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Case study: A selective tactile naming deficit for letters and numbers due to interhemispheric disconnection

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ABSTRACT

The role of white matter pathways in cognition is a topic of active investigation that is vital to both the fields of clinical neurology and cognitive neuroscience. White matter pathways provide critical connectivity amongst numerous specialized brain regions thereby enabling higher level cognition. While the effects of dissections and lesions of the corpus callosum have been reported, it is less understood how unilateral focal white matter lesions may impact cognitive processes. Here, we report a unique case study in which a small left lateralized stroke in the white matter adjacent to the body of the corpus callosum selectively impaired the ability to name letters and numbers presented to the ipsilesional, left hand. Naming of letters, numbers and objects was tested in both the visual and tactile modalities in both hands. Diffusion-weighted imaging showed a marked reduction in white matter pathway integrity through the body of the corpus callosum. Clinically, this case highlights the significant impact that a focal white matter lesion can have on higher-level cognition, specifically the integration of verbal and tactile information. Moreover, this case adds to prior reports on tactile agnosia by including DTI imaging data and emphasizing the role that white matter pathways through the body of the corpus callosum play in integrating tactile input from the right hemisphere with verbal naming capabilities of the left hemisphere. Finally, the findings also provoke fresh insight into alternative strategies for rehabilitating cognitive functioning when structural connectivity may be compromised.

1. Introduction

Norman Geschwind (1965) introduced the notion that impairments in many domains including language, action and emotion could arise from white matter pathway disconnection, as opposed to strictly cortical damage. This concept has since resulted in various disconnection hypotheses as explanations for a variety of neuropsychological disorders (the hodological approach per Catani and Ffytche, 2005). For example, both visuospatial neglect (Doricchi and Tomaiuolo, 2003; Doricchi et al., 2008) and various speech and language deficits (Bajada et al., 2015; Dick et al., 2013; Duffau, 2014; Ivanova et al., 2016) have been described as disconnection syndromes involving white matter fiber pathway disruption within either the right or left hemisphere, respectively. In particular, these studies have indicated the importance of stroke-related *intra*-hemispheric white matter pathway damage in cognitive processes such as language and attention. However, there has been far less research on the impact that unilateral focal lesions may have on *inter*-hemispheric white matter connectivity through the corpus callosum. Here, we describe a case of disconnection due to a small focal stroke adjacent to the corpus callosum.

The corpus callosum is the largest collection of white matter fibers, consisting of over 200 million axons that interconnect cortical areas in the two cerebral hemispheres (Aboitz et al., 1992; Innocenti, 1995; Schmahmann and Pandya, 2006). Studies of callosotomy and callosal agenesis patients, where the corpus callosum is surgically severed or underdeveloped, have demonstrated two important findings, namely that the corpus callosum is critical for interhemispheric transfer and that the two cerebral hemispheres are specialized for different cognitive processes (Bogen and Vogel, 1962; Gazzaniga et al., 1962; Wilson et al., 1977). Several studies, for example, have demonstrated that the corpus callosum plays a central role in transferring and integrating information between the left and right hemispheres of the brain (Banich, 1995; Banich and Shenker, 1994; Bloom and Hynd, 2005; Schulte and Müller-Oehring, 2010) and that callosal connectivity is related to

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interhemispheric transfer time (Reuter-Lorenz et al., 1995; Forster and Corballis, 1998; Iacoboni et al., 2000; Zaidel and Iacoboni, 2003; Paul et al., 2007). Meanwhile, other studies have highlighted the different functional specializations of the left and right cerebral hemispheres (for review see Gazzaniga, 2005; and Zaidel, 1991). For example, the right hemisphere appears to be superior for face recognition, visuospatial tasks, processing of global/holistic forms, and performing mental rotation (Bogen and Gazzaniga, 1965; Nebes, 1973; Gazzaniga and Smylie, 1983; Corballis and Sergent, 1988; Robertson et al., 1993). Similarly, in the vast majority of adults, the left hemisphere is specialized for most aspects of language (Lassonde et al., 1990; Reuter-Lorenz and Baynes, 1992; Gazzaniga, 2000). In addition, each hemisphere contains sensorimotor cortices that correspond to the contralateral side of the body. Together, these findings emphasize the role that the corpus callosum may play in linking information gathered through visual spatial and manual exploration of the physical environment with linguistic/communication abilities.

Brain imaging studies in healthy adults have confirmed many of the findings from callosotomy studies including evidence for hemispheric specialization (Bogen et al., 1988; Kanwisher et al., 1997; McCarthy et al., 1996; Pujol et al., 1999; Szaflarski et al., 2006; Thiebaut de Schotten et al., 2011; Sergent et al., 1992) and interhemispheric transfer time being associated with corpus callosum integrity (e.g. Clarke and Zaidel, 1994; Iacoboni and Zaidel, 2004). Importantly, fMRI studies by Fabri and colleagues (2001, 2011) have further demonstrated that activations associated with specific task modalities are associated with activation within discrete regions of the corpus callosum. Specifically, central-posterior portions of the body of corpus callosum have been associated with touch stimulation, while the splenium is more active during visual stimulation.

Recent advances in white matter imaging and tractography analysis techniques have provided a further means of studying connectivity and communication between different brain regions via specific white matter pathways. Tractography studies by Fabri and colleagues in healthy controls, for example, have confirmed that interhemispheric connections between homotopic areas of the cortex are organized within various segments of the corpus callosum. Of particular relevance to the current report, the midbody and posterior half of the body of the corpus callosum have been associated with motor and sensory control of the hands (Fabri et al., 2014). To date, however, there is little research on the impact that unilateral focal lesions may have on interhemispheric white matter connectivity through the corpus callosum, especially in regard to connections between non-homotopic regions.

The paucity of research in this area stems in part from the rarity of small focal infarcts that are confined to white matter regions. While strokes are a common cause of unilateral focal lesions, infarcts due to stroke are often sizable and have a wide range of behavioral consequences. Strokes impacting frontal or frontal-parietal cortices, for example, will often result in somatosensory and motor (hemiparesis) impairments, while other strokes can affect visual perception and language abilities, depending on the side and location of the lesion. Unilateral strokes resulting in well-confined infarcts involving primarily or only white matter pathways are rare. Such cases, however, can be especially informative in providing a greater understanding of the role of interhemispheric white matter pathways in cognition and perception.

In the case reported here, a patient with a small, unilateral focal lesion near the central body of the corpus callosum exhibited difficulty identifying a number that was traced onto her hand during a neurological exam. Her primary sensorimotor cortices and language areas were completely intact. Thus, in an effort to determine the degree to which callosal fibers were disrupted between the language dominant left hemisphere and primary sensory cortex in the right hemisphere, we analyzed diffusion-weighted imaging data using high angular resolution diffusion imaging (HARDI) deterministic tractography. This allowed us to determine the extent to which white matter pathways through the corpus callosum were compromised. In order to further explore the extent of this patient's tactile naming impairment, we also conducted a series of tactile naming tests (described below). This case is important as it highlights the potentially significant impact of a small white matter lesion on cognition, as well as the importance of callosal white matter fibers in establishing connectivity between different functional domains. In particular, this case suggests the corpus callosum may play a critical role in linking information gathered through manual exploration of the physical environment with linguistic/communication abilities.

2. Methods and materials

This research was approved by the Institutional Review Board at the VA Northern California Health Care System and was HIPAA compliant. Informed consent was obtained prior to data collection.

2.1. Case description

The patient was a right-handed, native-English speaking, female with 16 years of education who suffered a stroke at age 39 due to left carotid artery dissection. She had no prior neurologic history or history of substance abuse. Medical records indicated that the patient presented acutely with speech difficulties and right-sided sensorimotor symptoms. Primary complaints immediately after the stroke included weakness and decreased sensation in the dominant right hand, arm and foot; difficulty speaking; and an inability to continue her work as a graphic designer. The patient was referred to our stroke research program at 3 years post-onset, and a neurological exam was conducted at that time. During this exam, visual confrontation testing revealed a mild quadranopsia in the lower right visual field, mild weakness in the right hand and arm compared to the left, and difficulty identifying numbers that were traced onto the palm of her hands (tactile agraphesthesia).

2.1.1. Neuropsychological profile

An Edinburgh Handedness Inventory indicated that the patient was unequivocally right-hand dominant prior to the stroke (score 100/100). In addition, a series of neuropsychological tests were administered as part of a research battery. Table 1 shows the individual raw scores and normative percentiles (when available) for the neuropsychological assessments that were administered. Based on the Weschler Test of Adult Reading (WTAR), the patient had an estimated pre-morbid Verbal IQ of 102. To test for signs of hemispatial neglect, the Behavioral Inattention Test (BIT-Conventional) was administered. The patient scored in the unimpaired range, above the cutoff score (<128) for hemispatial neglect. In fact, no lateralized attentional bias was apparent on any of the individual BIT subtests (including clock drawing). Verbal short-term memory was assessed via the WAIS-IV Digit Span test revealing a normal forward digit span of 7 items. However, the Spatial Span score fell in the 5th percentile (impaired range). In addition, the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) was administered. All RBANS Index scores were within the low average to average range, except for the Attention Index which is based on Digit Span and Symbol Coding and was in the impaired range. Speech, language, and reading were all within normal limits as assessed by the Western Aphasia Battery (WAB; Kertesz, 1982). The patient received an overall WAB Aphasia Quotient (AQ) of 99.8/100, where the normal cutoff is >93.7. Scores on the individual subtests of the WAB AQ (Spontaneous Speech, Comprehension, Repetition & Naming – which included object naming) were all at ceiling. Scores on the WAB Cognitive Quotient subtests (Reading, Praxis, Drawing & Constructional Drawing) also approached ceiling.

Two-point sensory discrimination thresholds were tested at the time of tactile testing and were found to be normal for the patient's left and right palms (within 1 cm, for each) and left and right index fingers (5 mm and 5–6 mm, respectively). When asked about motor symptoms and hand use after her stroke, the patient reported more frequent use of her non-dominant, left hand due to right-handed weakness. She denied any

Table 1
Neuropsychological test scores grouped by cognitive domain. Raw or index scores and normative percentiles (when available) are shown. Where normative percentiles were not available, the raw score out of the total possible score is listed. WNL = Within Normal Limits, WTAR = Weschler Test of Adult Reading, CLQT = Cognitive Linguistic Quick Test, BIT-C = Behavioral Inattention Test-Conventional, RBANS = Repeatable Battery for the Assessment of Neuropsychological Status, WAB = Western Aphasia Battery, AQ = Aphasia Quotient.

Domain	Test	Score	Percentile	Clinical Range
Intellectual ability	WTAR (Pre-Morbid IQ)	32	46th	*Average*
	Raven's Coloured Progressive Matrices	28	10th	*Low average*
Executive functioning	CLQT	10	68th percentile	*WNL*
Attention & working memory	BIT-C	134/146		*No hemispatial neglect*
	RBANS Immediate Memory Index	83	13th	*Low average*
	RBANS Delayed Memory Index	81	10th	*Low average*
	RBANS Attention Index	64	1st	*Impaired*
	Digit Span Forward (WAIS-IV)	10	50th	*Average*
	Spatial Span (WMS-III)	9	5th	*Impaired*
Visuospatial/ Construction	RBANS Visuospatial/ Constructional Index	92	30th	*Average*
	WAB Drawing subtest	25/30		
	WAB Constructional Drawing subtest	25/30		
	WAB Praxis subtest	58/60		
Language	RBANS Language Index	95	37th	*Average*
	Western Aphasia Battery (WAB) AQ Total	99.8/100		*WNL*
	Spontaneous speech subtest	20/20		
	Comprehension subtest	10/10		
	Repetition subtest	9.9/10		
	Naming subtest (included objects)	10/10		
	WAB Reading subtest	99/100		

unwanted activity or interference from either hand and did not endorse any feelings of any body parts not belonging to her. Rather, she reported that she had full control of both hands despite some weakness and reduced sensation in her dominant right hand, consistent with her neurological exam. Based on these reports and the medical history obtained, there was no indication of alien hand syndrome (Scepkowski and Cronin-Golomb, 2003).

2.2. *Behavioral testing*

Several tests of Visual and Tactile naming were administered to the patient over the course of four sessions. Number stimuli included the digits 1–9, and letter stimuli included 23 uppercase letters from the English alphabet (Y, G, and F were omitted due to a high degree of similarity in the tactile domain to X, C, and E, respectively). The same numbers and letters were presented either visually or via tactile presentation in alternate tests. Object stimuli included a set of unique objects (e.g. fork, knife, spoon, paperclip, key, coin, rubber band, etc.) that could be held within one hand and palpated. Test type (Visual, Tactile) and Stimulus Type (Letters, Numbers, Objects) were blocked, while Hand (left, right) was always randomly interleaved within blocks. For all tests, stimulus order was randomized with the constraint that each stimulus was presented an equal number of times to each hand. There were no response time limits.

2.2.1. *Visual naming tests*

In order to assess visual naming, 24 physical objects, 23 wooden letters, and 9 numbers were used. The wooden stimuli were approximately 2 in. in height and 1.5 in. in width, depending on the particular stimulus. In all cases, each stimulus was visually presented one at a time and the patient was asked to name the item as it was presented in view. During these visual naming tests, the patient was not allowed to touch or interact with any of the stimuli. In a separate test session, the letter and number stimuli were also traced via stylus onto a blank piece of paper while the patient watched. In this case, the patient was asked to watch as each stimulus was traced in view and then to name the item. For the visual object and letter naming tests, each item was presented once for a total of 24 and 23 trials, respectively. For number naming, each item was presented twice for a total of 18 trials.

As an additional control for the tactile naming tests (described below), the letter and number stimuli were also traced onto the patient's hands in random order, while she watched. For letter naming, each letter was traced once onto each hand (23 trials per hand) in random order for a total of 46 trials. For number naming, each number was presented twice to each hand (18 trials per hand) in random order for a total of 36 trials.

2.2.2. *Tactile naming tests*

During the tactile naming tests, the patient wore an eye mask to prevent access to any visual information about the stimuli. In the passive condition, two blocks each of letters and numbers stimuli were traced via stylus approximately 2-inches in height onto the patient's palm. For letter naming, each block consisted of 23 trials administered to each hand for a total of 46 trials. For number naming, each block consisted of 18 trials administered to each hand for a total of 36 trials.

For comparison, two blocks of letters (46 trials per block, 23 per hand) and two blocks numbers (36 trials per block, 18 per hand) were also administered in an active palpation condition. In these blocks, the same wooden block stimuli used in the visual naming task above were placed directly into the patient's left or right hand to manually palpate and name. In addition, one block of object naming was conducted using 24 real-world objects which were each placed once into each hand in random order for naming (a total of 48 trials).

During the active palpation tasks, the participant often manually flipped items over or turned them upside down during exploration. For this reason, orientation-*only* errors were disregarded (e.g. a response of either 6 or 9 was scored as correct for both 6 and 9, and similarly for 2/5, M/W and Z/N).

2.2.3. *Control participant*

In order to compare the patient's performance to that of a healthy control, we also tested a right-handed, age-matched female with no neurological history on the tactile naming tests described above. The control participant performed one block each for tactile naming of letters and numbers, in both the traced and palpated conditions (for a total of 4 blocks). Each block was conducted using the same stimuli and procedures as outlined above. Diffusion Tensor Imaging was conducted in the control as well, as per the protocol described below.

2.3. *Brain imaging*

High resolution 3T MRI scans were acquired on a Siemens Magnetom Verio open-bore 3T MRI scanner using a 3D T1-weighted (T1W) MPRAGE (magnetization-prepared rapid gradient echo) protocol with 1

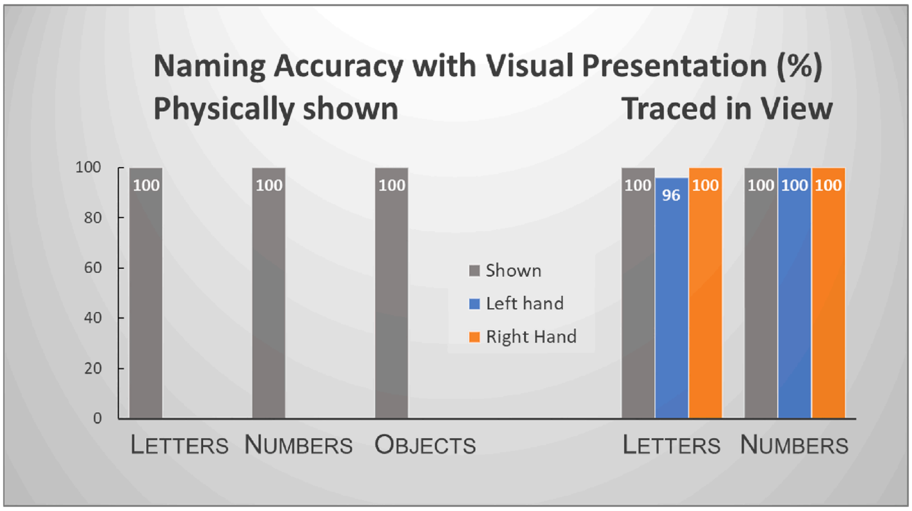

Fig. 1. Naming accuracy for letters, numbers, or objects that were visually presented to the patient (leftmost gray bars), or alternatively, traced in view onto a piece of paper (rightmost gray bars) or onto the patient's left or right palm (colored bars) while the participant watched. The latter condition (colored bars) was conducted as a control for the tactile naming conditions in which letter and number stimuli were traced via stylus onto the palms of the blindfolded participant.

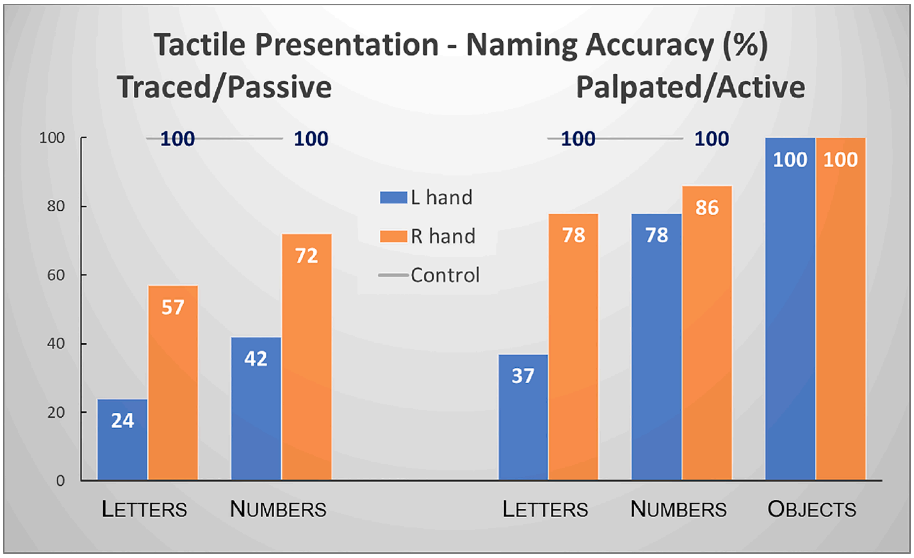

Fig. 2. Tactile naming accuracy for letters, numbers, and objects that were either passively traced onto the palmar surface of the hands (leftmost bars) or actively palpated (rightmost bars), always while the participant was blindfolded. The control participant performed at ceiling, as indicated by the gray lines.

mm 3 isotropic resolution (TR/TE/TI = 2400/3.16/1000 ms, flip angle = 8°; FOV = 256 mm; imaging matrix = 256 × 256; acquisition time = 4.5 min). Two T1W images were acquired and averaged to improve the contrast-to-noise ratio. FLAIR and fast spin echo T2-weighted (T2W) images were also acquired with the default Siemens pulse sequences to improve the visual assessment of brain lesions. Diffusion-weighted imaging (DWI) sequences were also collected with the parameters: T_R = 4500 ms, T_E = 79.0 ms, flip angle = 90°, b = 1200 s/mm^2, 64 directions, 11 b0, FOV = 220 mm, voxel size 2 × 2 × 2 mm, 72 axial slices, bandwidth = 1228 Hz/voxel, and GRAPPA factor = 2.

The participant's lesion was visualized and reconstructed using MRIcron software (Rorden and Brett, 2000). First, the lesion was traced directly onto the patient's native T1-weighted digital images, with yoked T2-weighted and FLAIR images to verify lesion boundaries. Lesions were then registered onto the Montreal Neurological Institute (MNI) template using the standard nonlinear spatial normalization procedure from statistical parametric mapping (SPM8). A cost function masking procedure was used to avoid distortions due to the presence of the lesion (Brett et al., 2001).

Tractography. DWI data were first pre-processed in FSL version 5.09 (Jenkinson et al., 2012) using a fieldmap correction for susceptibility induced distortions and then in ExploreDTI ver. 4.8.6 (Leemans et al., 2009) using eddy current and motion corrections. Next HARDI deterministic tractography based on constrained spherical deconvolution was implemented in StarTrack beta version (Dell'Acqua et al., 2013) with the following parameters: ALFA = 1.8, iterations = 300, n = 0.002, r = 15, ABS threshold = 0.003, step size (mm) = 0.5, angle threshold = 35, minimal length (mm) = 50. Finally, manual virtual tract dissections of the Corpus Callosum (CC), left Arcuate Fasciculus (AF), left Superior Longitudinal Fasciculus (SLF) and left Extreme Capsule (EmC) were done in native diffusion space in TrackVis ver. 0.6.1 (Wang et al., 2007) according to the following criteria.

CC streamlines were identified with a single seed ROI placed on the whole corpus callosum along several consecutive midsagittal slices and refined by removing any confounding cortico-spinal and cingulum fibers that were not part of the corpus callosum (all ROIs were drawn on the b0 map). AF was defined as fibers running dorsally between frontal and temporal lobes. AF was segmented by placing two ROIs: one on the coronal slice at the entrance to the frontal lobe (anterior to the central sulcus) and another one on the axial slice at the entrance to the temporal lobe (just below the Sylvain fissure). SLF was defined as a tract running between frontal and parietal lobes laterally to the AF. It was segmented using the same frontal ROI as the AF and an additional ROI placed posteriorly in the parietal lobe. EmC fibers were segmented by placing an ROI in the white matter underneath Broca's area and insular cortex and a second ROI underneath the middle-posterior portion of the superior temporal gyrus.

It was predicted that the patient's visual naming performance would be intact and that only tactile naming of stimuli would be impacted by the lesion. More specifically, it was hypothesized that naming of items presented to the left hand would be impaired relative to that of the right hand, due to compromised transfer of sensory information from the left hand to left hemisphere language regions.

3. Analysis and results

All behavioral analyses were conducted using R software 3.6.3 (R Project for Statistical Computing, RRID:SCR_001905; http://www.r-project.org/). McNemar's paired data tests were used to test for significant differences in performance between the patient's left and right hands across conditions. For these Chi-Squared tests, *p-values* were based on the asymptomatic estimate with correction and the *Wald confidence interval* was computed with an R function that is based on the technique described in Bonett and Price (2012). In addition, logistic mixed effects tests were conducted using v. 1.1–21-2 of the lme4 package in R (Bates et al., 2015) in order to test for other main effects and interactions. These analyses were conducted on individual trials rather than percentages. *Wald* z scores and *p-values* for the mixed effects analyses were produced by lme4's regression function "glmer". When possible, random slopes were included in the models, as reported below.

3.1. Visual naming

Consistent with performance on the WAB naming tasks, the patient performed at or near ceiling on all of the Visual naming tasks (both for stimuli presented visually or traced onto the palm of the hand while the participant watched). These data (see Fig. 1) confirmed that visual recognition of objects and alphanumeric shapes was intact.

3.2. Tactile naming

Tactile naming accuracy (while blindfolded) for passively traced letters and numbers differed between the two hands (see left side of Fig. 2, below). For letter naming, the patient accurately named 11/46 letters that were traced onto her left palm and 26/46 of those traced onto her right palm. For number naming, she accurately named 15/36 numbers that were traced onto her left hand and 26/36 of those traced onto her right hand. To test whether performance was reliably different between the two hands, McNemar's paired data Chi-Squared test was conducted to directly compare left- versus right-hand performance for letter and number naming in the passively traced condition where left- and right-hand trials were paired having the same item (specific number or letter), session (T1 vs. T2), and repetition number (see Table 2). The test found significantly worse tactile naming performance for letters and numbers that were traced onto the left hand, X^2 (1, N = 36) = 17.36, $p = 0.00003$, **CI** [0.191, 0.427]. Other main effects and interactions were analyzed using a mixed effects logistic regression model. Repeated measures included Hand (L, R), Stimulus Type (Letters, Numbers), Session (T1, T2), with Item (specific letters or numbers) as the random effect. Results revealed a significant main effect of Hand (*z-score* = 3.3, $p < 0.001$), with no other main effects or Hand × Stimulus Type interaction (all $p > 0.1$). The patient's errors were striking in that she often

Table 2

Top: McNemar's Chi-Square Test for Letters and Numbers that were passively traced onto the palmar surface of the hands. Bottom: McNemar's Chi-Square Test for Letters and Numbers that were actively palpated.

Passively Traced Numbers and Letters: Paired by Item & Session		Right Hand	
		Incorrect	Identified Correctly
Left Hand	Incorrect	25	31
	Identified Correctly	5	21
McNemar Test Chi-squared = 17.36, df=1 Asymptotic with correction *p* = 3.09 x 10^{-5} Wald confidence interval of off-diagonal proportion difference (Bonnet-Price corrected): [0.191, 0.427]			

Actively Palpated Numbers and Letters: Paired by Item & Session		Right Hand	
		Incorrect	Identified Correctly
Left Hand	Incorrect	8	29
	Identified Correctly	7	38
McNemar Test Chi-squared = 12.25, df=1 Asymptotic with correction *p* = 0.000465 Wald confidence interval of off-diagonal proportion difference (Bonnet-Price corrected): [0.142, 0.382]			

reported a letter that was very different from the one she was presented, such as reporting ‘M’ for an S, or reporting ‘L’ for an O.

Tactile naming performance for the actively palpated letters, numbers and objects is shown on the right in Fig. 2. For letter naming in this condition, the patient accurately named 17/46 using her left hand and 36/46 using her right hand. For number naming, she accurately named 28/36 using her left hand and 31/36 using her right hand. To test whether tactile letter and number naming performance differed based on the hand used, McNemar’s paired data Chi-Squared test was conducted to compare performance in the two hands in the active palpation condition. The Chi-Square test revealed a significant left-hand impairment for letter and number naming in the active palpation condition, X^2 (1, N = 36) = 12.25, $p = 0.0005$, **CI** [0.142, 0.382]. A mixed effects logistic regression model was used to examine tactile naming accuracy

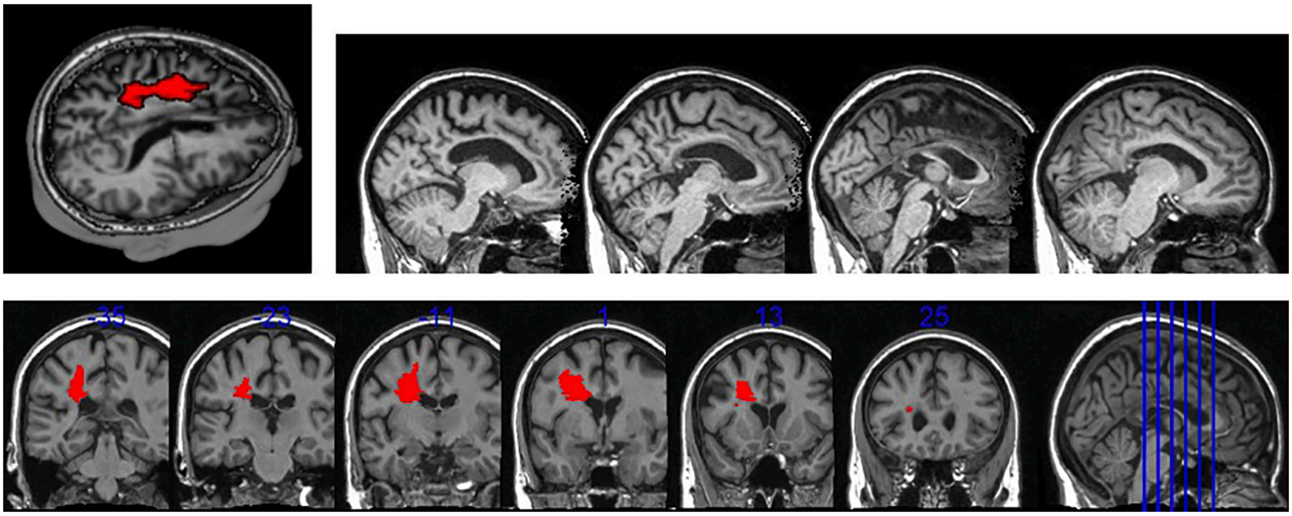

Fig 3. Left top panel: 3-D rendering of the left hemisphere infarct located adjacent to the midbody section of the corpus callosum. Right top panel: Midline sagittal MRI slices. Bottom panel: Multislice coronal view of the lesion reconstruction, with slice position indicated on the far right.

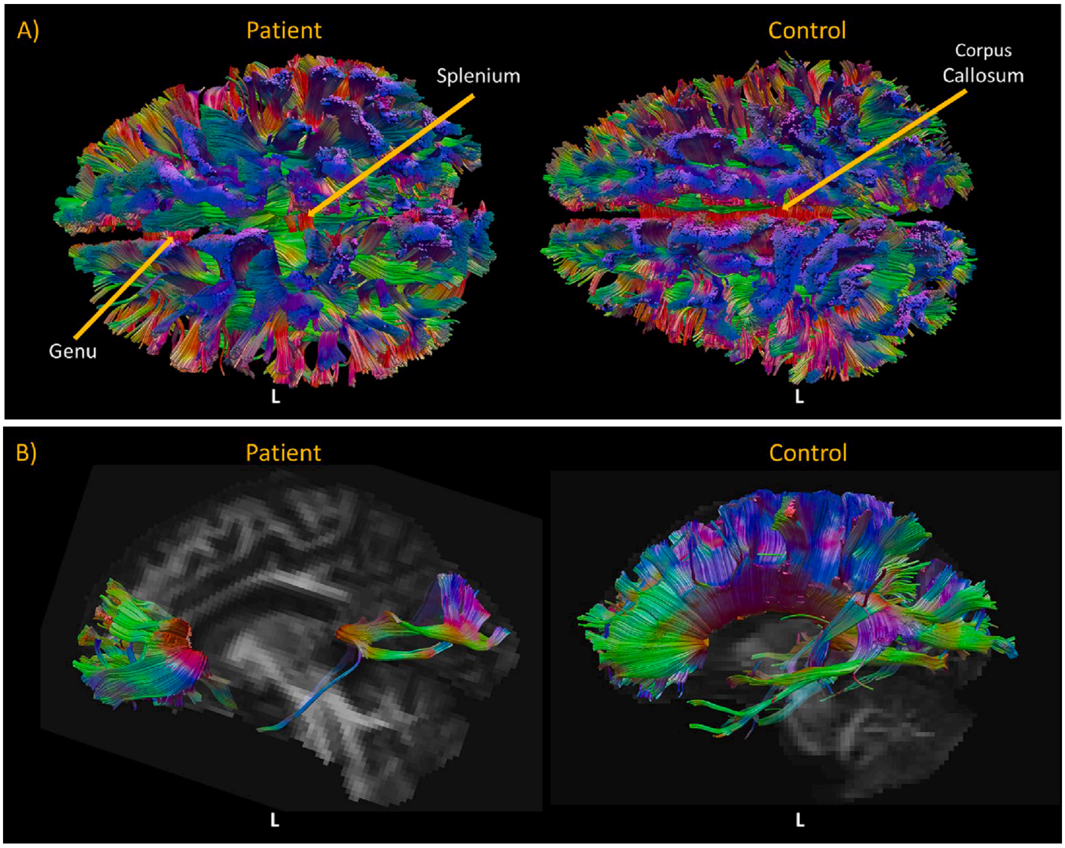

Fig. 4. Panel A: Whole-brain tractography viewed axially from above shows spared fiber tracts in the genu and splenium and an absence of tracts throughout the body of the corpus callosum in the patient (left) compared to that of an age- and sex-matched control (right). Panel B: Left lateral view of the corpus callosum fibers (viewed on a b0 image in native space) again revealing tracts only in most anterior and posterior portions of the corpus callosum in the patient. Conventional DTI color coding is used to show fiber orientation: red reflects tracts in the left–right direction, green in the antero-posterior direction, and blue in the inferior-superior direction. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

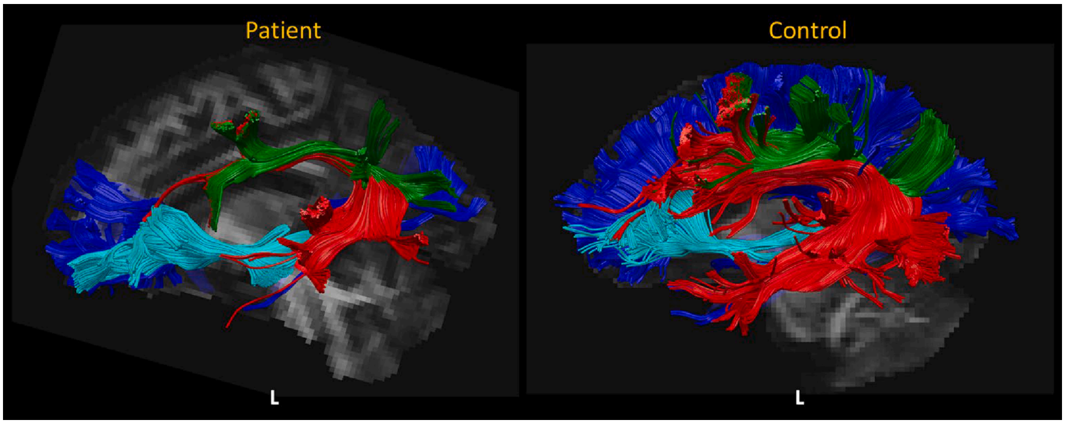

Fig. 5. Reconstruction of left hemisphere fiber tracts including the Arcuate Fasciculus (red), Superior Longitudinal Fasciculus (green), Extreme Capsule (cyan) and Corpus Callosum (dark blue). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

for alphanumeric stimuli across conditions (i.e. actively palpated or passively traced). Repeated measures included Condition (Traced, Palpated), Hand (L, R), and Stimulus Type (Letters, Numbers), with Item (specific letters or numbers) being the random effect. The mixed-effects model included both an intercept and slope with respect to Hand for each Item in case there were consistent Hand modulation differences between specific letters and numbers. Results revealed significant effects of Hand (*z-score* $= 5.0$, $p < 0.001$), Condition (*z-score* $= 3.2$, $p < 0.01$), and Stimulus Type (z-score $= 3.3$, $p < 0.001$). There were no Item specific effects and the Hand effect did not significantly interact with either Condition (Passively Traced vs. Actively Palpated) or Stimulus Type (all $p > 0.1$). Thus, in the actively palpated condition, performance was still reliably worse for letters and numbers presented to the left hand compared to the right hand.

Remarkably, the patient performed at ceiling in naming actively palpated objects (24/24 with each hand). Thus, an additional analysis combining tactile naming of all actively palpated letters, numbers, and objects was conducted to directly compare the three different stimulus types. A mixed effects logistic regression model with repeated measures of Stimulus Type (Letters, Number, Objects) and Hand (L, R), was used with Item being the random effect. Again, the mixed-effects model included both an intercept and slope with respect to Hand for each Item. Significant main effects of Hand (*z-score* $= 4.1$, $p < 0.001$) and Stimulus Type (*z-score* $= 3.5$, $p < 0.001$) were observed, but there was no significant Hand × Stimulus Type interaction ($p > 0.1$).

Unlike the patient, the age-matched control participant performed at ceiling (100% accuracy) on tactile naming of letters and numbers, regardless of which hand was used.

3.3. Imaging and tractography

Structural MRI revealed a small deep subcortical watershed infarct in the left hemisphere adjacent to the central body of the corpus callosum (lesion reconstruction shown in Fig. 3) and including the left superior corona radiata. The normalized lesion volume was 20.83 cc.

Reconstruction based on HARDI deterministic tractography revealed a marked reduction in the volume of the patient's corpus callosum. Specifically, streamlines extending laterally from the body of the corpus callosum were absent, while residual interhemispheric connectivity remained through the genu and splenium (shown in Fig. 4).

In addition, several left hemisphere fiber tracts relevant to language production, including the Arcuate Fasciculus (AF), Superior Longitudinal Fasciculus (SLF), and Extreme Capsule (EmC) were also reconstructed. Importantly, each of these left hemisphere language network fiber tracts could be reconstructed in the patient (illustrated in Fig. 5).

Although a reduction in tract counts was expected due to the presence of the white matter lesion, the tractography data revealed that the AF, SLF, and EmC could all be visualized in both hemispheres of the patient and had Mean FA values that were comparable to that of the control subject. The most striking finding from the tractography data, therefore, was the difference in CC fiber tracts in the patient versus the control. This difference is best captured by the reduced proportional volume and Mean FA of the CC fiber tracts in the patient compared to the control (see Table 3).

Table 3
Tractography metrics and mean FA data for the patient and an age- and sex-matched control participant. Tracts of interest include the Corpus Callosum (CC), along with the left hemisphere (Lh) language production network tracts including the Arcuate Fasciculus (AF), Superior Longitudinal Fasciculus (SLF), and the Extreme Capsule (EmC). Data for the Right hemisphere (Rh) tracts are shown to the right of the backslash /. *Proportional volume is the voxel volume of the tract relative to the total voxel count of the whole brain tractogram. SD = standard deviation.

Patient	AF (Lh/Rh)	SLF (Lh/Rh)	EmC (Lh/Rh)	CC	Whole brain tractogram
Track count	1425 / 807	858 / 773	1026 / 1049	5352	119,926
Volume (voxel count)	1455 / 1161)	1093 / 1013	1089 / 1602	4062	59,745
*Proportional Volume	0.0244 / 0.0194	0.0183 / 0.0170	0.0182 / 0.0268	0.0680	–
Mean FA	0.40 / 0.44	0.40 / 0.40	0.45 / 0.41	0.42	0.43
SD FA	0.13 / 0.11	0.13 / 0.12	0.13 / 0.13	0.13	0.16
Control	**AF (Lh/Rh)**	**SLF (Lh/Rh)**	**EmC (Lh/Rh)**	**CC**	**Whole brain tractogram**
Track count	6536 / 2735	2038 / 2997	345 / 894	49,695	191,436
Volume (voxel count)	4419 / 2875	2198 / 2399	1043 / 1561	24,425	82,905
*Proportional Volume	0.0533 / 0.0347	0.0265 / 0.0289	0.0126 / 0.0188	0.2946	–
Mean FA	0.48 / 0.46	0.45 / 0.45	0.40 / 0.43	0.55	0.48
SD FA	0.12 / 0.13	0.13 / 0.12	0.15 / 0.14	0.18	0.17

4. Conclusions and discussion

Over half a century of research has established that direct severing or under-development of the corpus callosum can impair interhemispheric transfer of information (Bogen and Gazzaniga, 1965; Bloom and Hynd, 2005; Fabri et al., 2001; Gazzaniga et al., 1962; Gazzaniga, 2000; Robertson et al., 1993; Reuter-Lorenz and Baynes, 1992; Schulte and

Müller-Oehring, 2010). Thus, it is also reasonable to expect that unilateral focal lesions adjacent to or impinging on the corpus callosum may also disrupt communication between the two hemispheres. The current case study presents a patient with a small left hemisphere infarct confined to the white matter adjacent to the midbody portion of the corpus callosum. Interestingly, behavioral testing indicated a selective tactile naming deficit for letters and numbers that were presented to the patient's *ipsilesional left* hand. Visual naming, visual object recognition, and language were all normal, confirming that this deficit could not be explained by more general impairments in verbal naming or visual object recognition. Instead, tactile information from the left hand, specifically for letters and numbers, was less accessible for identification via verbal naming.

Consistent with this interpretation, a spontaneous comment from the patient was particularly striking. After palpating and exploring a wooden number 6 in her left hand for some time, she offered a response of 'two', then switched her response to 'three'. Then, with some frustration, she said, "I can visualize it, but when I try to say it, it's just not right". When the experimenter then prompted her to draw what she was "visualizing" using her left hand, she correctly drew a 6. Thus, it appeared that tactile perception was intact, as also evidenced by her accurate haptic object identification. Rather, the problem appeared to be one of integrating specific tactile information from the right hemisphere with verbal naming abilities of the left hemisphere.

The idea that brain injury can result in a tactile-verbal disconnection is not new. In 1992 Endo et al. reported a case in which a unilateral subcortical lesion in the area of the left angular gyrus and posterior callosal radiations was hypothesized to have created a tactile-verbal disconnection, which the authors described as tactile *aphasia*. Understanding the specific pathways that might have been compromised or disconnected in that case, however, is complicated since the patient had also sustained a severe traumatic brain injury resulting in posterior subcortical damage thought to involve callosal radiations from the splenium as well as the posterior arcuate fasciculus, the external capsule, the inferior longitudinal fasciculus, and optic radiations. Moreover, DTI imaging was not available at that time. Thus, to our knowledge, our case is the only focal stroke case with tactile aphasia that has been presented in the literature along with DTI brain imaging showing the impact on specific white matter tracts.

In keeping with the hypothesis that our patient suffered from a tactile-verbal disconnection, DTI fiber tract reconstruction confirmed a lack of fiber tracts extending laterally from the body of the corpus callosum. This is consistent with other findings that somatosensory transfer of information, including that of the hands, likely relies on communication through the central to posterior portion of the body of the corpus callosum (Fabri et al., 2005; Hofer and Frahm, 2006; also see Fabri and colleagues, 2001, 2011, 2014). This is important since the hands play a critical, albeit possibly underappreciated, role in cognition and perception. Hands not only enable significant functionality in day-to-day activities, such as grasping, manipulating, and exploring objects, tools, and a myriad of surfaces, they are also important in guiding visual attention and perception (di Pellegrino et al., 1997; Reed et al., 2006; Schendel and Robertson, 2004).

It should be noted that the case reported here did not show any signs of alien hand syndrome which often consists of involuntary motor movements and/or apparent lack of ownership of the left hand in particular. Alien hand syndrome is rare and has been associated with medial frontal cortex lesions or a combination of frontal and collosal lesions (Banks et al., 1989 and Scepkowski and Cronin-Golomb, 2003, for a review). It is notable in the case reported here that there was little to no cortical damage and that white matter tracts passing through both the genu and splenium of the corpus callosum were visualized with diffusion tensor imaging. Although symptoms consistent with alien hand syndrome have been observed after callosotomy in the absence of cortical damage, such cases almost always exhibit intermanual conflict as the primary symptom (Feinberg et al., 1992). However, the patient studied here did not report or show any signs of intermanual conflict at any time since her stroke, or during any of the tactile naming tests conducted in this study.

Although it could be reasoned that right-handed individuals might have finer discrimination abilities on the surfaces of their dominant hand, it is unlikely that this could explain our patient's left-handed deficit for several reasons. For one, the patient's left hemisphere stroke resulted in weakness and decreased sensation in her contralesional *right* hand which should have biased the results in the opposite direction. Moreover, two-point sensory discrimination thresholds were found to be similar on the patient's left and right hands during the time of testing. Finally, testing of a healthy control participant (matched for age, gender and handedness) in both the active and passive conditions revealed performance at ceiling (100%) for both letter and number stimuli in both hands. Given these observations, the most parsimonious explanation is that tactile naming of stimuli presented to the patient's left hand likely suffered for reasons that were *not* of a purely sensory nature.

The fact that tactile naming accuracy was higher in this case for stimuli that were actively palpated, as compared to passively traced, is also noteworthy. One explanation could be order or practice effects with repeated exposure to the same set of alphanumeric stimuli. However, there were no effects of block order or trial order (within blocks). Another explanation for the higher naming accuracy of actively palpated items is that active tactile exploration may rely on different and/or more extensive brain networks. As reported by Homke and colleagues (2009), areas of the superior parietal lobule and intraparietal sulcus along with the ventral premotor cortex form an extensive fronto-parietal network for haptic object manipulation, with the anterior versus posterior portions of this network mapping onto the somatosensory versus action-related aspects of haptic recognition. Thus, active tactile manipulation may have resulted in the recruitment of a larger network of posterior brain regions which consequently may have been less vulnerable to disconnection.

The role of the hands in haptic recognition is particularly relevant to instances of tactile agnosia. Tactile agnosia is commonly defined as an impairment in recognizing objects after tactile exploration despite relatively intact sensory functioning and cognitive abilities. Unilateral tactile agnosia (affecting only one hand) has typically been associated with *contralateral* lesions involving the somatosensory cortex or other parietotemporal structures (Veronelli et al., 2014; Caselli, 1991, 1997; Reed et al., 1996; Homke et al., 2009), in addition to lesions to the corpus callosum (e.g. Balsamo et al., 2008; Marangolo et al., 1998). The case reported here is unique in that a chronic tactile naming deficit was observed for alphanumeric shapes presented to the *ipsilesional* left hand as a consequence of a focal pericallosal lesion in the left hemisphere. Thus, this case underscores the fact that white matter damage can result in the disconnection of otherwise intact cortices, such that an impairment may even be observed ipsilaterally, particularly in the case of the left hand which is controlled by the non-language dominant hemisphere. A difference in connectivity between the left and right hands and the language dominant hemisphere may partially explain why unilateral associative tactile agnosia is more commonly observed in the left hand (for right-hand dominant individuals).

The literature on tactile agnosia has also made a distinction between apperceptive agnosia and associative agnosia. Apperceptive agnosia is defined as a deficit in discriminating different tactile sensory features such as weight or texture. As such, apperceptive agnosia has been regarded as a perceptual deficit and has been associated in the literature with damage to supplementary motor and somatosensory cortices, as well as inferior parietal cortex (Caselli, 1997; Reed et al., 1996; Saetti et al., 1999). Associative agnosia, on the other hand, is defined as a deficit in associating tactile sensations with a particular object shape or name, despite spared perceptual abilities (Balsamo et al., 2008; Caselli, 1991; Casellim, 1993; Veronelli et al., 2014). Notably, our patient did not have sensory problems in the left hand and was able to identify objects held in the left hand, which rules out apperceptive agnosia. Thus, our case is more similar to cases of associative tactile agnosia, some of which have been observed following lesions involving the corpus callosum. For example, Balsamo et al., (2008) reported a case in which impaired recognition and naming of objects was observed in the left hand after a lesion to the posterior third of the trunk of the corpus callosum. In contrast, our case showed relatively intact *object* naming, but rather poor performance for letters and numbers. This begs the question as to whether there may be a dissociation between tactile recognition of objects versus other alphanumeric shapes.

However, before considering whether the brain may recruit different regions for tactile object recognition compared to tactual identification of alphanumeric shapes, it is important to acknowledge that there are some critical differences between alphanumeric stimuli and real-world objects. One difference is that letters and numbers differ from one another primarily in shape whereas real-world objects are inevitably more variable in shape, size, and texture. Furthermore, haptic object recognition may rely on both cutaneous sensory information as well as kinetic information from hand finger joint positions and movement (Gibson, 1962; Loomis and Lederman, 1986; Turvey and Carello, 2011). Handheld objects are certain to provide more of this latter type of information and as such may also be more readily associated with action schemas (e.g. what you do with a fork versus a pencil etc.). Thus, it is important to acknowledge that real-world objects provide more cues for differentiation via tactual manipulation than do alphanumeric stimuli.

Nonetheless, Veronelli et al. (2014) reported findings from a patient with a right hemisphere stroke who exhibited a pattern of impaired tactile object recognition, despite intact recognition of alphanumeric shapes. Meanwhile, our case involved a lesion of the *left* hemisphere and showed the opposite pattern, suggesting that there may be differences in brain regions needed for object versus letter naming. Another dissociation in haptic recognition of letters and objects was also described in a case report by Marangolo and colleagues (1998). Similar to our case, Marangolo et al.'s patient also demonstrated a left-handed impairment in matching and identifying letters (as well as colors), despite intact identification of real-world objects. Marangolo et al. reported that the patient's lesion was in the left cingulum, parallel to the corpus callosum, but also included a small lesion of the genu and a larger lesion of the splenium. The authors thus reasoned that the left hemisphere was necessary for letter/grapheme identification (but not for objects) and concluded that the lesion "probably interrupted the callosal pathways of the trunk within the left hemisphere" therefore interrupting the pathways linking the right sensorimotor cortex to the verbal left hemisphere. However, given the involvement of the genu and splenium the and the lack of DTI data from this 1998 case, it was not possible to discern which part of the corpus callosum may be most critical for linking right hemisphere somatosensory cortex to the left hemisphere language areas.

The case study reported here therefore helps confirm and refine prior postulations from prior case reports by Endo et al. (1992), Marangolo et al. (1998), and Veronelli et al. (2014). First, our case confirms that a focal unilateral pericallosal lesion can produce a tactile-verbal disconnection. Secondly, the current study adds to the evidence that letters may be a unique category of stimuli. Finally, the DTI data from the current case indicated that pathways throughout the body of the corpus callosum were patently disrupted, while those through the genu and splenium were spared. Thus, the current case refines and builds upon the prior studies by emphasizing the importance of the pathways through the midbody of the corpus callosum as being critical for tactile-verbal interaction.

Although interpretations must be made cautiously in a case study, our findings suggest that the specific difficulty in naming letters and numbers drawn on or placed in this individual's left hand is likely due to a disruption in the transfer of sensory information from the left hand to the language dominant left hemisphere. DTI data from this case revealed a marked reduction in white matter pathways through the midbody of the corpus callosum which have been shown to play a role in the interhemispheric transfer of tactile information (Fabri et al., 2005). Based on other recent human DTI and resting state functional connectivity analyses along with non-human primate tract tracing studies, it has been shown that left hemisphere frontal language areas including Broca's area are well connected with left temporal and parietal regions (Kelly et al., 2010). Fiber tracts supporting this connectivity include the Superior Longitudinal Fasciculus (SLF), Arcuate Fasciculus (AF) and the Extreme Capsule Fasciculus (ECF). Given that each of these language pathways could still be visualized in the left hemisphere of our patient and that she performed within normal limits on an extensive language battery, we conclude that the patient's lesion likely disconnected sensorimotor regions of the right hemisphere from access to the relatively intact left hemisphere language network.

With regard to the preserved tactile *object* recognition observed in our patient, prior case reports of bilateral tactile agnosia are noteworthy. For example, both Endo et al. (1992) and Nakamura et al. (1998) have reported cases of bilateral tactile agnosia in which objects could not be recognized via either hand. Since these cases had extensive bilateral lesions involving the parietal and temporal lobes (as well as portions of the arcuate fasciculus, inferior longitudinal fasciculus, and collosal radiations), the authors postulated that tactile agnosia for objects specifically requires a bilateral disconnection between somatosensory association cortex and the semantic memory stores in the inferotemporal cortex in both hemispheres. In other words, the semantic meaning of objects appears to be represented bilaterally in the brain. This is also consistent with neuroimaging studies that have implicated the lateral occipital complex bilaterally in visual object recognition (see Grill-Spector et al., 2001). In contrast, our case did not have bilateral damage, nor any damage within the inferotemporal or lateral occipital cortices in either hemisphere, which may explain the spared tactile object recognition capabilities.

Another way of understanding the current findings is in terms of separate ventral and dorsal streams for processing haptic information (Sathian, 2016). The tactile naming tasks used in the current study would be most consistent with reliance on the dorsally directed pathway which is involved in transmitting information from object features to the intraparietal sulcus and/or the lateral occipital complex for shape processing. Although these cortical regions were intact in our patient bilaterally, it is possible that connectivity between these regions was affected. However, given the location of the lesion within the left hemisphere, one would predict a greater impact on connectivity between parietal and occipital regions within the left hemisphere, thereby producing a greater deficit for items presented to the right hand. Instead, the deficit appeared to be unique to the left hand and predominantly affected letter naming.

Recent neuroimaging studies have implicated left lateralized activations during letter processing and identification. In particular, letter processing has been associated with activations in the left fusiform, left pars opercularis, and left parietal regions, consistent with possible word recognition and reading networks (Carreiras et al., 2015; Park et al., 2012). All together, these findings support the idea that recognition of letters may be left lateralized and therefore not as easily accessed when input is restricted to the right hemisphere (i.e., tactile stimulation of the left hand). Since the tactile naming of letters was most detrimentally impacted in the case reported here, this could be due to the fact that letter identification relies on different left-lateralized regions that may be part of a reading network. This is somewhat speculative as prior studies investigating brain activations associated with letter identification have only investigated visual or auditory stimulus presentations. However, if the left fusiform or visual word form area (VWFA) is involved in letter identification, one implication the current study is that this region may also be recruited when letters are processed via the tactile modality as well.

In summary, both lesion case studies and neuroimaging data seem to be converging on the notion that haptic recognition of objects involves bilateral neural circuitry involving the lateral occipital complex and inferotemporal cortices (Sathian, 2016; Endo et al., 1992; Nakamura et al., 1998). These areas were intact in both hemispheres in the case described here, so the fact that our patient showed no impairment in naming real word objects with either hand suggests that access to this circuitry within either hemisphere was sufficient for haptic object identification. In contrast, letters, which may require left-lateralized brain regions for identification appear to be more vulnerable to tactile naming impairments. The current case exemplifies this vulnerability by demonstrating a left-hand specific deficit in naming letters and numbers, despite intact tactile object recognition. This is broadly consistent with the interpretation that pathways through the midbody of the corpus callosum play a critical role in tactile letter naming, but not necessarily in object naming. Although, it is difficult to speculate from the present case study as to the specific regions (or final destinations) within the left hemisphere that must be accessed via connections through the corpus callosum, the tractography data suggest that fibers through the body of the corpus callosum may be essential for a collaborative interface between the tactile somatosensory cortices of the right hemisphere and the left hemisphere language/reading network.

Growing evidence now confirms that connectivity between different specialized areas of the brain is essential to enabling higher level cognition. The spared naming of actively palpated objects in the current case suggests that *more* complex stimuli or tasks (e.g. real world objects or active palpation in the case described here) recruit a broader (or potentially more bilateral) network of brain regions that may be less vulnerable to white matter pathway disconnection. This interpretation has implications for cognitive rehabilitation and suggests that more complex stimuli might be preferable for re-training, rather than starting with simple stimuli as is often the traditional approach.

CRediT authorship contribution statement

Krista Schendel: Conceptualization, Investigation, Project administration, Methodology, Formal analysis, Visualization, Writing - original draft. **Timothy J. Herron:** Formal analysis, Validation, Software, Writing - review & editing. **Brian Curran:** Data curation, Software, Formal analysis. **Nina F. Dronkers:** Funding acquisition, Resources. **Maria Ivanova:** Methodology, Software, Formal analysis, Visualization, Writing - review & editing. **Juliana Baldo:** Funding acquisition, Supervision, Conceptualization, Visualization, Writing - review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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