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ORIGINAL RESEARCH

Errors in proprioceptive matching post-stroke are associated with impaired recruitment of parietal, supplementary motor, and temporal cortices

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Abstract

Deficits in proprioception, the ability to discriminate the relative position and movement of our limbs, affect ~50% of stroke patients and reduce functional outcomes. Our lack of knowledge of the anatomical correlates of proprioceptive processing limits our understanding of the impact that such deficits have on recovery. This research investigated the relationship between functional impairment in brain activity and proprioception post-stroke. We developed a novel device and task for arm position matching during functional MRI (fMRI), and investigated 16 subjects with recent stroke and nine healthy age-matched controls. The stroke-affected arm was moved by an experimenter (passive arm), and subjects were required to match the position of this limb with the opposite arm (active arm). Brain activity during passive and active arm movements was determined, as well as activity in association with performance error. Passive arm movement in healthy controls was associated with activity in contralateral primary somatosensory (SI) and motor cortices (MI), bilateral parietal cortex, supplementary (SMA) and premotor cortices, secondary somatosensory cortices (SII), and putamen. Active arm matching was associated with activity in contralateral SI, MI, bilateral SMA, premotor cortex, putamen, and ipsilateral cerebellum. In subjects with stroke, similar patterns of activity were observed. However, in stroke subjects, greater proprioceptive error was associated with less activity in ipsilesional supramarginal and superior temporal gyri, and lateral thalamus. During active arm movement, greater proprioceptive error was associated with less activity in bilateral SMA and ipsilesional premotor cortex. Our results enhance our understanding of the correlates of proprioception within the temporal parietal cortex and supplementary/premotor cortices. These findings also offer potential targets for therapeutic intervention to improve proprioception in recovering stroke patients and thus improve functional outcome.

Keywords Proprioception · Stroke · Supramarginal gyrus · Functional magnetic resonance imaging · Somatosensory · Supplementary motor area

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Introduction

Following stroke, impairments specific to proprioception (our awareness of the position and movement of our body and limbs) occur in approximately 50% of individuals (Carey 1995; Carey et al. 1996; Connell et al. 2008; Dukelow et al. 2010; Semrau et al. 2013; Tyson et al. 2008). Proprioceptive impairments are associated with lesions to numerous different brain areas including the thalamus (Gutrecht et al. 1992; Kim 1992; Schmahmann 2003), posterior limb of the internal capsule (Meyer et al. 2016), and frontal and parietal cortices (Findlater et al. 2016; Kenzie et al. 2016, 2014). Although lesion analysis studies and case series have provided valuable evidence of the brain areas required for proprioception, they are unable to identify disruptions to brain function that are not

directly affected by the lesion. These brain areas become 'disconnected' from other areas and do not function normally, even though they are not directly damaged from the stroke. This is known as diaschisis (Seitz et al. 1999). Functional MRI offers a method to probe these functional disruptions in brain activity that result from stroke.

Beyond lesion studies, several paradigms have been developed to try to address which brain areas are involved in proprioceptive sensations in neurologically intact individuals. For example, passive limb movement during fMRI has been used to investigate proprioception (Mima et al. 1999; Radovanovic et al. 2001; Van de Winckel et al. 2005). Passive movement of the index finger, wrist, or elbow results in brain activation in contralateral primary sensorimotor cortices and bilateral secondary/association cortices (e.g. supplementary motor area (SMA), secondary somatosensory cortex (SII), insula, posterior parietal cortex) (Van de Winckel et al. 2005; Weiller et al. 1996). Another common paradigm used to assess limb movement sensation involves vibrating a muscle tendon between 80 and 100 Hz. This produces a strong illusion of muscle lengthening and in turn, limb movement (Goodwin et al. 1972; Roll and Vedel 1982). During fMRI, this type of illusion results in brain activations in contralateral primary motor (MI) and sensory (SI) cortices (Kavounoudias et al. 2008; Naito et al. 2002; Naito et al. 1999), bilateral secondary somatosensory cortex (SII), insula, supplementary motor (SMA), premotor areas, and ipsilateral cerebellum (Kavounoudias et al. 2008). Recently, Iandolo et al. (2018) investigated the neural correlates of proprioceptive matching at the ankle in healthy controls using fMRI. When compared to active ankle movements, proprioceptive matching movements showed stronger BOLD activations in S1, the supramarginal gyrus (SMG), superior parietal lobule, and superior frontal gyrus (Iandolo et al. 2018). Additionally, within these areas the authors found greater BOLD activations in the right hemisphere regardless of whether the right or left foot was performing the task, suggesting potential right hemisphere dominance in proprioceptive processing.

Some studies have investigated the brain activations related to proprioceptive impairments post-stroke. However, all have been done on stroke participants in the chronic stages post-stroke after potential neural reorganization has occurred. Ben-Shabat et al. (2015) performed a wrist position-sense test during fMRI of healthy controls and three individuals with proprioceptive impairments resulting from chronic stroke (greater than 16 months post-stroke). Subjects were specifically asked to pay attention to the position of the wrist that was being moved by the experimenter, as they were required to match the position with the opposite wrist upon hearing an auditory cue. The authors concluded that the right supramarginal gyrus (SMG) and dorsal premotor cortices were involved in the coding of proprioceptive information at the wrist in controls, and showed decreased task-related activation in the subjects with stroke. Further, Borstad et al. (2012) found that in a touch discrimination task in subjects with chronic stroke, activation in parietal cortex and precuneus were associated with better discrimination performance. Lastly, Van De Winckel et al. (2012) found that in eight chronic stroke patients, a passive left finger movement discrimination paradigm activated the right angular gyrus, left superior lingual gyrus, and right cerebellar lobule more than in healthy age-matched controls. The areas of the brain associated with proprioceptive processing are evidently widespread. Given the results by Ben-Shabat et al. (2015), our aim was to determine if the SMG and dorsal premotor cortices were involved in proprioception in a larger sample of subjects with sub-acute stroke, before potentially significant brain remodelling could occur.

Somatosensory retraining in the chronic stages post-stroke has been investigated with regard to changes in functional brain activity. Vahdat et al. (2019) assessed functional connectivity changes after a single robot-assisted training session in ten subjects post-stroke. They found that increased functional connectivity between ipsilesional and contralesional SMG was associated with better motor function following robot-assisted training. They also found that increased connectivity between contralesional S1, M1, and SMA was associated with better sensory function. Carey et al. (2016) also investigated changes in functional connectivity in chronic stroke after a sensory training intervention. Notably, subjects with lesions in S1 and S2 demonstrated decreased recruitment of precuneus cortex during a touch discrimination fMRI task that was associated with improvement in touch discrimination over time. An earlier PET study by Nelles et al. (2001) also demonstrated that changes in functional activation occur in patients post-stroke after a training intervention. They found that task-oriented motor training of the paretic arm post-stroke increased recruitment of brain areas in frontal and parietal cortices relative to stroke subjects who did not undergo training, even though functional improvements in arm function were not significant.

In healthy subjects, numerous parts of the brain involved in motor control respond to perceptions of limb movement, whether induced through passive movements or illusions. However, proprioceptive impairments can result from very specific lesion sites after stroke such as the posterior limb of the internal capsule, thalamus, or S1 (Findlater et al. 2016; Kenzie et al. 2016; Kenzie et al. 2014; Kim and Choi-Kwon 1996; Schmahmann 2003). Therefore, the question remains whether certain brain regions are more important for proprioceptive sensation following stroke than others. Based on the results from Ben-Shabat et al. (2015) and Iandolo et al. (2018), we hypothesized that decreased activation in the ipsilesional SMG and dorsal premotor cortex during a proprioceptive matching task would be associated with worse proprioceptive performance in subjects with stroke.

Methods

Subjects

Subjects with stroke ($n = 16$) who had clinically suspected proprioceptive impairment (based on passive joint motion assessment by a physical therapist) were approached for recruitment from the Foothills Medical Centre or Dr. Vernon Fanning Centre in Calgary, AB. Subjects were included if this was their only reported incident of stroke, were greater than 18 years old, and could follow the task instructions. Exclusion criteria were: previous stroke, stroke affecting both hemispheres in the brain, upper extremity orthopedic issues, neuropathy, or apraxia (using the Test for Upper Limb Apraxia (TULIA)) (Vanbellingen et al. 2010), or if cognitive/language impairments prevented subjects from understanding the task instructions. Healthy right-handed only age-matched control subjects ($n = 9$) with no history of neurological disease/injury were also recruited to perform the arm position-matching task and additional control tasks (described below). All subjects provided written informed consent prior to study participation. This research was approved by the University of Calgary Conjoint Health Research Ethics Board.

Clinical assessment

A battery of clinical assessments was performed to identify various impairments resulting from stroke. Proprioception was assessed using the Thumb Localizing Test (TLT) (Hirayama et al. 1999). The examiner moved subject's stroke-affected limb to a random position above eye level with the subject blindfolded. Subjects were instructed to use the opposite arm to grasp the thumb of the stroke-affected limb. The TLT is graded on a four-point scale from zero (no impairment) to three (unable to locate thumb). Upper limb motor impairment was assessed using the Chedoke-McMaster Stroke Assessment (CMSA) for the Upper Extremities (Gowland et al. 1993). Subjects perform a number of movements, which are scored by a trained observer. Scores on the CMSA range from one (flaccid paralysis) to seven (normal motor function). Visuospatial neglect was assessed using the conventional subtests of the Behavioral Inattention Test (BIT). The BIT is scored out of 146, with visuospatial neglect defined as a score less than 130 (Halligan et al. 1991). Overall disability was assessed with the Functional Independence Measure (FIM) (Keith et al. 1987), with a total score of 126 indicating complete independence with activities of daily living and lower scores indicating greater dependence. Lastly, handedness in all subjects was assessed with the Modified Edinburgh Handedness Inventory (Oldfield 1971). This questionnaire asked individuals their preference for hand use (prior to the stroke) in a variety of daily activities (e.g. using scissors, throwing, writing). Scores range from −100 (strong left hand dominance) to 100 (strong right hand dominance), with zero indicating no preference for using the left or right hand. These assessments were performed on the same or consecutive days as the robotic assessment.

Imaging parameters

All subjects were scanned on a 3 T MRI scanner (Discovery MR750, GE Healthcare, Waukesha, WI) with a 12-channel head coil. High-resolution anatomical images were acquired using a 3D fast spoiled gradient recalled echo brain volume imaging sequence (TR: 6.656 ms, TE: 2.928 ms, matrix: 256 × 256, FA: 10°, 1x1x1mm voxel size) along with a 3D T2-weighted fluid-attenuated inversion-recovery (FLAIR) sequence for stroke subjects (TR: 4200 ms, TE: 75 ms, matrix: 256 × 150, FA: 90°, 1x1x1.5 mm voxel size). For each of the task-based fMRI sequences, five minutes (150 volumes) of T2*-weighted gradient echo, echo planar images were acquired (36 slices, TR: 2000 ms, TE: 30 ms, matrix: 64 × 64, FA: 70°, 3.75 × 3.75x4mm voxel size, interslice gap: 0 mm). The choice to acquire 150 volumes was based on a balance between statistical power and subject fatigue (which is often a major functional limitation following stroke). A high-order shim was used to minimize magnetic field inhomogeneity. After six dummy scans to reach steady state, 150 volumes were collected.

Position-matching fMRI device and task

The purpose of the position matching task was for subjects to mirror match the position of a passively moved arm with the opposite arm, using only proprioceptive information. In subjects with stroke, the passive arm was always the stroke-affected arm and the active arm was always the opposite arm. In healthy control subjects, both arms were tested. A custom made apparatus was designed and fabricated from acrylic for use in this study, based on the dimensions of the GE scanner used (Fig. 1). The device was positioned over each subject's torso, with both arms secured to arm trays using two Velcro straps (2.5 cm wide) per arm. Velcro straps were secured at the wrist and forearm. The device allowed elbow flexion/extension movements, from full elbow extension to 35° of flexion (range = 35°) with minimal resistance. Once subjects positioned their arm in a new position, the small amount of resistance between the arm tray and the base enabled the arm to remain in the new position with minimal effort by the subject. The stroke affected arm was moved and held in position by the experimenter for the duration of the task. The device was fitted to each subject by having the fulcrum of each arm tray aligned with the medial epicondyles of the subjects' elbows. Once fitted to the subject, the base of the device was secured in place to the scanner bed using nylon pegs to prevent any superior or inferior movement (relative to

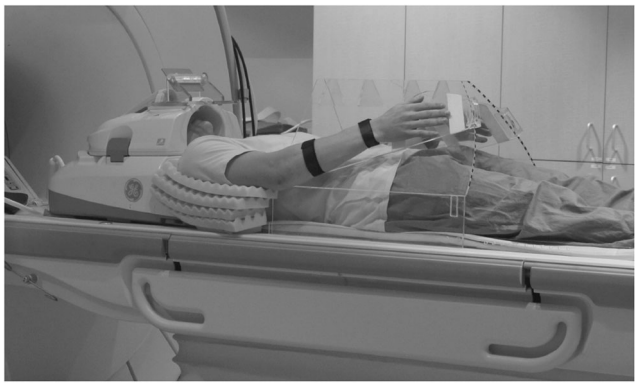

Fig. 1 Device used for the position-matching task in the MRI scanner. Subjects' arms were strapped to arm trays using two Velcro straps. The device allowed elbow flexion and extension movements from full elbow extension to 35 degrees of flexion. The fulcrum of the arm trays were aligned with the medial epicondyle of each elbow. A mirror mounted on the head coil was adjusted to allow viewing of a projection screen at the back of the MRI scanner. Dashed markings on the edge of the device near the fingertips indicated the angle of the arm trays.

the subject) of the device during scanning. Foam padding was placed under the upper arms of each individual to align the shoulders, elbows, and index fingers in a straight line with the arm trays at full elbow extension. Angle markings at the edge of the device near the fingertips allowed for measurement of elbow angles by aligning the arm trays to the appropriate mark on the device. Angles were indicated for every one-degree of elbow flexion. Each run was recorded via a video camera (Sony Handycam NEX-VG10) set-up in the scanner control room. Recordings were analyzed after completion of each scanning session to quantify position-matching performance. Arm positions were recorded once the arm was in the final position at the end of each movement. Positional accuracy (i.e. the difference in arm angles between the two arms) was measured to the nearest degree for each trial and averaged across all 20 trials.

During the position-matching task, subjects fixed their gaze on a cross in the center of a circle, presented via a mirror and projector. The inside of this circle changed color from an initial grey (duration = 7–9 s), to yellow (duration = 3.5–5.5 s), then to blue (duration = 2 s). Visual cues were coded and presented using Presentation® software (Version 18.0, Neurobehavioral Systems, Inc., Berkeley, CA, www.neurobs.com). The first yellow visual cue always appeared seven seconds after the start of image acquisition. During the yellow cue, the experimenter moved the subject's passive arm by ±10° of elbow flexion, in a pseudorandom order over a period of one second. Subjects were instructed to match the final position of the passive arm with their active arm, as soon as they saw the circle change from yellow to blue. After two seconds, the blue circle changed back to grey, signalling for subjects to maintain their arm position on the device until the next trial. Subjects always had 2 s to perform the active arm movements. A total of 20 trials were performed for each run, with yellow and grey cue durations randomly jittered across trials (yellow cue: 3.5–5.5 s, blue cue: 2 s, grey cue: 7–9 s). The cue durations were jittered in order to sample at different points on the hemodynamic response curve, given our scanner parameters (TR = 2 s). Subjects practiced the task outside of the scanner immediately prior to scanning, to ensure they understood the task instructions. Immediately prior to the functional scan, subjects were reminded of the task instructions.

Control position-matching tasks

Three additional tasks were performed by a sub-set of healthy control participants ($n = 8$), using the same visual cues, timings, and scanner parameters as in the position-matching task (see section 1.2.3. for imaging parameters and section 1.2.7 for statistical analyses). Subjects with stroke did not perform these control tasks. Control subjects performed the arm position-matching task as described above in addition to these control tasks. One control subject only completed the position-matching task and did not complete these control experiments due to subject time constraints. In between each run, subjects were reminded of the task instructions for the subsequent scan.

Control task 1: Visual stimuli

The first task simply involved presentation of the visual cues. Subjects were instructed to lie still and focus their gaze on the central cross while the circle changed colors. The purpose of this task was to identify brain activity related to the visual cues only, to determine if the visual cues had a significant impact on BOLD activations during the position-matching task. A single run of 150 volumes was collected for each subject for this task.

Control task 2: Single arm movement

The second control task involved movement of a single arm by the subject, without matching to a contralateral arm position. Subjects were instructed to lie still when they saw the yellow cue then move only their active arm to a different position when they saw the blue visual cue. Subjects were instructed to move as little or as much as they liked, with no right or wrong position. Subjects moved only one arm per run and the arm that was not moved remained at full elbow extension for the duration of the run. The purpose of this task was to identify brain activity in relation to arm movements without a specific proprioceptive-matching component. Both right and left arms were tested on separate runs, using 20 trials per run (i.e. 20 trials per arm).

Control task 3: Position-matching motor imagery

The final control task was a motor imagery paradigm. The purpose of this task was to identify brain activity related to subjects imagining performing proprioceptive matching, as previous literature has demonstrated similar patterns of brain activity during both motor imagery and motor execution (Hétu et al. 2013). During the yellow cue, the experimenter moved the subjects' passive arm by ±10° of elbow flexion pseudorandomly. Subjects were instructed to imagine moving the active arm to the mirrored location on the device, as soon as they saw the blue cue, without actually moving their arm. The 'motor imagery' arm was maintained at full elbow extension for the duration of the task. Right and left arms were tested on separate runs, with 20 trials per run (i.e. one run per arm).

Image preprocessing

Anatomical and functional images were processed using FEAT (FMRI Expert Analysis Tool) version 6.0, as part of FSL (FMRIB's Software Library, www.fmrib.ox.ac.uk/fsl). T1-weighted anatomical images and T2*-weighted functional images were first skull stripped using the brain extraction tool (BET) in FSL. Since 12 subjects had a right hemisphere stroke, the images for subjects with a left hemisphere stroke ($n = 4$) were flipped about the midsagittal axis prior to spatial normalization, to allow for group-level analyses. The middle volume of subjects' functional images was registered to each subject's corresponding high resolution structural image using FLIRT (FMRIB's Linear Image Registration Tool) (Jenkinson et al. 2002; Jenkinson and Smith 2001) and then normalized to the MNI template brain using FSL's boundary based registration (Greve and Fischl 2009). The following processing steps were then performed on the functional images: motion correction using MCFLIRT (Jenkinson et al. 2002), slice timing correction for interleaved slice acquisition using Fourier-space time-series phase-shifting, spatial smoothing (6 mm FWHM), high-pass temporal filtering (Gaussian-weighted least-squares straight line fitting, with sigma = 45 s), and grand-mean intensity normalisation. Then, each subject's functional images were analyzed with a Probabilistic Independent Component Analysis (Beckmann and Smith 2004) using MELODIC (Multivariate Exploratory Linear Decomposition into Independent Components) version 3.14, as part of FSL, to identify noise components. Noise components from each subject's scan were identified through visual inspection of the thresholded component spatial maps, as per the procedure outlined in Kelly et al. (2010). These components were removed from each functional run using the fsl_regfilt function. These 'denoised' functional images were then used in subsequent statistical analyses to identify BOLD activations associated with each task stimulus.

Lesion markings were drawn on the FLAIR images for each subject using MRIcron software (Rorden et al. 2007) (http://www.mccauslandcenter.sc.edu/mricro/mricron/) by trained researchers (JK and SF) and reviewed by a study physician with experience in reviewing stroke neuroimaging (SD). Clinical diagnostic images for each subject were performed according to the acute stroke protocol at the Foothills Medical Centre. Diagnostic images included a non-contrast computed tomography scan and/or FLAIR and diffusion weighted images (DWI). FLAIR images were marked based on the areas of hyperintensity seen on DWI (indicating the boundary of the lesion). FLAIR images and lesion markings were normalized to the Montreal Neurological Institute template brain using FLIRT and a FLAIR specific template available at (http://glahngroup.org) (Winkler et al. 2012). In subjects where a FLAIR image was not collected at the time of fMRI ($n = 2$), the clinical diagnostic FLAIR was used.

fMRI data analysis

The fMRI time-series data were statistically analyzed in FSL using FILM (FMRIB's Improved Linear Model) with local autocorrelation correction (Woolrich et al. 2001). Our regressors of interest included the stimuli occurring during yellow and blue visual cues (e.g. passive and active arm movements). These were modeled separately, each convolved with a double-gamma hemodynamic response function with one-second stimulus duration. Stimulus onset was aligned with the presentation of the visual cues (e.g. yellow cue onset = passive arm stimuli and blue cue onset = active arm stimuli), which were consistent across all subjects and all tasks. We did not include motion parameters as nuisance regressors in our analysis as we choose to use Independent Component Analysis (ICA) denoising to remove noise components due to motion, cardiac, respiratory, and CSF signal. No additional nuisance regressors were included in the single-subject analyses. The outputs (i.e. parameter estimates) from these analyses were then used for higher-level group analyses.

FMRIB's Local Analysis of Mixed Effects (FLAME) stage one (Beckmann et al. 2003; Woolrich 2008; Woolrich et al. 2004) was used for group analyses. Performance on the arm position-matching task was demeaned across subjects and included as an additional covariate (the degree of error was used as an additional covariate for both the passive movement and active matching stimuli). Performance was quantified as the average degrees of error between the passive and active limbs across all trials. The first-level main effects of the control tasks were contrasted by paired t-tests to account for within subject mean effects. Seven subjects with stroke performed within the control range of performance (i.e. equal or less mean error than the worst control) on the arm position-matching task during scanning. Since stroke subjects had clinically suspected proprioceptive deficits at the time of recruitment,

there was likely some proprioceptive recovery between recruitment and scanning. Thus, we further separated our subjects into controls, stroke subjects with impairment (those who demonstrated more mean error than the control range), and stroke subjects without impairment (those with equal or less mean error than the control range) and compared the mean difference in activation across these groups using F-tests. The areas of significant activation from the F-tests were then used as a mask for post-hoc comparisons of activation between groups (unpaired t-tests). Prior to correction for multiple comparisons, all t and F statistics were converted to z-scores for the purposes of cluster correction. Our activation maps are based on these z-scores. Statistical images were corrected for multiple comparisons using an initial cluster forming threshold of $z > 2.3$ followed by Gaussian random field theory to determine each cluster's estimated significance level. The estimated significance level for each cluster was then compared to a cluster probability threshold of $p = 0.01$ (Worsley 2001). Confirmatory scatter plots were created for significant clusters where applicable. For clusters of significance, the mean contrast of parameter estimate (COPE) values (i.e. brain activations) for each subject were extracted using the 'tsplotc' output from our group analyses. These data were then plotted against mean position matching error for each subject to indicate the relationship between brain activation and proprioceptive error across our sample for those clusters.

Results

Demographic and clinical information for stroke subjects is presented in Table 1. The average age of control subjects was 59 ± 11 years (female: 6, male: 3; right-handed: 9). The average age of stroke subjects was 64 ± 10 years. Each subject's lesion location is presented in Fig. 2. In all subjects, absolute head displacement during the position-matching task was less than 1.2 mm. Thus, no data had to be discarded due to excessive head motion. One subject demonstrated left-sided visuospatial neglect (subject #6. BIT score = 100). For the ICA denoising, an average of 48 components were extracted from each subject (control = 42, stroke = 54) with 19 components

Table 1 Individual subject demographic, lesion, and clinical assessment information for subjects with stroke and controls. Proprioceptive matching errors are presented as mean ± standard deviation

Subject	Age	Sex	Hand	Timeline 1/2/3	Lesion Volume (cm^3)	Stroke Type/Hem	Proprioceptive Errors (°)	BIT	TLT	CMSA (C/I)	FIM	MAS
Stroke												
1	69	F	R	6/8/2	1.7	I/L	3.4 ± 2.0	145	2	7/7	117	0
2	84	M	R	3/25/21	1.45	I/L	3.1 ± 2.6	143	0	7/7	121	0
3	75	M	R	9/36/27	0.2	I/R	2.4 ± 2.3	145	0	7/7	124	0
4	60	F	R	31/38/7	11.5	H/R	9.3 ± 7.0**	132	2	3/7	73	0
5	36	F	M	12/15/3	28.3	I/R	12.5 ± 3.5**	141	0	7/7	118	0
6	64	M	R	17/25/8	69.3	I/R	12.1 ± 6.0**	100	1	6/6	115	0
7	69	M	R	21/27/6	3.6	I/R	3.9 ± 3.2	143	0	2/7	84	2
8	58	M	R	22/30/9	74.7	H/R	5.1 ± 3.4	141	0	5/7	114	0
9	62	M	R	21/29/8	3.8	I/L	1.0 ± 1.0	144	0	5/7	105	0
10	52	F	R	30/29/1	38.5	H/R	11.9 ± 7.9**	140	1	1/7	77	1+
11	67	M	R	29/26/3	8.3	H/R	4.1 ± 2.9	142	3	5/6	75	1
12	62	M	R	7/11/4	34.4	I/R	9.8 ± 5.6**	135	1	5/6	106	0
13	72	M	R	19/21/2	1.6	I/R	11.6 ± 5.4**	143	2	4/7	96	0
14	61	F	R	21/25/4	54.8	H/R	10.0 ± 5.8**	143	3	4/7	80	0
15	71	F	R	61/24/37	2.9	I/R	6.4 ± 3.6**	142	0	7/7	124	0
16	62	M	R	5/4/1	2.0	I/L	9.4 ± 5.4**	143	2	6/6	121	0
Control												
1	33	F	R	–	–	–	2.6 ± 1.6	–	–	–	–	–
2	64	F	R	–	–	–	2.4 ± 1.8	–	–	–	–	–
3	51	F	R	–	–	–	2.8 ± 1.8	–	–	–	–	–
4	67	M	R	–	–	–	4.1 ± 1.9	–	–	–	–	–
5	67	M	R	–	–	–	4.3 ± 2.1	–	–	–	–	–
6	59	F	R	–	–	–	4.1 ± 2.6	–	–	–	–	–
7	60	M	R	–	–	–	2.5 ± 2.1	–	–	–	–	–
8	66	F	R	–	–	–	3.5 ± 2.1	–	–	–	–	–
9	64	F	R	–	–	–	5.1 ± 3.4	–	–	–	–	–

Proprioceptive errors for controls subjects is an average between the two trials testing the right and left arms

R Right; *M* Mixed handedness, *I* Ischemic; *H* Hemorrhagic; *Hem* Hemisphere; *BIT* Behavioral Inattention Test; *TLT* Thumb Localizing Test; *CMSA* Chedoke McMaster Stroke Assessment Impairment Inventory for the upper extremity (values presented are for the Contralesional and Ipsilesional limbs); *FIM* Functional Independence Measure; *MAS* Modified Ashworth Scale; *Timeline 1* Days between stroke and clinical assessment; *2* days between stroke and MRI; *3* days between clinical assessment and MRI

**Indicates subject with proprioceptive impairment. I.e. performed worse than all control subjects

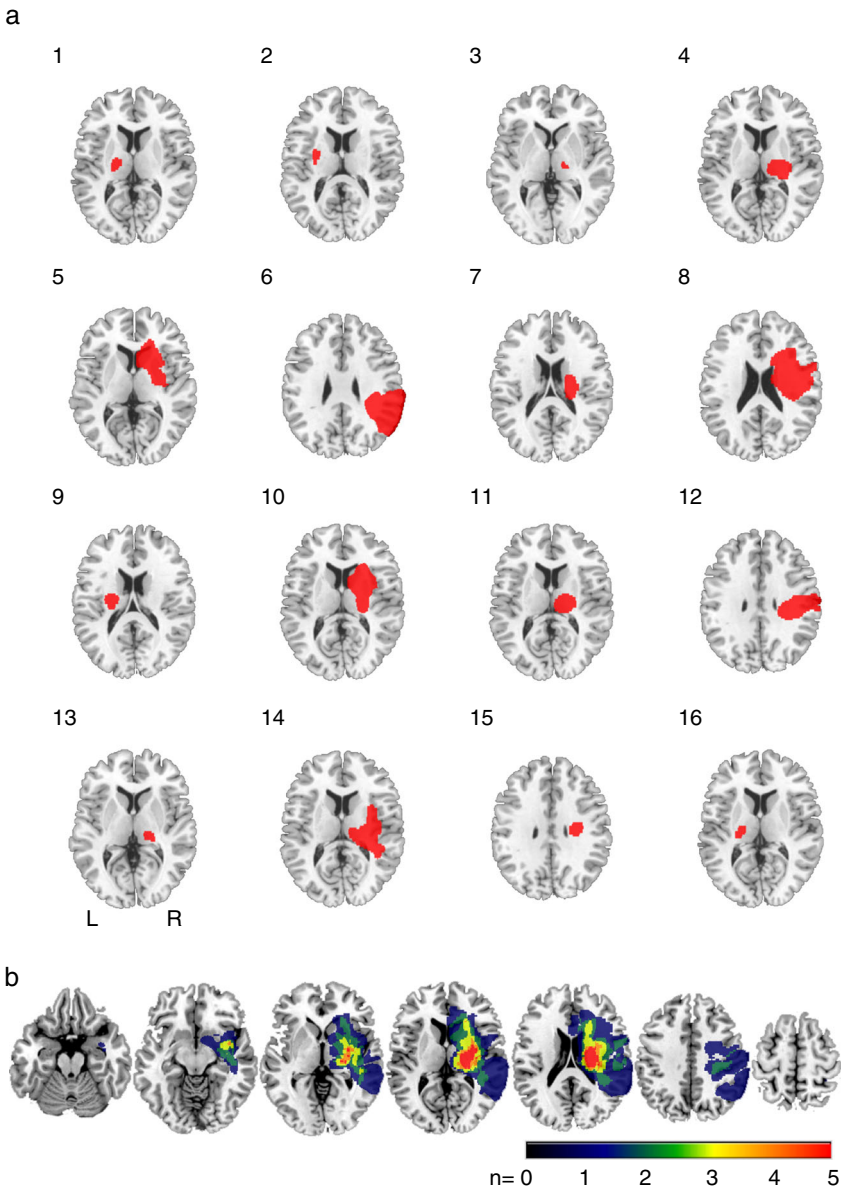

Fig. 2 Lesion distribution in subjects with stroke. **a** Individual lesion locations (red) are presented on the Montreal Neurological Institute template brain at the largest axial cross-section of the lesion. Subject # indicated at top left of each slice. Slices are displayed in anatomical coordinates, with the left side of the image representing the left side of the brain **b**. Overlap of all lesions after flipping of left hemisphere lesions about the midsagittal axis. Color bar indicates number of overlapping lesions

identified as noise on average and removed from the data (control = 13, stroke = 25).

Position matching task performance

No subjects reported discomfort or an inability to tolerate the position-matching device, and all were able to complete the task. All subjects reported that they could not see the device or their arms during scanning. Neurologically intact control subjects demonstrated mean errors of 4.0° ± standard deviation = 1.2° when matching the left arm to the passively moved right arm position and mean errors of 3.3° ± 1.0° when matching the right arm to the passively moved left arm position. This difference was not statistically significant (paired t-test. $t(9) = 1.6$, $p = 0.14$). Subjects with stroke were worse at matching arm position compared to controls ($t(23) = 2.99$, $p = 0.007$) with a mean error of 7.3° ± 4.0°.

Position-matching fMRI task

Control subject data are presented in Fig. 3 and represents the mean activation for control subjects during the position-matching task. Passive arm movements were associated with widespread activation in bilateral sensorimotor areas including: contralateral SI, MI, and premotor cortices, and bilateral SMA, superior parietal cortex, putamen, thalamus, and ipsilateral cerebellum (Fig. 3. A (passive left arm movement), B (passive right arm movement)). Decreased BOLD signal was also observed in the cerebellum during passive movement, primarily in the

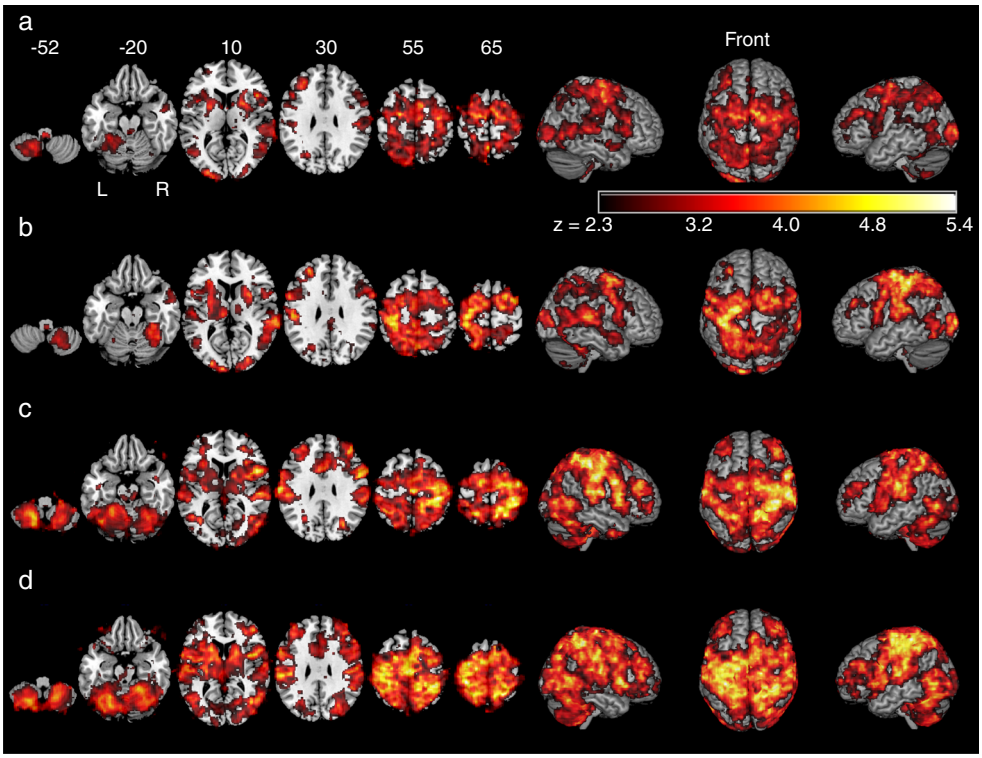

Fig. 3 Images of mean brain activity for control subjects ($n = 9$) during the position-matching task (event related design). Each of the following stimuli were modeled independently using a general linear model, with each movement/trial (20 per run) representing a single event. **a** Passive left arm movement. **b** Passive right arm movement. **c** Active left arm matching **d**. Active right arm matching. Statistical images were thresholded using an initial cluster forming threshold of $z > 3.1$ and a (corrected) cluster significance threshold of $p = 0.01$. MNI z-coordinates are presented above each axial slice. Surface rendered whole brain images are presented in the right three columns.

contralateral superior posterior lobe. Active arm matching resulted in widespread activation across bilateral sensory and motor areas (Fig. 3. C (active left arm matching), D (active right arm matching)), predominantly in the contralateral hemisphere. Performance on the position-matching task in control subjects (the difference between passive and active arm positions for each trial) was then analyzed. Only during passive right arm movement were greater matching errors associated with decreased activation in a small number of voxels in bilateral occipital cortices (not shown). In all other conditions there were no associations between proprioceptive errors and BOLD activations for controls.

In subjects with stroke, no significant differences were found in BOLD activation between left and right hemisphere stroke subjects for passive or active movements after comparison with two group unpaired t-test (cluster forming threshold $z > 2.3$, corrected cluster significance threshold $p = 0.01$). Thus, we felt confident in reflecting the images of those with left hemisphere lesions to the right hemisphere for group comparisons. Similar to controls, in subjects with stroke the passive arm movements activated bilateral sensorimotor areas, with peak activations in: contralateral SI and MI as well as bilateral SMA, superior parietal cortices, and ipsilateral cerebellum (Fig. 4a). Active arm matching was associated with bilateral brain activation, notably in contralateral SI, MI, SMG, bilateral thalamus, and ipsilateral cerebellum (Fig. 4b). Interestingly, the degree of error on the position-matching task was negatively associated with BOLD activations in two distinct areas (Fig. 5a, b). During the passive arm movement portion of the task, greater matching errors were associated with less BOLD activation in the contralateral SMG and superior temporal gyri (Fig. 5a, c, blue areas). During the active position-matching portion of the task, greater matching errors were associated with less activation in the ipsilateral dorsal premotor cortex and bilateral supplementary motor areas (Fig. 5b, d). Scatter plots depict the average individual subject brain activation versus position matching error for each of these two clusters.

Control fMRI tasks

Control task 1: Visual stimuli

Presentation of both yellow and blue visual stimuli resulted in increased activation only in primary visual cortices bilaterally (Supplementary Fig. 1. A). There were no differences in activation patterns elicited by these two visual stimuli.

Control task 2: Single arm movement

The second control task required subjects to move one limb to any new position on the device, without matching any reference position (Supplementary Fig. 1. B & C). When modeled independently, left and right arm movements resulted in widespread activation in bilateral sensorimotor networks including frontal and parietal cortices, thalamus and the cerebellum.

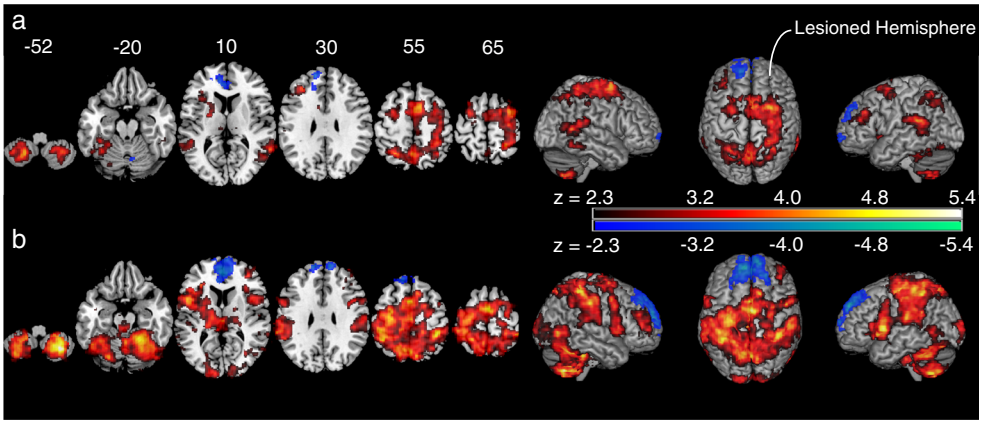

Fig. 4 Images of mean brain activity for subjects with stroke ($n = 16$) while performing the position-matching task (event related design). Each of the following stimuli were modeled independently using a general linear model, with each movement/trial (20 per run) representing a single event. **a** Passive arm movement. **b** Active arm matching. Statistical images were thresholded using an initial cluster forming threshold of $z > 2.3$ and a (corrected) cluster significance threshold of $p = 0.01$. Negative associations with the task stimulus are presented in blue. MNI coordinates are presented above each axial slice. Surface rendered whole brain images are presented in the right three columns.

Contrasting active position-matching from the first experiment with this active arm movement revealed several clusters of increased activation in frontal, parietal, and cerebellar areas (Supplementary Fig. 2. A & B).

Control task 3: Position-matching motor imagery

The third control task required control subjects to imagine moving one arm to match the position of the opposite,

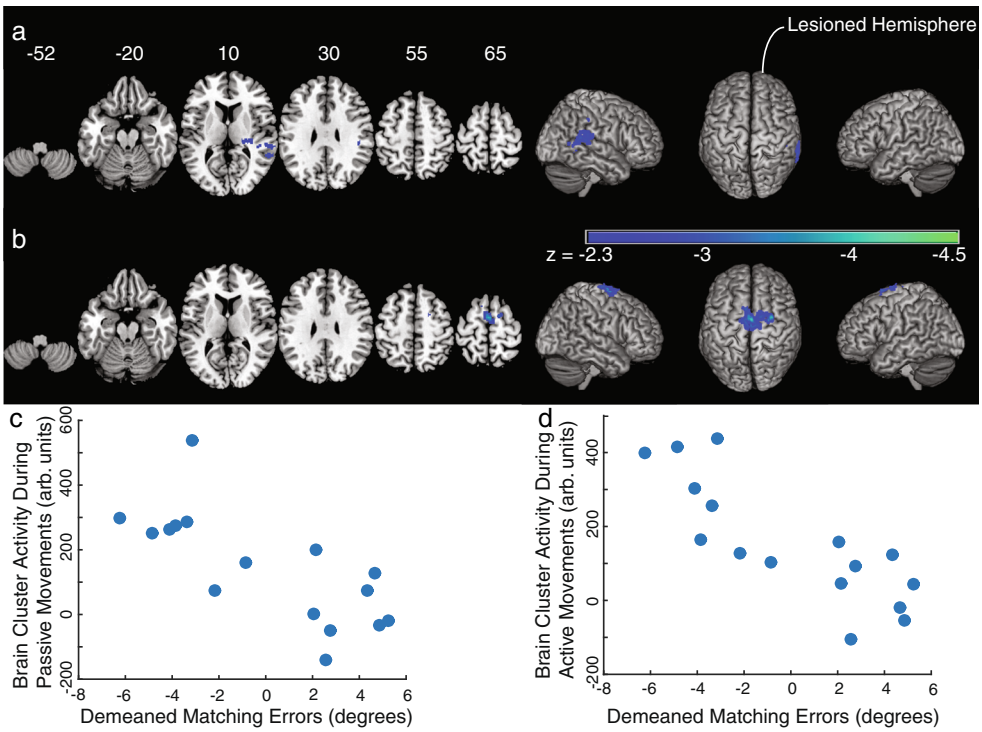

Fig. 5 Images of brain activity for subjects with stroke (n = 16), with position-matching error modeled as the regressor of interest during (**a**) passive arm movement and (**b**) active arm matching. Statistical images were thresholded using an initial cluster forming threshold of $z > 2.3$ and a (corrected) cluster significance threshold of $p = 0.01$ A/B. In all cases, activity magnitude decreased with increasing error. MNI coordinates are presented above each axial slice. Surface rendered whole brain images are presented in the right three columns. (**c**) Scatter plot of average brain activation from cluster a (Passive movement) and magnitude of error on the proprioceptive matching task for each subject. (**d**) Scatter plot of average brain activation from cluster b (Active matching) and magnitude of error on the proprioceptive matching task for each subject. Individual subject raw data were extracted from 'tsplotc' output files from group level analyses and represent the individual mean contrast of parameter estimates for the given cluster of voxels.

passively moved arm. Imagined movements of left and right arms resulted in similar frontal, parietal and cerebellar activations when compared to actual arm movements (Supplementary Fig. 1. D & E). Contrasting active position-matching from the first experiment with activity during motor imagery revealed several clusters of increased activation in primary somatosensory and motor cortices, as well as clusters in parietal opercular areas (Supplementary Fig. 2. C & D).

Three group difference

Some subjects with stroke fell within the range of control performance (i.e. equal or less mean error than the worst control) on the position-matching task ($n = 7$, Table 1). Thus, we separated our subjects into three groups: control subjects ($n = 9$), stroke subjects without proprioceptive impairment (n = 7), and stroke subjects with proprioceptive impairment (n = 9) for group comparison. First, we used F-tests to identify differences in activation between these three groups during passive and active arm stimuli (Fig. 6a, c). Both passive and active arm movements showed differences in activation in frontal and parietal areas bilaterally, and subcortical structures (e.g. basal ganglia and cerebellum). Unpaired t-tests comparing control subjects to stroke subjects without impairment demonstrated none (passive arm movement) or few (active arm matching, Fig. 6d) differences in activation. Comparisons between control subjects and stroke subjects with impairment (Fig. 6b, e) demonstrated larger differences in activation in bilateral frontal, parietal, and subcortical structures. No differences in activation were identified between the two stroke groups. Further, stroke subjects (impaired and unimpaired) had no areas of greater activation relative to control subjects during passive or active arm movements.

Discussion

This study has utilized a novel device for testing arm proprioception during fMRI. Similar to previous research in healthy controls (Ben-Shabat et al. 2015), passive arm movements elicited brain activity in contralateral SI, MI, and bilateral SMA, premotor cortex, SII, and putamen, while active arm movements elicited relatively greater activity in contralateral SI, MI, SMA, and ipsilateral cerebellum. However, during passive arm movement in stroke subjects, greater matching error was associated with less activity in contralateral SMG,

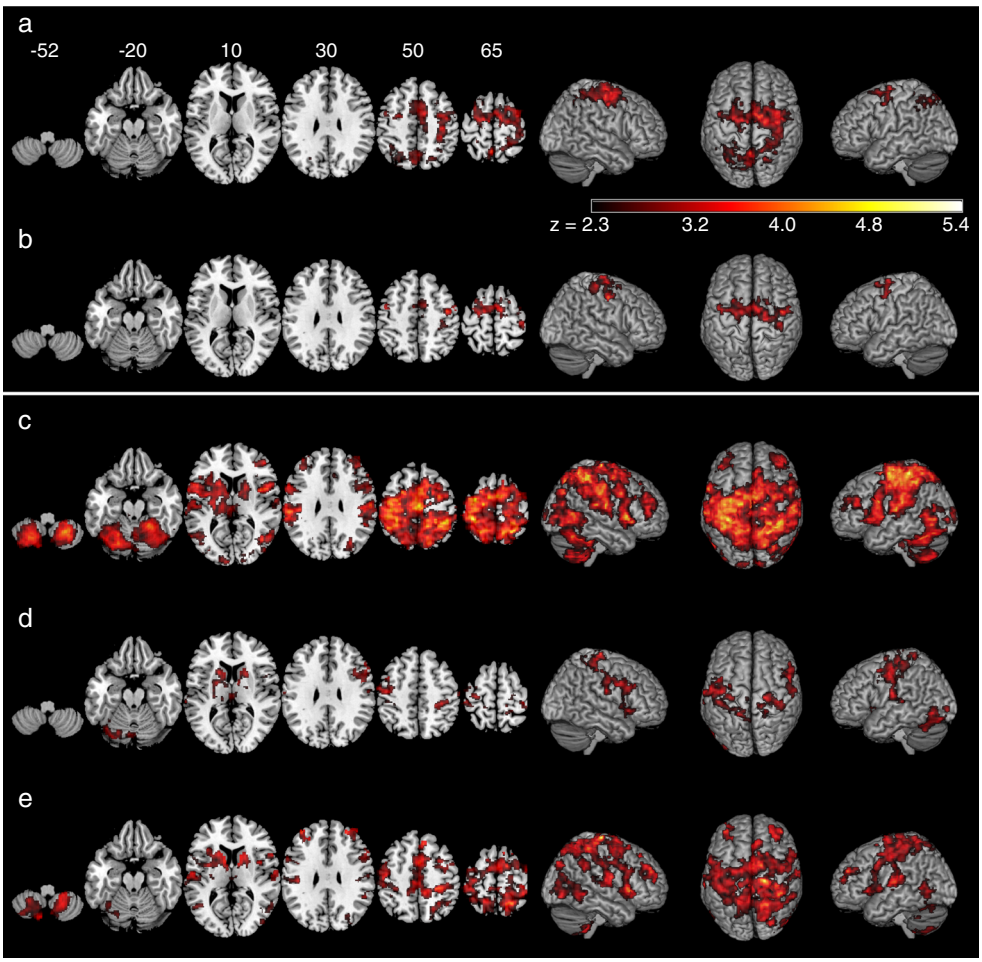

Fig. 6 Images of the difference in brain activity between three groups (control, stroke without proprioceptive impairment, and stroke with proprioceptive impairment). **a** F-test between the three groups during passive arm movement. **b** Control > stroke with impairment during passive arm movement. **c** F-test between the three groups during active arm matching stimuli. **d** Control > stroke without impairment during active arm matching. **e** Control > stroke with impairment during active arm matching. Post-hoc comparisons were masked by the corresponding interaction map (significant areas on F-test). All statistical images were thresholded using an initial cluster forming threshold of z > 2.3 and a (corrected) cluster significance threshold of p = 0.01. X > Y indicates areas where X had significantly greater BOLD activation than Y. MNI coordinates are presented above each axial slice. Surface rendered whole brain images are presented in the right three columns

superior temporal gyrus, and lateral thalamus. Additionally, during active arm matching in stroke subjects, greater matching error was associated with less activity in bilateral SMA and ipsilateral premotor cortex. These results support our hypothesis that the SMG, superior temporal gyrus, supplementary motor and premotor cortices are critical regions involved in processing proprioceptive information from the upper limbs. Furthermore, the SMG, superior temporal gyrus, and lateral thalamus are likely involved in the perception of limb position, while the SMA and premotor cortices are more likely involved in using this proprioceptive information to guide subsequent movement of the opposite limb.

Previous functional imaging studies in healthy individuals using passive upper limb movement perceptions have shown contralateral activity in SI, MI, SMA (Bernard et al. 2002; Mima et al. 1999; Weiller et al. 1996), bilateral activations in SII, insula, parietal cortices, and putamen (Yang et al. 2009). These areas, as well as ipsilateral cerebellum (Kavounoudias et al. 2008), are similarly activated by vibration-induced illusions of movement (Naito et al. 2016; Naito et al. 1999; Radovanovic et al. 2001). Our task in healthy controls also activated these sensorimotor areas contralaterally (SI, MI) and bilaterally (SMA, premotor, SII, parietal cortices, putamen, cerebellum) (Fig. 3). Across all subjects with stroke, we observed largely similar patterns of activation during passive and active arm movements (Fig. 4a, b), yet these subjects demonstrated impaired proprioception during the fMRI task (Table 1). These results were likely driven, in part, by the fact that only some of the subjects had proprioceptive impairments at the time of testing (Fig. 6).

Since our sample of subjects with stroke had varying degrees of proprioceptive impairment (Table 1, Fig. 2) we were able to determine that the activity in SMG/superior temporal gyrus (contralateral to the moving arm) as well as bilateral SMA/ipsilateral premotor cortex was negatively associated with the degree of impairment (Fig. 5a, b). In our subjects with stroke, it is interesting that traditional somatosensory areas (e.g. SI, SII, posterior parietal cortex) were not associated with the degree of proprioceptive impairment, given the known involvement of these areas in somatosensory processing. Further, we did not observe an association between proprioceptive impairment and brain activity in the insula, which has recently been implicated in lesion analysis studies of somatosensory and proprioceptive impairments (Findlater et al. 2016; Kenzie et al. 2016; Meyer et al. 2016). Based on these results, increased activity in these traditional somatosensory areas during passive limb movement does not necessarily indicate that the individual is correctly interpreting the somatosensory information. Rather, the recruitment of higher-order brain areas (e.g. superior and inferior parietal cortex) appears to play a larger role than S1 with regard to performance on our proprioceptive matching task. This is not totally surprising given the complexity of our task in terms of brain processing (i.e. interpretation of the sensory stimuli, holding that information in working memory, transferring that information to the opposite hemisphere, coordinating a motor action and comparing that action with the proprioceptive information of the opposite limb). The only objective measure we have of an individual's performance on this task is the degree of error in matching limb position. Therefore, if a subject performed poorly on this task we are unable to determine where in this processing pathway the disruption occurred. Furthermore, brain activation with a single joint proprioceptive matching task may look different than the bimanual task we choose to use. In the present study, we did not perform a single limb proprioceptive matching task in stroke subjects given the confounding motor deficits.

Passive movement of the stroke-affected arm would presume to encode the positional information that subjects use to guide movement of the opposite limb (Ben-Shabat et al. 2015). Since there was a slight delay (3.5–5.5 s) between passive and active movements in our task, we were able to separate the brain activity associated with the passive and active components of our task by modelling the hemodynamic response to these two stimuli separately. During passive arm movement, increased activity in the ipsilesional SMG, superior temporal gyrus, and thalamus was associated with less error in position matching. This suggests these areas are important for the processing of positional information from the arm to guide a subsequent movement. In contrast, using this positional information to accurately match positions with the opposite limb (active matching) involved bilateral supplementary motor and ipsilesional premotor cortices. These areas play multiple roles in motor planning and voluntary behavior (Nachev et al. 2008), but also play a sensory role (Lim et al. 1994). This suggests a crucial role for these areas in guiding arm movements to proprioceptively defined locations.

In the study by Ben-Shabat et al., each subjects' wrist was passively moved to a certain position, and subjects were asked to actively match this position with the opposite wrist. Only the passive movements (i.e., 'encoding of position') were analyzed, and it was found that the right SMG and premotor cortices were significantly involved with both right and left wrist position sense. The SMG showed decreased activity during this task in three subjects with chronic stroke and persistent proprioceptive impairments, strengthening the importance of the SMG in proprioceptive impairments post-stroke.

Several control tasks were also performed in healthy control subjects (Supplementary Figs. 1 & 2) to ensure that the brain activity we observed was primarily due to proprioceptive processing and not confounding elements of the stimuli or tasks such as visual cues or motor imagery. When the brain activity during each of our control tasks (vision only, motor only, and motor imagery) were compared to the brain activity during our proprioceptive matching task (Supplementary Fig. 2), there were no areas exhibiting greater activity during the control tasks.

This suggests that our proprioceptive task may involve some element of motor imagery, and that motor imagery and motor execution recruit very similar brain networks. However, we did not perform this task with stroke subjects and therefore cannot conclude that this association is the same following stroke, especially with the potential neural reorganization that may occur following stroke. Additionally, we compared brain activity during active proprioceptive matching and single arm movements of the same arm (Control task #2. Supplementary Fig. 2. A & B). This contrast attempted to remove the motor component of arm movement (since both stimuli required active movement of the same arm), thus isolating brain activity associated with proprioceptive matching. Increased brain activity was observed in bilateral SMA and parietal cortices, as well as pre-motor, S1, and M1 cortices contralateral to the moved arm. These brain areas appear to be essential components of a complex proprioceptive network.

We performed a follow-up analysis comparing three groups (Fig. 6. Controls, stroke subjects without proprioceptive impairment, and stroke subjects with proprioceptive impairment). Large differences in activation were observed between controls and stroke subjects with impairment (Fig. 6b, e) but relatively few differences were observed between controls and stroke subjects without proprioceptive impairment (Fig. 6d). Hence, the differences we observed between groups from F-tests (Fig. 6a, c) was largely due to the contrast between controls and stroke subjects with proprioceptive impairments. Since all of our subjects with stroke had clinically suspected proprioceptive deficits at the time of initial presentation, the stroke subjects without impairment at the time of scanning (~30 days post stroke) had likely undergone some functional recovery during this time period (Murphy and Corbett 2009). This functional recovery was associated brain activations resembling that of control subjects (indicated by the lack of difference in brain activations between these two groups). We suspect we simply did not have a sufficient sample size to identify differences in activation between impaired and unimpaired stroke subjects. However, the differences in brain activation we did observe between these three groups (simply based on proprioceptive performance), supports the use of this task to probe proprioceptive networks in the human brain.

Recent work in our lab has concluded that lesions to frontal, parietal and superior temporal areas are associated with proprioceptive impairments following stroke (Findlater et al. 2016; Kenzie et al. 2016). Some locations of brain activity associated with proprioceptive impairments in the current study (i.e., SMG and superior temporal gyrus) were damaged in only two of our 16 subjects (Fig. 2), and the SMA/premotor cortices were not damaged in any subjects. Thus, it is unlikely that lesions in these locations solely explain our findings. Most subjects had subcortical strokes affecting the thalamus, internal capsule, and/or basal ganglia (Fig. 2). Therefore, impaired proprioception likely resulted from disconnection between afferent signals and brain areas important for proprioceptive processing (i.e., diaschisis). Lesions may have also disrupted the connections between cortical areas important for the integration of proprioceptive information.

Another recent lesion analysis study demonstrated that impaired somatosensory function is associated with lesions to the insula, SII/parietal operculum, superior thalamic radiation, putamen, and internal capsule (Meyer et al. 2016). Some of these areas are traditionally thought of as association areas, where multiple sensory inputs (i.e., somatosensory, visual, auditory) are integrated to provide us with a representation of our body and environment. For example, in subjects with subcortical stroke and touch impairments, decreased activation during a tactile stimulus (measured by fMRI) in ipsilesional SI, SII, contralesional thalamus, and frontal, parietal, and occipital regions were associated with worse tactile discrimination abilities (Carey et al. 2011). These findings highlight the distributed network that is involved in processing somatosensory information from the upper limbs. Furthermore, passive limb movements have previously been shown to activate contralateral M1 in healthy controls, an area traditionally thought of as being involved with 'motor' processing (Bernard et al. 2002; Yang et al. 2009). Given the tight coupling of sensory and motor processing for optimal feedback control of voluntary movements (de Lafuente and Romo 2002; Naito et al. 2016; Scott 2004), it is not surprising to see 'motor' areas such as M1 and cerebellum being activated by passive movement of a limb.

The present study was limited by the small sample size (n = 16 stroke subjects), limited runs of the task paradigm (one run of 20 trials per subject with stroke), and relatively few control subjects (n = 9). However, our control subjects were carefully selected to best match the age of our stroke subjects. Additionally, activation patterns across control subjects were quite consistent for each task. The number of runs was primarily limited by subject's potential mental and physical fatigue, as well as coordinating therapy schedules with MR scanner availability. Stroke subject's affected arms were also moved manually by the experimenter during the task, which limits our ability to standardize the movements experienced by each subject. However, this has the advantage of being less resource intensive/ technically challenging while being able to stop the task if the subject was to complain of pain (which no subject did). While spasticity is a concern following stroke, it usually manifests many weeks after stroke, and was not a limiting factor in our subjects performing the task (See Table 1 – Modified Ashworth Scale). Additionally, given the novelty of our device, reliability and validity of the measure was not determined. Further, four of our subjects demonstrated mild ipsilesional motor impairment (CMSA = 6/7 indicating near normal movements, with abnormalities observed in rapid or complex movements). Since our task was performed at a single joint and relatively straightforward we feel this had minimal affect on our

results, but cannot be excluded as a confounding factor. Lastly, we have limited ability to comment on activation differences that relate to recovery of function, since we only assessed subjects at one time point. Future studies on proprioceptive impairments should assess brain activity at multiple time points over the course of recovery.

Conclusion

Our findings suggest that proprioceptive impairments post-stroke may be a result of either impaired sensation of limb position (involving SMG, superior temporal gyrus, and lateral thalamus), or impaired utilization of proprioceptive information to guide subsequent movements (involving supplementary motor and premotor cortices). We have further elucidated the functional correlates of proprioception in the temporal parietal cortex as well as supplementary/premotor cortices. These results offer potential therapeutic targets for neurostimulation to enhance functional recovery for those affected by stroke.

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Compliance with ethical standards

Competing interests The authors have no competing interests to declare.

Declarations of interest None.

References

Beckmann, C. F., & Smith, S. M. (2004). Probabilistic independent component analysis for functional magnetic resonance imaging. *IEEE Transactions on Medical Imaging, 23*, 137–152.

Beckmann, C. F., Jenkinson, M., & Smith, S. M. (2003). General multilevel linear modeling for group analysis in FMRI. *Neuroimage, 20*, 1052–1063. https://doi.org/10.1016/S1053-8119(03)00435-X.

Ben-Shabat, E., Matyas, T. A., Pell, G. S., Brodtmann, A., & Carey, L. M. (2015). The right Supramarginal gyrus is important for proprioception in healthy and stroke-affected participants: A functional MRI study. *Frontiers in Neurology, 6*, 248. https://doi.org/10.3389/fneur.2015.00248.

Bernard, R. A., Goran, D. A., Sakai, S. T., Carr, T. H., McFarlane, D., Nordell, B., Cooper, T. G., & Potchen, E. J. (2002). Cortical activation during rhythmic hand movements performed under three types of control: An fMRI study. *Cognitive, Affective, & Behavioral Neuroscience, 2*, 271–281. https://doi.org/10.3758/CABN.2.3.271.

Borstad, A., Schmalbrock, P., Choi, S., & Larsen, D. S. (2012). Neural correlates supporting sensory discrimination after left hemisphere stroke. *Brain Research, 1460*, 78–87. https://doi.org/10.1016/j.brainres.2012.03.060.

Carey, L. (1995). Somatosensory loss after stroke. *Crit. Rev. Phys. Rehabil. Med., 7*, 51–91.

Carey, L. M., Oke, L. E., & Matyas, T. a. (1996). Impaired limb position sense after stroke: A quantitative test for clinical use. *Archives of Physical Medicine and Rehabilitation, 77*, 1271–1278.

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. *Neurorehabilitation and Neural Repair, 25*, 443–457. https://doi.org/10.1177/1545968310395777.

Carey, L. M., Abbott, D. F., Lamp, G., Puce, A., Seitz, R. J., & Donnan, G. A. (2016). Same intervention-different reorganization: The impact of lesion location on training-facilitated somatosensory recovery after stroke. *Neurorehabilitation and Neural Repair, 30*, 988–1000. https://doi.org/10.1177/1545968316653836.

Connell, L. a., Lincoln, N. B., & Radford, K. a. (2008). Somatosensory impairment after stroke: Frequency of different deficits and their recovery. *Clinical Rehabilitation, 22*, 758–767. https://doi.org/10.1177/0269215508090674.

Dukelow, S. P., Herter, T. M., Moore, K. D., Demers, M. J., Glasgow, J. I., Bagg, S. D., Norman, K. E., & Scott, S. H. (2010). Quantitative assessment of limb position sense following stroke. *Neurorehabilitation and Neural Repair, 24*, 178–187. https://doi.org/10.1177/1545968309345267.

Findlater, S. E., Desai, J. A., Semrau, J. A., Kenzie, J. M., Rorden, C., Herter, T. M., Scott, S. H., & Dukelow, S. P. (2016). Central perception of position sense involves a distributed neural network – Evidence from lesion-behaviour analyses. *Cortex, 79*, 42–56. https://doi.org/10.1016/j.cortex.2016.03.008.

Goodwin, G. M., McCloskey, D. I., & Matthews, P. B. (1972). Proprioceptive illusions induced by muscle vibration: Contribution by muscle spindles to perception? *Science, 175*, 1382–1384.

Gowland, C., Stratford, P., Ward, M., Moreland, J., Torresin, W., Van Hullenaar, S., Sanford, J., Barreca, S., Vanspall, B., & Plews, N. (1993). Measuring physical impairment and disability with the Chedoke-McMaster stroke assessment. *Stroke., 24*, 58–63. https://doi.org/10.1161/01.STR.24.1.58.

Greve, D. N., & Fischl, B. (2009). Accurate and robust brain image alignment using boundary-based registration. *Neuroimage, 48*, 63–72. https://doi.org/10.1016/j.neuroimage.2009.06.060.

Gutrecht, J. A., Zamani, A. A., & Pandya, D. N. (1992). Lacunar thalamic stroke with pure cerebellar and proprioceptive deficits. *Journal of Neurology, Neurosurgery, and Psychiatry, 55*, 854–856. https://doi.org/10.1136/jnnp.55.9.854.

Halligan, P. W., Cockburn, J., & Wilson, B. A. (1991). The behavioural assessment of visual neglect. *Neuropsychol. Rehabil. An Int. J., 1*, 5–32.

Hétu, S., Grégoire, M., Saimpont, A., Coll, M., Eugène, F., Michon, P.-E., & Jackson, P. L. (2013). The neural network of motor imagery : An ALE meta-analysis. *Neuroscience and Biobehavioral Reviews, 37*, 930–949.

Hirayama, K., Fukutake, T., & Kawamura, M. (1999). "Thumb localizing test" for detecting a lesion in the posterior column-medial lemniscal system. *Journal of the Neurological Sciences, 167*, 45–49.

Iandolo, R., Bellini, A., Saiote, C., Marre, I., Bommarito, G., Oesingmann, N., Fleysher, L., Mancardi, G. L., Casadio, M., & Inglese, M. (2018). Neural correlates of lower limbs proprioception: An fMRI study of foot position matching. *Hum. Brain Mapp. n/a-n/a., 39*, 1929–1944. https://doi.org/10.1002/hbm.23972.

Jenkinson, M., & Smith, S. M. (2001). A global optimization method for robust affine registration of brain images. *Med. Imaging 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. https://doi.org/10.1016/S1053-8119(02)91132-8.

Kavounoudias, A., Roll, J. P., Anton, J. L., Nazarian, B., Roth, M., & Roll, R. (2008). Proprio-tactile integration for kinesthetic perception: An fMRI study. *Neuropsychologia, 46*, 567–575. https://doi.org/10.1016/j.neuropsychologia.2007.10.002.

Keith, R. A., Granger, C. V., Hamilton, B. B., & Sherwin, F. S. (1987). The functional Independence measure: A new tool for rehabilitation. *Adv. Clin. Assess., 1*, 6–18.

Kelly, R. E., Alexopoulos, G. S., Wang, Z., Gunning, F. M., Murphy, C. F., Morimoto, S. S., Kanellopoulos, D., Jia, Z., Lim, K. O., & Hoptman, M. J. (2010). Visual inspection of independent components: Defining a procedure for artifact removal from fMRI data. *Journal of Neuroscience Methods, 189*, 233–245. https://doi.org/10.1016/j.jneumeth.2010.03.028.

Kenzie, J. M., Semrau, J. a., Findlater, S. E., Herter, T. M., Hill, M. D., Scott, S. H., & Dukelow, S. P. (2014). Anatomical correlates of proprioceptive impairments following acute stroke: A case series. *Journal of the Neurological Sciences, 342*, 52–61. https://doi.org/10.1016/j.jns.2014.04.025.

Kenzie, J. M., Semrau, J. A., Findlater, S. E., Yu, A. Y., Desai, J. A., Herter, T. M., Hill, M. D., Scott, S. H., & Dukelow, S. P. (2016). Localization of impaired kinesthetic processing post-stroke. *Frontiers in Human Neuroscience, 10*. https://doi.org/10.3389/fnhum.2016.00505.

Kim, J. S. (1992). Pure sensory stroke. Clinical-radiological correlates of 21 cases. *Stroke., 23*, 983–987. https://doi.org/10.1161/01.STR.23.7.983.

Kim, J. S., & Choi-Kwon, S. (1996). Discriminative sensory dysfunction after unilateral stroke. *Stroke., 27*, 677–682.

de Lafuente, V., & Romo, R. (2002). A hidden sensory function for motor cortex. *Neuron, 36*, 785–786.

Lim, S. H., Dinner, D. S., Pillay, P. K., Luders, H., Morris, H. H., Klem, G., Wyllie, E., & Awad, I. A. (1994). Functional anatomy of the human supplementary sensorimotor area: Results of extraoperative electrical stimulation. *Electroencephalography and Clinical Neurophysiology, 91*, 179–193. https://doi.org/10.1016/0013-4694(94)90068-X.

Meyer, S., Kessner, S. S., Cheng, B., Bonstrup, M., Schulz, R., Hummel, F. C., De Bruyn, N., Peeters, A., Van Pesch, V., Duprez, T., Sunaert, S., Schrooten, M., Feys, H., Gerloff, C., Thomalla, G. G., Thijs, V., & Verheyden, G. (2016). Voxel-based lesion-symptom mapping of stroke lesions underlying somatosensory deficits. *NeuroImage Clin., 10*, 257–266. https://doi.org/10.1016/j.nicl.2015.12.005.

Mima, T., Sadato, N., Yazawa, S., Hanakawa, T., Fukuyama, H., Yonekura, Y., & Shibasaki, H. (1999). Brain structures related to active and passive finger movements in man. *Brain, 122*, 1989–1997. https://doi.org/10.1093/brain/122.10.1989.

Murphy, T.H., Corbett, D., 2009. Plasticity during stroke recovery : from synapse to behaviour 10. https://doi.org/10.1038/nrn2735.

Nachev, P., Kennard, C., & Husain, M. (2008). Functional role of the supplementary and pre-supplementary motor areas. *Nature Reviews. Neuroscience, 9*, 856–869. https://doi.org/10.1038/nrn2478.

Naito, E., Ehrsson, H. H., Geyer, S., Zilles, K., & Roland, P. E. (1999). Illusory arm movements activate cortical motor areas: A positron emission tomography study. *The Journal of Neuroscience, 19*, 6134–6144.

Naito, E., Roland, P. E., & Ehrsson, H. H. (2002). I feel my hand moving: A new role of the primary motor cortex in somatic perception of limb movement. *Neuron, 36*, 979–988. https://doi.org/10.1016/s0896-6273(02)00980-7.

Naito, E., Morita, T., & Amemiya, K. (2016). Body representations in the human brain revealed by kinesthetic illusions and their essential contributions to motor control and corporeal awareness. *Neuroscience Research, 104*, 16–30. https://doi.org/10.1016/j.neures.2015.10.013.

Nelles, G., Entzen, W. J., Ueptner, M. J., Ller, S. M., & Diener, H. C. (2001). Arm training induced brain plasticity in stroke studied with serial positron emission tomography. *Neuroimage, 13*, 1146–1154. https://doi.org/10.1006/nimg.2001.0757.

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

Radovanovic, S., Korotkov, A. D., Ljubisavljevic, M., Kataeva, G. V., Roudas, M. S., Lyskov, E., Medvedev, S. V., & Johansson, H. (2001). Brain activation during different types of proprioceptive inputs. A pet study. *Society for Neuroscience – Abstracts, 27*, 124.

Roll, J. P., & Vedel, J. P. (1982). Kinaesthetic role of muscle afferents in man, studied by tendon vibration and microneurography. *Experimental Brain Research*, 177–190.

Rorden, C., Karnath, H.-O., & Bonilha, L. (2007). Improving lesion-symptom mapping. *Journal of Cognitive Neuroscience, 19*, 1081–1088. https://doi.org/10.1162/jocn.2007.19.7.1081.

Schmahmann, J. D. (2003). Vascular syndromes of the thalamus. *Stroke., 34*, 2264–2278. https://doi.org/10.1161/01.STR.0000087786.38997.9E.

Scott, S. S. H. S. H. (2004). Optimal feedback control and the neural basis of volitional motor control. *Nature Reviews. Neuroscience, 5*, 532–546. https://doi.org/10.1038/nrn1427.

Seitz, R. J., Azari, N. P., Knorr, U., Binkofski, F., Herzog, H., & Freund, H.-J. (1999). The role of Diaschisis in stroke recovery. *Stroke, 30*, 1844–1850. https://doi.org/10.1161/01.STR.30.9.1844.

Semrau, J.A., Herter, T.M., Scott, S.H., Dukelow, S.P., 2013. Robotic identification of kinesthetic deficits after stroke. Stroke 44, 3414–3421. https://doi.org/10.1161/STROKEAHA.113.002058.

Tyson, S. F., Hanley, M., Chillala, J., Selley, A. B., & Tallis, R. C. (2008). Sensory loss in hospital-admitted people with stroke: Characteristics, associated factors, and relationship with function. *Neurorehabilitation and Neural Repair, 22*, 166–172. https://doi.org/10.1177/1545968307305523.

Vahdat, S., Darainy, M., Thiel, A., & Ostry, D. J. (2019). A single session of robot-controlled proprioceptive training modulates functional connectivity of sensory motor networks and improves reaching accuracy in chronic stroke. *Neurorehabilitation and Neural Repair, 33*, 70–81. https://doi.org/10.1177/1545968318818902.

Van de Winckel, A., Sunaert, S., Wenderoth, N., Peeters, R., Van Hecke, P., Feys, H., Horemans, E., Marchal, G., Swinnen, S. P., Perfetti, C., & De Weerdt, W. (2005). Passive somatosensory discrimination tasks in healthy volunteers: Differential networks involved in familiar versus unfamiliar shape and length discrimination. *Neuroimage, 26*, 441–453. https://doi.org/10.1016/j.neuroimage.2005.01.058.

Van De Winckel, A., Wenderoth, N., De Weerdt, W., Sunaert, S., Peeters, R., Van Hecke, W., Thijs, V., Swinnen, S. P., Perfetti, C., & Feys, H. (2012). Frontoparietal involvement in passively guided shape and length discrimination: A comparison between subcortical stroke patients and healthy controls. *Experimental Brain Research, 220*, 179–189. https://doi.org/10.1007/s00221-012-3128-2.

Vanbellingen, T., Kersten, B., Van Hemelrijk, B., Van De Winckel, A., Bertschi, M., Müri, R., De Weerdt, W., & Bohlhalter, S. (2010). Comprehensive assessment of gesture production: A new test of upper limb apraxia (TULIA). *European Journal of Neurology, 17*, 59–66. https://doi.org/10.1111/j.1468-1331.2009.02741.x.

Weiller, C., Jüptner, M., Fellows, S., Rijntjes, M., Leonhardt, G., Kiebel, S., Müller, S., Diener, H. C., & Thilmann, A. F. (1996). Brain representation of active and passive movements. *Neuroimage, 4*, 105–110. https://doi.org/10.1006/nimg.1996.0034.

Winkler, A., Kochunov, P., Glahn, D., 2012. FLAIR Templates [WWW Document]. URL http://glahngroup.org

Woolrich, M. (2008). Robust group analysis using outlier inference. *Neuroimage, 41*, 286–301. https://doi.org/10.1016/j.neuroimage.2008.02.042.

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. https://doi.org/10.1006/nimg.2001.0931.

Woolrich, M. W., Behrens, T. E. J., Beckmann, C. F., Jenkinson, M., & Smith, S. M. (2004). Multilevel linear modelling for FMRI group analysis using Bayesian inference. *Neuroimage, 21*, 1732–1747. https://doi.org/10.1016/j.neuroimage.2003.12.023.

Worsley, K.J., 2001. Statistical analysis of activation images, in: P., J., P.M., M., S.M., S. (Eds.), Functional MRI: An introduction to methods. OUP.

Yang, D. S., Hong, J. H., Byun, W. M., Kwak, S. Y., Ahn, S. H., Lee, H., Hwang, C. H., & Jang, S. H. (2009). Identification of the medial lemniscus in the human brain: Combined study of functional MRI and diffusion tensor tractography. *Neuroscience Letters, 459*, 19–24. https://doi.org/10.1016/j.neulet.2009.04.058.