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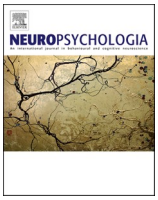

Intact tactile detection yet biased tactile localization in a hand-centered frame of reference: Evidence from a dissociation

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ABSTRACT

We examined the performance of an individual with subcortical damage, but an intact somatosensory thalamocortical pathway, to examine the functional architecture of tactile detection and tactile localization processes. Consistent with the intact somatosensory thalamocortical pathway, tactile detection on the contralesional hand was well within the normal range. Despite intact detection, the individual demonstrated substantial localization biases. Across all localization experiments, he consistently localized tactile stimuli to the left side in space relative to the long axis of his hand. This was observed when the contralesional hand was palm up, palm down, rotated 90° relative to the trunk, and when making verbal responses. Furthermore, control experiments demonstrated that this response pattern was unlikely a motor response error. These findings indicate that tactile localization on the body is influenced by proprioceptive information specifically in a hand-centered frame of reference. Furthermore, this also provides evidence that aspects of tactile localization are mediated by pathways outside of the primary somatosensory thalamocortical pathway.

1. Introduction

Processing somatosensory information involves detecting a stimulus and representing its location in space. Several models have been proposed on the functional organization between tactile detection and tactile localization (Harris et al., 2004). One dimension that these models differ on is whether tactile detection and localization share a common sensory process (single process model) or involve separate processes (multiple process models). Evidence for multiple process models primarily came from brain-damaged individuals, with one group of cases able to detect tactile stimuli with substantial impairments in tactile localization, up to having no knowledge of stimulus location (Anema et al., 2009; Birznieks et al., 2012, 2016; Halligan et al., 1995; Rapp et al., 2002; White et al., 2010), whereas the other group was thought to provide judgments on stimulus locations on the body despite reporting not feeling touch ("numb touch"; Paillard et al., 1983; Rossetti et al., 2001). These observations form a double-dissociation, leading to a proposal that tactile detection and localization are independent and parallel processes.

However, there are methodological concerns regarding both aspects of this double dissociation. For individuals with impaired detection and intact localization (numb touch), one concern is that this may not be a true dissociation but is instead due to response bias in making "yes-no" responses for tactile detection. If tactile detection and localization have different response criteria, such that the detection criterion is more conservative while the localization criterion is more liberal, individuals could demonstrate such a behavioral dissociation even within a single process model (see Harris et al., 2004; Medina and Coslett, 2016 for a discussion).

Furthermore, previous cases of brain-damaged individuals with "intact" detection and impaired tactile localization are not clearly unimpaired in tactile detection. These individuals have either mild to severe impairments in tactile detection, or incomplete evidence regarding their tactile detection abilities. For example, one individual with no ability to localize tactile stimuli (Halligan et al., 1995) could only detect 33% of all tactile stimuli. Individuals in more recent studies of tactile localization also report mild impairments in tactile detection relative to their ipsilesional hand or age-matched healthy controls (Birznieks et al., 2012, 2016; White et al., 2010; Anema et al., 2009). The individuals reported in Rapp et al. (2002) could reliably detect light taps delivered to their contralesional hand. However, their tactile detection thresholds were not tested systematically, hence it is unknown whether they were

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truly unimpaired at tactile detection. These results could be consistent with a single process model in which tactile detection needs to utilize less resources compared to tactile localization. Moderate damage to a single process in this model would result in a mild detection deficit and a more profound tactile localization deficit. Strong evidence for a single dissociation between tactile detection and localization would ideally be an individual with completely normal tactile detection and with severely impaired tactile localization. This type of strong single dissociation is unlikely explained by a single process model. In this manuscript, we report such a case.

Individuals with normal detection yet impaired localization can also inform mechanisms underlying tactile localization. With impairments in both tactile detection and localization in previous cases, errors in tactile localization could be caused by degraded quality of sensory input, or be related specifically to impairments in tactile localization separate from stimulus quality (Harris et al., 2004). It is thus difficult to infer mechanisms specific to the localization process from those individuals. On the other hand, in individuals with completely normal tactile detection yet impaired localization, errors in tactile localization would be solely due to impaired stimulus location representation. These error patterns can then be utilized to understand how the location of tactile stimuli is represented.

When localizing a tactile stimulus on the skin surface, stimulus location can be represented in a somatotopic reference frame, based on fixed locations on the skin surface (Penfield and Boldrey, 1937). For example, a stimulus presented to the left index finger would be represented in the same location regardless of the position of that finger relative to the body or external space. However, when adding information from proprioception, tactile stimuli can also be represented relative to an external reference frame (e.g. Azañón and Soto-Faraco, 2008; Heed et al., 2015; Medina et al., 2019; Yamamoto and Kitazawa, 2001). Here, "external reference frame" refers to a category of body-centered reference frames that are not somatotopic, with the midline of body parts extending into external space. For example, in a trunk-centered external representation, changing hand position relative to the trunk would change the representation of location of a tactile stimulus on the left index finger.

There is evidence that detection of tactile stimuli on the hand can be modulated by body position, indicating effects of information from an external frame of reference on tactile performance. Moscovitch and Behrmann (1994) studied a group of individuals who failed to detect the contralesional stimulus when bilateral stimuli were presented (tactile extinction). To examine if tactile extinction in these individuals occurred in a somatotopic or external frame of reference, two stimuli were simultaneously presented on the ulnar and radial side of the ipsilesional wrist (to ensure detection), with the ipsilesional palm facing up or down. If these participants demonstrated tactile extinction in a somatotopic frame of reference, they would have failed to respond to tactile stimuli on the same side of the hand, somatotopically defined (e.g. the ulnar stimulus), regardless of hand posture. Alternatively, if tactile extinction in these individuals occurred based on an external reference frame, participants would have failed to report the tactile stimulus on the contralesional side in space relative to the wrist midline regardless of hand posture. In 11 individuals with tactile extinction, extinguished stimuli were always on the contralesional side in space relative to the wrist midline, providing evidence that information in an external frame of reference affects tactile processing (see also Aglioti et al., 1999; Moro et al., 2004; Tinazzi et al., 2000). In a different condition in which individuals experience bilateral sensations when only presented with a unilateral stimulus (synchiria), the rate of synchiria decreased when both hands moved to the ipsilesional side in trunk- and head-centered frames of reference, indicating that tactile detection rates (here, for phantom stimuli) can vary as a function of hand position in multiple external frames of reference (Medina and Rapp, 2008).

The studies discussed in the previous paragraph provide evidence that information from an external frame of reference affects the rate of tactile detection. Is tactile *localization* on the body surface also influenced by externally-based representations? It is commonly assumed that a tactile stimulus is first localized on the body surface in somatotopic space, with information from proprioception and other modalities then utilized to localize the stimulus in external space (Longo et al., 2010; Medina and Coslett, 2010). One possibility is that mapping touch to a location in somatotopic space is encapsulated, such that the perceived location on the skin surface is not influenced by other processes (i.e. body position in external space). This account is intuitive, as our perception of the location of touch on the body does not seem to vary as a function of body position. However, evidence from neurologically-intact individuals demonstrates that this may not be the case. One study investigated if tactile localization on the fingers and hands operate in different reference frames (Haggard et al., 2006). In the experiment, participants placed their two hands either vertically aligned, or palm facing each other with fingers interwoven. In each trial a tactile stimulus was presented to one of the eight fingers (thumbs excluded), and participants were asked to report either which hand, or which finger regardless of hand, was stimulated. They found that interweaving fingers decreased hand identification accuracy but did not affect finger identification, concluding that assigning stimuli to the hands takes into account information from external space, such that participants made more errors when finger position in external space is less distinguishable (see also Riemer et al., 2010). In another study, participants were more accurate localizing tactile stimuli among fingers when they were separated versus touching each other (Overvliet et al., 2011), indicating that tactile localization on the skin surface is influenced by proprioceptive information (see also Badde et al., 2019; Ho and Spence, 2007; Medina et al., 2018).

Despite evidence from these studies, it remains unclear in which reference frames proprioceptive information could influence tactile perception. Individuals with tactile extinction fail to respond to contralesional stimuli relative to the wrist or hand midline (Moscovitch and Behrmann, 1994), indicating that tactile locations can be represented with regards to these body parts. Furthermore, studies that manipulated hand posture (palms up versus down) have demonstrated that left and right can be encoded based on an external frame of reference (e.g. Moscovitch and Behrmann, 1994). There are two potential interpretations for these results. One is that stimulus locations can be encoded in a hand-centered reference frame, in which the midline is parallel to the long axis of the hand regardless of hand position relative to the body. For example, imagine an individual presented with bilateral tactile stimuli to the left wrist with the hand rotated 90° relative to the trunk midline. If the extinction operates in a hand-centered frame of reference, then the participant would fail to respond to the stimuli that are farther from the viewer in external space, but still leftward in a hand-centered frame of reference. A second possibility is that these stimuli are encoded based on the relative position of the two stimuli (see Aglioti et al., 1999; Medina and Rapp, 2008). In this frame of reference, left-right assignment is inherited from the body midline of the viewer, and any two stimuli are encoded based on the relative position of the two stimuli. In the aforementioned example with the hand rotated 90° relative to the trunk, an individual with tactile extinction in this frame of reference would not make errors, given that the two stimuli are parallel in this frame of reference. Previous studies of tactile extinction did not test individuals with the hand rotated 90°. From these studies, the evidence for hand-centered representations is unclear.

This manuscript reports an individual with a subcortical lesion, but no evident cortical damage, who demonstrated intact tactile detection with severely impaired tactile localization. Given the lesion location, we first examined what fiber tracts were damaged using diffusion tensor imaging (DTI), finding an intact pathway from thalamus to S1 that likely subserved his intact tactile detection. We then report five experiments to address two primary questions. First, we presented a series of tests to examine whether this case demonstrates truly intact tactile detection along with impaired tactile localization (Experiments 1 & 2). We found

that tactile detection thresholds on the contralesional hand were well within the range of normal performance. Surprisingly, the individual made large, systematic errors in tactile localization, providing a strong single dissociation that is unlikely accounted for by a single process model.

Second, his impaired tactile localization with normal detection provide opportunity to study mechanisms specific to the localization process. Specifically, we investigated if tactile *localization* on the contralesional hand is affected by hand position in external space, and if so, in which frame of reference is the localization deficit (Experiments 3 & 4). For these purposes, we examined tactile localization in this individual while manipulating hand posture. Across all experiments, the individual mislocalized stimuli to the left side in an external, hand-centered frame of reference defined by the hand proximodistal axis, regardless of if the hand was straight or rotated 90° relative to the body. In somatotopic reference frame, these localization judgments varied dramatically based on hand posture, clustering around the little finger when the hand was palm facing down, and around the thumb when the hand was palm facing up. To our knowledge, this is the first report of tactile localization on the skin surface being strongly affected by proprioceptive information in a brain-damaged individual. We report his proprioceptive performance in Experiments 5, and then discuss a potential relationship between his biases in proprioception and tactile localization. Finally, we discuss the possible mechanism and neural correlates of his tactile localization biases.

2. Case history

At the beginning of our testing, DS was a 46-year-old right-handed male who suffered a subcortical infarct restricted to the white matter of the right hemisphere four years before the investigation. MRI revealed damage to the superior and anterior corona radiata (Fig. 1). The lesion consisted of cystic fluid-filled cavitation (shown in yellow in Fig. 1, bottom) surrounded by gliosis (shown in red in Fig. 1, bottom). As detailed in the Appendix, DTI tractography showed that projections from the thalamus and the primary somatosensory cortex (S1) hand area on the post-central gyrus were intact, as were the connections between S1 and the secondary somatosensory cortex (S2) in the parietal operculum. Furthermore, tractography showed that lesion likely damaged pathways from the thalamus to the superior frontal gyrus and frontal eye field.

The individual was initially weak in the left arm and leg after the stroke, but his strength had recovered when we first tested him. In addition, he described signs of alien/anarchic hand symptoms in his contralesional (left) hand for a few months after the stroke. He described episodes in which the left hand would grasp objects and perform tasks without him realizing it. For example, when he was standing in front of the mirror, he would look up and find his left hand reaching for a bar of soap. These signs of alien hand symptoms had subsided by our initial testing session. During our final experiments (five years after our initial testing), he did not demonstrate any obvious motor deficits in his hands.

3. Experiment 1: Assessing tactile detection

Given that his thalamus and primary somatosensory cortices were intact, along with the pathway from thalamus to S1 in the damaged hemisphere, we expected normal tactile detection on the contralesional hand. We therefore tested tactile detection threshold on both hands, with the ipsilesional hand as control. Tactile detection threshold was tested in two sessions that were five years apart. All data from this experiment and subsequent experiments can be found on the Open Science Framework, see https://osf.io/8q5jr/. All research was approved by the Institutional Review Board at the University of Delaware.

3.1. Procedure

The individual was seated in front of a table with the tested hand placed on the table, aligned with body midline and palm facing up. There were two blocks in each testing session, one for each hand. The individual was asked to close his eyes throughout each block. Tactile detection threshold was measured by presenting Semmes-Weinstein monofilaments to the palmar side of the tip of the middle finger (North Coast Medical Inc., CA, USA). The monofilament set contains 20 intensities ranging from 0.008 to 300 g, which are then log-transformed to values ranging from 1.65 to 6.65. We use the log-transformed values below in reporting detection thresholds. A weighted 1-down, 1-up staircase procedure was used: Each block started with the thickest filament. If the individual detected the stimulus, the filament intensity was decreased by two scale levels for the next trial, otherwise the filament intensity was increased by one scale level. To differentiate hits from false alarms, catch trials where the experimenter would approach the individual's hand with the filament without actually touching the hand were interspersed among actual trials. After each trial, the experimenter asked "Did you feel anything?" and the individual verbally responded *Yes* or *No*. We planned to stop the staircase procedures after 10 reversals

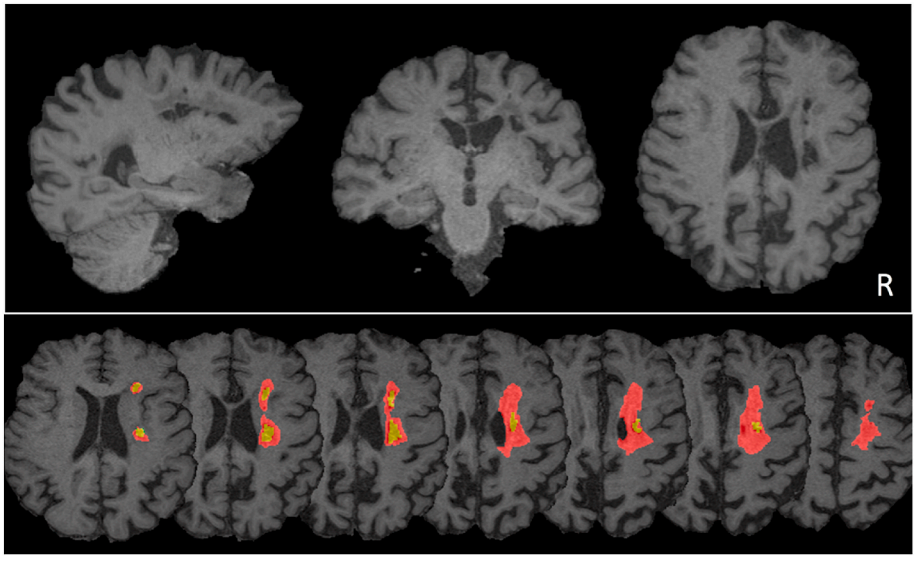

Fig. 1. T1-weighted MRI image for DS. Top: The lesion shown in representative slices in each view. Bottom: Axial sections from ventral to dorsal showing area in the lesion consisting of fluid-filled cavities (yellow) and gliosis (red). Unless otherwise noted, all brain images below are displayed in neurological conventions, with the left hemisphere displayed on the left side of the brain image, and right hemisphere right side. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

and calculate detection threshold as the average intensity at all 10 reversals. However, due to experimenter error, we continued beyond 10 reversals on the tested blocks (see Table 1 for details). Given that the threshold estimate becomes more stable with more reversals, we report thresholds calculated from averaging all reversal points.

3.2. Results

We report tactile detection threshold on both hands tested in both investigations (Table 1), calculated as the average log-transformed scale across all trials where the direction (i.e. increasing or decreasing) of the staircase procedure reversed. False alarm rates are also reported.

Tactile detection thresholds below 2.83 are considered as normal (North Coast Medical Inc., CA, USA). In a study with a large sample size (N = 130, age 7–75 years, mean 41 years), detection thresholds ranged from 1.65 to 3.84, most frequently at 2.83 (Hage et al., 1995). As shown in Table 1, the detection thresholds on both hands were within the normal range and practically identical.

4. Experiment 2: Tactile localization

Having found a normal tactile detection threshold on DS's contralesional hand, we then tested his tactile localization ability. Past studies reported cases who could detect touch but not accurately localize (Halligan et al., 1995; Birznieks et al., 2012, 2016; White et al., 2010; Anema et al., 2009). It is therefore possible that DS has impaired tactile localization in spite of completely intact detection. More importantly, impaired tactile localization with normal detection would provide novel evidence that tactile detection and localization are dissociable processes.

4.1. Procedure

The tested hand was placed on the table, aligned with the body midline and palm facing down. For each hand, we used a filament that was four intensities above the hand's threshold (log-transformed value of 4.08 for both hands) to ensure that stimuli were detectable. In cases where the detection threshold did not map to a filament, the closest thicker filament was considered as the threshold filament. In each trial, the experimenter stimulated one of the 22 predetermined locations (Fig. 2, black labels) on the hand dorsum with the individual's eyes closed (as in Rapp et al., 2002). Then the individual opened his eyes and pointed to where he felt the touch using his untested hand. A second experimenter recorded the individual's responses on a standardized hand illustration (hand drawings in Fig. 2). The second experimenter, for this and all other experiments, was blind to the expected pattern of results. In trials where the individual did not feel the stimulus, the locations were marked as missed.

We tested DS's tactile localization during two separate sessions. In each session, two blocks were conducted on each hand with the order counter-balanced in an ABBA design. Within each block there were 22 trials, with one trial per location in a randomized order. In total four trials were tested for each location on each hand. All testing sessions were videotaped. Recorded responses on the hand drawing were confirmed with the videos offline.

Table 1
Tactile detection threshold on each hand, collected from two testing sessions.

	Left (contralesional) hand		Right (ipsilesional) hand	
	Session 1			
	Threshold (15 reversals)	False alarm rate	Threshold (17 reversals)	False alarm rate
Filament scale	2.45	0.14 (1/7)	2.46	0 (0/8)
	Session 2			
	Threshold (14 reversals)	False alarm rate	Threshold (17 reversals)	False alarm rate
Filament scale	2.80	0 (0/7)	3.13	0 (0/7)

*Thresholds are log-transformed intensities.

4.2. Analyses

Since single-case data can violate various assumptions in standard parametric statistics, we analyzed our data using permutation tests. In some cases, we were interested in whether DS's localization judgments were biased in a particular direction. To examine this, we used one-sample permutation tests to examine if the bias for his localization judgments was significantly different from zero. To do this, we took the bias for each localization judgment and, in each permutation, randomly flipped the sign of each observation, with the assumption that observations would be randomly below or above zero under the null hypothesis. For comparing localization judgments across hands or experimental manipulations, we used permutation tests in which each permutation randomly shuffled the relationship between the localization judgment and tested hand/experimental condition. The actual mean localization bias was then compared to mean localization bias from each permutation, with the two-tailed permutation *p*-value being the percentage of permutations in which the absolute mean bias was larger than the absolute actual mean bias.

Permutation tests were performed using the DAAG package in R (https://cran.r-project.org/web/packages/DAAG/DAAG.pdf) with 100,000 permutation iterations for each analysis.

4.3. Results

Actual and perceived target locations for each hand are shown in Fig. 2. Overall, 15 out of 88 (17.0%) stimuli on the contralesional (left) hand and 24 out of 88 (27.3%) stimuli on the ipsilesional (right) hand were not detected. The detection rate did not differ between the two hands (Fisher's exact $p = .146$). Trials in which tactile stimuli were not detected were excluded from subsequent analyses.

Next, localization biases were calculated as the difference between responses and actual locations in medial-lateral and proximal-distal directions. For both hands, negative values denote biases lateral to the body midline, i.e. towards the little finger, and proximal to the body, i.e. towards the wrist. As shown in Fig. 2, perceived stimulus locations on the contralesional hand (left panel) shifted dramatically towards the little finger and wrist. One-sample permutation tests revealed a significant lateral ($p < .001$, $M = -19.3$ mm, $SD = 24.0$ mm) and proximal bias ($p < .001$, $M = -31.7$ mm, $SD = 29.3$ mm). For the control ipsilesional (right) hand (Fig. 2, right), there was a slight but significant bias towards the little finger, ($p < .001$, $M = -2.23$ mm, $SD = 4.95$ mm), with no significant bias in proximodistal direction ($p = .954$, $M = 0.41$ mm, $SD = 15.0$ mm). Two-sample permutation tests revealed significantly greater lateral and proximal biases on the left (contralesional) versus right hand ($ps < .001$).

4.4. Discussion

Despite normal tactile detection, we found large localization errors on his contralesional hand. Compared with his ipsilesional right hand, localization judgments for his left hand strongly clustered in the ulnar and proximal directions (see Fig. 2). To our knowledge, this is the first case that shows completely normal detection with largely impaired localization.

In addition to the contrast between tactile detection and localization, DS's errors clustered on one side of the hand in the mediolateral direction. One question regarding his tactile localization performance is the reference frame of his localization bias. One possibility is that this bias is somatotopic, such that DS will mislocalize towards the little

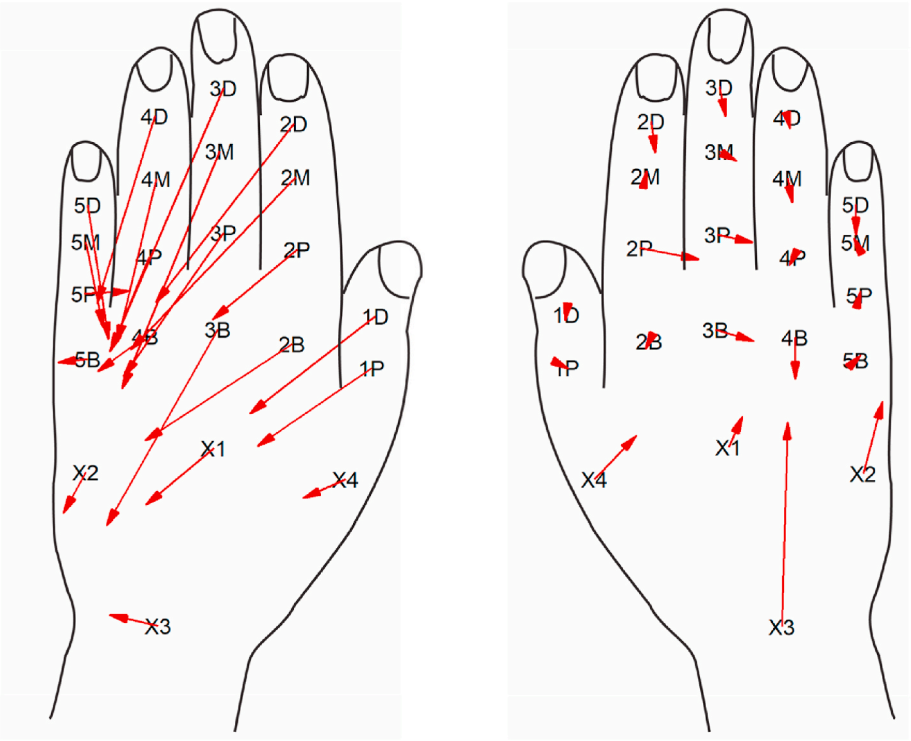

Fig. 2. Tactile localization performance of each hand in Experiment 2. Black labels denote stimulus locations. Red arrows point from each stimulus location to the perceived stimulus location.

finger regardless of hand position. However, tactile information can also be represented in one of many external reference frames. A simple manipulation to examine this is changing hand position from palm down to palm up. If the bias is somatotopic and towards the ulnar side of the hand, then localization judgments will be biased towards the little finger regardless of hand posture. If his localization errors are based on an external representation, responses will be biased towards the left side of the hand regardless of hand posture, being the thumb when the hand is palm up. These questions were addressed in Experiment 3.

5. Experiment 3: investigation of spatial reference frame in tactile localization errors

We performed a series of experiments in a new testing session, manipulating hand posture to examine whether DS's localization bias occurred in a somatotopic or external reference frame. Due to time constraints, we only tested his contralesional (left) hand.

In addition, we tested both the hand dorsum and palm in the same block. In the brains of non-human primates, dorsum and palm surface representations in S1 are distributed differently: The surface of the palm is largely represented in continuous cortical areas whereas the dorsal surface is represented by smaller non-continuous cortical "islands" (Merzenich et al., 1984). It is therefore possible that representations of the dorsum and palm surfaces are differentially affected by brain damage. However, there is sparse evidence on how tactile localization performance on the two hand surfaces is affected after stroke, except for one study showing biases towards the hand center on both surfaces for two individuals (Rapp et al., 2002). In Rapp et al. (2002), stimuli were only tested one surface at a time, not allowing for errors across the surfaces of the hand. We tested both dorsum and palm in the same block to examine if directional biases in DS are consistent across surfaces.

5.1. Experiment 3a

This experiment was performed to replicate the previous tactile localization pattern observed on the hand dorsum, and to examine what pattern would be observed after stimulating the palm.

5.1.1. Procedure

The procedure was the same as in Experiment 2 except for the following differences. First, we only tested the contralesional (left) hand. Second, DS's forearm was resting on a foam block such that we were able to stimulate the palm surface from below (Fig. 3a). Finally, we used a clearly suprathreshold filament (scale of 5.18) to ensure tactile detection. We tested 22 locations on each hand surface, with one trial per location. All locations were tested in one block in randomized order. We were not able to test location X3 (at the base of the palm) as it was covered by the foam block. Accordingly, this location was not included in the analyses.

5.1.2. Results

Actual and perceived stimulus locations are shown in Fig. 3b. Consistent with Experiment 2, overall there was a significant bias towards the little finger ($p < .001$, $M = -28.8$ mm, $SD = 25.5$ mm) and the wrist ($p < .001$, $M = -39.5$ mm, $SD = 33.1$ mm). Two-sample permutation tests did not reveal significant differences between the hand dorsum and palm in both mediolateral and proximodistal bias ($ps > .9$).

There were also trials where DS perceived tactile stimuli delivered to the palm surface as on the dorsum (Fig. 3, blue arrows on the dorsal surface), and vice versa (Fig. 3, red arrows on the palmar surface), which we term "cross-surface errors". Overall, 1 out of 22 (4.5%) dorsum stimuli were perceived as on the palm, and 18 out of 21 (85.7%) palm stimuli were perceived as on the dorsum. A Fisher's exact test revealed significantly more cross-surface errors for stimuli delivered to palm versus dorsum ($p < .001$).

5.1.3. Discussion

In this experiment, we replicated our previous finding that DS mislocalized tactile stimuli on the hand dorsum towards the little finger and the wrist. In addition, localization biases were consistent across the

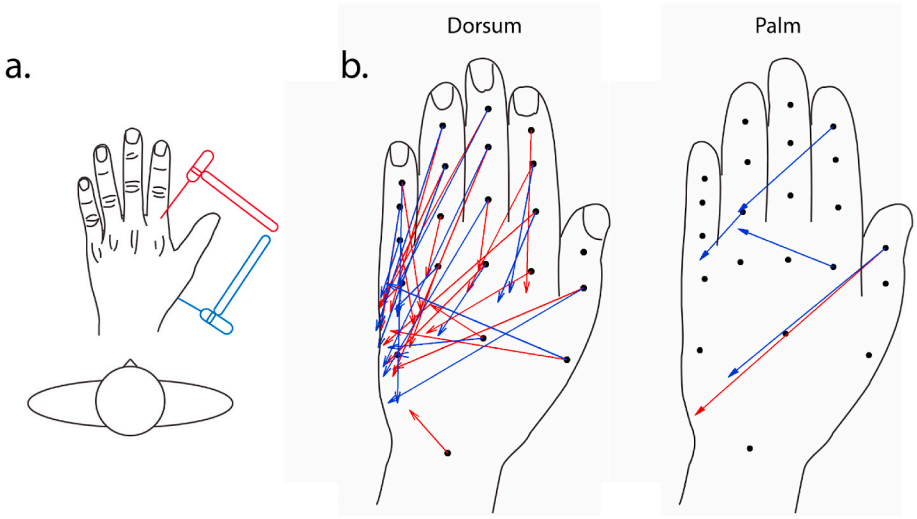

Fig. 3. a. Hand posture in Experiment 3a. DS was stimulated on the dorsum (filament in red) and palm surfaces (filament in blue) in the same block with the hand positioned palm facing down. b. Localization bias in Experiment 3a shown by arrows pointing from the actual (black dots) to perceived stimulus locations on each surface. Consistent with the filament colors in a., red arrows denote localization judgments for stimuli delivered to the dorsum surface, blue arrows are localization judgments for stimuli on the palm surface. The palm surface on the right is displayed as if viewed from the top, through the dorsum surface. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

dorsum and palm surfaces.

There are multiple interpretations of DS's localization errors in terms of which frame of reference they occurred. One possibility is that those biases occur in somatotopic space, such that errors would be towards the little finger regardless of hand position in space. Alternatively, those biases might occur in external space, such that they are on the left side relative to the hand proximodistal axis. On this assumption, tactile localization judgments would be biased in the ulnar direction when the contralesional (left) hand is palm down, but would shift towards the thumb when placed palm up. We tested these possibilities in Experiment 3b.

One surprising and novel finding was that when stimuli could be presented to either surface, DS mislocalized the majority of stimuli that were delivered to the palm as on the dorsum. However, since the hand was positioned palm facing down, it is possible that DS made more dorsal responses because a) this surface was stimulated more in past experiments, and could be more likely to be stimulated or b) because of the relative ease in pointing to the dorsal surface, which was facing up. We further investigated these cross-surface errors in the following experiments.

5.2. Experiment 3b

5.2.1. Procedure

The procedure was the same as in Experiment 3a except that the contralesional (left) hand was placed palm facing up (Fig. 4a). We did not test locations X1 and X3 on the dorsum because they were covered by the foam block. Accordingly, these locations were not included in the analyses.

5.2.2. Results

Actual and perceived stimulus locations are shown in Fig. 4b. There was still a significant lateral ($p = .002$, $M = -13.4$ mm, $SD = 25.6$ mm) and proximal bias ($p < .001$, $M = -39.3$ mm, $SD = 38.8$ mm), but on the skin surface judgments shifted towards the thumb. Together with the results from Experiment 3a, these results provide evidence for a bias that is not based on a somatotopic representation, but instead on some type of external representation. Two-sample permutation tests between the dorsum and palm surfaces did not reveal a significant difference in mediolateral ($p = .551$) or proximodistal bias ($p = .553$).

As in Experiment 3a, there were cross-surface errors on both surfaces. Overall, 1 out of 20 (5%) dorsum stimuli were perceived as on the palm, and 15 out of 22 (68.2%) palm stimuli were perceived as on the dorsum; a significant difference in cross-surface errors for palm versus

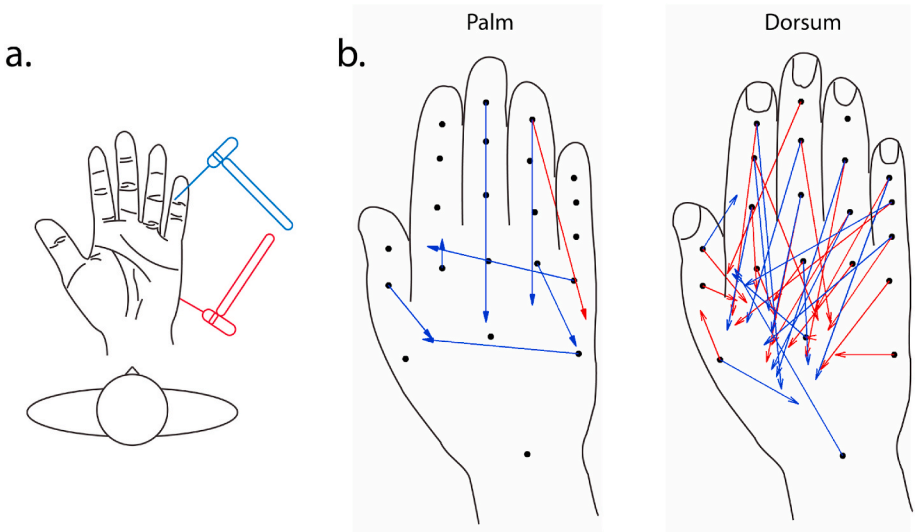

Fig. 4. a. Hand posture in Experiment 3b. b. Localization bias in Experiment 3b shown by arrows pointing from the actual (black dots) to perceived stimulus locations on each surface. Consistent with the filament colors in a., red arrows denote localization judgments for stimuli delivered to the dorsum surface, blue arrows are localization judgments for stimuli on the palm surface. The dorsum surface on the right is displayed as if viewed from the top, through the palm surface. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

dorsum stimuli (Fisher's exact test, $p < .001$). This is consistent with Experiment 3a, indicating that cross-surface errors occurred in a somatotopic space and are not affected by hand posture.

5.2.3. Discussion

In this experiment, we tested if DS's tactile localization errors occur in a somatotopic or an external reference frame. Across Experiment 3a and 3b, we found that perceived stimulus locations always shifted to the left side in space relative to the hand proximodistal axis, demonstrating biases in an external hand-centered frame of reference. Our case indicates that errors in tactile localization on the skin surface can occur in a non-somatotopic representation. Accordingly, judgments on the skin surface varied with hand posture, towards the pinky when the hand was palm facing down (Experiment 3a), and towards the thumb when the hand was palm facing up (Experiment 3b), demonstrating a strong influence of proprioceptive information. We also replicated a finding from Experiment 3a that DS localized the majority of palm stimuli to the dorsum, even when the dorsum was facing down and less easy to point to. This confirmed that cross-surface errors were perceptual errors, with a bias towards sensing touch on the hand dorsum even when the palm was stimulated.

In Experiment 3a and 3b, the contralesional (left) hand was aligned with the body midline. It was therefore unclear if the leftward biases were relative to the hand proximodistal axis (in a hand-centered frame of reference) or relative to the body midline (trunk-centered frame of reference). In addition, as discussed earlier, since the hand long axis has been aligned with the viewer's perspective, it is unclear if the left-right was relative to a body part itself, or general left-right along the transverse axis with respect to the viewer. In Experiment 3c, we addressed these questions by rotating the hand by 90° towards the body, such that the hand-centered (defined by the hand proximodistal axis) frame of reference was misaligned from trunk-centered (defined by body midline) frames of reference and the viewer's perspective (Fig. 5a). With the hand placed palm down, if previous localization errors were made on the left side specifically relative to the hand itself, i.e. relative to the hand proximodistal axis, we expect perceived stimulus locations to shift towards the little finger. If localization errors were made on the left side of a trunk-centered frame of reference or based on the viewer, we expect shifts towards the wrist.

5.3. Experiment 3c

5.3.1. Procedure

The procedure was the same as Experiment 3a, except that the contralesional (left) hand was rotated 90° such that the mediolateral hand axis was aligned with the body midline (Fig. 5a). We did not test location X3 (base of the palm) because it was covered by the foam block. Location 2B on the dorsum was excluded from the analysis due to a recording error.

5.3.2. Results

Actual and perceived stimulus locations are shown in Fig. 5b. To be consistent with Experiments 3a and 3b, localization errors were still coded in hand space, with negative values denoting biases towards the little finger and wrist. Overall, there was still a significant bias towards the little finger ($p < .001$, $M = -29.0$ mm, $SD = 23.7$ mm) and wrist ($p < .001$, $M = -49.4$ mm, $SD = 33.8$ mm). No differences in mediolateral ($p = .371$) or proximodistal ($p = .109$) bias between the hand palm and dorsum surfaces were found.

As for cross-surface errors, overall 2 out of 21 (9.5%) dorsum stimuli were perceived as on palm, and 3 out of 21 (14.3%) palm stimuli were perceived as on dorsum. There was no significant difference in cross-surface error rate between stimuli delivered to hand dorsum and palm (Fisher's exact test, $p = 1$). These findings differ from Experiment 3a and 3b, in which there were more cross-surface errors made on stimuli delivered to palm vs. dorsum, although the reason for such an improvement is not clear.

5.3.3. Discussion

When DS's contralesional hand was rotated 90°, tactile localization judgments again shifted leftward relative to the hand proximodistal axis, indicating that tactile localization errors occur in a hand-centered frame of reference instead of a trunk-centered or other viewer-based external frames of reference. Taken together, Experiments 3a to 3c showed that perceived tactile stimulus locations on the skin surface were strongly affected by proprioceptive information in external space. Specifically, tactile localization judgments shifted towards the left side of the hand itself, whether the hand was palm down (Experiment 3a), palm up (Experiment 3b) or rotated 90° (Experiment 3c).

In these experiments, DS responded by manually pointing with his ipsilesional hand to his contralesional hand. Is it possible that the

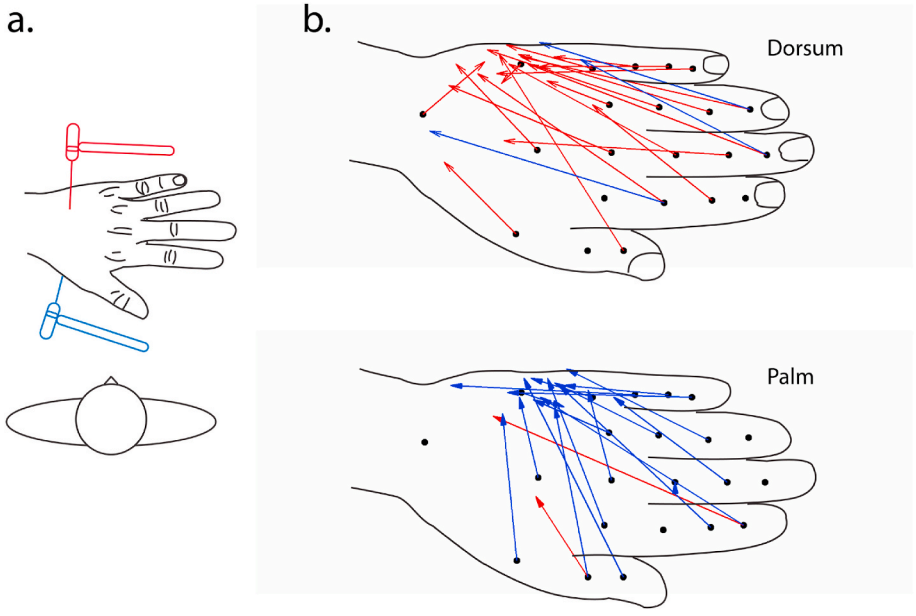

Fig. 5. a. Hand position and posture during Experiment 3c. b. Localization bias in Experiment 3c shown by arrows pointing from the actual (black dots) to perceived stimulus locations on each surface. Consistent with the filament colors in a., red arrows denote localization judgments for stimuli delivered to the dorsum surface, blue arrows are localization judgments for stimuli on the palm surface. The palm surface on the bottom is displayed as if viewed from the top, through the dorsum surface. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

observed errors were based on a motor deficit, and not a perceptual deficit? First, even though the ipsilesional hand was unaffected by his stroke, there might still be gross deficits that cause errors in pointing movements. In addition, previous literature reported a case who was more accurate in localizing touch when pointing to a hand image versus pointing to his own stimulated hand (Anema et al., 2009), indicating that there could be errors specifically associated with pointing to one's own body. We therefore ran two control experiments to test DS's general pointing ability, as well as examining whether his tactile localization errors generalized to other response modalities.

6. Experiment 4: Are the observed biases motor or perceptual?

6.1. Experiment 4a

To test if the observed tactile localization biases were based on a motor deficit, we instructed DS to point to visual targets with his ipsilesional (right) hand, the hand with which he made pointing responses in Experiment 3. In addition, to examine if he had a deficit specific to pointing to body-related objects, we instructed DS to point to visual targets shown either in different quadrants drawn on a piece of paper or at different locations on a hand drawing.

6.1.1. Procedure

DS was tested on pointing to different locations on the table in front of him. Each location was within one of twelve quadrants in a 4 × 3 grid, spanning −33.8 cm–33.8 cm in the transverse direction relative to the body midline and 5 cm–55.7 cm in the proximodistal direction (Fig. 6). This grid was not visible to DS. A laser pointer was mounted to a tripod. In each trial, DS was asked to close his eyes while the experimenter positioned the tripod-mounted laser pointer to aim within one of the quadrants. Then DS was asked to open his eyes and look at the laser dot for approximately 2 s. The laser pointer was then turned off and DS immediately pointed to where the laser dot was with his ipsilesional right hand. A picture was taken on the position of the laser pointer as well as where DS pointed to code the distance between the pointed position and actual location of the visual target. Three trials were presented for each quadrant, with the specific target locations within the quadrant varying across trials. One trial (middle row, the second quadrant from right) was excluded from the analysis due to an experimenter error (picture of the target location not taken).

In a second version of the experiment, the procedure was the same except for the following differences. First, we placed a standard hand drawing of the dorsum of the left hand in front of DS. In each trial, the laser dot was shown on one of the 22 locations (one trial per location) as in the tactile localization experiments (there were no target positions labeled on the drawing), with stimulus presentation and localization judgments done in the same manner as in the first block. A second experimenter recorded the location of the pointing response on a different hand drawing.

6.1.2. Results

For pointing to visual targets in quadrants, we calculated the distance between the actual visual stimulus and the localization judgment in proximodistal and mediolateral directions respectively. Positive values denote errors towards the right and distal relative to the body. One-sample permutation tests were performed to examine if the pointing errors significantly differed from zero. There was a slight but significant bias towards the right side of space ($p = .047$, $M = 2.28$ mm, $SD = 6.52$ mm). No significant proximodistal errors were found ($p = .166$, $M = 2.5$ mm, $SD = 10.4$ mm). Since the tactile localization biases were to the left side of the proximodistal hand axis and proximal to the wrist, those biases were unlikely to be explained by general pointing errors in external space.

In addition, DS accurately pointed to all 22 locations on the hand drawing with no observable errors (i.e. his finger touched the target location on every trial). These findings provide additional evidence that the tactile localization errors could not be attributed as pointing errors.

6.2. Experiment 4b

To examine if his tactile localization errors generalized to other response modalities, we had DS respond to tactile stimuli by verbally describing perceived stimulus locations.

6.2.1. Procedure

This experiment was done in three blocks, each with a different hand posture. In the first block, the contralesional (left) hand was placed palm facing down, aligned with the body midline (same as Experiment 3a). In the second block, the hand was placed palm facing up, aligned with the body midline (same as Experiment 3b). In the third block, the hand was placed palm facing down, rotated 90° (same as Experiment 3c).

Due to time constraints and to reduce difficulties in verbally describing locations, we only tested the distal and proximal segments of each finger on each surface (Fig. 7a). The procedure of each trial was the same as in Experiment 3, except that DS verbally described on which surface (dorsum, palm) he felt stimuli, as well as the location on that surface. To enable quantification of mediolateral localization bias (see Analyses below), we encouraged DS to describe stimulus location in the mediolateral direction by referencing which finger, or in between which two fingers, the felt stimulus location was aligned with. For example, if a stimulus was perceived at the label "R" in Fig. 7a, it would be described as "top side (i.e. dorsum), *in line with ring finger* and close to wrist". A second experimenter wrote down his verbal responses. Each location was tested once in each block.

6.2.2. Analyses

Given that our primary question examined whether DS still

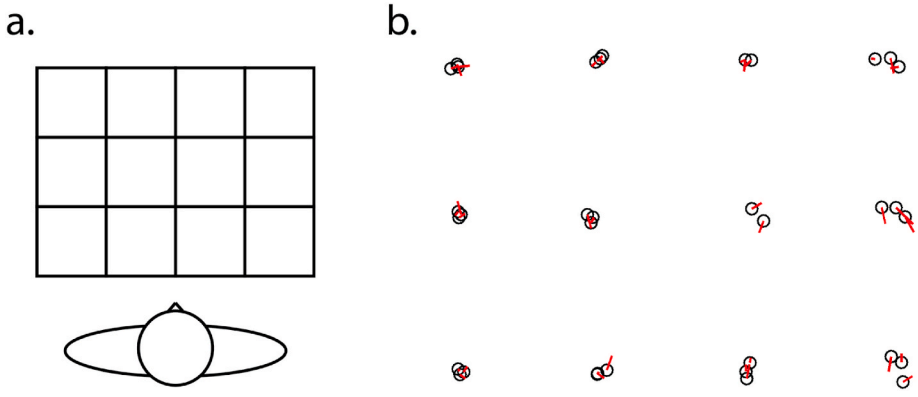

Fig. 6. a. Illustration of the setup in Experiment 4a. DS was asked to point to visual targets presented in different quadrants defined by a 4 × 3 grid. The grid lines are displayed only for illustration purposes and were not visible to DS during the experiment. b. DS's pointing performance is shown by red lines starting from each actual visual-stimulus location (black circles) to the pointed location. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

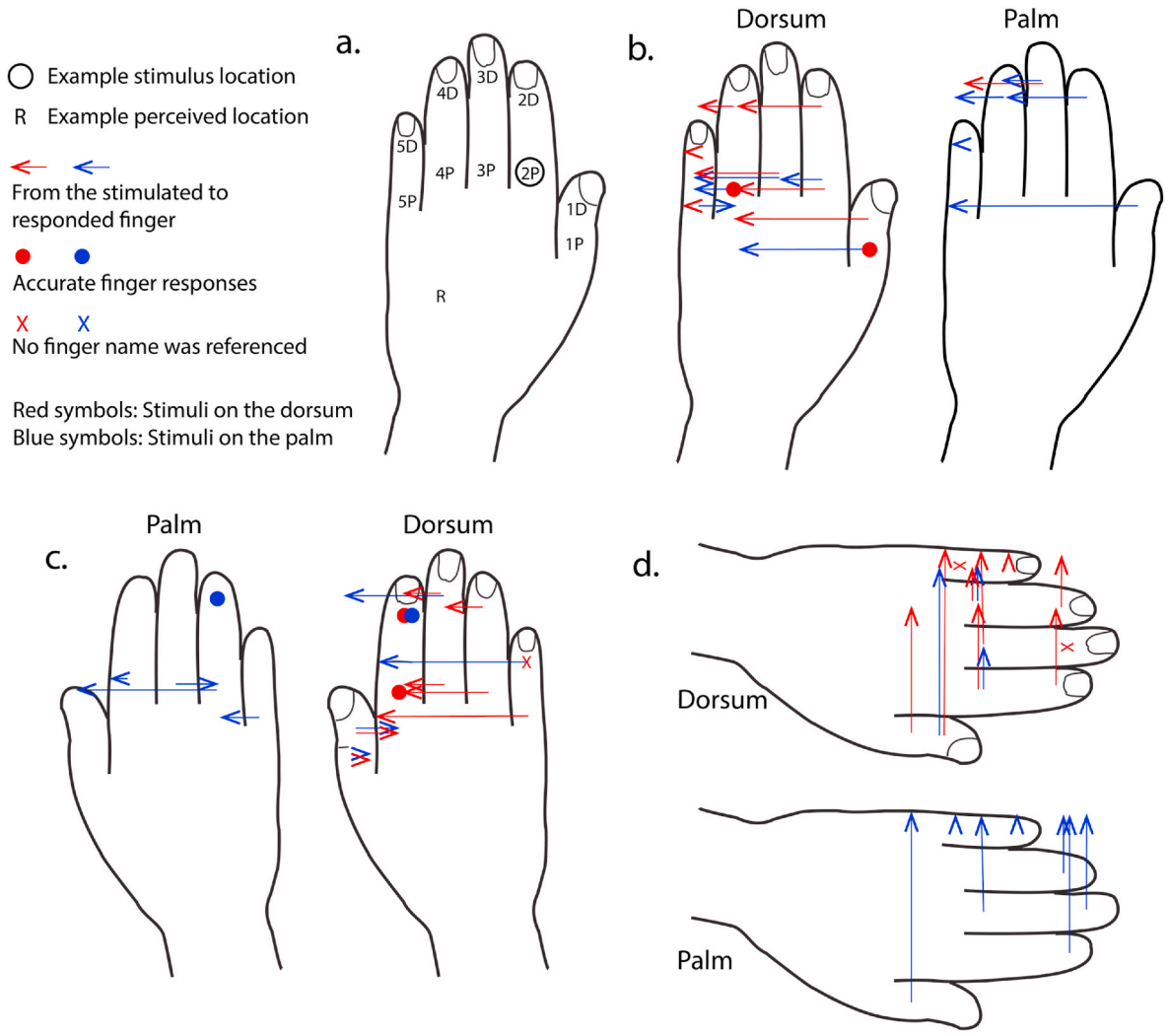

Fig. 7. a. Stimulus locations in Experiment 4b. In an example trial, location 2P (circled) is stimulated, and DS may perceive it at the letter R, describing it as in line with the ring finger and close to the wrist. b., c., and d. Performance on block 1, 2, and 3 respectively. Each arrow starts from the stimulated location and ends at the responded finger. All arrows are along the mediolateral direction because only mediolateral bias is considered. Filled circles denote accurate finger responses. X's indicate no finger was referenced in DS's response. As with previous figures, red symbols denote responses for stimuli delivered to the dorsum surface, blue symbols denote responses for stimuli delivered to the palm surface. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

demonstrated leftward biases relative to the hand proximodistal axis with verbal responses, we only analyzed tactile localization errors in the mediolateral direction. The fingers were coded as 1 to 5 from thumb to the little finger. Localization bias was calculated as the distance in finger units between the stimulated finger and response finger, with negative values denoting ulnar biases. For example, if the stimulus was on the index finger and the response were on (or aligned with) the ring finger, this trial would have a mediolateral bias of −2 finger units. If DS referred to a location between two fingers, that location was coded as the average finger number (e.g. 3.5 for locations between the middle and ring finger). In trials where DS reported feeling touch on the side of the hand, locations were coded as the number of the corresponding outer finger plus or minus 0.5 (e.g. 5.5 for the side surface of the little finger).

As with previous experiments, permutation tests were performed on localization errors. Trials in which DS did not specify a finger in his response (3 out of 60) were excluded from the analyses. It is worth noting that whereas we coded judgments in terms of fingers, in most cases DS perceived the stimulus as on the palm or dorsum areas of the hand.

6.2.3. Results

For all blocks, one-sample permutation tests revealed a significant bias towards the left side in space relative to the hand proximodistal axis (block 1: $p < .001$, $M = -1.45$ finger units, $SD = 1.22$ finger units; block 2: $p = .047$, $M = -0.71$ finger units, $SD = 1.39$ finger units; block 3: $p < .001$, $M = -1.33$ finger units, $SD = 2.14$ finger units). No significant differences between the palm and dorsum surface were found in any block ($ps > .8$). These results are consistent with DS's tactile localization performance when he manually pointed to perceived tactile locations, indicating that the previous findings generalize to different response modalities, and could not be attributed as pointing errors. Finally, DS also made cross-surface errors when making verbal responses (Table 2; Fig. 7, red arrows or circles on the palm surface and vice versa), indicating that these errors were also perceptual and independent of response modality.

6.2.4. Discussion

In two experiments, we ruled out the possibility that DS's tactile localization errors were due to a motor deficit. First, when pointing to remembered visual targets in quadrants with the right (ipsilesional) hand, DS showed overall *rightward* biases relative to the body. Given that

Table 2
Results from Fisher's exact tests on cross-surface errors in Experiment 4b.

	Dorsum stimuli localized to palm	Palm stimuli localized to dorsum	Fisher's exact test comparing surfaces
Block 1: Palm down	1/10	5/10	$p = .141$
Block 2: Palm up	0/10	5/10	$p = .032$
Block 3: Palm down, rotated 90°	0/10	3/10	$p = .211$

the tactile localization biases were towards the *left* of the hand proximodistal axis, these biases are unlikely to be explained by motor pointing errors. Second, DS pointed accurately to remembered visual targets shown on a hand drawing, indicating that his tactile localization biases could not be explained by pointing errors specific to body-related objects. In addition to motor deficits, these findings also rule out the possibility that DS's tactile localization bias was caused by spatial neglect. Past studies reported brain-damaged individuals with hemispatial neglect who drew numbers on a clock all in the non-neglected hemisphere (Chen and Goedert, 2012; Di Pellegrino, 1995). Similarly, it is possible that DS was neglecting the right side of the hand space and fit the entire hand surface to the left side, only making judgments on the left side. That DS could point accurately to locations spanning both hemispaces indicate intact spatial attention and rules out this account. Finally, Experiment 4b showed a similar pattern of localization errors when DS made verbal responses compared to manually pointing to perceived stimulus locations, indicating that his tactile localization errors reflected general perceptual biases instead of response errors.

So far we have shown that DS made tactile localization errors consistently to the left side in space relative to the hand proximodistal axis. One question is if DS showed similar biases in other behavioral examinations that might explain his tactile localization biases. Although the mechanism is unclear given limited data, we found that when asked to judge location of the left (contralesional) hand in external space, DS made similar proximal and lateral errors. We report data from a proprioceptive judgment task to provide complementary information on his deficits and use this to motivate potential explanations in the discussion.

7. Experiment 5: Landmark localization

As part of a battery of tests, we presented DS with the landmark localization task as in Longo and Haggard (2010). Although this task is typically used to examine biases within the hand, an overall shift in localization judgments in this task can also be used to examine his ability to represent body position in external space. Data were collected over two testing sessions.

7.1. Procedure

At the beginning of each block, DS's tested hand was placed on the table, palm facing down and aligned with the body midline. To ensure that he did not move the hand during a block, we placed rubber cylinders between his fingers and around his hand. A picture of the hand was taken to later code the actual position of the hand. The hand was then occluded under a white board (50 cm × 50 cm) suspended 10 cm above his hand. His forearm and shoulder were covered with a black fabric to prevent DS from inferring hand position based on visual information.

In each trial, the experimenter verbally said a landmark on the hand (i.e. tip of your middle finger), and DS responded using a pointer to identify the location on the white board that was directly above the perceived landmark. We then took a picture of the localization judgment and coded them offline (as in Medina and Duckett, 2017). We examined landmark localization at 10 positions (tip and knuckle of each finger), three trials per location in a block. Another picture of the hand was taken at the end of each block. Comparing pictures taken before and after each block confirmed that the hand did not move during each block.

Each hand was tested in two blocks in each testing session, ordered in ABBA design. The first session started with the left hand, and the second session started with the right hand.

7.2. Results

The distance between the actual and perceived location of the landmarks was coded in millimeters (Fig. 8) and then compared against zero using one-sample permutation tests. For both hands, negative values denote lateral and proximal biases. For the contralesional (left) hand, there was a significant lateral ($p < .001$, $M = -63.3$ mm, $SD = 30.3$ mm) and proximal bias ($p < .001$, $M = -51.5$ mm, $SD = 42.4$ mm). For the right hand, there was a significant lateral bias ($p < .001$, $M = -17.5$ mm, $SD = 26.1$ mm), but no significant shift in proximodistal direction ($p = .395$, $M = -2.40$ mm, $SD = 30.8$ mm). Two-sample permutation test showed significantly larger lateral and proximal biases ($ps < .001$) in the left hand versus the right hand.

7.3. Discussion

In this experiment, we found significant lateral and proximal shifts in perceived landmark locations on the contralesional left hand. Importantly, the direction of his landmark judgments is consistent with the direction of his tactile localization bias in previously reported experiments. We discuss the implication of these consistent biases in the General discussion section below.

8. General discussion

We report the tactile detection and localization performance of a unique case whose behavior informs us regarding models of tactile processing. First, DS demonstrated normal tactile detection with substantially impaired localization, demonstrating a strong single dissociation. Second, we found that on the contralesional hand, perceived stimulus locations on the skin surface were strongly affected by hand posture, with an ulnar bias when the hand was palm facing down, and a radial bias when the hand was palm facing up. To our knowledge, this is the first reported case showing perceived tactile location on the skin surface changes as a function of hand position. This finding provides evidence that localizing touch on the body does not only occur in somatotopic space, but also takes into account information from external space.

Past studies reported brain-damaged individuals who could detect touch but made large tactile localization errors (Halligan et al., 1995; Birznieks et al., 2012, 2016; White et al., 2010; Anema et al., 2009; Harris et al., 2004; Harris et al., 2004; Rapp et al., 2002). These cases could be explained by a single process model in which tactile detection and localization share a common process, but tactile detection uses less resources than localization. However, in a single process model, a strong single dissociation with completely normal tactile detection and substantially impaired localization (as in DS) would be highly unlikely. For this pattern to fit a single-process model, there would need to be a very large differential in the amount of resources needed for the two tasks – with damage resulting in a profound localization deficit and no measurable detection deficit. Although theoretically possible, it is unlikely for a single process model to predict both partial dissociation as in previously reported cases, and a strong dissociation as in DS, after brain damage. Instead, these results are broadly consistent with a multiple process model in which tactile detection and localization are dissociable processes.

There are two types of multiple process models – a serial model in which tactile information is first processed for detection and is subsequently utilized for localization, and a model in which tactile

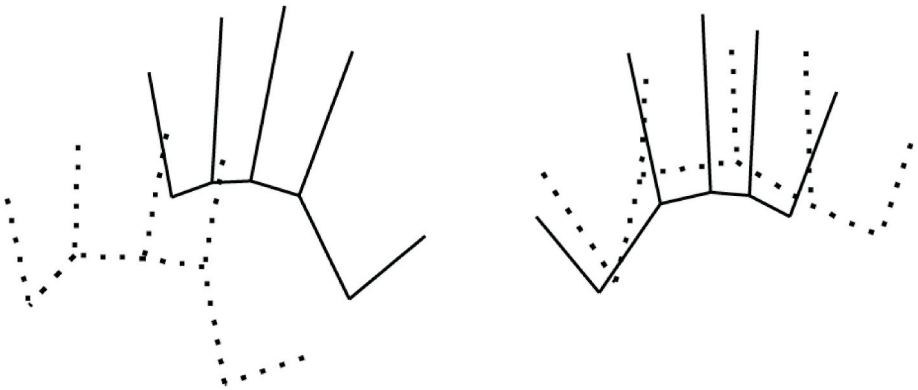

Fig. 8. Actual (solid lines) and perceived (dashed lines) landmark locations on the left (left panel) and right (right panel) hand. Landmarks are connected by straight lines to display the hand shapes.

information is processed for detection and localization in parallel (see Harris et al., 2004 for a discussion). Our results are consistent with either serial or parallel processing models, as both models can predict intact tactile detection and impaired localization. Strong evidence for the parallel model would be a clear double dissociation between tactile detection and localization. However, a double dissociation would not be predicted by the serial model, as participants with impaired detection and intact localization would not be expected if localization is performed after detection.

A clear single dissociation between tactile detection and localization also has implications on the neural correlates of the tactile localization process. Whereas most previous cases suffered brain damage along pathways from the thalamus to S1 (Halligan et al., 1995; Birznieks et al., 2012; White et al., 2010; Rapp et al., 2002), DS had an intact thalamocortical pathway, along with no parietal damage. This demonstrates that tactile localization deficits can be caused by lesions outside of the traditional thalamocortical pathway to S1, indicating the existence of additional pathways specific to tactile localization. Specifically, given that DS's localization errors occurred in an external, hand-centered frame of reference, the additional pathway might be responsible for mapping stimulus location to skin surface based on this frame of reference (this will be discussed in more detail later in the discussion).

The second important finding is that DS's tactile localization biases occurred in external space, always towards the left side based on the hand's proximodistal axis. Critically, these biases were not likely motor response errors during pointing or hemispatial neglect, as DS could accurately point to remembered visual targets, and demonstrated similar localization biases when making verbal responses. In addition, since tactile stimuli in the experiments were far beyond his detection threshold, localization errors were unlikely due to sensory noise. These findings provide strong evidence that tactile localization on the skin surface does not only utilize information from somatotopic space, but also information regarding current body posture. Previous studies have also provided evidence that proprioceptive information is considered during tactile localization, such that the pattern of localization errors was modulated by body posture (Badde et al., 2019; Haggard et al., 2006; Ho and Spence, 2007; Riemer et al., 2010). Taken together, these findings suggest that external information can influence the perceived location of tactile stimuli on the skin surface.

In addition to contrasting somatotopic versus external frames of reference, we also provide clear evidence that DS's tactile localization errors occurred in an external frame of reference specifically centered on the hand proximodistal axis. Previous studies reported spatial representations centered on the hand proximodistal axis. For example, tactile extinction has occurred for stimuli on the contralesional side with regards to the wrist midline (Moscovitch and Behrmann, 1994), a reference frame that overlaps with the hand proximodistal axis in the current study. In addition, studies of the tactile Simon effect showed that participants were faster and more accurate in judging intensity of a tactile stimulus when the stimulus occurred on the same side as the responding effector, with the side of tactile location defined relative to the hand proximodistal axis (Medina et al., 2019). However, since in these studies the hand/wrist proximodistal axes were always aligned with the viewer's perspective, the "left" and "right" sides could also be assigned from the viewer's perspective, but not relative to the hand/wrist axis per se. In the current study, by rotating the hand 90° and still observing localization biases towards the left side of the hand proximodistal axis, we confirmed that DS's localization errors occurred specifically relative to the hand proximodistal axis, providing strong evidence for a hand-centered frame of reference in representing tactile locations.

So far we have discussed two major findings from DS: A strong single dissociation between tactile detection and localization, and localization errors in an external frame of reference specifically centered on the proximodistal axis of the hand. An unanswered question is why DS mislocalizes touch towards the left side of the hand, regardless of hand posture. Given limited evidence, we cannot make a strong claim. However, we suggest one possible interpretation given DS's performance on the landmark localization task (Experiment 5). As shown in Experiment 5, DS made substantial leftward and proximal errors on his contralesional left hand. Importantly, proprioceptive biases on the contralesional hand were in the same directions as his tactile localization biases. One possibility is that his tactile localization biases stem from feedback processes from representations in external space to somatotopic representations. When the hand is touched, the brain not only represents tactile location on the skin surface, but also maps the location to external space by integrating proprioceptive information (Fig. 9, red arrow). Given leftward and proximal biases in proprioception, after being mapped to external space, touch may be represented in space to the left and proximal to the actual hand position (Fig. 9, gray circle). This biased external representation could then feed back to a somatotopic representation. Because of proprioceptive bias, where the touch is represented in external space only slightly overlaps with the actual hand position (Fig. 9, green area). However, there is a clear constraint that a touch must have occurred on the hand surface. Given the external biases and skin surface constraints, during the feedback process the touch is projected to the leftmost and proximal part of the skin surface, leading to tactile localization biases (Fig. 9, green area). In normal cases, biases from feedback processes may be much less weighted by information from somatotopic space, making the effect of proprioceptive errors not noticeable. Nevertheless, DS's lesion may have affected the relative weighting between somatotopic representation and effects of proprioceptive biases, leading to magnified localization errors. On this explanation, one possible mechanism for proprioceptive information to influence tactile localization is by feedback processes from representations of tactile location in external space to a somatotopic

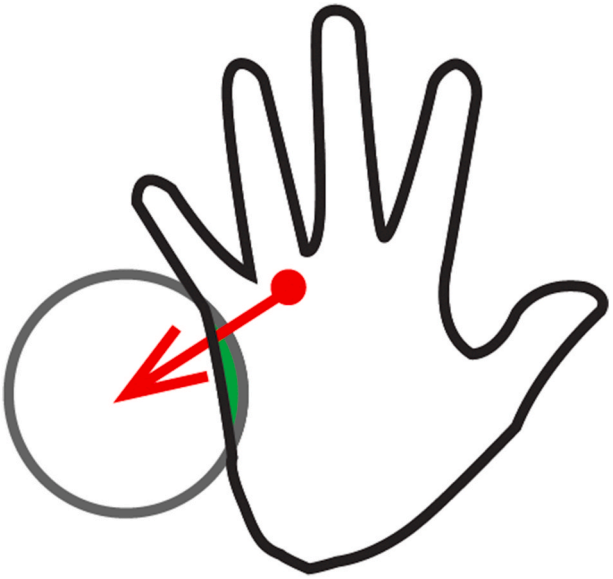

Fig. 9. Illustration of a potential explanation of DS's tactile localization bias. The red dot on the hand denote stimulus location. The red arrow denotes mapping of stimulus location from the somatotopic reference frame to external space, given proximal and lateral/leftward proprioceptive bias from Experiment 5. The gray circle represents a noise range where the stimulus would be perceived in external space, given noise in proprioception. Stimulus location in external space then feeds back to the skin surface. The green area denotes where the stimulus location in external space overlaps with the skin surface. Given the constraint that touch could only occur on the skin surface, when mapped back from external space to the skin surface, touch is localized to the green area. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

representation, biasing perception on the skin surface. An alternative account is that external information may not influence perception in a somatotopic reference frame per se, but is integrated during the response stage (Badde and Heed, 2016). On this account, in the case of DS the brain represents stimulus location on the skin surface (Fig. 9, red dot) and in external space (Fig. 9, gray circle) separately without mutual influence. However, when making responses, the two spatial codes are integrated, in this case with a stronger weight on the external code, leading to biased localization judgments towards the perceived stimulus location in external space. We note that both of these accounts are speculative. Future studies are needed to investigate the effect of proprioceptive biases on tactile localization on the body.

DS's behavioral results and lesion location also provide novel insights on the neural correlates of tactile localization. First, using transcranial magnetic stimulation, previous studies found that the primary somatosensory cortex, and parietal cortex more generally, play a causal role in localizing touch on the skin surface (Porro et al., 2007; Seyal et al., 1997). Nevertheless, DS had no damage to parietal cortical areas or pathways from thalamus to S1, indicating additional neural correlates for tactile localization. Second, whereas past literature has focused on motor deficits after corona radiata infarcts (Cho et al., 2007; Kim and Pope, 2005; Kwon et al., 2011; Roby-Brami et al., 2003; Shelton and Reding, 2001; Song, 2007), we report for the first time substantial – and selective – tactile localization errors after corona radiata lesion. From our tractographic analyses (see Appendix), DS's lesion of the superior and anterior corona radiata likely disrupted pathways from the thalamus to the frontal eye field and partially, superior frontal gyrus. These areas have not been reported to directly relate to tactile localization. Given limited evidence, it is difficult to infer the neural mechanism of DS's deficits. Here we discuss literature that may be relevant.

The frontal eye field is involved in eye movements, but may also encode proprioceptive information. Single-cell studies on primates demonstrated that neurons in the frontal eye field are active preceding saccade movements or upon cues predictive of subsequent saccades (Bruce and Goldberg, 1985). One neural mechanism is that the thalamus relays corollary discharge to the frontal eye fields before the saccade is initiated, based on which neurons in the frontal eye field shift their receptive fields based on the future fixation (Sommer and Wurtz, 2006). Lesions in the frontal eye field resulted in delayed endogenously induced saccades towards the contralesional hemispace in humans (Henik et al., 1994) and a delayed manual response towards contralateral visual targets in monkeys (Crowne et al., 1981). Interestingly, the magnitude of the saccade activity of the frontal eye field neurons was modulated by hand position, with stronger modulation effects when the location of visual saccade target varied within vs. outside the reachable space of the hand (Thura et al., 2011). These findings indicate that neurons in the frontal eye field also encode proprioceptive information about the hand. In daily life, coordination between visual information and hand movements is ubiquitous. To achieve this, eye-centered visual information and hand-centered coordinates need to be transformed and aligned. Given that the frontal eye field encodes both eye-centered and proprioceptive information, it may be involved in coordinate transformations. It is unclear in which reference frame is the information aligned, but it is possible that disrupted connections between the thalamus and frontal eye fields impaired coordinate transformation at some stages, which then introduced errors in hand location representation in external space. Such impairments might be caused by disrupted pathways between the thalamus and frontal eye field, or consequential corticocortical connections between the frontal eye field and other regions (Elston and Rosa, 1998; Thura et al., 2011). Misrepresentation of hand position may have then led to tactile localization errors, as outlined in the previous paragraph.

With regards to the partially disrupted thalamus-superior frontal gyrus pathway, neuroimaging studies have reported activation in the superior frontal gyrus during tactile spatial pattern discrimination and tactile localization (Hegner et al., 2010; Takahashi et al., 2013), indicating that these frontal regions are involved in tactile spatial processing. For example, during a tactile temporal order judgment task, bilateral middle frontal gyri were more activated compared with a control task (Takahashi et al., 2013). We note that with limited data and prior evidence, it is not possible to infer the neural mechanism of DS's deficits, and our accounts are speculative. Future studies are needed to investigate the function of these pathways in somatosensory processing. That said, these results suggest the potential role of the frontal eye field and/or superior frontal gyrus in tactile localization.

Finally, we report for the first time mislocalization of tactile stimuli across surfaces. Specifically, DS was substantially more likely to mislocalize tactile stimuli to dorsal side when stimulated on palmar side, compared to the opposite direction. Unfortunately, we do not have enough evidence from DS or prior literature to explain why such errors occurred. Most previous tactile localization studies only present stimuli to one surface. Contextual constraints in past studies (e.g. top-down knowledge that tactile stimuli are only being presented to one surface) may either alter responses or perceptual processes to limit reported stimuli to one side. It is possible that such biases could also be observed in other individuals with brain damage, or in neurologically-intact individuals. We believe that it is valuable to examine both palm and dorsum surfaces to fully understand tactile localization processes for the entire hand.

CRediT authorship contribution statement

Yuqi Liu: Conceptualization, Methodology, Formal analysis, Investigation, Writing - original draft. **Alexandria O'Neal:** Methodology, Investigation, Formal analysis. **Robert D. Rafal:** Formal analysis, Writing - original draft, Supervision. **Jared Medina:** Conceptualization, Methodology, Writing - original draft, Supervision, Project administration.

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Appendix

Lesion analysis with probabilistic tractography

Image acquisition and processing

Diffusion-weighted images were acquired using a 3.0 T Siemens Magnetom Prisma scanner at the University of Delaware Center for Biomedical and Brain Imaging. An echo planar sequence (TE = 106.0 ms, TR = 5300 ms, voxel size = 1.4 × 1.4 × 4 mm, 35 sagittal slices) included 64 diffusion-directions with a diffusion weighting of b = 1000. A T1-weighted structural image was acquired using an MPRAGE sequence (TR = 2080.0 ms, TE = 4.64 ms, flip angle = 7°, voxel size = 0.7 × 0.7 × 0.7 mm, 208 sagittal slices).

Images were processed and analyzed using the FSL package (FMRIB Software Library v5.0, Oxford, UK). For preprocessing, the diffusion-weighted images were first corrected for eddy currents and susceptibility. After brain extraction BET tool of FSL, the T1-weighted structural image was co-registered to the diffusion space.

Probabilistic Tractography

Tractography analyses were performed using the FDT diffusion toolbox in FSL. First, diffusion parameters were estimated using the BEDPOSTX tool. Next, tractography was done using the ProbtrackX tool (number of samples = 5000, curvature threshold = 0.2). In addition, a whole-brain map of fractional anisotropy (FA) values was obtained using the DTIFIT toolbox in FSL.

Structural MRI (Fig. 1) revealed that DS had damage restricted to white matter, and that the primary somatosensory cortex (S1) in the post-central gyrus, as well as thesecondary somatosensory cortex (S2) in the parietal operculum were spared. The first goal of these tractographic analyses was to determine whether connections between the thalamus and S1 and those connecting S1 and S2 were intact. As detailed below preserved tactile detection in DS was associated with preservation not only of S1 and S2 but also the white matter tracts connecting S1 to thalamus and to S2. The second goal of the tractography was to demonstrate what structures were disconnected by the destruction of white matter in the corona radiata of the right hemisphere.

Connections of the primary somatosensory cortex

We first virtually dissected connections between S1 and the thalamus, and connections between S1 and S2. Figure A1 shows the masks used for probabilistic tractography.

The masks for S1 were manually drawn on axial slices of the hand area of the post-central gyrus of both hemispheres. The hand area knob of the primary motor cortex in the precentral gyrus served as a landmark to identify the hand area of S1. Masks for the dissection of connections to S2 in each hemisphere were manually drawn on coronal slices across the parietal operculum. The thalamus seed masks were obtained from the Harvard-Oxford Subcortical Structural Atlas, obtained from FSL's Atlas Tools, co-registered to DS's structural space.

For each connection in each hemisphere, probabilistic tractography was run twice using one mask as a seed mask and another mask as target (waypoint and termination mask), and then reversing the process using the other mask as seed. An exclusion mask for this and subsequent tractography included exclusion of streamlines crossing the midsagittal plane or the axial plane just above the optic chiasm. In addition, for tractography of connections between S1 and S2, the exclusion mask also was drawn over the entire insular cortical ribbon. From each tractography analysis, a streamline map was generated where the value of each voxel represents the number of samples that went through that voxel from the seed space. This map was then thresholded such that only voxels that contained at least 10% of the maximal number of samples were kept (Azadbakht et al., 2015). When probabilistic tractography revealed streamlines for both dissections, the resulting streamlines were compared for consistency, and were binarized in order to map overlapping voxels for use in visualization and computation of mean fractional anisotropy (FA).

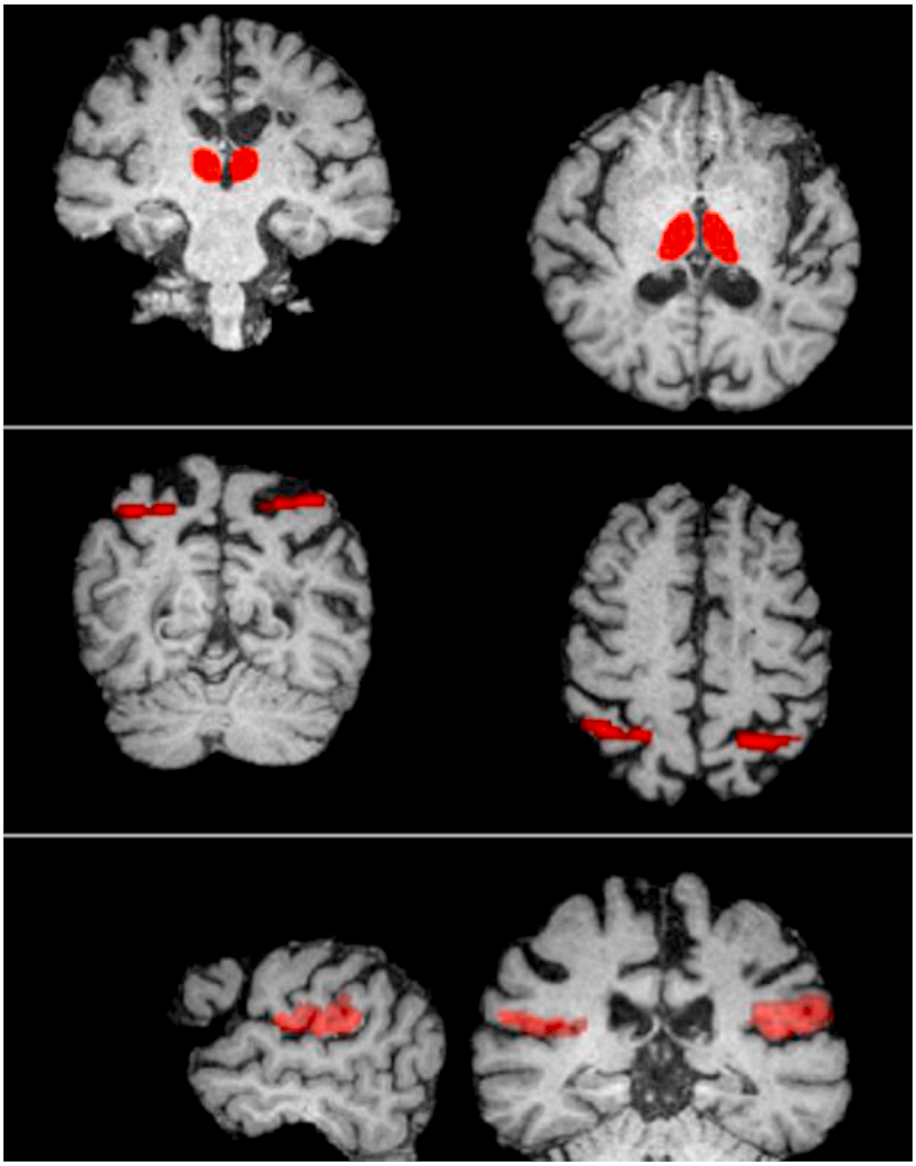

Fig. A1. Masks used in probabilistic tractography to generate streamlines between thalamus and S1, and connections between S1 and S2. Top: Coronal (left) and axial (right) slices showing thalamus mask. Middle: Coronal (left) and axial (right) slices showing manually drawn masks on the hand area S1 cortex. Bottom: Sagittal (left) and coronal (right) slices showing manually drawn masks of the parietal operculum (S2).

Figure A2 displays the results of the tractography analyses. In both hemispheres, streamlines started from the ventral-lateral part of the thalamus and travelled posteriorly to S1. These findings indicate that pathways from the thalamus to S1 were not affected by the lesion.

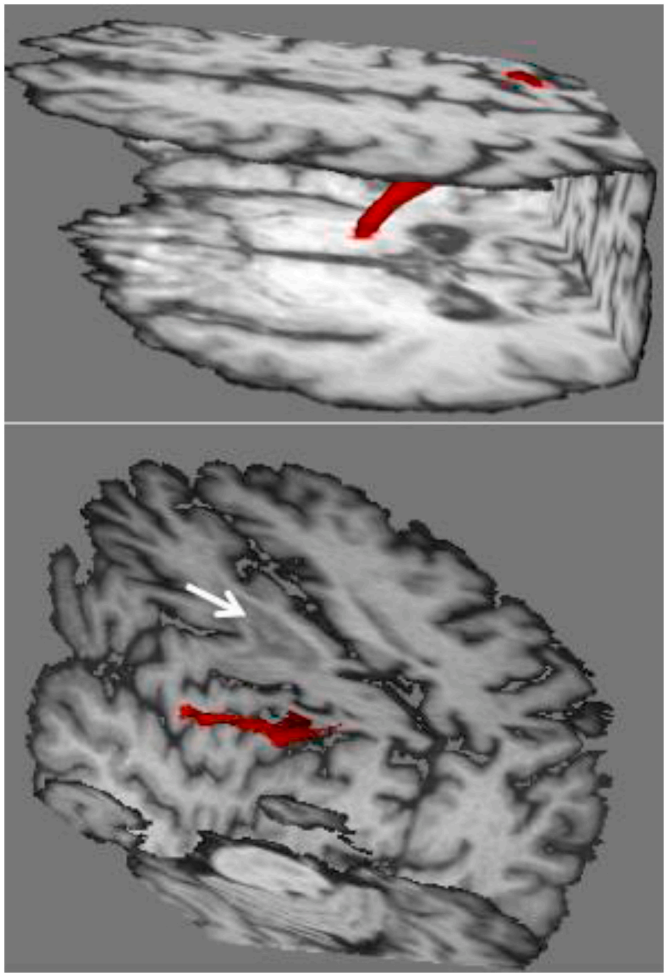

Fig. A2. Probabilistic tractography in the lesioned right hemisphere between S1 hand area and the thalamus (top) and S2 (bottom). The gliotic area of the lesion is evident in the bottom figure (white arrow). The streamlines in the right hemisphere were symmetrical with those generated in the left hemisphere (not shown).

Tractographic study to estimate thalamocortical projections damaged, and spared, by the stroke

To examine what connections were likely to have been destroyed by the lesion, the lesion mask (see Fig. 1) was reflected onto the left (contralesional) hemisphere to generate a mirrored lesion mask using the FSLswapdim utility of FSL. This mask was used as a waypoint mask in a series of virtual dissections conducted in diffusion space of the intact left hemisphere. The resulting streamline was then reflected onto the right hemisphere to estimate the typography of the fibers that could have been damaged by the stroke. It should be understood that this procedure is an estimate of potentially damaged fibers because it assumesthat homologous fibers in the two hemispheres were symmetric premorbid, and that tissue retraction due to gliosis had a minimal effect on the course of the fibers.

First, the left thalamus mask (Figure A1) was used as a seed mask and the mirrored lesion mask in the left hemisphere was used as waypoint mask. The goal was to determine the thalamic efferents that had traversed the lesioned region prior to the stroke, and to identify their cortical targets. The resulting streamline was reflected onto the right hemisphere. Figure A3 shows that thalamic projections through apparently lesioned tissue would have terminated in the premotor cortex, frontal eye field and the superior frontal gyrus prior to the stroke.

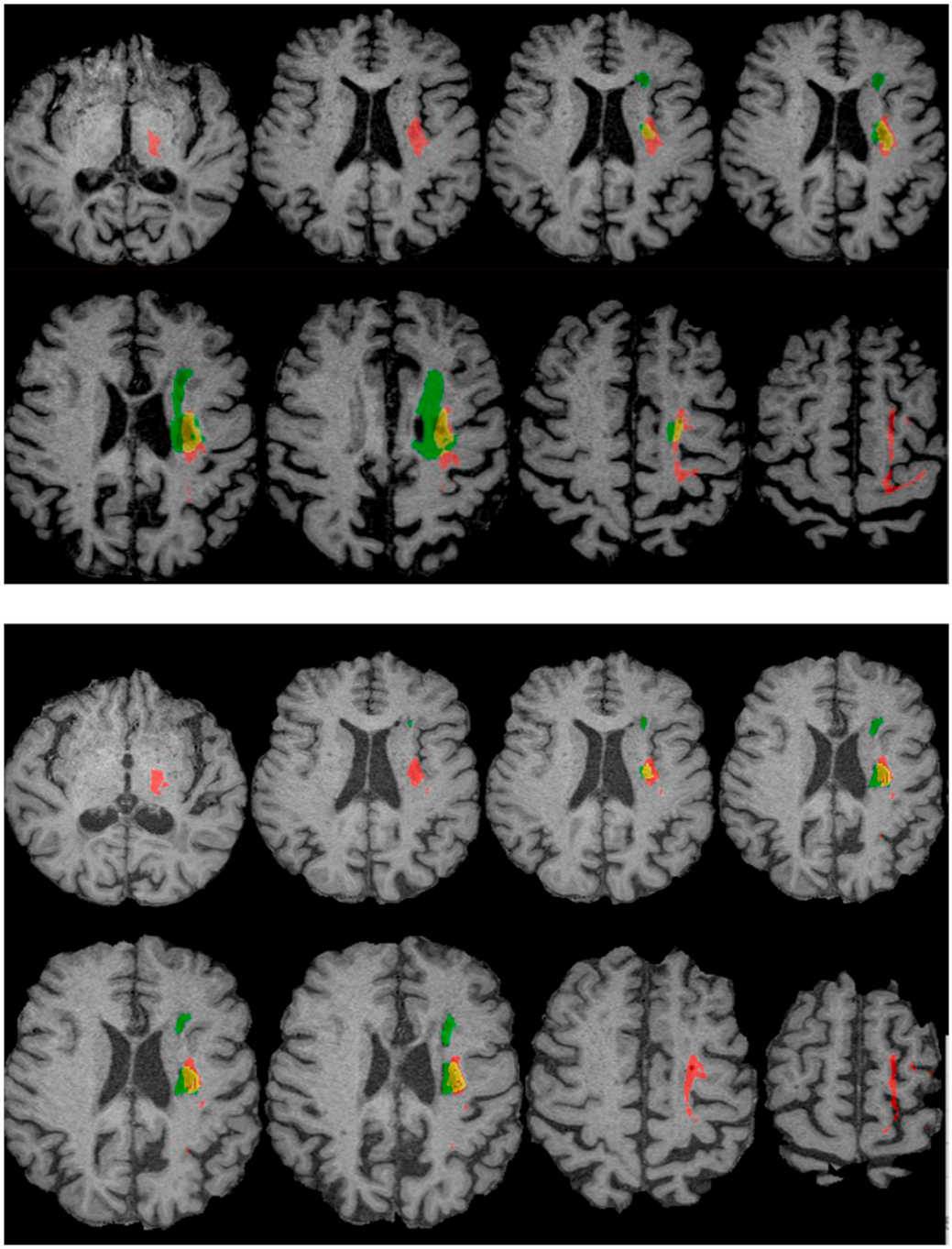

Fig. A3. T1-weighted axial slices (from ventral on top left to dorsal on bottom right in each panel) showing thalamic projections (in red) that had passed through lesioned tissue (green) prior to the stroke. The region where the fibers could have been damage by the stroke is shown in yellow. Top Panel: Shows fibers that could have been disrupted by any part of the lesion. Bottom Panel: Shows where fibers would have been transected by the cystic component of the lesion.

Thalamic projections to premotor cortex

The previous analysis suggested that some connections between thalamus and premotor cortex would have had to pass through tissue that appears gliotic on T1-weighted MRI. Since the functions of premotor cortex in motor preparation operate in a hand-centered reference frame of the type distorted in this individual, we performed a virtual dissection of connections between thalamus and premotor cortex. While premotor cortex is traditionally conceptualized as having motor functions, it may also process pure sensory information. There is evidence that neurons in the premotor cortex encodes visual information independent of hand action. Song and McPeek (2010) have recorded from dorsal premotor cortex neurons with responses time-locked to visual stimulus onset rather than to reach movement onset. They reported that these sensory premotor cortex neurons signaled target selection, and were physiologically distinct, with narrow action potentials, from movement-related neurons which had broader action potentials. It is possible that the premotor cortex also encodes tactile information for haptically-guided hand movements.

To determine whether thalamic projections to premotor cortex had been destroyed by the lesion, probabilistic tractography was implemented using the thalamic seed mask (shown in Figure A1), and premotor cortex as a target mask in the ipsilesional hemisphere. Premotor cortex masks were drawn in each hemisphere using anatomical landmarks specified by Ahdab et al. (2014). This was achieved by manually drawing a mask on sagittal

slices that masked the rostral and caudal banks of the precentral sulcus. Figure A3 shows the masks of the premotor cortices (green) and the tractography demonstrating streamlines in both hemispheres (red streamlines). The anterior part of the streamline in the right hemisphere appear to pass through gliotic tissue.

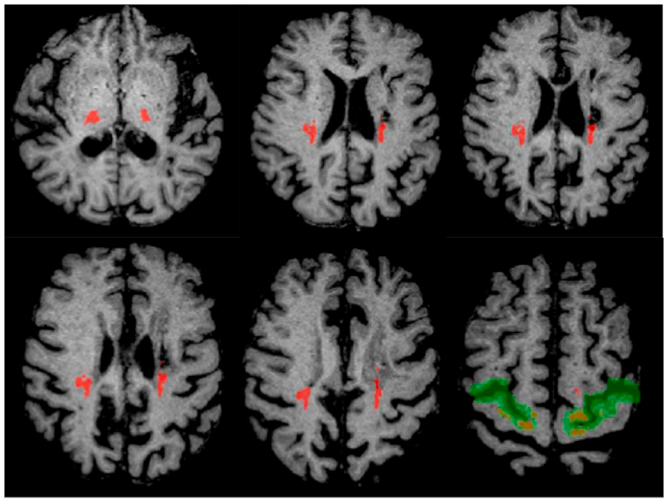

Fig. A4. Thalamic projections to premotor cortex are shown in red on a series of T1-weighted axial slices from ventral to dorsal. The premotor cortex target mask is shown in green. The thalamus seed masks are shown in Figure A1.

Thalamic projections to the superior frontal gyrus (SFG)

Because the analysis shown in Figure A3 suggested that some thalamic projections to the superior frontal gyrus may have been damaged by the stroke, tractography was implemented to identify fibers that may have been damaged and those that had been spared. The thalamic seed masks are shown in Figure A2, and the mask of the superior frontal gyrus is shown in green in Figure A5. Figure A5 shows preservation of some thalamic projections to the superior frontal gyrus in both hemispheres (red). An estimate of destroyed white matter tissue (yellow) was achieved by reflecting the thresholded (10%) and binarized streamline connecting the thalamus to the SFG from the intact left hemisphere to the right hemisphere; and then subtracting the thresholded and binarized streamline between thalamus and the SFG in the damaged right hemisphere.

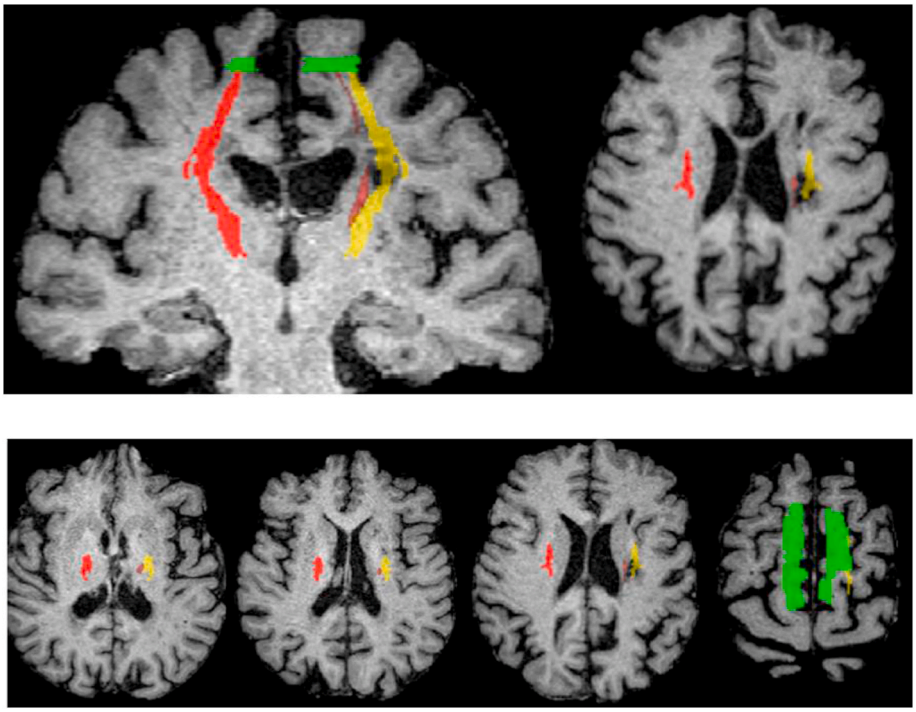

Fig. A5. Top panel: Thalamic projections to the superior frontal gyrus in both hemispheres (red) shown on T1-weighted. Bottom panel: The same projections shown on axial slices from ventral (left) to dorsal (right). The superior frontal gyrus target masks are shown in green. The thalamus seed masks are shown in Figure A1. An estimate of destroyed white matter tissue (yellow) was achieved by reflecting the thresholded (10%) and binarized streamline connecting the thalamus to the SFG from the intact left hemisphere (in red) to the right hemisphere; and then subtracting the thresholded and binarized streamline between thalamus and the SFG in the damaged right hemisphere.

Thalamic projections to the frontal eye field (FEF)

Electrophysiological recordings and inactivation studies have shown that the medio-dorsal thalamic nucleus of the thalamus transmits oculomotor

corollary discharge signals from the superior colliculus to the frontal eye field (Sommer and Wurtz, 2006). In monkeys these fibers originate from neurons on the lateral border of the medio-dorsal nucleus of the thalamus and synapse on frontal eye field neurons between the end of the principle sulcus and the curve of the arcuate sulcus.

To determine whether thalamic projections to the frontal eye field were intact in the lesioned right hemisphere, probabilistic tractography was implemented in both hemispheres using a mask generously overlapping the border of the mediodorsal thalamic nucleus shown in yellow in Figure A6, and a mask over the posterior part of the middle frontal gyrus, shown in blue in Figure A6. Connections between the medio-dorsal thalamic nucleus and the frontal eye field in the undamaged left hemisphere are shown in blue in Figure A6. No streamline was generated in the right hemisphere (using either thalamus mask or FEF mask, as seed), suggesting that thalamo-cortical projections to the frontal eye field may have been destroyed. To estimate the premorbid course of these projections, the streamline from the left hemisphere was reflected onto the right hemisphere. Figure A6 shows that the estimated topography of premorbid thalamocortical projections had traversed the region destroyed by the cystic component of the lesion (yellow).

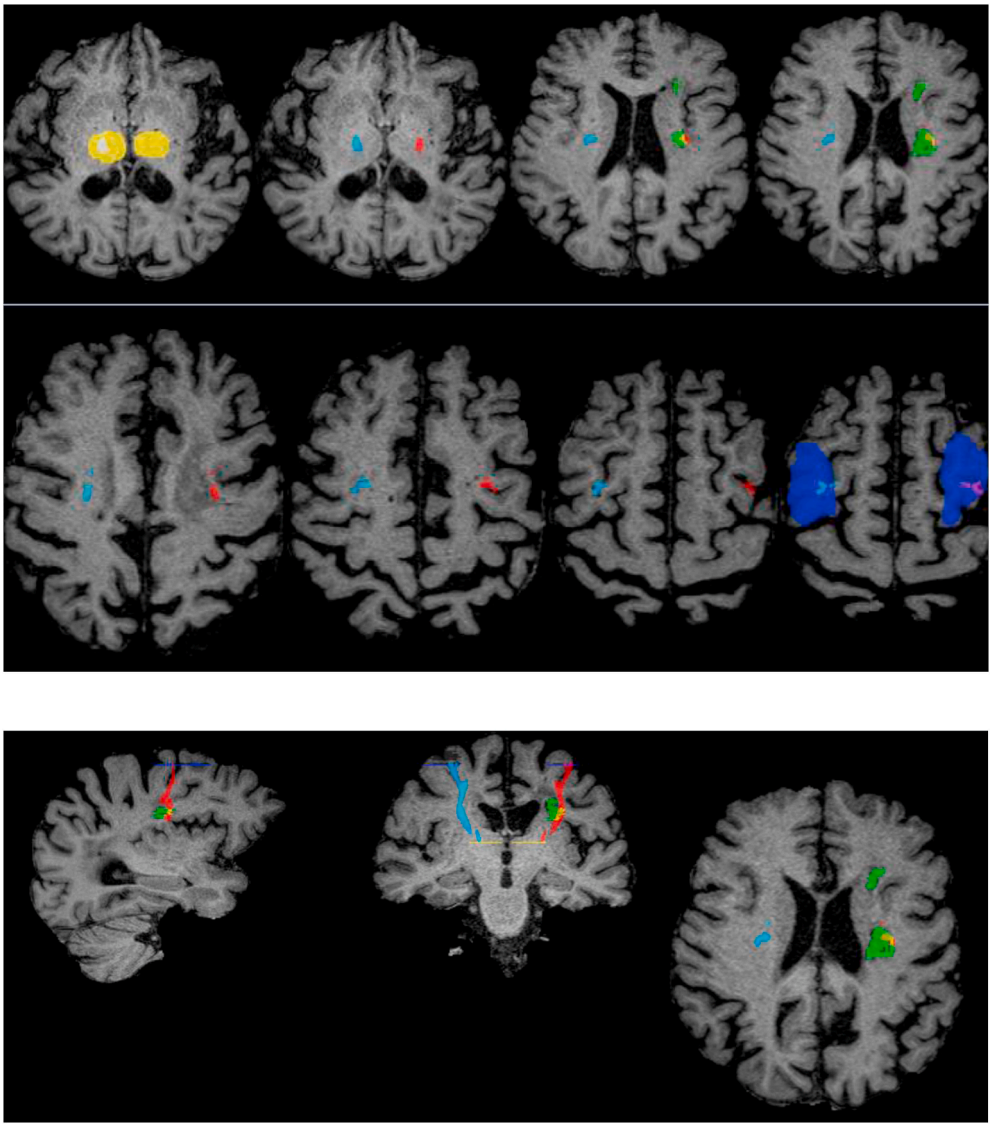

Fig. A6. Connections between the medio-dorsal nucleus of the thalamus and the frontal eye field in the left hemisphere are shown in light blue. Missing connections between thalamus and frontal eye field in the right hemisphere (depicted in red) were demonstrated by reflecting the streamline in the left hemisphere (light blue) onto the right hemisphere. The right hemisphere connections (red) are shown to have been transected (yellow) where they traversed the region destroyed by the cystic component of the lesion (green). The seed masks covering the medio-dorsal thalamic nuclei are shown in yellow (top left) and the frontal eye field masks in dark blue. Top Panel: Axial sections from ventral (top left) to dorsal (bottom right). The yellow region surrounded by green shows the connections between the thalamus and frontal eye field that were transected by the cystic component of the lesion (green). Bottom Panel: Three views (left: sagittal, middle: coronal, right: axial) showing transection (yellow) of thalamic connections with the frontal eye field.

Connections between Brodmann's area 5 and premotor cortex

Brodmann's area 5 is a region of somatosensory cortex (with some neurons being also visually responsive, Padberg et al. (2005)), posterior to area 2 which, superiorly, it displaces. Area 5 connections and physiological response properties implicate it as a neural substrate critical for the kind of hand-centered somatotopic mapping under consideration in the case of this individual. Individual neurons in area 5 receive afferents from proprioception-responsive neurons in primary sensory area 3 (Duffy and Burchfiel, 1971) of both hemispheres. These neurons respond to movements from multiple joints on both sides of the body; and some cells have exhibited convergence between touch and kinesthesis (Duffy and Burchfiel, 1971). With changing limb position, reach movement directional tuning of area 5 neurons rotate in space such that they predict rotation of the arm necessary

to perform the task (Ferraina and Bianchi, 1994). Sakata, Takaoka, Kawarasaki and Shibutani (1973) concluded that "area 5 is the site of higher order processing of somesthetic information, and may give rise to the neural code of position and form of body and tactile objects in 3-dimensional space."

Since an interruption of area 5 projections to premotor cortex could potentially distort an action-based topographic somatosensory map, tractography was implemented in both hemispheres to examine whether those projections could have been damaged by the stroke. For this virtual dissection, masks of area 5 were manually drawn on several successive slices of the T1-weighted image, using the postcentral gyrus as a landmark. The masks included the posterior banks of the most superior part of the postcentral gyrus (yellow in Figure A7). The masks of premotor cortices are shown in Figure A4.

Figure A7 shows that connections between area 5 and premotor cortices appear to be intact and that the course of the connecting streamline was posterior to any region of damaged brain tissue (red streamlines in Figure A7).

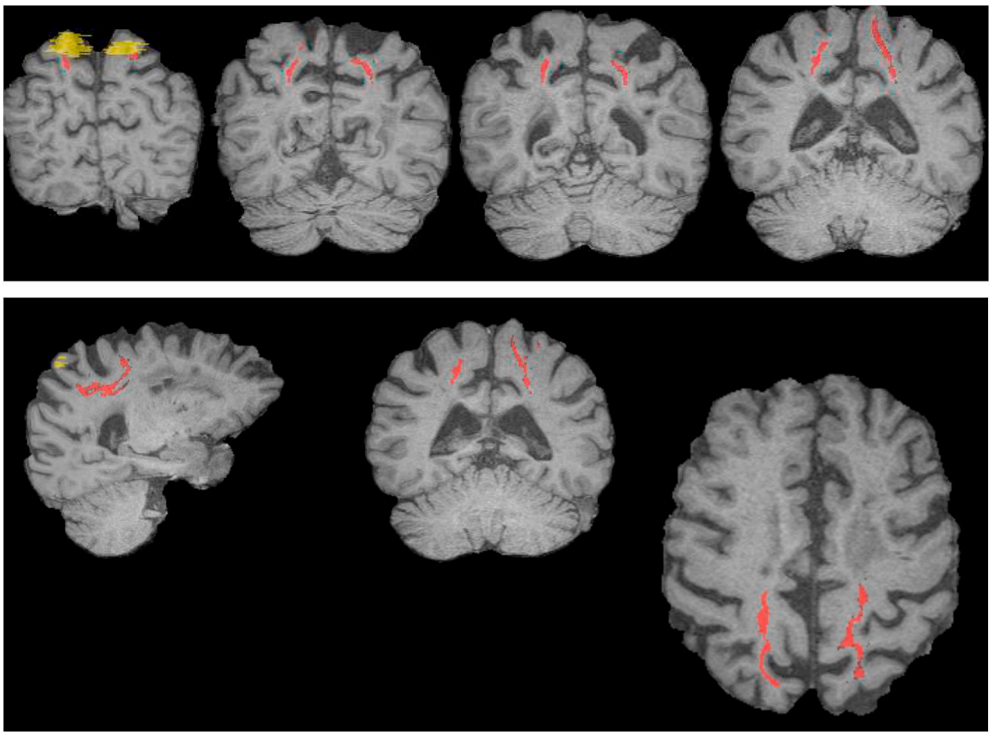

Fig. A7. Connections between area 5 and premotor cortex in both hemispheres shown in red. The area 5 seed mask is shown in yellow on top left. The top row shows a series of coronal slices from posterior to anterior. The bottom row additionally shows sagittal and axial slices demonstrating that the course of the connections between area 5 and premotor cortex was posterior to the lesion and intact.

Summary of tractographic observations

Probabilistic tractography demonstrated that the following relevant pathways were spared by the lesion:

Thalamic projections to S1 (Figure A2, top).

Connections between S1 and S2 (Figure A2, bottom).

Connections between area 5 and premotor cortex (Figure A7).

Thalamic projections to premotor cortex may have also been spared. However, the most posterior part of the streamline passed through gliotic tissue, and white matter integrity of this part of the streamline may be functionally compromised.

Probabilistic tractography suggests that the right hemisphere connections between the dorsomedial nucleus of the thalamus and the frontal eye field may have been completely destroyed by the stroke (Figure A6).

Thalamic projections to the superior frontal gyrus (Figure A5) have been compromised by the stroke. While some fibers appear to have been preserved, most of the pathway was destroyed by the stroke.

Table A1 shows mean FA values for all streamlines.

Table A1
Mean FA values for streamlines in each hemisphere.

	Right FA	Left FA	Hemispheric Asymmetry
Thalamus-S1	.410	.380	−0.03
S1–S2	.318	.303	−0.015
Thalamus-Premotor	.366	.408	0.042
Thalamus-SFG	.276	.362	0.086
Area 5-Premotor	.382	.408	0.026

Author contributions

All authors developed the study question and designed the experiments. Y. Liu and A. O'Neal performed data collection. Y. Liu performed analyses and prepared the manuscript draft. J. Medina and R.D. Rafal supervised data analyses and provided critical revisions to the manuscript. All authors

approved the final version of the manuscript.

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