Original Research Article

ASNR AMERICAN SOCIETY OF NEUROREHABILITATION

Neurorehabilitation and
Neural Repair
1–11

DOI: 10.1177/1545968320940982
journals.sagepub.com/home/nnr
SAGE

Change in Right Inferior Longitudinal Fasciculus Integrity Is Associated With Naming Recovery in Subacute Poststroke Aphasia

Marieke Blom-Smink, MSc[1,2], Marjolein Verly, PhD[3], Kerstin Spielmann, PhD[1,2], Marion Smits, MD, PhD[2], Gerard M. Ribbers, MD, PhD[1,2], and Mieke W. M. E. van de Sandt-Koenderman, PhD[1,2]

Abstract

Background. Despite progress made in understanding functional reorganization patterns underlying recovery in subacute aphasia, the relation between recovery and changes in white matter structure remains unclear. *Objective*. To investigate changes in dorsal and ventral language white matter tract integrity in relation to naming recovery in subacute poststroke aphasia. *Methods*. Ten participants with aphasia after left-hemisphere stroke underwent language testing and diffusion tensor imaging twice within 3 months post onset, with a 1-month interval between sessions. Deterministic tractography was used to bilaterally reconstruct the superior longitudinal fasciculus (SLF), inferior fronto-occipital fasciculus (IFOF), inferior longitudinal fasciculus (ILF), middle longitudinal fasciculus (MdLF), and uncinate fasciculus (UF). Per tract, the mean fractional anisotropy (FA) was extracted as a measure of microstructural integrity. Naming accuracy was assessed with the Boston Naming Test (BNT). Correlational analyses were performed to investigate the relationship between changes in FA values and change in BNT score. *Results*. A strong positive correlation was found between FA change in the right ILF within the ventral stream and change on the BNT ($r = 0.91$, $P < .001$). An increase in FA in the right ILF was associated with considerable improvement of naming accuracy (range BNT change score: 12-14), a reduction with limited improvement or slight deterioration. No significant correlations were found between change in naming accuracy and FA change in any of the other right or left ventral and dorsal language tracts. *Conclusions*. Naming recovery in subacute aphasia is associated with change in the integrity of the right ILF.

Keywords

aphasia, stroke, diffusion tensor imaging, white matter tracts, naming

Introduction

Aphasia is a common consequence of damage to the language-dominant left hemisphere and is prevalent in about 30% of stroke survivors.[1] Neuroimaging has increased our understanding of the reorganization patterns underlying language recovery following stroke. Most studies have focused on the integrity and activity of cortical areas in language processing. More recently, however, the importance of the white matter tracts connecting these areas has been pointed out.[2,3]

Current neuroanatomical models of language connectivity assume that language is processed along dorsal and ventral pathways.[4,5] The superior longitudinal fasciculus (SLF), comprising the arcuate fasciculus (AF), is a major white matter tract connecting temporo-parietal with frontal language cortices within the strongly left-dominant dorsal stream.[5] The ventral stream is more bilaterally organized[4] and includes the inferior fronto-occipital fasciculus (IFOF),

[1]Rijndam Rehabilitation, Rotterdam, The Netherlands
[2]Erasmus MC, University Medical Center Rotterdam, Rotterdam, The Netherlands
[3]KU Leuven, ExpORL, Leuven, Belgium

Supplementary material for this article is available on the *Neurorehabilitation & Neural Repair* website along with the online version of this article.

Corresponding Author:
Gerard M. Ribbers, Erasmus MC, University Medical Center Rotterdam, Department of Rehabilitation Medicine, PO Box 2040, 3000 CA Rotterdam, Zuid-Holland 3001KD, The Netherlands.
Email: g.ribbers@erasmusmc.nl

inferior longitudinal fasciculus (ILF), middle longitudinal fasciculus (MdLF), and uncinate fasciculus (UF).[5] Whereas the dorsal stream is assumed to support phonological processing[5] and motor-articulatory computations,[6] the ventral stream is associated with lexical-semantic processing.[4,5]

Diffusion tensor imaging (DTI) is a noninvasive brain imaging technique providing measures of white matter structure. To date, only a handful of studies have used this technique to investigate changes in structural connectivity in aphasia recovery.[7-12] Most of these studies were performed in the chronic stage[7,9-11] and provided evidence of therapy-induced structural plasticity in the left[7,10] or right[9] AF within the dorsal stream. Within the ventral stream, the role of only the ILF[11] and UF[10] has been investigated. Whereas language recovery following treatment of chronic aphasia was found to be supported by changes in the integrity of the left ILF,[11] no therapy-induced structural changes have been observed for the UF in either hemisphere.[10] Recently, Jang et al[8] examined structural changes in the left and right dorsal stream from the early to the chronic stage, reporting an association between increase in volume of the damaged left AF and recovery from aphasia over the first year after stroke. Conversely, Keser et al[12] revealed that an increase in the integrity of the right AF from the acute (<2 weeks) to the chronic (6-12 months) stage was associated with poorer naming recovery. To our knowledge, the relationship between changes in structural connectivity and language recovery in the first months post onset is as yet unclear. As most improvement in language function occurs in the subacute stage, a better understanding of the changes in white matter structure underlying language outcomes at this stage of stroke recovery is warranted.

The present observational study aimed to investigate recovery of naming within 3 months post onset in relation to changes in language white matter tract integrity. Whereas most DTI studies selected specific tracts in either the dorsal or the ventral stream, we evaluated changes in dorsal and ventral language streams in the left and right hemispheres. We studied a group of aphasic patients in the subacute stage who were scanned twice with a time interval of approximately 1 month.

Methods

Participants

Ten participants (7 men; mean age: 61.8 ± 7.8 years) with aphasia due to first-ever left-hemisphere stroke completed the study. They were all enrolled in a stroke rehabilitation program, including speech-language therapy (SLT). Individually tailored SLT was provided in individual and group sessions, and comprised intensive naming treatment,[13] cognitive-linguistic therapy, communicative treatment, and/or counseling and coaching of patients and proxies. Naming therapy comprised of 2 weeks of daily 45-minute individual sessions.[13] The naming therapy protocol was based on Cueing Hierarchy Therapy.[14] For detailed description of the therapy protocol, see Spielmann et al.[13]

All participants were within 3 months post onset at the time of the study, had Dutch as their native language, were right-handed prior to stroke as assessed with the Edinburgh Handedness Inventory,[15] had normal hearing, and normal or corrected-to-normal vision. None of the participants had (1) severe aphasia (Shortened Token Test[16] [TT] correct score <9 and Aphasia Severity Rating Scale[17] [ASRS] score = 0-1), (2) minimal aphasia (Shortened TT correct score >28 and ASRS score = 4-5), (3) a history of other neurological, cognitive or psychiatric disorders, (4) substance abuse, or (5) any contraindications to magnetic resonance imaging (MRI). Baseline characteristics of the participants are listed in Table 1.

The participants were a convenience subsample recruited from a multicenter randomized controlled trial (RCT) on transcranial direct current stimulation (tDCS) in subacute aphasia rehabilitation[13] that showed no effect of tDCS versus sham.[18] The participants in the present study were all recruited from the in- and outpatient rehabilitation clinic of Rijndam Rehabilitation, Rotterdam, The Netherlands, had no contraindications to MRI, agreed to participate in the neuroimaging part of the trial, and underwent DTI scanning twice. Figure 1 presents the flowchart of the participant selection.

In the present study, we explored the relationship between naming recovery and changes in language white matter tract integrity irrespective of tDCS condition, because the RCT showed no effect of tDCS versus sham, neither immediately after the intervention nor at 6 months follow-up.[18] The decision to collapse the data was further justified by the fact that the participants in this study, when grouped into 2 groups (tDCS and sham), also showed no significant differences in naming recovery (Supplementary Table 1) or in change in tract integrity for any of the tracts of interest (Supplementary Table 2).

The study was approved by the Medical Ethics Committee of the Erasmus MC, University Medical Center Rotterdam, The Netherlands, and all participants provided written informed consent in accordance with the Declaration of Helsinki.

Language Measure

Naming accuracy was assessed with the 60-item Boston Naming Test[19] (BNT). In the Dutch version, item 57 ("trellis") is not included, due to its low naming agreement in a Dutch norm group.[20] In deviation from the standard BNT administration procedure,[19] incorrect responses were not followed up with cues. The spontaneous responses were scored as either correct or incorrect, based on a list with

Table 1. Demographic and Clinical Characteristics for Each Participant.

Participant ID	Age (years)	Sex	Education (years)	TT (0-36)	ASRS (0-5)	DTI (days post stroke)		BNT (days post stroke)		Stroke type	Lesion volume (mL)	Lesion site (LH)
						First	Second	First	Second			
P01	69	M	11.0	26.5	3	43	78	41	77	Hemorrhage	19.58	INS, SC (min)
P02	73	M	16.0	25.5	3	20	62	18	50	Infarction	5.57	SC
P03	56	M	13.0	28.0	4	15	50	17	50	Infarction	28.50	IFG, INS (min), STG (min)
P04	66	F	8.5	11.0	2	44	90	44	76	Hemorrhage	38.55	STG, ANG/SMG
P05	60	M	17.0	30.0	2	55	90	50	85	Infarction	27.02	IFG, INS, ANG/SMG, SC
P06	64	F	20.0	27.5	3	64	95	62	96	Infarction	23.59	INS, HES (min), ANG/SMG
P07	63	M	9.5	24.5	4	37	70	37	71	Infarction	16.77	INS, STG, ANG/SMG
P08	67	M	15.0	28.5	3	50	92	52	86	Infarction	25.77	INS, STG, ANG/SMG
P09	51	M	15.0	18.5	1	33	82	37	68	Infarction	154.57	IFG, INS, SMA (prob), SC
P10	49	F	10.0	27.5	4	35	82	36	69	Infarction	27.49	INS

Abbreviations: M, male; F, female; TT, Shortened Token Test; ASRS, Aphasia Severity Rating Scale; DTI, diffusion tensor imaging; BNT, Boston Naming Test; LH, left hemisphere; First, first session/assessment; Second, second session/assessment; INS, insula; SC, striatocapsular region; IFG, inferior frontal gyrus; STG, superior temporal gyrus; ANG, angular gyrus; SMG, supramarginal gyrus; HES, Heschl's gyrus; SMA, supplementary motor area; min, minimal; prob, probably.

target names and synonyms.[21] In accordance with the Dutch scoring system,[21] semantically correct responses with at least 2/3 of the phonemes produced correctly were scored correct. The language outcome measure was change in BNT scores. The first assessment was performed at a mean of 39.4 ± 14.1 days post onset (range: 17-62 days post onset) and the second assessment at a mean of 72.8 ± 14.8 days post onset (range: 50-96 days post onset).

Image Acquisition and Processing

The first scanning session was performed at a mean of 39.6 ± 15.0 days post onset (range: 15-64 days post onset) and the second scanning session at a mean of 79.1 ± 14.5 days post onset (range: 50-95 days post onset).

Images were acquired on the same whole-body 3.0-T Discovery MR750 system (GE Healthcare), using an 8-channel head coil, at Erasmus MC, University Medical Center Rotterdam. DTI data were acquired using an optimized single-shot spin-echo echo-planar imaging pulse sequence (repetition time [TR] = 7925 ms; echo time [TE] = 81.9 ms; field of view [FOV] = 240 mm; matrix size = 128 × 224; slice thickness = 2.5 mm; in-plane pixel size = 1.9 × 1.9 mm^2; 59 contiguous sagittal slices; acquisition time = 4:53 minutes). Diffusion gradients were applied in 32 noncollinear directions (b = 1000 s/mm^2) and 4 nondiffusion weighted images were acquired.

Pre- and postprocessing of the DTI data were performed using ExploreDTI (http://www.ExploreDTI.com) by an experienced rater (MV), who was blinded to the language test results of the participants. Preprocessing consisted of subject motion and eddy current correction. During this step, the b-matrix was corrected for the rotational component of subject motion.[22] The data quality summary as implemented in ExploreDTI and the native data were visually inspected to check for apparent motion artefacts. Subsequently, the diffusion tensors were estimated using nonlinear least squares fitting. Whole brain tractography was performed using a uniform 2 mm seed point resolution, and the following termination thresholds were applied: fractional anisotropy (FA) <0.2, angle <30°, and fiber tract length <50 mm. Deterministic tractography was used to reconstruct the dorsal and ventral tracts for both hemispheres in native space. Using the FA color-coded maps, regions of interest (ROIs) were drawn manually on the coronal and axial slices based on a priori anatomical knowledge. The ROIs were defined according to the ROI reconstruction protocols of Catani et al[23] for the SLF; of Wakana et al[24] for the IFOF, ILF, and UF; and of Makris et al[25] for the MdLF. When necessary, NOT ROIs were placed to exclude fibers from neighboring tracts. The ROIs were defined as follows:

For the SLF (Figure 2a), the axial slice where the anterior and posterior parts of the corpus callosum meet, was identified. Then, a single SEED ROI was drawn in the white matter region located in the posterior portion of the slice and lateral to the corona radiata. Only voxels with an anterior-posterior directionality were included in the ROI.[23]

For the IFOF (Figure 2b), the most anterior coronal slice where the left and right genu of the corpus callosum join, was identified. Then, on this slice, the whole hemisphere was selected using a SEED ROI. Following this, the midpoint between the posterior edge of the cingulum and the posterior edge of parieto-occipital sulcus was identified in the sagittal plane. An AND ROI was drawn around the full occipital lobe on the corresponding coronal slice.[24]

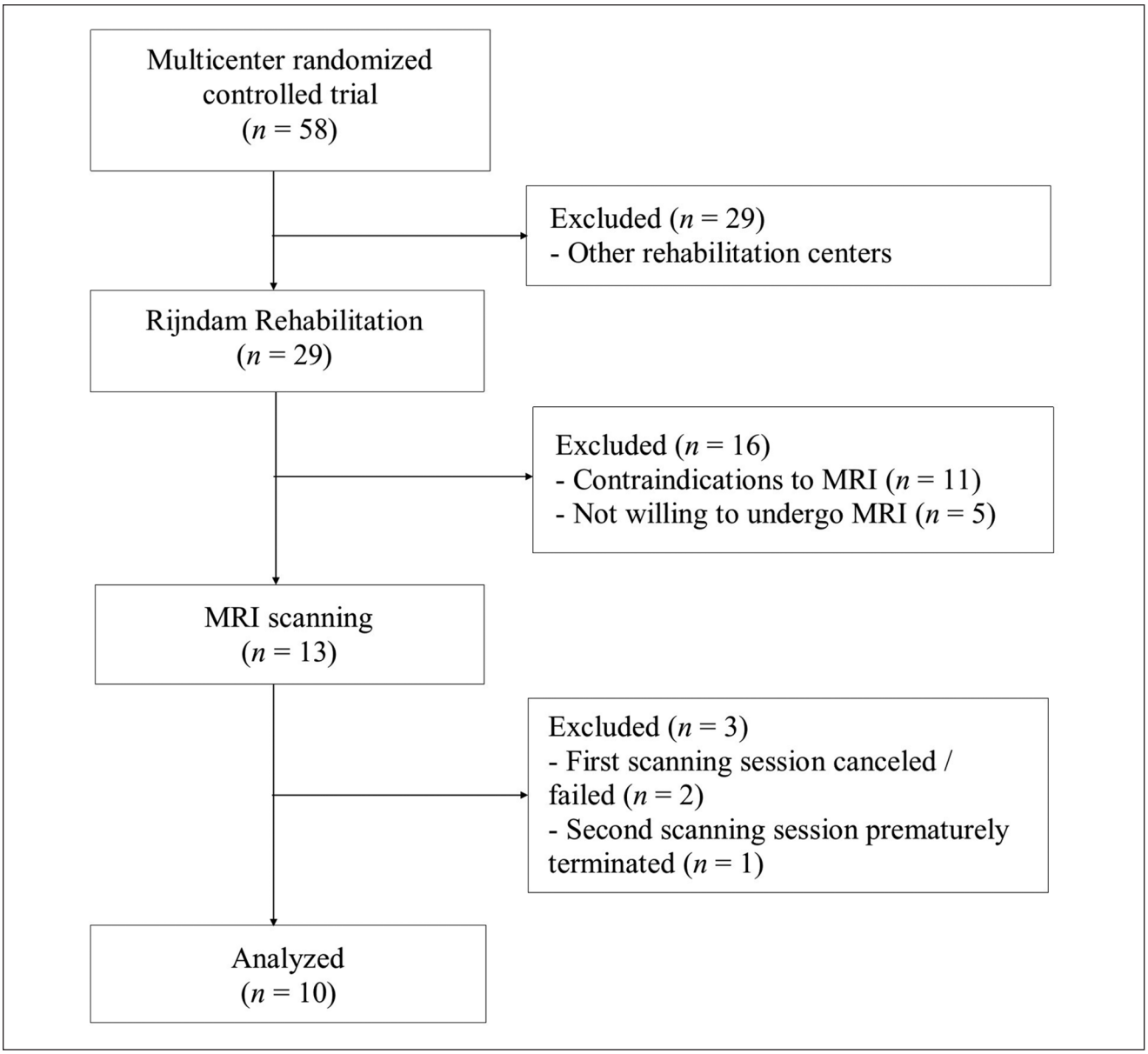

Figure 1. Flowchart of participant selection.

For the ILF (Figure 2c), a coronal slice was selected at the posterior edge of the cingulum, identified on a sagittal slice. Then, a SEED ROI was selected comprising the entire hemisphere. The second ROI —an AND ROI— included the entire temporal lobe on the most posterior coronal slice where the temporal lobe is not connected to the frontal lobe.[24]

For the MdLF (Figure 2d), SEED ROIs were drawn in the superior temporal gyrus white matter, inferior from the SLF fibers and superior to the ILF fibers, on 3 coronal slices. The first slice was the most anterior slice on which the middle cerebellar peduncle is still visible. The second slice was the most anterior slice where the corticospinal tract covers the middle cerebellar peduncle. The third slice was the most anterior slice showing both the transverse pontine fibers and the superior cerebellar peduncle.[25]

For the UF (Figure 2e), the most anterior coronal slice on which the fornix is still visible was identified. Then, a SEED ROI was placed in the anterior-posterior white matter inferolateral from the anterior portion of the internal capsule. Finally, on the same slice, an AND ROI was drawn in the anterior-posterior white matter of the full temporal lobe.[24]

Along each white matter tract, the mean value for FA was extracted as an indirect measure of microstructural integrity. FA describes the degree of directional dependence

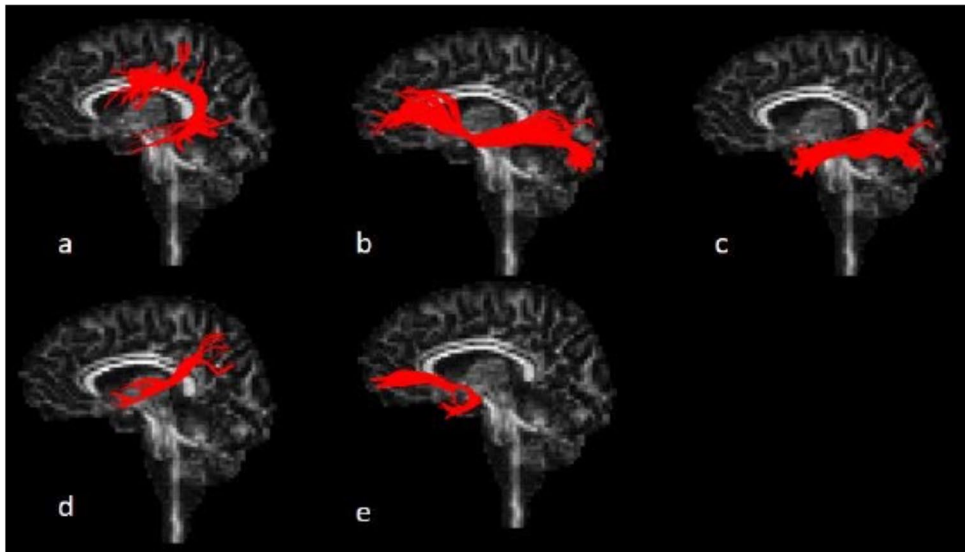

Figure 2. Reconstruction of left-hemisphere dorsal and ventral language white matter tracts using deterministic tractography: (a) superior longitudinal fasciculus (SLF); (b) inferior fronto-occipital fasciculus (IFOF); (c) inferior longitudinal fasciculus (ILF); (d) middle longitudinal fasciculus (MdLF); (e) uncinate fasciculus (UF); Figure courtesy of M. Verly (2017; doctoral thesis, p. 303).

of water diffusion in fiber tracts, with values ranging from 0 (isotropic diffusion) to 1 (diffusion in one direction); higher values indicate a higher degree of directional organization and coherence of fiber tracts. FA is thought to reflect myelination and/or axonal density[26] and is a measure that is very sensitive to microstructural changes.[27]

Statistical Analysis

Statistical analyses were performed using IBM Statistical Package for Social Sciences for Windows, version 23. To analyze changes in FA values for each of the white matter tracts from the first to the second scanning session and to analyze change in BNT scores from the first to the second assessment, we used paired-samples *t* tests. To investigate the relationship between changes in FA values and change in BNT score, we calculated Pearson's correlations. The significance level was set at $\alpha = .05$; probability values calculated for Pearson's correlations were corrected for multiple comparisons (10×).

Results

Deterministic tractography was successful for all tracts in all participants, except for 1 tract; due to the lesion, the left SLF could not reliably be identified in 3 participants (P06, P08, and P10), and, therefore, analyses for the left SLF were performed on 7 participants.

At the group level, no significant changes in FA were found for any of the left and right hemisphere white matter tracts from the first to the second scanning session (Table 2). Figure 3 presents the individual tractography results at the first and second scanning session.

For the left SLF (Figure 3A, left panel), 2 participants (P02, P07) showed an increase in FA (FA change: 0.001 and 0.025, respectively), 4 participants (P01, P03, P05, P09) showed a decrease (range FA change: −0.017 to −0.004), and 1 participant (P04) showed no FA change. For the right SLF (Figure 3A, right panel), 6 participants (P01, P02, P03, P07, P09, P10) showed an increase (range FA change: 0.001 to 0.045), 3 participants (P05, P06, P08) showed a decrease (range FA change: −0.012 to −0.004), and 1 participant (P04) showed no FA change.

For the left IFOF (Figure 3B, left panel), 4 participants (P02, P05, P08, P10) showed an increase (range FA change: 0.008 to 0.032), and 6 participants (P01, P03, P04, P06, P07, P09) showed a decrease (range FA change: −0.017 to −0.007). For the right IFOF (Figure 3B, right panel), 4 participants (P02, P04, P05, P07) showed an increase (range FA change: 0.003 to 0.012), and 6 participants (P01, P03, P06, P08, P09, P10) showed a decrease (range FA change: −0.018 to −0.001).

For the left ILF (Figure 3C, left panel), 2 participants (P07, P08) showed an increase (FA change: 0.01 and 0.009, respectively), and 8 participants (P01, P02, P03, P04, P05, P06, P09, P10) showed a decrease (range FA change: −0.059 to −0.001). For the right ILF (Figure 3C, right panel), 3 participants (P03, P05, P06) showed an increase (range FA change: 0.011 to 0.028), and 7 participants (P01, P02, P04, P07, P08, P09, P10) showed a decrease (range FA change: −0.021 to −0.001).

Table 2. Mean (SD) Fractional Anisotropy for Each White Matter Tract at First and Second Scanning Sessions, and Comparisons Between Fractional Anisotropy at First and Second Scanning Sessions.

	First	Second		
	FA, mean (SD)	FA, mean (SD)	*t*	*P*
SLF left	0.390 (0.022)	0.390 (0.027)	0.000	>.999
SLF right	0.453 (0.028)	0.461 (0.023)	−1.501	.168
IFOF left	0.448 (0.054)	0.448 (0.043)	0.019	.985
IFOF right	0.491 (0.032)	0.490 (0.028)	0.423	.683
ILF left	0.433 (0.026)	0.423 (0.033)	1.599	.144
ILF right	0.459 (0.031)	0.459 (0.040)	0.078	.940
MdLF left	0.402 (0.041)	0.401 (0.036)	0.113	.912
MdLF right	0.431 (0.019)	0.430 (0.019)	0.177	.863
UF left	0.404 (0.029)	0.399 (0.027)	1.092	.303
UF right	0.421 (0.023)	0.418 (0.019)	0.543	.600

Abbreviations: First, first scanning session; Second, second scanning session; FA, fractional anisotropy; SLF, superior longitudinal fasciculus; IFOF, inferior fronto-occipital fasciculus; ILF, inferior longitudinal fasciculus; MdLF, middle longitudinal fasciculus; UF, uncinate fasciculus.

For the left MdLF (Figure 3D, left panel), 6 participants (P02, P03, P05, P07, P08, P09) showed an increase (range FA change: 0.001 to 0.037), and 4 participants (P01, P04, P06, P10) showed a decrease (range FA change: −0.042 to −0.001). For the right MdLF (Figure 3D, right panel), 4 participants (P03, P07, P09, P10) showed an increase (range FA change: 0.001 to 0.039), 5 participants (P01, P04, P05, P06, P08) showed a decrease (range FA change: −0.019 to −0.005), and 1 participant (P02) showed no FA change.

For the left UF (Figure 3E, left panel), 3 participants (P02, P04, P06) showed an increase (range FA change: 0.008 to 0.021), and 7 participants (P01, P03, P05, P07, P08, P09, P10) showed a decrease (range FA change: −0.021 to −0.002). For the right UF (Figure 3E, right panel), 5 participants (P01, P02, P05, P06, P07) showed an increase (range FA change: 0.003 to 0.017), and 5 participants (P03, P04, P08, P09, P10) showed a decrease (range FA change: −0.036 to −0.003).

At the group level, the BNT score improved significantly from 34.8 (SD = 15.7) at the first assessment to 40.5 (SD = 15.1) at the second assessment, $t(9) = -3.0$, $P = .015$. Figure 4 presents the individual naming results at the first and second assessment. Six participants (P1, P3, P5, P6, P7, P9) showed improvement on the BNT (range BNT change score: 5 to 14), 2 participants (P4, P10) showed limited improvement (BNT change score: 2 and 1, respectively), and 2 participants (P2, P8) showed a slight decline (BNT change score: −3 and −1, respectively).

No significant correlations were found between FA change in the left hemisphere tracts and change in BNT score. For the right hemisphere tracts, a moderate negative correlation was found between FA change in the SLF and change in BNT score ($r = -0.65$, $P = .044$). However, this correlation did not survive a correction for multiple testing. A strong positive correlation was found between FA change in the ILF and change in BNT score ($r = 0.91$, $P < .001$; Figure 5); an increase in FA was associated with a considerable improvement on the BNT (range BNT change score: 12 to 14), a decrease in FA was related to a limited improvement or slight decline in BNT scores. Table 3 shows the results of the correlational analyses. See Supplementary Figure 1 for the scatterplots of the correlational results.

Discussion

In this observational study, we investigated changes in tract integrity in the left and right dorsal and ventral language streams in relation to naming recovery in subacute aphasia. Naming recovery appeared to be related to FA change in the ILF within the ventral stream in the unaffected right hemisphere, and unrelated to changes in both the ventral and dorsal streams in the left hemisphere.

The ILF is an important component of the ventral semantic system, transferring visual information from the occipital to the anterior temporal lobe,[5] and is proposed to be involved in visual object recognition[5,28] and in mapping lexical labels onto object representations.[28] Our finding that the right ILF was involved in naming recovery is in line with a functional neuroimaging study in poststroke aphasia reporting activation of right hemisphere cortical areas that are connected by the ILF.[29] Abel et al[29] showed that during in-scanner picture naming cortical activation extended to the right hemisphere, including visual cortex and areas in the temporal lobe.

In contrast to our study, most previous DTI studies on aphasia recovery established a relationship between language recovery and changes in structural connectivity within the left[7,8,10] or right dorsal stream.[9,12] Although 4 of these 5 studies differed from our study in the tasks used to investigate aphasia recovery,[7-10] 3 of these studies reported on a relationship between structural changes and spoken language production,[7,9,10] including naming[7,10] or picture description.[9] The fourth study[8] found a relationship with a summary score for spoken language comprehension and production. Unlike our study, most of these studies examined therapy-induced white matter plasticity in the chronic stage[7,9,10] and/or exclusively focused on the dorsal stream,[7-9,12] which may explain the discrepancy in findings. It is worth noting that, although our finding regarding the right SLF did not reach significance after multiple testing correction, it is consistent with the observational study by Keser et al,[12] demonstrating that increased tract integrity within the right dorsal stream was associated with less improvement on the BNT.

One previous study has investigated the role of the left and right ILF in recovery of naming after stroke and

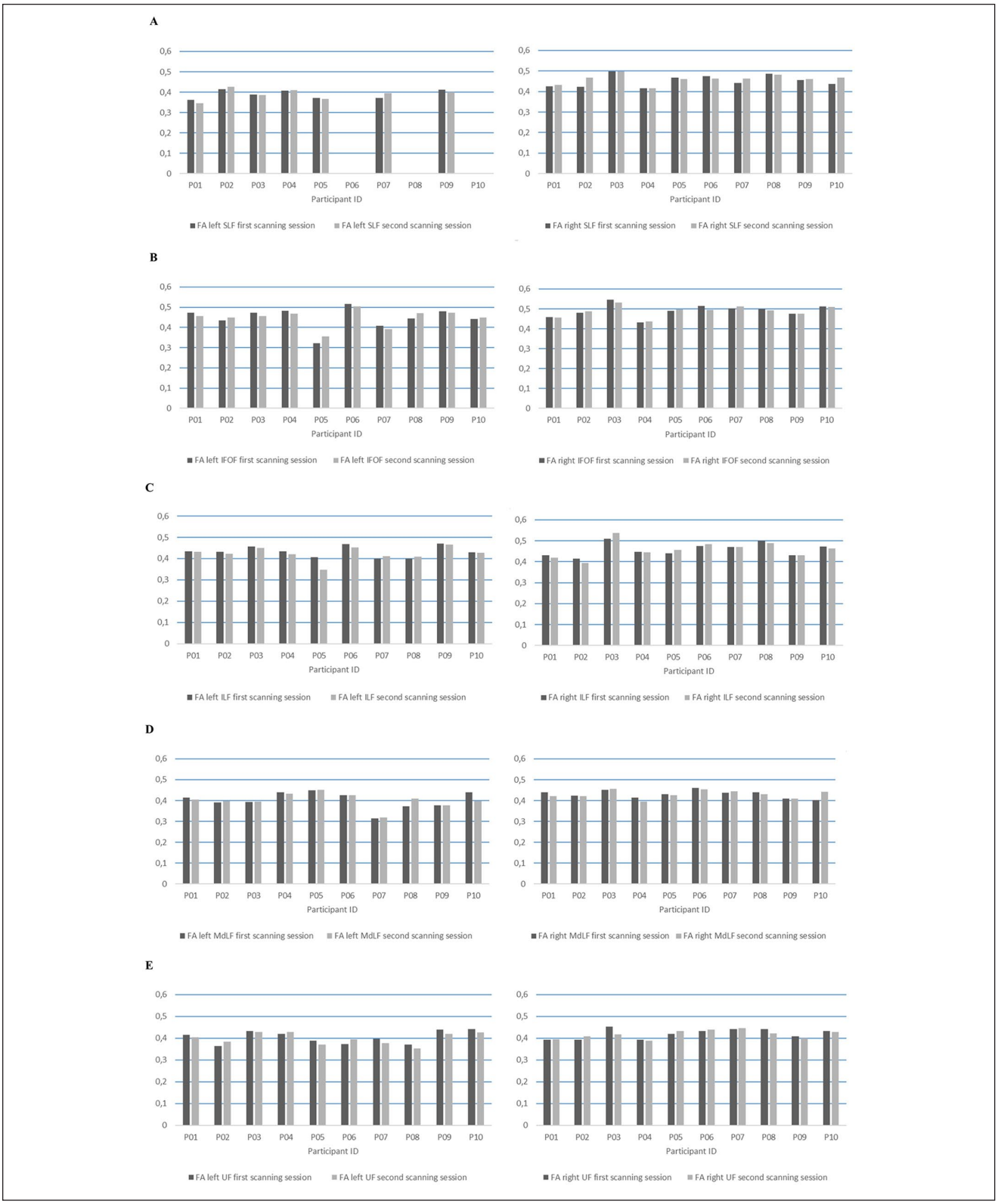

Figure 3. Fractional anisotropy (FA) values of the (A) left, respectively right, superior longitudinal fasciculus (SLF), (B) left, respectively right, inferior fronto-occipital fasciculus (IFOF), (C) left, respectively right, inferior longitudinal fasciculus (ILF), (D) left, respectively right, middle longitudinal fasciculus (MdLF), and (E) left, respectively right, uncinate fasciculus (UF) for each participant at first (dark gray) and second scanning session (light gray).

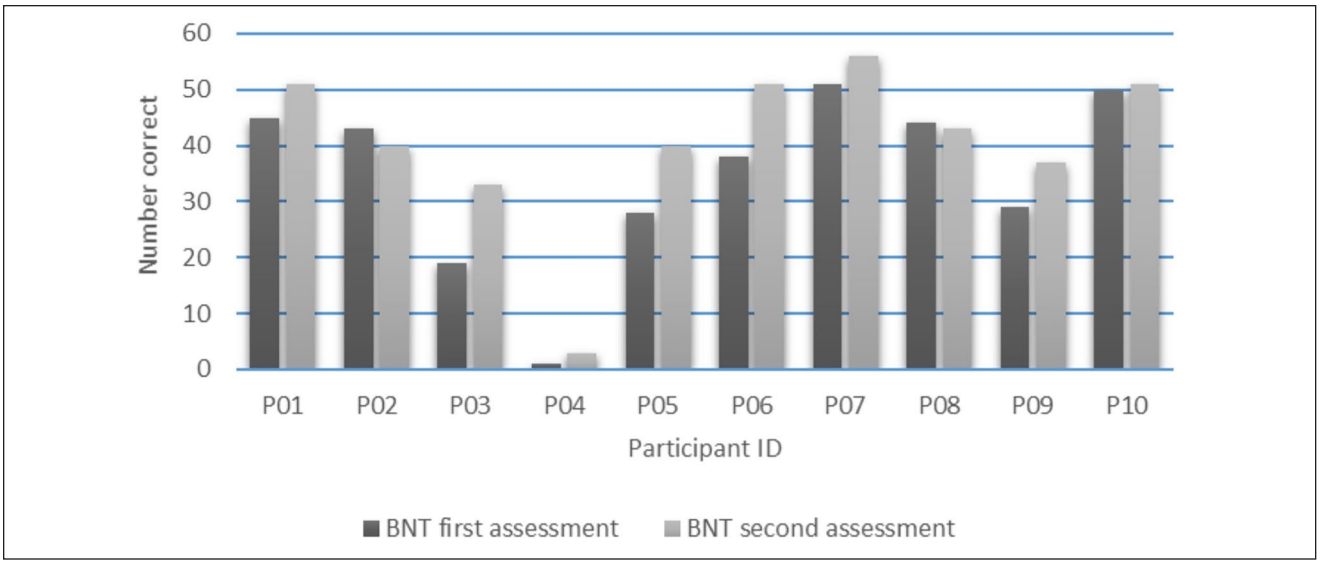

Figure 4. Boston Naming Test (BNT) scores for each participant at first (dark gray) and second assessment (light gray).

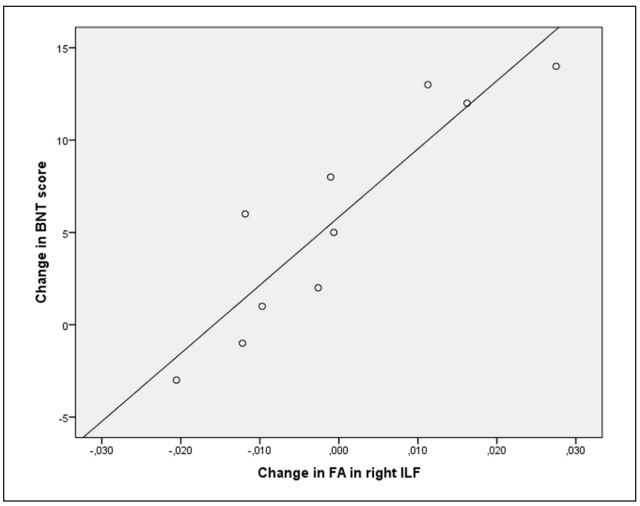

Figure 5. Scatterplot showing the correlation between change in fractional anisotropy (FA) in the right inferior longitudinal fasciculus (ILF) from first to second scanning session and change in Boston Naming Test (BNT) score from first to second assessment.

Table 3. Correlation Coefficients (*P* Value) Between Change in Fractional Anisotropy for Each White Matter Tract From First to Second Scanning Session and Change in Boston Naming Test Scores From First to Second Assessment.

White matter tract	Pearson's *r* (*P*)
SLF left	–0.423 (.344)
SLF right	–0.646 (.044)
IFOF left	–0.317 (.372)
IFOF right	–0.482 (.159)
ILF left	–0.454 (.188)
ILF right	0.907 (<0.001)*
MdLF left	–0.044 (0.905)
MdLF right	–0.131 (0.718)
UF left	–0.019 (0.958)
UF right	–0.189 (0.601)

*$P < .005$ (Bonferroni-corrected), significant correlation.

reported an association between therapy-induced naming improvement in chronic aphasia and structural plasticity in the ILF in the lesioned left hemisphere.[11] While this study pointed to the left ILF, we found a relationship with structural changes in the right ILF. This discrepancy may be related to a difference in time after stroke for the participants. Whereas the study by McKinnon et al[11] was performed in patients who were at least 12 months poststroke, we studied a group of patients who were within 3 months post onset. Based on functional neuroimaging studies, it has been suggested that hemispheric contributions to aphasia recovery may change over time.[30,31] In a longitudinal study, Saur et al[30] observed strongly reduced activation in both hemispheres in the first days post onset, followed by increased bilateral activation with recruitment of right homologue language areas during the next 2 weeks, and restoration of left-hemisphere language dominance after 4 to 12 months. Van de Sandt-Koenderman et al[31] reported that patients in the subacute stage of stroke (<3 months post onset) showed bilateral or right-lateralized language activation, whereas chronic patients (>12 months post onset) showed bilateral or left-lateralized language activation patterns.

Our findings underscore that the bilateral representation of the ventral stream enables the unaffected right hemisphere to compensate for compromised language function

in the left hemisphere.[4] This is in line with functional neuroimaging studies, reporting that the right hemisphere may play a role in compensating for language deficits in the first months after stroke.[32,33] Several studies have suggested that right hemisphere recruitment may depend on lesion volume[32-34] and lesion site.[32-35] In the present study, the involvement of the right ILF seems to be independent of lesion volume, as the 3 participants (P3, P5, P6) who showed considerable naming improvement and an increase in FA had similar lesion volumes as 2 (P8, P10) of the 3 participants who showed a decrease in FA and limited improvement or a slight decline in naming accuracy. The participant (P2) who showed the largest FA decrease and the largest deterioration of naming accuracy had the smallest lesion volume of all participants. Whether the relationship between naming recovery and change in right ILF integrity was driven by lesion site remains unclear given the heterogeneous lesion profiles of the participants.

Interestingly, the changes in the right ILF found in the present study appeared to go in 2 directions. Whereas an increase in FA was associated with a considerable improvement on the BNT, a decrease in FA was related to a limited improvement or even a slight decline in BNT scores. A reduction in tract integrity in the unaffected right hemisphere was an unexpected finding. However, Ivanova et al[36] observed a lower mean FA in several right-hemisphere white matter tracts, including the ILF, in chronic aphasic patients too; a finding thought to be a reflection of remote neurodegeneration effects after stroke. Our finding is also in line with a study in a general population of stroke patients, reporting a relationship between reduced white matter integrity in the nonlesioned hemisphere at 3 months post onset, which was attributed to demyelination, and poor cognitive recovery.[37] Hence, our finding that some participants showed a decrease versus others showing an increase in integrity of the right ILF suggests that there might be 2 different underlying neural mechanisms at play: remote degeneration with a reduction in tract integrity and lack of recovery in some participants, and an increase in integrity in others, which might reflect adaptive white matter plasticity in the unaffected hemisphere. White matter plasticity underlying behavioral improvements has also been found in the healthy adult brain and has been suggested to reflect activity-dependent myelination.[38,39] It remains unknown what drives remote degeneration in some participants and white matter plasticity in others.

Within the ventral stream, none of the other language white matter tracts examined, including the UF, appeared to play a role in subacute naming recovery. The absence of results for the UF are in accordance with the results found by Van Hees et al[10] in chronic aphasia, showing no structural changes in the left or the right UF following naming treatment.

This study has several limitations. A first limitation is the small sample size. Our results, providing the first indication of a role of the right ventral stream in early naming recovery, need to be confirmed with larger samples. Another limitation is that the participants were predominantly male (7 men, 3 women). Given the evidence for sex differences in white matter tracts related to language,[40-42] this imbalance might have introduced bias. This is particularly prominent for the analyses of the left SLF. Due to the presence of the lesion in the SLF, the left SLF could not be reconstructed in 3 participants, which excluded 2 of the 3 female participants' data. A third limitation is that the time post onset at which the behavioral and tractography data were obtained varied across individuals and between measurements. These differences in the timing of data collection hamper the interpretation of the structure-function relationships, as both aphasia recovery[43] and changes in structural integrity[3] may occur rapidly in the first months after stroke. A fourth limitation is that some of the participants received tDCS, whereas others did not, which might potentially have influenced the behavioral and neural results at the individual level. However, when grouped into 2 groups (tDCS and sham), the participants showed no significant differences in naming recovery (Supplementary Table 1) or in change in tract integrity for any of the tracts of interest (Supplementary Table 2). Furthermore, when examining the scatterplots showing the correlation between FA change in each of the tracts and change in BNT score with visualization of experimental condition (Supplementary Figure 1), we found no evidence of confounding by tDCS, as the participants assigned to either the experimental or control condition were randomly distributed across each of the plots. Last, DTI tractography provides only indirect measures of white matter tissue properties, and, hence, uncertainty exists about the correspondence between DTI measures and underlying neuroanatomical factors.[44]

In conclusion, the present findings provide preliminary evidence of a relationship between change in white matter integrity in the right ventral stream and naming recovery in subacute aphasia. Whereas an increase in the integrity of the right ILF was associated with a considerable improvement of naming accuracy, a reduction was related to a limited improvement or a slight deterioration of naming accuracy. The present findings add to the understanding of the neural mechanisms underlying recovery from aphasia and highlight the need to examine changes in the bilateral ventral white matter pathways in studies investigating recovery of language after stroke.

Acknowledgments

We thank the MRI technologists for their contribution to the project. Special thanks are given to the participants for their commitment to the study.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was supported by Erasmus MC Cost-Effectiveness Research (Grant Number: 2012-12112) and the Dutch Brain Foundation (Grant Number: 2013(1)-97).

ORCID iD

Marieke Blom-Smink https://orcid.org/0000-0001-5679-0759

References

1. Laska AC, Hellblom A, Murray V, Kahan T, Von Arbin M. Aphasia in acute stroke and relation to outcome. *J Intern Med*. 2001;249:413-422.
2. Kiran S. What is the nature of poststroke language recovery and reorganization? *ISRN Neurol*. 2012;2012:786872.
3. Thiel A, Zumbansen A. The pathophysiology of post-stroke aphasia: a network approach. *Restor Neurol Neurosci*. 2016;34:507-518.
4. Hickok G, Poeppel D. The cortical organization of speech processing. *Nat Rev Neurosci*. 2007;8:393-402.
5. Dick AS, Bernal B, Tremblay P. The language connectome: new pathways, new concepts. *Neuroscientist*. 2014;20:453-467.
6. Hickok G. The functional neuroanatomy of language. *Phys Life Rev*. 2009;6:121-143.
7. Breier JI, Juranek J, Papanicolaou AC. Changes in maps of language function and the integrity of the arcuate fasciculus after therapy for chronic aphasia. *Neurocase*. 2011;17:506-517.
8. Jang SH, Cho IT, Lim JW. Recovery of aphasia and change of injured arcuate fasciculus in the dominant hemisphere in stroke patients. *NeuroRehabilitation*. 2017;41:759-764.
9. Schlaug G, Marchina S, Norton A. Evidence for plasticity in white-matter tracts of patients with chronic Broca's aphasia undergoing intense intonation-based speech therapy. *Ann N Y Acad Sci*. 2009;1169:385-394.
10. Van Hees S, McMahon K, Angwin A, de Zubicaray G, Read S, Copland DA. Changes in white matter connectivity following therapy for anomia post stroke. *Neurorehabil Neural Repair*. 2014;28:325-334.
11. McKinnon ET, Fridriksson J, Glenn GR, et al. Structural plasticity of the ventral stream and aphasia recovery. *Ann Neurol*. 2017;82:147-151.
12. Keser Z, Sebastian R, Hasan KM, Hillis AE. Right hemispheric homologous language pathways negatively predicts poststroke naming recovery. *Stroke*. 2020;51:1002-1005.
13. Spielmann K, van de Sandt-Koenderman WM, Heijenbrok-Kal MH, Ribbers GM. Transcranial direct current stimulation in post-stroke sub-acute aphasia: study protocol for a randomized controlled trial. *Trials*. 2016;17:380.
14. Linebaugh CW, Shisler RJ, Lehner L. Cueing hierarchies and word retrieval: a therapy program. *Aphasiology*. 2005;19:77-92.
15. Oldfield RC. The assessment and analysis of handedness: the Edinburgh inventory. *Neuropsychologia*. 1971;9:97-113.
16. De Renzi E, Faglioni P. Normative data and screening power of a shortened version of the Token Test. *Cortex*. 1978;14:41-49.
17. Goodglass H, Kaplan E. *The Assessment of Aphasia and Related Disorders*. Lea & Febiger; 1972.
18. Spielmann K, van de Sandt-Koenderman WME, Heijenbrok-Kal MH, Ribbers GM. Transcranial direct current stimulation does not improve language outcome in subacute poststroke aphasia. *Stroke*. 2018;49:1018-1020.
19. Kaplan E, Goodglass H, Weintraub S. *The Boston Naming Test*. Lea & Febiger; 1983.
20. Heesbeen IME, Van Loon-Vervoorn WA. Boston Benoemingstest: Uitbreiding van de Nederlandse normen, gecorrigeerd voor opleiding en leeftijd [Boston Naming Test: Extension of the Dutch norms, adjusted for education and age]. In: IME Heesbeen. *Diagnostiek en herstelmeting van taalproblemen na niet-aangeboren hersenletsel* [Diagnostics and recovery measurement of language problems after non-congenital brain injury]. Universal Press; 2001.
21. Van Loon-Vervoorn WA. *De Boston Benoemingstaak: Een test voor woordvinding bij afasie* [The Boston naming test: a test of word-finding in aphasia]. 4th ed. Utrecht University; 2005.
22. Leemans A, Jones DK. The B-matrix must be rotated when correcting for subject motion in DTI data. *Magn Reson Med*. 2009;61:1336-1349.
23. Catani M, Thiebaut de Schotten M. A diffusion tensor imaging tractography atlas for virtual in vivo dissections. *Cortex*. 2008;44:1105-1132.
24. Wakana S, Caprihan A, Panzenboeck MM, et al. Reproducibility of quantitative tractography methods applied to cerebral white matter. *Neuroimage*. 2007;36:630-644.
25. Makris N, Preti MG, Asami T, et al. Human middle longitudinal fascicle: variations in patterns of anatomical connections. *Brain Struct Funct*. 2013;218:951-968.
26. Beaulieu C. The basis of anisotropic water diffusion in the nervous system — a technical review. *NMR Biomed*. 2002;15:435-455.
27. Alexander AL, Lee JE, Lazar M, Field AS. Diffusion tensor imaging of the brain. *Neurotherapeutics*. 2007;4:316-329.
28. Catani M, Mesulam M. The arcuate fasciculus and the disconnection theme in language and aphasia: history and current state. *Cortex*. 2008;44:953-961.
29. Abel S, Weiller C, Huber W, Willmes K, Specht K. Therapy-induced brain reorganization patterns in aphasia. *Brain*. 2015;138(pt 4):1097-1112.
30. Saur D, Lange R, Baumgaertner A, et al. Dynamics of language reorganization after stroke. *Brain*. 2006;129(pt 6):1371-1384.
31. Van de Sandt-Koenderman MWME, Mendez Orellana CP, van der Meulen I, Smits M, Ribbers GM. Language lateralisation after Melodic Intonation Therapy: an fMRI study in subacute and chronic aphasia. *Aphasiology*. 2018;32:765-783.

32. Anglade C, Thiel A, Ansaldo AI. The complementary role of the cerebral hemispheres in recovery from aphasia after stroke: a critical review of literature. *Brain Inj*. 2014;28: 138-145.
33. Cocquyt E-M, De Ley L, Santens P, Van Borsel J, De Letter M. The role of the right hemisphere in recovery of stroke-related aphasia: a systematic review. *J Neurolinguist*. 2017;44: 68-90.
34. Skipper-Kallal LM, Lacey EH, Xing S, Turkeltaub PE. Right hemisphere remapping of naming functions depends on lesion size and location in poststroke aphasia. *Neural Plast*. 2017;2017:8740353.
35. Stockert A, Wawrzyniak M, Klingbeil J, et al. Dynamics of language reorganization after left temporo-parietal and frontal stroke. *Brain*. 2020;143:844-861.
36. Ivanova MV, Isaev DY, Dragoy OV, et al. Diffusion-tensor imaging of major white matter tracts and their role in language processing in aphasia. *Cortex*. 2016;85:165-181.
37. Dacosta-Aguayo R, Grana M, Fernandez-Andujar M, et al. Structural integrity of the contralesional hemisphere predicts cognitive impairment in ischemic stroke at three months. *PLoS One*. 2014;9:e86119.
38. Scholz J, Klein MC, Behrens TE, Johansen-Berg H. Training induces changes in white-matter architecture. *Nat Neurosci*. 2009;12:1370-1371.
39. Engvig A, Fjell AM, Westlye LT, et al. Memory training impacts short-term changes in aging white matter: a longitudinal diffusion tensor imaging study. *Hum Brain Mapp*. 2012;33:2390-2406.
40. Hagmann P, Cammoun L, Martuzzi R, et al. Hand preference and sex shape the architecture of language networks. *Hum Brain Mapp*. 2006;27:828-835.
41. Kanaan RA, Allin M, Picchioni M, et al. Gender differences in white matter microstructure. *PLoS One*. 2012;7:e38272.
42. Jung M, Mody M, Fujioka T, Kimura Y, Okazawa H, Kosaka H. Sex differences in white matter pathways related to language ability. *Front Neurosci*. 2019;13:898.
43. El Hachioui H, Lingsma HF, van de Sandt-Koenderman ME, Dippel DWJ, Koudstaal PJ, Visch-Brink EG. Recovery of aphasia after stroke: a 1-year follow-up study. *J Neurol*. 2013;260: 166-171.
44. Catani M, Allin MP, Husain M, et al. Symmetries in human brain language pathways correlate with verbal recall. *Proc Natl Acad Sci U S A*. 2007;104:17163-17168.