarginal | −48 -24 18 | 103 | 4.30/3.87 | 0.001 |
| | L mid occipital | −33 -96 9 | 63 | 4.26/3.84 | 0.018 |
| Control > L hem lesion group | | | | | |
| S1 Left | R mid temporal | 39–63 24 | 131 | 6.08/5.07 | < 0.001 |
| | L mid occipital | −36 -93 12 | 153 | 6.01/5.02 | < 0.001 |
| | R postcentral | 51–27 57 | 100 | 5.49/4.70 | 0.002 |
| | L mid occipital | −45 -72 3 | 128 | 5.43/4.66 | < 0.001 |
| | L sup parietal | −21 -72 45 | 52 | 4.66/4.13 | 0.039 |
| Control > R hem lesion group | | | | | |
| S1 Left | R parietal operculum | 60–18 21 | 161 | 4.90/4.30 | < 0.001 |
| S2 Left | R parietal operculum | 60–21 21 | 193 | 4.53/4.04 | < 0.001 |
| S2 Right | R mid occipital | 24–96 3 | 51 | 4.75/4.19 | 0.042 |
| | L mid occipital | −24 -99 6 | 224 | 4.64/4.11 | < 0.001 |
| | L sup temporal | −51 0–3 | 63 | 4.46/3.98 | 0.018 |
| R hem lesion group > Control | | | | | |
| S1 Right | R Inf Parietal | 42–60 57 | 108 | 4.78/4.21 | 0.001 |
| R hem lesion group > L hem lesion group (SVC C > L contrast) | | | | | |
| S1 Left | L sup parietal | −21 -84 51 | 9 | 4.02/3.65 | 0.037 |
| | L mid occipital | −42 -72 9 | 20 | 3.94/3.59 | 0.010 |
| | L mid occipital | −39 -90 9 | 11 | 3.87/3.54 | 0.028 |
| R hem lesion group > L hem lesion group (SVC R > C contrast) | | | | | |
| S1 Right | R angular | 45–60 54 | 6 | 3.88/3.55 | 0.011 |
| | R inf parietal | 48–54 39 | 2 | 3.83/3.51 | 0.023 |
| | R angular | 63–54 33 | 4 | 3.69/3.40 | 0.016 |

Note: C = Control, L = Left hemisphere lesion group, R = Right hemisphere lesion group. k = cluster size. SVC = small volume correction. SVC analysis between lesion sub groups is based on regions of difference identified in stroke lesion subgroup compared to healthy controls.

tactile perception is warranted.

### 4.1.4. Right lesion group

*4.1.4.1. Right lesion group compared to controls.* In contrast to the left lesion group, the right lesion group showed increases and decreases in FC when compared to healthy controls. Differences included decreased FC from contra-lesional S1 and S2 to the ipsi-lesional S2. In addition, FC was decreased from the ipsi-lesional S2 to bilateral mid occipital and contra-lesional superior temporal regions. The right lesion group showed greater connectivity within hemisphere from ipsi-lesional (right) S1 to the right inferior parietal lobe (rIPL).

Involvement of bilateral S2 changes are important given the regions putative functions. The S2 region of the somatosensory network has been described as an association and information integration area (Eickhoff et al., 2010; Thoma et al., 2007; Wu et al., 2014). Non-primate and primate studies (Hihara et al., 2015; Wong et al., 2015) have shown S2 to be responsive to multiple sensory inputs, including auditory and visual. Human studies (Bremmer et al., 2001; Gazzola and Keysers, 2009) have shown S2 to respond to visual motion stimuli. Others have suggested S2 and auditory corticies to be linked (Kleber et al., 2016) based on evidence of anatomical connection (Ro et al., 2013), reports of tactile stimuli activating regions of the auditory cortex (Schürmann et al., 2006), auditory stimuli activating S2 (Lang et al., 2011) and interactions between the two (Iguchi et al., 2007; Seghier

et al., 2015). Furthermore, S2 has been suggested to facilitate inter-hemisphere interactions (Chung et al., 2014; Klingner et al., 2010). Despite the similarity of lesion damage between the two groups, only the right subgroup showed disruption of inter-hemispheric FC between ipsi-lesional S1 and S2 with the contra-lesional S2. Decreased FC was found from the right ipsi-lesional S2 seed to contra-lesional superior temporal gyrus and bilateral visual areas.

The right hemisphere lesion group showed significantly increased FC from the right S1 seed to the rIPL. This region is part of the Frontoparietal Control Network (FCN), a network that may act as intermediary between DAN and Default Mode networks (Vincent et al., 2008). Studies have found the region to have increased activation of the IPL during tasks that require inhibition of responses, such as the stop signal task (Aron and Poldrack, 2006) and suppression of visual response (Aso et al., 2016). This region has also been associated with multi-modal sensory information integration (Beauchamp et al., 2010; Gentile et al., 2011; Renier et al., 2009). Animal models have shown anatomical connections between the IPL and somatosensory regions (Cavada and Goldman-Rakic, 1989), while Avanzini et al. (2016) found the IPL to be part of a larger phase associated somatosensory network. Bilateral differences in function have also been suggested (Zhang and Li, 2014), with the left IPL involved in language processes while the right is associated with spatial attention. To speculate, the increased FC from the right S1 seed may suggest that when processing somatosensory information, inhibition of conflicting sensory information and increased reliance on attentional systems could be enhancing the somatosensory information (Johansen-Berg et al., 2000). Further, post-stroke, the recruitment of cortical regions to compensate for damage in adjacent areas is now well established (Green, 2003; Grefkes and Ward, 2014; Ward, 2011). Despite both groups having lesion damage located around S2, only the right lesion group showed decreased FC between left somatosensory seeds and the right S2 compared to controls. This interpreted disruption may have shifted S2 functions to the neighbouring rILP. For the left lesion group, this shift may have been unnecessary due to minimally disrupted bilateral S2 FC.

*4.1.4.2. Right lesion group compared to left lesion group-level.* The right lesion group showed greater FC compared to the left hemisphere group from ipsi-lesional and contra-lesional S1. Increased FC was evident from the contra-lesional left S1 seed to the left superior parietal and mid occipital regions. Controls also exhibited increased FC between these regions when compared to the left lesion group. Links between the somatosensory and visual systems have been documented in animals (Guipponi et al., 2015; Hihara et al., 2015) and humans (Amedi et al., 2005; Sathian and Lacey, 2007). For example, blind individuals show responses in the visual cortex while reading Braille (Amedi et al., 2003). Weisser et al. (2005) showed that temporary sight-deprived participants showed increased tactile acuity compared to controls and changes within the intraparietal sulcus and mid occipital regions. In sighted individuals, Tal et al. (2016) showed the inferior lateral occipital cortex (LOC) was selectively activated to contralateral tactile stimulation of the hand and upper torso. Furthermore, this activity was thought to be driven by S1. Our results show that both controls and the right lesion group had increased FC between the left S1 seed and right mid occipital region, which overlaps with the inferior LOC. This may suggest links between the visual and somatosensory systems are disrupted with lesion damage to the left hemisphere, but not with damage to the right. In healthy individuals, Tal et al. (2016) suggest this link may have formed with increased reliance on tools in everyday life, yet within the context of stroke implications of the disruption between these two regions is unclear.

### 4.2. Laterality index

Symmetric patterns of FC have been established for healthy adult participants in the somatosensory system (Bannister et al., 2015; Burton
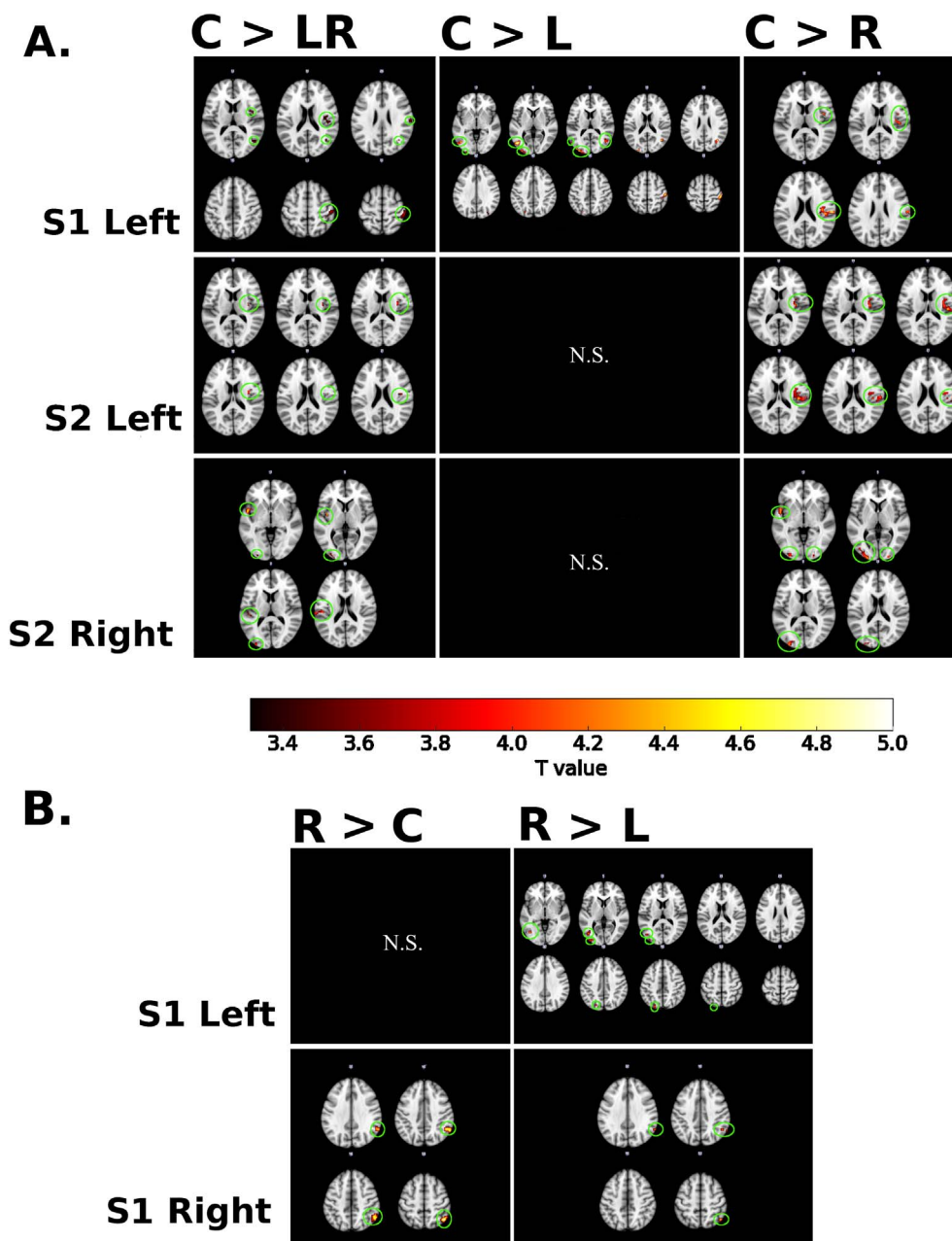
**Fig. 6.** Images of increased FC between controls and lesion subgroups (6a) and increased FC between lesion subgroups and controls or respective lesion subgroups (6b). N·S. = no significant difference.

et al., 2009; Hodkinson et al., 2016). Our findings support a symmetrical pattern of inter-hemispheric connectivity for S1 and S2 in older healthy controls as evidenced by LI values close to zero. The hypothesis of disruption of inter-hemispheric FC for the stroke groups was partially supported, with a subset of the seed maps showing an increased laterality effect. The left lesion group showed an increased LI for contra-lesional (right) S1 and S2 compared to controls. In comparison, the right lesion group only showed an increased LI for contra-lesional (left) S2 compared to controls. Interestingly increased laterality was evident for contra-lesional S2 for both groups.

In animal models, Bauer et al. (2014) found gradated, focal lesioning of the somatosensory cortex produced decreased FC in ipsi- and contra-lesional hemispheres when seeded from the ipsi-lesional hemisphere, while contra-lesional hemisphere FC was decreased between hemispheres but relatively stable within-hemisphere. Currently there is little data in human studies relating to the role laterality of resting state

FC plays in the somatosensory system and the impact on post-stroke recovery. Our results show that substantial amounts of heterogeneity exists for LI score across both hemispheres from both primary and secondary somatosensory regions in chronic stroke survivours. This may be a useful measure in identifying individual differences in tactile recovery profile post-stroke.

### 4.3. Limitations

An unavoidable limitation of this study was the impact of the lesion on the seed. Ideally the signal provided by the seed is minimally disrupted by the tissue damage and the seed is primarily within a region of viable cortical tissue to minimise the noise component of the lesion through averaging of the signal over voxels. Our study had a specific focus on S1 and S2 regions with seeds independently derived from activation maps from a cohort of healthy participants. The stroke

**Table 5**

Laterality Index values for seed maps for left lesion, right lesion and healthy control groups.

| Seed | L hem lesion | R hem lesion | Healthy control |
|---|---|---|---|
| S1 ipsi-lesional hemisphere | 0.21 (0.27)/0.16 (0.19) | 0.33 (0.26)/0.21 (0.16) | 0.05 (0.15)/0.03 (0.11) |
| S1 contra-lesional hemisphere | 0.38 (0.23)/0.36 (0.29) | 0.31 (0.26)/0.21 (0.16) | 0.10 (0.15)/0.08 (0.12) |
| S2 ipsi-lesional hemisphere | 0.10 (0.24)/0.07 (0.12) | 0.29 (0.29)/0.18 (0.17) | 0.06 (0.10)/0.06 (0.08) |
| S2 contra-lesional hemisphere | 0.36 (0.25)/0.35 (0.16) | 0.35 (0.17)/0.34 (0.23) | 0.09 (0.13)/0.09 (0.15) |

Mean (SD)/Median (MAD) values are presented. Note: ipsi-lesional refers to the seed map with the seed placed in the same hemisphere as the lesion. Contra-lesional refers to the seed map with the seed placed in the opposite hemisphere to the lesion. For control participants where no impairment exists, the left hemisphere has been designated "ipsi-lesional" and the right hemisphere "contra-lesional". A laterality index near zero indicates symmetrical or bilateral activity. Higher values indicate more lateralised function, i.e. increased activity of the seed hemisphere compared to the homologous seed in the opposite hemisphere.

participants however had extensive lesions within S1 and S2 with approximately 50% of the ipsi-lesional seeds potentially impacted by the lesion. Nevertheless, the focal impact of the lesion on the brain regions of interest is part of the problem. Additionally, the method of normalising data in part to remove artifact and increase signal in low signal to noise voxels amplified the noise component of seeds partially or fully within the lesioned area. This noise component however is assumed to be white, which would potentially decrease the correlation between seed and cortical areas. Despite these limitations, both lesion groups produced FC within a spatially similar somatosensory network to the healthy controls and past studies (Bannister et al., 2015), with differences consistent with the hypotheses.

Additionally, evidence from this and previous studies suggest attentional systems may be involved in with alterations of tactile perception post stroke. While we gathered a diverse range of tactile sensitivity measures, we did not use any clinical tests that measure attention. Exploration of attentional subdomains may be useful in explaining a portion variance in tactile function observed.

As a general methodological limitation, it must also be mentioned that the BOLD signal is an indirect measure of neural activity and considered to be a mix of signals originating from neural and membrane sources (Logothetis et al., 2001). How information derived from BOLD translates to excitatory and inhibitory processes is still not understood. As FC is calculated from task negative BOLD signal, interpretation of increases and decreases of connectivity at the group level is currently ill-defined.

### 4.4. Summary and conclusion

In conclusion functional connectivity was altered in chronic stroke survivors with somatosensory impairment compared to age and sex matched healthy controls, with greater inter-hemispheric FC from left S1 and bilateral S2 in healthy controls. Stroke survivors with left hemisphere lesion had decreased FC from ipsi-lesional left S1 while those with right hemisphere lesion had decreased FC from bilateral S2, and contra-lesional left S1. They also showed greater intra-hemispheric connectivity than the controls and left lesion group. FC changes were found both within the somatosensory functional network and in interactions with other, associated functional networks.

Our results suggest that further consideration should be given to the role attentional processes play in post-stroke tactile dysfunction. Additionally, somatosensory FC profiles may be altered depending on the hemisphere damaged, despite similar levels of tactile impairment. Further exploration of post-stroke changes in FC of the somatosensory system should factor in hemisphere as a covariate.

### Clinical trial registration
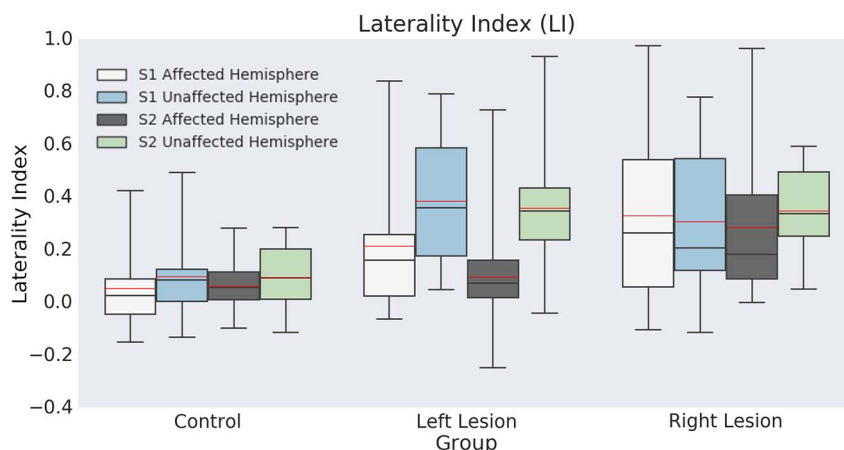
ANZCTR number ACTRN12605000609651.



**Fig. 7.** Laterality Index (LI) for each seed map for controls (left column), left hemisphere lesion group (middle column) and right hemisphere lesion group (right column). Note: N.S = Not significant.

## Ethics

Approval from Austin Human Ethics Committee (H2013/04915), La Trobe University Human Ethics Committee, Northern Health Human Ethics Committee.

## References

Ackerley, R., Borich, M., Oddo, C.M., Ionta, S., 2016. Insights and perspectives on sensory-motor integration and rehabilitation. Multisens. Res. 29 (6), 607–633. http://dx.doi.org/10.1163/22134808-00002530.

Amedi, A., Raz, N., Pianka, P., Malach, R., Zohary, E., 2003. Early "visual" cortex activation correlates with superior verbal memory performance in the blind. Nat. Neurosci. 6 (7), 758–766. http://dx.doi.org/10.1038/nn1072.

Amedi, A., von Kriegstein, K., van Atteveldt, N.M., Beauchamp, M.S., Naumer, M.J., 2005. Functional imaging of human crossmodal identification and object recognition. Exp. Brain Res. 166 (3–4), 559–571. http://dx.doi.org/10.1007/s00221-005-2396-5.

Aron, A.R., Poldrack, R.A., 2006. Cortical and subcortical contributions to Stop signal response inhibition: role of the subthalamic nucleus. J. Neurosci. 26.

Ashburner, J., Friston, K.J., 2005. Unified segmentation. NeuroImage 26 (3), 839–851. http://dx.doi.org/10.1016/j.neuroimage.2005.02.018.

Aso, T., Nishimura, K., Kiyonaka, T., Aoki, T., Inagawa, M., Matsuhashi, M., Yoshikazu, T., Fukuyama, H., 2016. Dynamic interactions of the cortical networks during thought suppression. Brain Behav. 6 (8). http://dx.doi.org/10.1002/brb3.503.

Avants, B.B., Tustison, N.J., Song, G., Cook, P.A., Klein, A., Gee, J.C., 2011. A reproducible evaluation of ANTs similarity metric performance in brain image registration. NeuroImage 54 (3), 2033–2044. http://dx.doi.org/10.1016/j.neuroimage.2010.09.025.

Avanzini, P., Abdollahi, R.O., Sartori, I., Caruana, F., Pelliccia, V., Casaceli, G., ... Orban, G.A., 2016. Four-dimensional maps of the human somatosensory system. Proc. Natl. Acad. Sci. 113 (13), E1936–E1943.

Bannister, L.C., Crewther, S.G., Gavrilescu, M., Carey, L.M., 2015. Improvement in touch sensation after stroke is associated with resting functional connectivity changes. Front. Neurol. 6 (JUL). http://dx.doi.org/10.3389/fneur.2015.00165.

Bates, D., Mächler, M., Bolker, B., Walker, S., 2015. Fitting linear mixed-effects models using lme4. J. Stat. Softw. 1 (1). http://dx.doi.org/10.18637/jss.v067.i01.

Bauer, A.Q., Kraft, A.W., Wright, P.W., Snyder, A.Z., Lee, J.-M., Culver, J.P., 2014. Optical imaging of disrupted functional connectivity following ischemic stroke in mice. NeuroImage 99, 388–401. http://dx.doi.org/10.1016/j.neuroimage.2014.05.051.

Beauchamp, M.S., Pasalar, S., Ro, T., 2010. Neural substrates of reliability-weighted visual-tactile multisensory integration. Front. Syst. Neurosci. 4 (25). http://dx.doi.org/10.3389/fnsys.2010.00025.

Behzadi, Y., Restom, K., Liau, J., Liu, T.T., 2007. A component based noise correction method (CompCor) for BOLD and perfusion based fMRI. NeuroImage 37 (1), 90–101. http://dx.doi.org/10.1016/j.neuroimage.2007.04.042.

Biswal, B.B., Mennes, M., Zuo, X.-N., Gohel, S., Kelly, C., Smith, S.M., Milham, M.P., 2010. Toward discovery science of human brain function. Proc. Natl. Acad. Sci. 107 (10), 4734–4739. http://dx.doi.org/10.1073/pnas.0911855107.

Bremmer, F., Schlack, A., Shah, N.J., Zafiris, O., Kubischik, M., Hoffmann, K., ... Fink, G.R., 2001. Polymodal motion processing in posterior parietal and premotor cortex: a human fMRI study strongly implies equivalencies between humans and monkeys. Neuron 29 (1), 287–296.

Brookes, M.J., Wood, J.R., Stevenson, C.M., Zumer, J.M., White, T.P., Liddle, P.F., Morris, P.G., 2011. Changes in brain network activity during working memory tasks: a magnetoencephalography study. NeuroImage 55 (4), 1804–1815. http://dx.doi.org/10.1016/j.neuroimage.2010.10.074.

Brott, T., Adams, H.P., Olinger, C.P., Marler, J.R., Barsan, W.G., Biller, J., ... Hertzberg, V., 1989. Measurements of acute cerebral infarction: a clinical examination scale. Stroke 20 (7), 864–870.

Burton, H., Dixit, S., Litkowski, P., Wingert, J.R., 2009. Functional connectivity for somatosensory and motor cortex in spastic diplegia. Somatosens. Mot. Res. 26 (4), 90–104. http://dx.doi.org/10.3109/08990220903335742.

Carey, L.M., Oke, L.E., Matyas, T.A., 1997. Impaired touch discrimination after stroke: a quantitative test. J. Neurologic. Rehabil. 11 (4), 219–232. http://dx.doi.org/10.1177/154596839701100404.

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 (5), 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 (5), 443–457. http://dx.doi.org/10.1177/1545968310395777.

Carey, L.M., Seitz, R.J., Parsons, M., Levi, C., Farquharson, S., Tournier, J.-D., ... Connelly, A., 2013. Beyond the lesion: neuroimaging foundations for post-stroke recovery. Future Neurol. 8 (5), 507–527. http://dx.doi.org/10.2217/fnl.13.39.

Carter, A.R., Astafiev, S.V., Lang, C.E., Connor, L.T., Rengachary, J., Strube, M.J., ... Corbetta, M., 2010. Resting inter-hemispheric fMRI connectivity predicts performance after stroke. Ann. Neurol. 67 (3), 365–375. http://dx.doi.org/10.1002/ana.21905.

Carter, A.R., Shulman, G.L., Corbetta, M., 2012. Why use a connectivity-based approach to study stroke and recovery of function? NeuroImage 62 (4), 2271–2280. http://dx.doi.org/10.1016/j.neuroimage.2012.02.070.

Cavada, C., Goldman-Rakic, P.S., 1989. Posterior parietal cortex in rhesus monkey: II.

Evidence for segregated corticocortical networks linking sensory and limbic areas with the frontal lobe. J. Comp. Neurol. 287 (4), 422–445. http://dx.doi.org/10.1002/cne.902870403.

Chung, Y.G., Han, S.W., Kim, H.-S., Chung, S.-C., Park, J.-Y., Wallraven, C., Kim, S.-P., 2014. Intra- and inter-hemispheric effective connectivity in the human somatosensory cortex during pressure stimulation. BMC Neurosci. 15, 43. http://dx.doi.org/10.1186/1471-2202-15-43.

Cole, D.M., Smith, S.M., Beckmann, C.F., 2010. Advances and pitfalls in the analysis and interpretation of resting-state FMRI data. Front. Syst. Neurosci. 4. http://dx.doi.org/10.3389/fnsys.2010.00008.

Cox, R.W., 1996. AFNI: software for analysis and visualization of functional magnetic resonance neuroimages. Comput. Biomed. Res. 29 (3), 162–173. http://dx.doi.org/10.1006/cbmr.1996.0014.

Dinomais, M., Chinier, E., Lignon, G., Richard, I., Ter Minassian, A., Tich, S.N.T., 2013. The effect of video-guidance on passive movement in patients with cerebral palsy: fMRI study. Res. Dev. Disabil. 34 (10), 3487–3496. http://dx.doi.org/10.1016/j.ridd.2013.07.008.

Doyle, S., Bennett, S., Fasoli, S.E., McKenna, K.T., 2010. Interventions for sensory impairment in the upper limb after stroke. Cochrane Database Syst. Rev. 6, CD006331. http://dx.doi.org/10.1002/14651858.CD006331.pub2.

Eickhoff, S.B., Stephan, K.E., Mohlberg, H., Grefkes, C., Fink, G.R., Amunts, K., Zilles, K., 2005. A new SPM toolbox for combining probabilistic cytoarchitectonic maps and functional imaging data. NeuroImage 25 (4), 1325–1335. http://dx.doi.org/10.1016/j.neuroimage.2004.12.034.

Eickhoff, S.B., Paus, T., Caspers, S., Grosbras, M.-H., Evans, A.C., Zilles, K., Amunts, K., 2007. Assignment of functional activations to probabilistic cytoarchitectonic areas revisited. NeuroImage 36 (3), 511–521. http://dx.doi.org/10.1016/j.neuroimage.2007.03.060.

Eickhoff, S.B., Grefkes, C., Fink, G.R., Zilles, K., 2008. Functional lateralization of face, hand, and trunk representation in anatomically defined human somatosensory areas. Cerebral Cortex (New York, N.Y.: 1991) 18 (12), 2820–2830. http://dx.doi.org/10.1093/cercor/bhn039.

Eickhoff, S.B., Jbabdi, S., Caspers, S., Laird, A.R., Fox, P.T., Zilles, K., Behrens, T.E.J., 2010. Anatomical and functional connectivity of cytoarchitectonic areas within the human parietal operculum. J. Neurosci. 30 (18), 6409–6421. http://dx.doi.org/10.1523/JNEUROSCI.5664-09.2010.

Eimer, M., Forster, B., Van Velzen, J., 2003. Anterior and posterior attentional control systems use different spatial reference frames: ERP evidence from covert tactile-spatial orienting. Psychophysiology 40 (6), 924–933.

Eklund, A., Nichols, T.E., Knutsson, H., 2016. Cluster failure: why fMRI inferences for spatial extent have inflated false-positive rates. Proc. Natl. Acad. Sci. 113 (28), 7900–7905. http://dx.doi.org/10.1073/pnas.1602413113.

Friston, K.J., Williams, S., Howard, R., Frackowiak, R.S., Turner, R., 1996. Movement-related effects in fMRI time-series. Magn. Reson. Med. 35 (3), 346–355.

García-Larrea, L., Lukaszewicz, A.-C., Mauguière, F., 1995. Somatosensory responses during selective spatial attention: the N120-to-N140 trasition. Psychophysiology 32 (6), 526–537. http://dx.doi.org/10.1111/j.1469-8986.1995.tb01229.x.

Gazzola, V., Keysers, C., 2009. The observation and execution of actions share motor and somatosensory voxels in all tested subjects: single-subject analyses of unsmoothed fMRI data. Cerebral Cortex (New York, N.Y.: 1991) 19 (6), 1239–1255. http://dx.doi.org/10.1093/cercor/bhn181.

Gentile, G., Petkova, V.I., Ehrsson, H.H., 2011. Integration of visual and tactile signals from the hand in the human brain: an FMRI study. J. Neurophysiol. 105 (2), 910–922. http://dx.doi.org/10.1152/jn.00840.2010.

Gorgolewski, K., Burns, C.D., Madison, C., Clark, D., Halchenko, Y.O., Waskom, M.L., Ghosh, S.S., 2011. Nipype: a flexible, lightweight and extensible neuroimaging data processing framework in python. Front. Neuroinform. 5. http://dx.doi.org/10.3389/fninf.2011.00013.

Gotts, S.J., Saad, Z.S., Jo, H.J., Wallace, G.L., Cox, R.W., Martin, A., 2013. The perils of global signal regression for group comparisons: a case study of autism spectrum disorders. Front. Hum. Neurosci. 7. http://dx.doi.org/10.3389/fnhum.2013.00356.

Green, J.B., 2003. Brain reorganization after stroke. Top. Stroke Rehabil. 10 (3), 1–20. http://dx.doi.org/10.1310/H65X-23HW-QL1G-KTNQ.

Grefkes, C., Fink, G.R., 2014. Connectivity-based approaches in stroke and recovery of function. Lancet Neurol. 13 (2), 206–216. http://dx.doi.org/10.1016/S1474-4422(13)70264-3.

Grefkes, C., Ward, N.S., 2014. Cortical reorganization after stroke: how much and how functional? Neuroscientist 20 (1), 56–70. http://dx.doi.org/10.1177/1073858413491147.

Guipponi, O., Cléry, J., Odouard, S., Wardak, C., Ben Hamed, S., 2015. Whole brain mapping of visual and tactile convergence in the macaque monkey. NeuroImage 117, 93–102. http://dx.doi.org/10.1016/j.neuroimage.2015.05.022.

Hihara, S., Taoka, M., Tanaka, M., Iriki, A., 2015. Visual responsiveness of neurons in the secondary somatosensory area and its surrounding parietal operculum regions in awake Macaque monkeys. Cereb. Cortex 25 (11), 4535–4550. http://dx.doi.org/10.1093/cercor/bhv095.

Hodkinson, D.J., Veggeberg, R., Kucyi, A., van Dijk, K.R.A., Wilcox, S.L., Scrivani, S.J., ... Borsook, D., 2016. Cortico–cortical connections of primary sensory areas and associated symptoms in migraine. eNeuro 3 (6). http://dx.doi.org/10.1523/ENEURO.0163-16.2016.

Hothorn, T., Bretz, F., Westfall, P., 2008. Simultaneous inference in general parametric models. Biom. J. 50 (3), 346–363. http://dx.doi.org/10.1002/bimj.200810425.

Hyvärinen, J., Poranen, A., Jokinen, Y., 1980. Influence of attentive behavior on neuronal responses to vibration in primary somatosensory cortex of the monkey. J. Neurophysiol. 43 (4), 870–882.

Iguchi, Y., Hoshi, Y., Nemoto, M., Taira, M., Hashimoto, I., 2007. Co-activation of the

secondary somatosensory and auditory cortices facilitates frequency discrimination of vibrotactile stimuli. Neuroscience 148 (2), 461–472. http://dx.doi.org/10.1016/j.neuroscience.2007.06.004.

Johansen-Berg, H., Christensen, V., Woolrich, M., Matthews, P.M., 2000. Attention to touch modulates activity in both primary and secondary somatosensory areas. Neuroreport 11 (6), 1237–1241.

Jones, A., Forster, B., 2014. Neural correlates of endogenous attention, exogenous attention and inhibition of return in touch. Eur. J. Neurosci. 40 (2), 2389–2398. http://dx.doi.org/10.1111/ejn.12583.

Kastrup, A., Baudewig, J., Schnaudigel, S., Huonker, R., Becker, L., Sohns, J.M., ... Witte, O.W., 2008. Behavioral correlates of negative BOLD signal changes in the primary somatosensory cortex. NeuroImage 41 (4), 1364–1371. http://dx.doi.org/10.1016/j.neuroimage.2008.03.049.

Kessner, S.S., Bingel, U., Thomalla, G., 2016. Somatosensory deficits after stroke: a scoping review. Top. Stroke Rehabil. 23 (2), 136–146. http://dx.doi.org/10.1080/10749357.2015.1116822.

Kleber, B., Veit, R., Moll, C.V., Gaser, C., Birbaumer, N., Lotze, M., 2016. Voxel-based morphometry in opera singers: increased gray-matter volume in right somatosensory and auditory cortices. NeuroImage 133, 477–483. http://dx.doi.org/10.1016/j.neuroimage.2016.03.045.

Klingner, C.M., Hasler, C., Brodoehl, S., Witte, O.W., 2010. Dependence of the negative BOLD response on somatosensory stimulus intensity. NeuroImage 53 (1), 189–195. http://dx.doi.org/10.1016/j.neuroimage.2010.05.087.

Lang, S., Yu, T., Markl, A., Müller, F., Kotchoubey, B., 2011. Hearing others' pain: neural activity related to empathy. Cogn. Affect. Behav. Neurosci. 11 (3), 386–395. http://dx.doi.org/10.3758/s13415-011-0035-0.

Lee, S.D., Jung, Y., Chung, Y.A., Lee, W., 2016. Neural substrates in secondary somatosensory area for the perception of different tactile sensations. Int. J. Imaging Syst. Technol. 26 (1), 85–91. http://dx.doi.org/10.1002/ima.22160.

Logothetis, N.K., Pauls, J., Augath, M., Trinath, T., Oeltermann, A., 2001. Neurophysiological investigation of the basis of the fMRI signal. Nature 412 (6843), 150.

Maldjian, J.A., Laurienti, P.J., Kraft, R.A., Burdette, J.H., 2003. An automated method for neuroanatomic and cytoarchitectonic atlas-based interrogation of fMRI data sets. NeuroImage 19 (3), 1233–1239. http://dx.doi.org/10.1016/S1053-8119(03)00169-1.

Maldjian, J.A., Laurienti, P.J., Burdette, J.H., 2004. Precentral gyrus discrepancy in electronic versions of the Talairach atlas. NeuroImage 21 (1), 450–455. http://dx.doi.org/10.1016/j.neuroimage.2003.09.032.

Meador, K.J., Allison, J.D., Loring, D.W., Lavin, T.B., Pillai, J.J., 2002. Topography of somatosensory processing: cerebral lateralization and focused attention. J. Int. Neuropsychol. Soc. 8 (3), 349–359. http://dx.doi.org/10.1017/S1355617702813169.

van Meer, M.P.A., van der Marel, K., Wang, K., Otte, W.M., el Bouazati, S., Roeling, T.A.P., ... Dijkhuizen, R.M., 2010. Recovery of sensorimotor function after experimental stroke correlates with restoration of resting-state inter-hemispheric functional connectivity. J. Neurosci. 30 (11), 3964–3972. http://dx.doi.org/10.1523/JNEUROSCI.5709-09.2010.

Oldfield, R.C., 1971. The assessment and analysis of handedness: the Edinburgh inventory. Neuropsychologia 9 (1), 97–113.

Oliphant, T.E., 2007. Python for scientific computing. Comput. Sci. Eng. 9 (3), 10–20.

Ovadia-Caro, S., Margulies, D.S., Villringer, A., 2014. The value of resting-state functional magnetic resonance imaging in stroke. Stroke 45 (9), 2818–2824. http://dx.doi.org/10.1161/STROKEAHA.114.003689.

Park, C., Chang, W.H., Ohn, S.H., Kim, S.T., Bang, O.Y., Pascual-Leone, A., Kim, Y.-H., 2011. Longitudinal changes of resting-state functional connectivity during motor recovery after stroke. Stroke 42 (5), 1357–1362. http://dx.doi.org/10.1161/STROKEAHA.110.596155.

R Core Team, 2013. R: A Language and Environment for Statistical Computing. R Foundation for Statistical Computing, Vienna, Austria Retrieved from. http://www.R-project.org/.

Rehme, A.K., Grefkes, C., 2013. Cerebral network disorders after stroke: evidence from imaging-based connectivity analyses of active and resting brain states in humans. J. Physiol. 591 (1), 17–31. http://dx.doi.org/10.1113/jphysiol.2012.243469.

Rehme, A.K., Eickhoff, S.B., Rottschy, C., Fink, G.R., Grefkes, C., 2012. Activation likelihood estimation meta-analysis of motor-related neural activity after stroke. NeuroImage 59 (3), 2771–2782. http://dx.doi.org/10.1016/j.neuroimage.2011.10.023.

Renier, L.A., Anurova, I., De Volder, A.G., Carlson, S., VanMeter, J., Rauschecker, J.P., 2009. Multisensory integration of sounds and vibrotactile stimuli in processing streams for "What" and "Where". J. Neurosci. 29 (35), 10950–10960. http://dx.doi.org/10.1523/JNEUROSCI.0910-09.2009.

Ro, T., Ellmore, T.M., Beauchamp, M.S., 2013. A neural link between feeling and hearing. Cerebral Cortex (New York, N.Y.: 1991) 23 (7), 1724–1730. http://dx.doi.org/10.1093/cercor/bhs166.

Sathian, K., Lacey, I., 2007. Journeying beyond classical somatosensory cortex. Can. Can. J. Exp. Psychol. 61 (3), 254–264.

Schaefer, H.S., Putnam, K.M., Benca, R.M., Davidson, R.J., 2006. Event-related functional magnetic resonance imaging measures of neural activity to positive social stimuli in pre- and post-treatment depression. Biol. Psychiatry 60 (9), 974–986.

Schäfer, K., Blankenburg, F., Kupers, R., Grüner, J.M., Law, I., Lauritzen, M., Larsson, H.B.W., 2012. Negative BOLD signal changes in ipsi-lateral primary somatosensory cortex are associated with perfusion decreases and behavioral evidence for functional inhibition. NeuroImage 59 (4), 3119–3127. http://dx.doi.org/10.1016/j.neuroimage.2011.11.085.

Schürmann, M., Caetano, G., Hlushchuk, Y., Jousmäki, V., Hari, R., 2006. Touch activates human auditory cortex. NeuroImage 30 (4), 1325–1331. http://dx.doi.org/10.1016/j.neuroimage.2005.11.020.

Seghier, M.L., 2008. Laterality index in functional MRI: methodological issues. Magn. Reson. Imaging 26 (5), 594–601. http://dx.doi.org/10.1016/j.mri.2007.10.010.

Seghier, M.L., Hope, T.M.H., Prejawa, S., Jones, Parker, Ōiwi, Vitkovitch, M., Price, C.J., 2015. A trade-off between somatosensory and auditory related brain activity during object naming but not reading. J. Neurosci. Off. J. Soc. Neurosci. 35 (11), 4751–4759. http://dx.doi.org/10.1523/JNEUROSCI.2292-14.2015.

Smith, S.M., Fox, P.T., Miller, K.L., Glahn, D.C., Fox, P.M., Mackay, C.E., ... Beckmann, C.F., 2009. Correspondence of the brain's functional architecture during activation and rest. Proc. Natl. Acad. Sci. 106 (31), 13040–13045. http://dx.doi.org/10.1073/pnas.0905267106.

Smith, S.M., Vidaurre, D., Beckmann, C.F., Glasser, M.F., Jenkinson, M., Miller, K.L., ... Van Essen, D.C., 2013. Functional connectomics from resting-state fMRI. Trends Cogn. Sci. 17 (12), 666–682. http://dx.doi.org/10.1016/j.tics.2013.09.016.

Sommerfeld, Disa Kathryn, von Arbin, Magnus H., 2004. The impact of somatosensory function on activity performance and length of hospital stay in geriatric patients with stroke. Clin. Rehabil. 18 (2), 149–155. http://dx.doi.org/10.1191/0269215504cr710oa.

Steinmetz, P.N., Roy, A., Fitzgerald, P.J., Hsiao, S.S., Johnson, K.O., Niebur, E., 2000. Attention modulates synchronized neuronal firing in primate somatosensory cortex. Nature 404 (6774), 187–190. http://dx.doi.org/10.1038/35004588.

Tal, Z., Geva, R., Amedi, A., 2016. The origins of metamodality in visual object area LO: bodily topographical biases and increased functional connectivity to S1. NeuroImage 127, 363–375. http://dx.doi.org/10.1016/j.neuroimage.2015.11.058.

Thoma, R.J., Hanlon, F.M., Huang, M., Miller, G.A., Moses, S.N., Weisend, M.P., ... Cañive, J.M., 2007. Impaired secondary somatosensory gating in patients with schizophrenia. Psychiatry Res. 151 (3), 189–199. http://dx.doi.org/10.1016/j.psychres.2006.10.011.

Tomasi, D., Volkow, N.D., 2011. Association between functional connectivity hubs and brain networks. Cereb. Cortex 21 (9), 2003–2013. http://dx.doi.org/10.1093/cercor/bhq268.

Tzourio-Mazoyer, N., Landeau, B., Papathanassiou, D., Crivello, F., Etard, O., Delcroix, N., ... Joliot, M., 2002. Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. NeuroImage 15 (1), 273–289. http://dx.doi.org/10.1006/nimg.2001.0978.

Vincent, J.L., Kahn, I., Snyder, A.Z., Raichle, M.E., Buckner, R.L., 2008. Evidence for a frontoparietal control system revealed by intrinsic functional connectivity. J. Neurophysiol. 100 (6), 3328–3342. http://dx.doi.org/10.1152/jn.90355.2008.

Vossel, S., Geng, J.J., Fink, G.R., 2014. Dorsal and ventral attention systems. Neuroscientist 20 (2), 150–159. http://dx.doi.org/10.1177/1073858413494269.

van der Walt, S., Colbert, S.C., Varoquaux, G., 2011. The NumPy array: a structure for efficient numerical computation. Comput. Sci. Eng. 13 (2), 22–30.

Ward, N.S., 2011. Assessment of cortical reorganisation for hand function after stroke. J. Physiol. 589 (23), 5625–5632. http://dx.doi.org/10.1113/jphysiol.2011.220939.

Ward, N.S., Cohen, L.G., 2004. Mechanisms underlying recovery of motor function after stroke. Arch. Neurol. 61 (12), 1844–1848. http://dx.doi.org/10.1001/archneur.61.12.1844.

Wegner, K., Forss, N., Salenius, S., 2000. Characteristics of the human contra-versus ipsilateral SII cortex. Clin. Neurophysiol. 111 (5), 894–900.

Weinstein, S., 1993. Fifty years of somatosensory research. J. Hand Ther. 6 (1), 11–22. http://dx.doi.org/10.1016/S0894-1130(12)80176-1.

Weisser, V., Stilla, R., Peltier, S., Hu, X., Sathian, K., 2005. Short-term visual deprivation alters neural processing of tactile form. Exp. Brain Res. 166 (3–4), 572–582. http://dx.doi.org/10.1007/s00221-005-2397-4.

Wong, C., Chabot, N., Kok, M.A., Lomber, S.G., 2015. Amplified somatosensory and visual cortical projections to a core auditory area, the anterior auditory field, following early- and late-onset deafness. J. Comp. Neurol. 523 (13), 1925–1947. http://dx.doi.org/10.1002/cne.23771.

Woo, C.-W., Krishnan, A., Wager, T.D., 2014. Cluster-extent based thresholding in fMRI analyses: pitfalls and recommendations. NeuroImage 91, 412–419. http://dx.doi.org/10.1016/j.neuroimage.2013.12.058.

Wu, Q., Li, C., Li, Y., Sun, H., Guo, Q., Wu, J., 2014. SII and the fronto-parietal areas are involved in visually cued tactile top-down spatial attention: a functional MRI study. Neuroreport 25 (6), 415–421. http://dx.doi.org/10.1097/WNR.0000000000000128.

Zhang, S., Li, C.-S.R., 2014. Functional clustering of the human inferior parietal lobule by whole-brain connectivity mapping of resting-state functional magnetic resonance imaging signals. Brain Connect. 4 (1), 53–69. http://dx.doi.org/10.1089/brain.2013.0191.