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Diffusion-tensor imaging of major white matter tracts and their role in language processing in aphasia

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ABSTRACT

A growing literature is pointing towards the importance of white matter tracts in understanding the neural mechanisms of language processing, and determining the nature of language deficits and recovery patterns in aphasia. Measurements extracted from diffusion-weighted (DW) images provide comprehensive *in vivo* measures of local microstructural properties of fiber pathways. In the current study, we compared microstructural properties of major white matter tracts implicated in language processing in each hemisphere (these included arcuate fasciculus (AF), superior longitudinal fasciculus (SLF), inferior longitudinal fasciculus (ILF), inferior frontal-occipital fasciculus (IFOF), uncinate fasciculus (UF), and corpus callosum (CC), and corticospinal tract (CST) for control purposes) between individuals with aphasia and healthy controls and investigated the relationship between these neural indices and language deficits.

Thirty-seven individuals with aphasia due to left hemisphere stroke and eleven age-matched controls were scanned using DW imaging sequences. Fractional anisotropy (FA), mean diffusivity (MD), radial diffusivity (RD), axial diffusivity (AD) values for each major white matter tract were extracted from DW images using tract masks chosen from standardized atlases. Individuals with aphasia were also assessed with a standardized language test in Russian targeting comprehension and production at the word and sentence level.

Abbreviations: DTI, diffusion tensor imaging; DF, diffusion-weighted; FA, fractional anisotropy; MD, mean diffusivity; AD, axial diffusivity; RD, radial diffusivity; AF, arcuate fasciculus; SLF, superior longitudinal fasciculus; ILF, inferior longitudinal fasciculus; IFOF, inferior frontal-occipital fasciculus; UF, uncinate fasciculus; MdLF, middle longitudinal fasciculus; CST, corticospinal tract; CC, corpus callosum; MNI, Montreal Neurological Institute.

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Individuals with aphasia had significantly lower FA values for left hemisphere tracts and significantly higher values of MD, RD and AD for both left and right hemisphere tracts compared to controls, all indicating profound impairment in tract integrity. Language comprehension was predominantly related to integrity of the left IFOF and left ILF, while language production was mainly related to integrity of the left AF. In addition, individual segments of these three tracts were differentially associated with language production and comprehension in aphasia. Our findings highlight the importance of fiber pathways in supporting different language functions and point to the importance of temporal tracts in language processing, in particular, comprehension.

1. Introduction

Aphasia is an acquired neurogenic communication disorder leading to deficits in oral and written language comprehension and production (Hallowell & Chapey, 2008). Aphasia in most instances occurs after damage due to stroke or traumatic-brain injury to perisylvian areas in the dominant hemisphere. As early as the 19th century, it was acknowledged that damage to both cortical areas and subcortical fiber pathways (white matter tracts) could lead to language deficits. Carl Wernicke (1874) described a syndrome resulting from a disconnection of Broca's and Wernicke's areas, that would later become known as 'conduction aphasia' (Catani & Mesulam, 2008). At the end of the 19th century, Lichtheim (1885), building on Wernicke's work, further extended the descriptions of disconnection syndromes in language and outlined two additional types of aphasia, transcortical sensory and transcortical motor, that resulted from disconnection of the concept center from other language areas, although he did not provide anatomical specifications for these syndromes in his work. Further, contemporary re-examination of classical cortical aphasia cases (e.g., Leborgne patient) using modern neuroimaging techniques have demonstrated extensive white matter involvement (Dronkers, Plaisant, Iba-Zizen, & Cabanis, 2007; Thiebaut de Schotten et al., 2015). Recent lesion studies repeatedly show that lesions associated with comprehension and production deficits in aphasia can be located in subcortical white matter (Bates et al., 2003; Kümmerer et al., 2013).

Still today, relatively little is known about the functional significance of fiber pathways in language processing, in general, and their contributions to aphasia syndromes, in particular (for review see Bajada, Lambon Ralph, & Cloutman, 2015; Dick, Bernal, & Tremblay, 2014). However, recent advances in diffusion imaging techniques now afford the opportunity to investigate microstructural tissue properties and white matter integrity *in vivo* in individuals with various brain pathology, including aphasia. Within this novel avenue of research, accumulating evidence shows that differential fiber pathway damage (Hosomi et al., 2009; Kim & Jang, 2013; Kim et al., 2011; Rosso et al., 2015) and premorbid anatomical variations in tract structure (Forkel, Thiebaut de Schotten, Dell'Acqua, et al., 2014) can serve as important prognostic factors for patterns of language recovery following stroke. Measured changes in the macro- and microstructure of fiber pathways have also been used as physiological markers of observed behavioral changes following training (Geva, Correia, & Warburton, 2011; Scholz, Klein, Behrens, & Johansen-Berg, 2009). To advance our knowledge of how language is processed in the brain and to gain insights into the neural mechanisms of language recovery in aphasia, further investigation of the functional roles of fiber pathways is required.

1.1. *Role of different white matter tracts in language processing*

1.1.1. *Dorsal tracts*

Historically, the arcuate fasciculus (AF) has been regarded as the main tract involved in language. The importance of this tract was highlighted in the first network model of language processing by Carl Wernicke (even though initially Wernicke was mistaken regarding its anatomical location) (Catani & Mesulam, 2008). The AF and the superior longitudinal fasciculus (SLF) are fiber bundles that run longitudinally within each cerebral hemisphere and connect frontal cortex with postrolandic areas, the temporal and inferior parietal lobes, respectively. Once these fibers bundle together to pass over the ventricles, they become difficult to distinguish from one another and have previously been referred to by the same name. However, Petrides and Pandya (1988) – in the rhesus monkey brain using radiographic techniques – and later Makris et al. (2005) – in the human brain using diffusion tensor imaging (DTI) – isolated the two tracts and demonstrated their distinct trajectories. Specifically, Makris et al. (2005) delineated four separate segments of the SLF in the human brain, with the fourth subdivision being the AF. Based on recent neuroimaging techniques and electrostimulation studies, two- and three-pathway models of the AF have been proposed (Brauer, Anwander, Perani, & Friederici, 2013; Catani, Jones, & Ffytche, 2005; Glasser & Rilling, 2008). For instance, Catani et al. (2005) demonstrated functional segregation of the AF, with the direct (long) branch presumably supporting phonological processing and indirect (short) branches – lexical-semantic processing. Data no longer unequivocally support the classical depiction of this tract as directly and exclusively connecting Wernicke's with Broca's area. It has been shown that in the frontal lobe the tract actually reaches to the precentral gyrus rather than to the

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Broca's area (Brown et al., 2014; for review see; Bernal & Ardila, 2009), though the exact terminations of this tract remain to be determined (Makris et al., 2005).

Undoubtedly, the AF in the dominant left hemisphere is important for language, as damage to this tract leads to a broad array of aphasia symptoms (Bates et al., 2003; Dronkers, Redfern, & Knight, 2000; Dronkers, Turken, Baldo, Curran, & Knight, 2015; Dronkers et al., 2007), though its specific functions remain to be established. The integrity of the AF, as indexed via fractional anisotropy (FA), was related to difficulties in repetition and comprehension, however, when damage to cortical language areas was taken into account, only the link with repetition remained significant (Breier, Hasan, Zhang, Men, & Papanicolaou, 2008). In the same study, the SLF was also related to repetition abilities (Breier et al., 2008). Kümmerer et al. (2013), using voxel based lesion-symptom mapping, also showed that a lesion within the posterior temporoparietal periventricular white matter within the projection of the AF and dorsal SLF was associated with repetition deficits. Marchina et al. (2011) demonstrated that AF lesion load significantly predicted impairment in rate, informativeness and overall efficiency of spontaneous speech and naming ability. Lesions to the anterior segment of the AF were related to decreased speech fluency (Fridriksson, Guo, Fillmore, Holland, & Rorden, 2013). Wilson et al. (2011) in a study of primary progressive aphasia reported that decreased integrity of the SLF including its AF component was related to expressive and receptive syntactic processing difficulties. Grossman et al. (2013) also demonstrated that accurate grammatical expression was related to integrity of the SLF (and also the inferior longitudinal fasciculus; ILF) in primary progressive aphasia. During electrostimulation of this tract in awake surgery, speech arrest and naming difficulties, specifically phonemic paraphasias, are observed (Bello et al., 2008; Duffau et al., 2002; Maldonado et al., 2011). Finally, changes in the integrity of the AF both in the dominant (Breier, Juranek, & Papanicolaou, 2011) and non-dominant hemispheres (Schlaug, Marchina, & Norton, 2009) as a result of speech therapy for production deficits in aphasia have been reported. Limited studies have consistently demonstrated a positive relationship between these neural and behavioral changes: with a larger change in FA and tract volume revealed in patients with greater language gains (Schlaug et al., 2009; van Hees et al., 2014). Forkel, Thiebaut de Schotten, Kawadler et al. (2014) showed that the volume of the AF in the right (intact) hemisphere in the acute stage of recovery was predictive of overall language recovery 6-months post-onset. Additionally, the AF also seems to play an important role in language acquisition in children (Bernal & Ardila, 2009; Yeatman et al., 2011), as possibly the ability to learn novel words depends on audio-motor integration that in turn is contingent on efficient connection and communication between pre- and post-rolandic language areas provided by the long branch of the AF (López-Barroso et al., 2013). To date no other fiber pathways have been studied in the search for neural substrate of language improvement or acquisition. In summary, emerging data suggest that the AF is critical for speech fluency, phonological processing and, possibly, syntactic analysis. Further investigation is required to look into its role in language processing in greater detail. Importantly, future studies should be more consistent in spatially distinguishing the AF from the SLF and differentiating their functional roles.

1.1.2. *Ventral tracts*

Given the widespread array of areas now known to be involved in language processing, the AF cannot be the only white matter pathway supporting language processing. Still only within the last 10 years have neuroimaging and electrostimulation studies begun to highlight the importance of ventral white matter tracts in language processing (Catani et al., 2005; Dronkers et al., 2015; Duffau, Moritz-Gasser, & Mandonnet, 2013; Turken & Dronkers, 2011; see also; Bajada et al., 2015; Dick et al., 2014), such as the ILF, inferior frontal-occipital fasciculus (IFOF), uncinate fasciculus (UF), and middle longitudinal fasciculus (MdLF). Surprisingly, damage to some of these tracts was initially described in 1895 by Dejerine and Dejerine-Klumpke in their post mortem dissections of individuals suffering from aphasia (Krestel, Annoni, & Jagella, 2013): they observed degeneration of the UF, ILF, and IFOF in the autopsy of three patients with aphasia and were the first to describe ventral and dorsal fiber pathways related to language disorders (Dejerine & Dejerine-Klumpke, 1901).

The ILF and IFOF are long intrahemispheric association fibers that run the length of the temporal lobe. The ILF connects the occipital lobe with the anterior portions of the middle and inferior temporal gyri, temporal pole and limbic structures, while the IFOF runs medial to the ILF in the temporal lobe and connects inferior and medial occipital lobe with the inferior orbitofrontal cortex (Catani & Thiebaut de Schotten, 2008). The two pass near each other in the temporal lobe and the extent of their segregation remains unclear (Forkel, Thiebaut de Schotten, Kawadler, et al., 2014). Semantic paraphasic errors were elicited during intraoperative direct electrical stimulation to the IFOF (Bello et al., 2008; Mandonnet, Nouet, Gatignol, Capelle, & Duffau, 2007), but not the ILF in neurosurgical patients (Mandonnet et al., 2007). Similarly in another study, a double-dissociation was demonstrated for these tracts: stimulation of the ILF lead exclusively to visual object recognition and reading difficulties, whereas stimulation of the IFOF caused anomia, but no visual impairments (Gil-Robles et al., 2013). Other researchers have also pointed to more involvement of the IFOF in language, particularly semantic processing, with the ILF as more related to visual deficits (Fernández-Miranda et al., 2008) and possibly providing an indirect route for semantic processing (Duffau et al., 2013). Further, altered white matter integrity of the ILF (and UF) in patients with semantic dementia (Agosta et al., 2010) and the semantic variant of primary progressive aphasia (Agosta et al., 2013) has also been demonstrated. In primary progressive aphasia, integrity of the ILF was related to accurate grammatical expression, while mean length of utterance was related to the IFOF (Grossman et al., 2013). Voxel-based lesion-symptom mapping has shown that comprehension deficits were associated with lesions to the temporoprefrontal region, particularly the projection of the ventral extreme capsule (Kümmerer et al., 2013). It appears that, in humans, the IFOF passes through a section of the extreme capsule (Catani & Thiebaut de Schotten, 2012), thus providing evidence for its involvement in language comprehension.

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Previous DTI studies in stroke patients have not explored the specific relationship between the integrity of these temporal tracts and language processing, though subcortical temporal regions are considered important in determining aphasia severity (Rosso et al., 2015), and, in particular, in supporting language comprehension (Dronkers, Wilkins, Van Valin, Redfern, & Jaeger, 2004; Turken & Dronkers, 2011).

The functional role of another ventral tract, the UF, in language processing also remains mostly unspecified, with speculations regarding its function being again largely based on its anatomical position, i.e., a direct short connection between anterior temporal and inferior frontal areas that are known to be important for language (Catani & Thiebaut de Schotten, 2008). It has been suggested that the UF may share cortical terminations with the ILF and thus provide an indirect semantic processing route (Duffau et al., 2013) assisting in tasks requiring connections from temporal to frontal regions, such as with lexical retrieval, semantic association, and aspects of naming (Lu et al., 2002). However, the UF terminates in the more ventral and orbital regions of the frontal lobe (Catani & Thiebaut de Schotten, 2012) and evidence supporting a UF role in specific aspects of linguistic processing remains controversial. In primary progressive aphasia and semantic dementia, loss of integrity in the UF has been documented, though its relation to particular aspects of language processing is still to be established (Agosta et al., 2013, 2010; Catani et al., 2013; Grossman et al., 2013). Further intraoperative subcortical mapping of the UF has led to semantic paraphasias (Bello et al., 2008). DTI and tract-lesion overlap studies in aphasia that considered the integrity of the UF have not been able to detect any specific relationship with language processing (Breier et al., 2008; Marchina et al., 2011), with only one study showing that integrity of the UF (as indexed via tract lesion load) was predictive of both speech fluency and semantic processing (Basilakos et al., 2014).

Another tract that runs within the temporal lobe is the MdLF. This fiber pathway purportedly connects the caudal and inferior parietal lobe with the anterior superior temporal gyrus and sulcus, and potentially the temporal pole (Makris et al., 2013). However, it is problematic to fully differentiate and isolate the MdLF from immediately adjacent fiber tracts, such as the AF and IFOF. To date there is no direct evidence regarding the role of this tract in language and its functional role in humans remains to be ascertained (De Witt Hamer, Moritz-Gasser, Gatignol, & Duffau, 2011; Duffau et al., 2013; Wang et al., 2013).

In summary, given the existing neuroimaging, electrostimulation, and lesion evidence, of the temporal tracts, the ILF and the IFOF, and possibly the UF, seem to be important for lexical-semantic processing with a specific functional role for each tract yet to be determined.

1.1.3. *Other white matter tracts*

One more potentially important pathway for language processing is an intralobar tract: the frontal aslant tract, identified by Catani and colleagues (Catani et al., 2012, 2013), that connects Broca's area with the supplementary motor area, pre-supplementary motor area and anterior cingulate. In stroke-induced aphasia, Basilakos et al. (2014) showed that damage to the inferior portion of the aslant tract was most predictive of speech fluency. However, this portion of the aslant tract overlaps with the most anterior segment of the AF thus obfuscating a clear interpretation of the findings. Future investigations will need to further specify the anatomical location of the frontal aslant tract and determine its possible unique contributions to language processing.

1.2. *Limitations of existing studies of white matter tracts and language processing*

In sum, despite recent advances, much remains unknown about the specific functional roles of various fiber pathways. One possible reason is that the aforementioned studies in aphasia investigated the integrity and relationship to language of a limited set of fiber pathways (usually AF, SLF and sometimes UF) within one hemisphere. Another possible reason is that previous approaches have treated fiber pathways as uni-functional entities, whereas white matter tracts in fact consist of both long and short fibers that transmit information between distant and adjacent regions, respectively. As these connect different cortical regions, their functions are also likely to differ. This issue was first highlighted by the fathers of aphasiology: in describing disconnection syndromes in aphasia, Carl Wernicke wrote that 'aphasia may be caused by any disruption of this pathway, the clinical picture, however, may vary considerably and is related to the specific segment of the pathway involved' (as cited in Catani & Mesulam, 2008). For instance, the differential role of long- versus short-range connections in the ventral visual stream has already been proposed (Rudrauf et al., 2008). In the language system this has not been systematically attempted; existing studies aim to determine the functional role of the whole tract, rather than its subsections. Another reason why the linguistic roles of fiber pathways have yet to be elucidated is that few indices of microstructural tissue properties are usually taken into account, with FA and possibly mean diffusivity (MD) considered. While FA reflects the magnitude of directional diffusivity and thus is potentially indicative of overall tract integrity in cases of brain disorders explicitly impacting white matter, other indices, such as axial diffusivity (AD; the 1st largest eigenvalue) and radial diffusivity (RD; average of the 2nd and 3rd eigenvalues) should be considered (Alexander, Lee, Lazar, & Field, 2008). Song et al. (2002, 2003) proposed that these indices reflect different neural mechanisms: an increase in RD is indicative of demyelination, while an increased AD reflects axonal degeneration. These metrics are used extensively in other areas, for instance in research on healthy aging (Bennett & Madden, 2014) and motor outcome following stroke (Auriat, Borich, Snow, Wadden, & Boyd, 2015; Lindenberg, Zhu, Rüber, & Schlaug, 2012), but so far have been predominantly excluded from DTI studies of language.

1.3. *Goals and hypotheses of the current study*

The current study strives to overcome these limitations and provide a first comprehensive investigation of the functional

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roles of major fiber pathways in relation to language in aphasia. The integrity of the AF, SLF, IFOF, ILF, and UF were explored as their contribution to language processing has been previously established, though their exact roles remain to be ascertained. The MdLF and the frontal aslant tract were not considered in the present study as they are not currently included in standardized atlases of white matter tracts (Eickhoff et al., 2005; Mori, Wakana, Nagae-Poetscher, & van Zijl, 2005; Natbrainlab tractography based atlas (accessed 12.20.2015)–http://www.natbrainlab.co.uk/#!atlas-maps/ch5f), perhaps because their potential role in language and their exact anatomy await further specification. We did, however, consider the corpus callosum (CC), as it supports communication between the two hemispheres and might play an important role in compensatory recruitment or secondary degeneration of the contralateral regions. To control for the possible confounding influence of lesion load, we decided to additionally consider one other tract that is often directly damaged in stroke or has secondary axonal degeneration but is not considered part of the language connectome: the corticospinal tract (CST). We explored the integrity of the selected white matter tracts in both hemispheres to determine the contribution of fiber pathways in the left lesioned hemisphere to aphasic language deficits and possible changes of fiber pathways in the right, intact hemisphere.

The first aim of the study was to examine the microstructural properties of selected major white matter tracts bilaterally in individuals with aphasia as compared to a control group with four main DTI indices: FA, MD, AD and RD – extracted from diffusion-weighted (DW) images. These metrics together provide comprehensive *in vivo* measures of microstructural properties of white matter tracts (Alexander et al., 2008). We anticipated that for all left hemisphere tracts including the CC there would be significant pathological reduction in FA and increases in MD, RD, AD compared to the control group. We did not expect to see differences in DTI indices of the right hemisphere tracts between groups.

The second aim was to relate the integrity of these tracts to language processing at the word and sentence level. At this level of analysis we expected to find a pattern that would be consistent with dorsal–ventral models of language processing (Bornkessel-Schlesewsky, Schlesewsky, Small, & Rauschecker, 2015; Poeppel, Emmorey, Hickok, & Pylkkänen, 2012; Saur et al., 2008), i.e., dorsal tracts would be more associated with production deficits, while ventral tracts – with comprehension. Naturally, the control fiber pathway – CST – was not expected to be related to language abilities.

The third aim was to subdivide tracts that demonstrated a significant relationship with language measures, into smaller segments and correlate our DTI metrics for these segments with language measures. Here, in contrast to the whole-tract analysis above, we envisaged that a more complex picture would emerge, with specific segments of both ventral and dorsal tracts contributing simultaneously to expressive and receptive language processing.

The current study provides the first comprehensive investigation of all major fiber pathways in a large group of individuals with post-stroke aphasia and is the first one to consider the differential role of small tract segments.

2. Materials and methods

2.1. Participants

Thirty-seven individuals (18 males, 19 females; M_{age} = 54 years, SD = 10.53, age range: 34–78 years) with various types of aphasia were recruited at the Center for Speech Pathology and Neurorehabilitation in Moscow, Russia. All participants were right-handed and native speakers of Russian. All individuals in this group had aphasia resulting from single or multiple left-hemisphere strokes (bilateral strokes were excluded), the latest being not earlier than four months prior to scanning (M = 26.38, SD = 21.40 months post-onset; range: 4–100 months). None of the participants had diagnosed neurodegenerative disorders, epilepsy, other psychiatric disorders or history of alcohol or drug abuse. Each person with aphasia was examined by a speech-language pathologist and a neuropsychologist of the Center, and their language deficit was classified according to the system of Alexander Luria (Luria, 1980). Aphasia subtypes were distributed among patients as follows: 13 fluent, 20 non-fluent, 4 mixed.

For the control group, 11 age-matched neurologically-healthy right-handed native speakers of Russian (6 males, 5 females; M_{age} = 53 years, SD = 8.56, age range: 35–65 years) participated in our study. There was no significant difference in age between the aphasia and the control groups [$t(46) = .310$, $p = .758$]. The study was approved by the Ethics Committee of the National Research University Higher School of Economics, Moscow, Russia; all individuals gave informed consent prior to participation.

2.2. Language assessment

All participants in the aphasia group were examined by a speech-language pathologist with the Assessment of Speech in Aphasia (ASA, Tsvetkova, Akhutina, & Pylaeva, 1981), a traditional quantitative Russian language battery for aphasia that includes ratings of conversational speech, and a series of production and comprehension subtests. For this study, the results of the subtests targeting comprehension and production at the word and sentence level were used and are described in detail below.

2.2.1. Comprehension subtests

The single word noun and verb auditory comprehension subtests each consists of 30 items requiring the participant to match words to pictures within a 10-picture visual array. At the beginning of the task, single words are presented aurally, and then two-word and three-word strings are given. The lexical items vary by frequency, and the distractors change in hierarchically-increasing complexity (from non-related to phonetically-related to semantically-related). For each item (both single words and series of words) the participant can receive the following scores: 1 for correctly chosen pictures in the right order following single word presentation; .5 for incorrect order and for failure to correct the mistake after it was indicated, and for a correct answer after repeated word presentation; or 0 otherwise.

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The sentence comprehension subtest consists of 15 items. The participant is required to match an aurally-presented sentence to a target picture choosing amongst alternatives. The items vary by the frequency of words, grammatical complexity of the sentences, and complexity of the alternative choices (from two to six distractors of different degree of relation to the target). Items are presented in order of increasing difficulty and are scored as follows: 2 for a correct answer after single sentence presentation; 1 for a correct answer after repeated presentation; or 0 otherwise.

The subtest involving the execution of commands consists of 10 instructions varying in length, grammatical complexity, and word frequency. The participant has to follow the commands by performing certain actions or carrying out manipulations with real objects. The possible scores for each item are: 3 for a correct performance after single instruction presentation; 1.5 for correct performance after repeated instruction presentation; or 0 otherwise.

2.2.2. *Production subtests*

Confrontation naming subtests of objects and actions consist of 30 items each. The black-and-white line drawings are presented to the participant, and she/he has to name them in one word. The target words vary by frequency, length and phonetic complexity, and are presented in order of complexity, from frequent, short and phonetically-simple to non-frequent, long and phonetically-complex. The possible ratings for each item are: 1 for naming the target word, regardless of the presence of verbal search; .5 for literal or verbal paraphasias, saying the word by syllables, using multi-word expressions containing the target word, or requiring a contextual cue for the correct response; 0 for severe literal or verbal paraphasias, or no response.

The sentence construction subtest consists of 15 items in which the participant has to produce sentences based on pictorial stimuli. The pictures are presented in order of ascending complexity requiring production of syntactically and semantically more complex sentences. The performance for each item is assessed as follows: 2 points are given for a complete grammatically-correct sentence, regardless of literal paraphasias that do not impede sentence comprehension; 1 point for using verbal paraphasias, mild grammatical or word order errors, verb arguments omissions, or incorrect temporal verb inflection; 0 for severe grammatical errors that distort the meaning of the sentence, or no response.

Noun and verb comprehension subtests were averaged into a score for comprehension of single words. Similarly, naming objects and actions subtests were averaged into a score for naming single words. Comprehension of sentences and execution of commands together made up the score of comprehension at the sentence level. Sentence production subtests contributed solely to the score on production at the sentence level. The score for each group of subtests varied from 0 to 30. Thus, altogether four scores reflecting comprehension and production at the word and sentence level were used to investigate the relationship between language processing and microstructural properties of white mater pathways.

2.3. *MRI data acquisition*

MRI data were acquired using a 1.5T Siemens Avanto scanner. For each participant, a high-resolution structural T_1 – weighted volume of the whole brain was acquired ($1 \times 1 \times 1$ mm voxels). DTI data were acquired using a spin echo, single shot EPI pulse sequence. Image parameters were as follows: acquisition matrix = 70×70, FOV = 192×192 mm^2, slice thickness = 2.7 mm, resulting in $2.7 \times 2.7 \times 2.7$ mm^3 voxels; TR = 6000 msec; TE = 95 msec; GRAPPA factor = 2; EPI factor = 70; b = 1000 sec/mm^2; number of gradient directions = 20; 1 non-diffusion weighted image was acquired before 20 diffusion weighted measurements; number of repetitions = 2.

2.4. *DTI data preprocessing and analysis*

The primary tool used for the preprocessing of the DTI data was the Oxford Centre for FMRIB Software Library (FSL; www.fmrib.ox.ac.uk/fsl) (Jenkinson, Beckmann, Behrens, Woolrich, & Smith, 2012). First, two non-weighted DW images were aligned and averaged. After that eddy current correction with the FSL tool "eddy_correct" gradient vectors rotation (Leemans & Jones, 2009) was performed. For tensor estimation, the Brain Extraction Tool from FSL (BET, Smith, 2002) and DTIFIT tool were used. BET thresholding value was .25 and tensor estimation was performed with the use of the weighted least squares algorithm.

Next, the T1 image was reoriented in the AC-PC direction and resliced to the MNI dimensions with the SPM-8 toolbox (http://www.fil.ion.ucl.ac.uk/spm). The resulting image is referred to as rT1_acpc. The lesion mask for aphasia patients was then drawn over the rT1_acpc image in Mricron (http://www.mccauslandcenter.sc.edu/mricro/mricron/). The lesion mask was used to improve co-registration between the FA and rT1_acpc images and between the rT1_acpc and MNI images using cost function masking (Brett, Leff, Rorden, & Ashburner, 2001). This cost function masking was the only difference in processing data from the aphasia and the control groups. Linear transformation (FLIRT, Jenkinson, Bannister, Brady, & Smith, 2002; Jenkinson & Smith, 2001) was used to transform FA and MD maps to the rT1_acpc space. To compute AD and RD we rotated tensors using the Camino tool (Alexander, Pierpaoli, Basser, & Gee, 2001; Cook et al., 2006) and then extracted eigenvalues.

Finally, analyses of DTI metrics of selected white matter tracts was done by extracting relevant DTI indices from DW images in regions constrained by tract masks warped from a standardized atlas to the individual's native space. This method is analogous to that of Zhang et al. (2010) and similar to the technique used by Lunven et al. (2015) in a study of visual neglect. The AF, SLF, ILF, IFOF, UF, and CST tract maps for both hemispheres were taken from the John Hopkins University White Matter Tractography atlas (Mori et al., 2005) and the CC tract maps (split into 3 parts: genu, body, splenium) were derived from the Juelich Histological Atlas (Eickhoff et al., 2005). As tract masks for the analyses were taken from probabilistic atlases, they were thresholded with the probability value of .25 in MNI space and then binarized as in the Lunven et al. study (2015). This stringent thresholding was

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done to reduce the individual variability within each tract (particularly at its terminations) and to obtain the core of the selected tracts, minimizing the inclusion of neighboring pathways. Only the left and right SLF tract masks were created slightly differently. In the John Hopkins University White Matter Tractography atlas the AF is considered a part of the SLF. Thus, to be able to differentiate the functional role of the SLF we subtracted the AF mask from the SLF mask followed by standard thresholding procedures described above. Left hemisphere tract masks are presented in MNI space in Fig. 1. Transformation of rT1_acpc to MNI was computed with the FNIRT tool of the FSL toolbox (Andersson, Jenkinson, & Smith, 2007) and then inverted and applied to tract masks (again cost function masking was used for the aphasia group). We eliminated the lower 10-percentile of the resulting tract mask in rT1_acpc space and took all the remaining voxels into the analysis. We then computed mean values of the DTI metrics (FA, MD, RD and AD) extracted from DW images within the tract masks in rT1_acpc space for further statistical analyses. To be clear, tract masks taken from standardized atlases were used simply as regions of interest to constrain the white matter pathways being investigated.

All statistical analyses were performed using IBM SPSS Statistics V 22. Intergroup comparisons of DTI indices were done using independent-samples *t*-tests. Where homogeneity of variance between the two groups was violated, the unequal variances *t*-test (the Welch *t*-test) was applied. Comparison of left and right hemisphere tracts in each group was done using paired-samples *t*-tests. Finally, for investigating the relationship between DTI indices and language measures, partial correlations were used. Initially, partial regression plots between language measures and mean DTI metrics were visually examined to confirm the absence of outliers and influential cases, while factoring out effects of age, time post-onset and lesion size. All statistical tests were two-tailed. To account for multiple comparisons, the significance level for all statistical comparisons performed was set to .01, unless otherwise stated.

To assess the quality of rT1_acpc normalization and the potential to use it for FA data extraction, we performed "double-warping" of rT1_acpc images (warping rT1_acpc to MNI, computing inverse transform and warping the warped rT1_acpc back). Three experts then visually assessed the quality of co-registration. The structures matched precisely up to the blur due to the interpolation. To demonstrate the validity of using T1 space for extracting FA values from tract masks, we performed correlational analysis between FA values extracted in T1 space and FA values extracted in MNI space for ILF, IFOF and AF tracts (right and left). Observed correlations were at the level of .98 or higher indicating an almost perfect match between the extracted values.

This atlas-based DTI metrics extraction preprocessing method for investigating the integrity of white matter tracts in individuals with aphasia has several important advantages over other conventional approaches to the extraction of DTI data. First, compared to selectively and subjectively placing the ROI within a tract (Breier et al., 2008; Sidaros et al., 2008), it allows for automated and non-subjective analysis of data from the whole tract (or segment). Second, it can be applied even when more traditional methods of DTI data analysis, such as tractography using seed ROIs or Tract Based Spatial Statistics (Smith et al., 2006) are not appropriate due to the lack of data in the lesion area and variability in lesion location making tract reconstruction (e.g., see van Hees et al., 2014; Kim & Jang, 2013) or extraction of tract skeletons impossible. For instance, in a study of stroke patients with visual neglect, Lunven et al. (2015) acknowledged that "lesions generally reduced the efficiency of the TBSS (Tract Based Spatial Statistics) preprocessing steps, which are optimized for brain without macroscopic lesions" (p. 7), and thus often proves to be less sensitive. The preprocessing algorithm utilized in the current study overcomes these limitations.

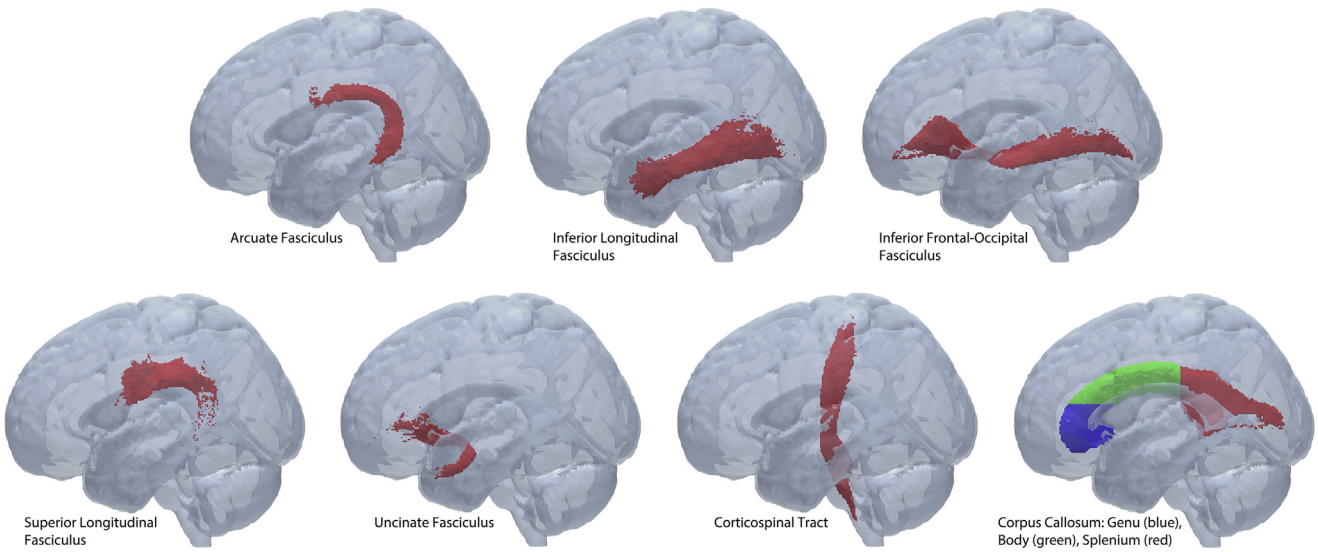

Fig. 1 – Left hemisphere tract masks used for extraction of DTI metrics (presented in MNI space).

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3. Results

3.1. Inter- and intragroup differences

The distribution of the lesion locations for all 37 individuals with aphasia can be seen in Fig. 2. The greatest degree of overlap is seen in the periventricular white matter underlying the frontal, temporal, and parietal lobes. In the cortex, the lesion overlap was greatest in the perisylvian cortex and insula. Descriptive statistics for all DTI indices for left and right hemisphere tracts for the aphasia and the control groups are presented in Table 1, as well as the results of between group comparisons.

As can be seen in Table 1, individuals with aphasia had greater variability of FA compared to the control group and had significantly lower FA in all the examined left hemisphere tracts. On other DTI indices, individuals with aphasia had significantly higher MD, AD, RD values for the left hemisphere tracts; with a less consistent picture and overall less prominent differences for the right hemisphere tracts. For illustrative purposes, average histograms of FA for the left and right AF, UF, ILF and IFOF for the aphasia and the control groups are presented in Fig. 3, where a clear leftward shift of the FA distribution can be observed for left hemisphere tracts in the aphasia group compared to controls.

When left and right hemisphere tracts in the control group were compared, no significant differences were detected for any of the DTI measures except for selected measures of ILF, SLF and CST. The right ILF had higher FA values than the left ILF [$t(10) = -4.85$, $p = .001$]. The left SLF had higher RD values than the right SLF [$t(10) = 3.26$, $p = .009$]. The left CST also had higher RD values than the right CST [$t(10) = 4.44$, $p = .001$]. Conversely, significant differences were detected for the aphasia group for all major tracts and all DTI indices (see Table 2). FA values were lower for the left hemisphere tracts compared to the right, while the inverse was true for the MD, RD, AD measures.

3.2. Correlational analysis

Next, correlational analyses were performed between DTI indices and language measures for the aphasia group while taking age, time post onset and lesion size (measured as the number of voxels in the lesion mask) into account. No significant results were obtained for major RH tracts; thus Table 3 only includes findings for left hemisphere tracts. As can be seen from the correlation coefficients presented in Table 3, only FA measures for the left AF, ILF, IFOF were significantly related to language measures. Observed correlations for these three main white matter tracts are demonstrated graphically with partial regression plots in Figure A of the Appendix. MD, AD and RD indices were not significantly related to any of the language measures, (except for a significant correlation between RD of the AF and CC splenium and naming), but there was a consistent negative direction in the relationship between these diffusion indices of the AF, ILF, IFOF and language measures.

In order to determine precisely which portions of the tract were contributing to these significant effects, the three tracts, AF, IFOF and ILF, were divided into segments roughly equivalent in size and investigated as to their individual relationships with language measures. Tract segmentation is illustrated in Fig. 4 and cut-off points in MNI space for tract segments are presented in Table 4. Partial correlations between FA metrics from these tract segments and language measures while taking age, months post-onset and lesion size into account are also shown in Table 4; for this secondary analysis significance level was set to .05. As can be seen, different portions of the tracts were selectively related to language measures, with some portions of the three tracts entirely unrelated to language comprehension or production. Most notably, the inferior ventral (temporal) portion of the AF was highly correlated with comprehension, while the middle (parietal) portion was related exclusively to production. Middle and posterior segments of the ILF and IFOF were correlated with language comprehension, while more anterior segments also demonstrated a relationship with production.

4. Discussion

4.1. Inter- and intra-group difference in microstructural properties of white matter tracts

The present study is the first to compare all basic DTI metrics across all major white matter tracts for both hemispheres in a large group of individuals with post-stroke aphasia and age-matched controls. Individuals with aphasia were found to have significantly lower FA values for all left hemisphere tracts and significantly higher values of MD, RD and AD for all left and some right hemisphere tracts compared to controls. In the vast majority of previous DTI studies in aphasia the FA metric was used to evaluate damage to white matter. MD, RD and AD metrics utilized in the current study provide a more comprehensive evaluation of the microstructure of fiber pathways. It has been proposed that RD increases following demyelization, as there is less restriction in perpendicular

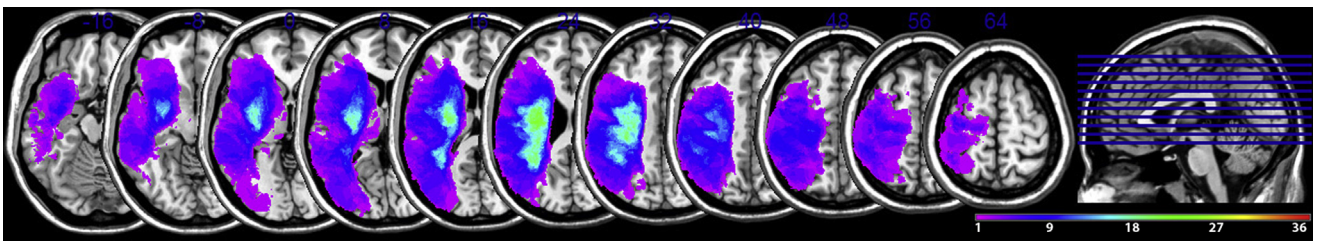

Fig. 2 – Lesion overlay for patients with aphasia ($n = 37$).

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Table 1 – Mean (SD) DTI indices for each white matter tract for the aphasia and the control groups, and results of between group comparisons.

	FA		MD [$\times 10^{-3}$ mm^2/sec]		AD [$\times 10^{-3}$ mm^2/sec]		RD [$\times 10^{-3}$ mm^2/sec]	
	Aphasia	Control	Aphasia	Control	Aphasia	Control	Aphasia	Control
AF left	.29 (.09)**	.42 (.01)	1.13 (.34)**	.75 (.02)	1.40 (.30)**	1.09 (.02)	.99 (.36)**	.57 (.02)
SLF left	.23 (.07)**	.33 (.02)	1.17 (.37)**	.79 (.02)	1.40 (.35)**	1.06 (.02)	1.06 (.38)**	.65 (.02)
IFOF left	.31 (.05)**	.39 (.02)	1.05 (.22)**	.81 (.02)	1.35 (.20)**	1.15 (.04)	.90 (.23)**	.62 (.02)
ILF left	.31 (.05)**	.37 (.02)	.96 (.16)**	.81 (.02)	1.25 (.15)**	1.12 (.04)	.82 (.17)**	.64 (.02)
UF left	.28 (.08)**	.35 (.03)	1.11 (.35)**	.83 (.03)	1.38 (.31)**	1.14 (.03)	.97 (.38)**	.67 (.04)
CST left	.39 (.09)**	.48 (.03)	1.05 (.26)**	.79 (.04)	1.44 (.22)**	1.21 (.04)	.85 (.28)**	.56 (.05)
AF right	.40 (.04)	.41 (.02)	.79 (.06)*	.75 (.02)	1.13 (.05)	1.07 (.04)	.63 (.06)**	.57 (.02)
SLF right	.34 (.03)	.34 (.02)	.81 (.05)	.78 (.02)	1.10 (.05)	1.06 (.03)	.66 (.05)	.64 (.03)
IFOF right	.37 (.03)*	.39 (.02)	.87 (.06)*	.82 (.03)	1.21 (.06)	1.17 (.04)	.70 (.06)**	.63 (.03)
ILF right	.37 (.03)*	.39 (.01)	.84 (.04)*	.80 (.03)	1.17 (.05)	1.13 (.04)	.68 (.04)**	.62 (.03)
UF right	.35 (.03)	.36 (.03)	.86 (.05)	.83 (.05)	1.18 (.05)	1.15 (.05)	.70 (.06)	.67 (.05)
CST right	.48 (.03)	.49 (.03)	.81 (.04)	.78 (.04)	1.25 (.05)	1.22 (.05)	.59 (.04)	.55 (.05)
CC body	.35 (.05)**	.42 (.04)	1.21 (.14)**	.99 (.11)	1.59 (.11)**	1.43 (.08)	1.01 (.15)**	.76 (.12)
CC genu	.38 (.05)	.42 (.04)	1.02 (.10)**	.9 (.06)	1.41 (.08)**	1.31 (.07)	.82 (.12)**	.68 (.07)
CC splenium	.39 (.06)**	.47 (.03)	1.23 (.12)**	1.05 (.09)	1.69 (.10)**	1.57 (.08)	.99 (.13)**	.77 (.10)

Note. Significance levels of comparisons between groups: ** $p \leq .001$; * $p < .01$.

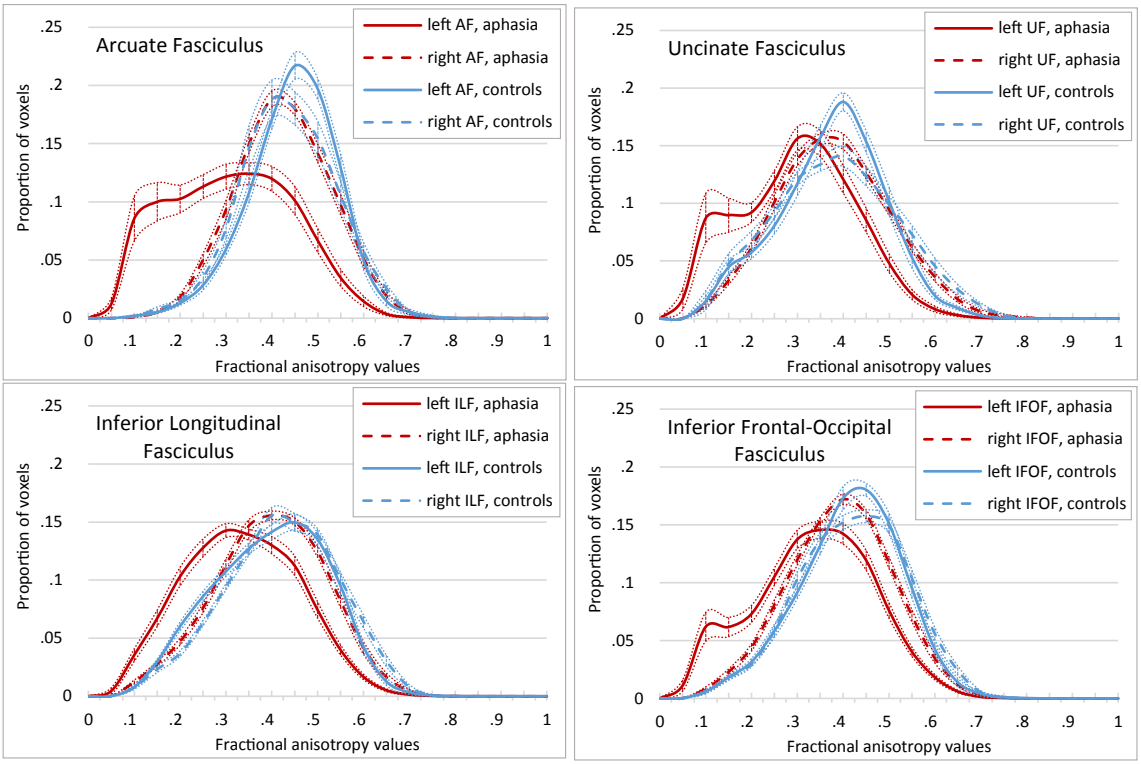

Fig. 3 – Average FA histograms for left (solid lines) and right (dashed lines) AF, UF, ILF and IFOF for the aphasia (red lines) and the control (blue lines) groups. Dotted lines represent the FA histograms one standard error above and below the mean.

movement (Klawiter et al., 2011; Song et al., 2002), while AD decreases in the acute stage following axonal injury (Song et al., 2003), with a subsequent increase indicative of reduced axonal density (Chen et al., 2008); although see Wheeler-Kingshott and Cercignani (2009) for a more cautious interpretation of AD and RD changes. Demonstrated increases in both metrics and, as a consequence, an increase in MD and decrease in FA most likely reflect loss of both axonal and myelin integrity due to direct injury and secondary axonal degeneration (Acosta-Cabronero, Williams, Pengas, & Nestor, 2010; Beaulieu, 2002; Chen et al., 2008; Lindenberg et al., 2012). Previously Catani et al. (2013) demonstrated increases in RD for the frontal aslant tract in individuals with a non-fluent variant of primary progressive aphasia. Increased values of MD, AD and RD have been reported for motor pathways in the ipsilesional hemisphere in stroke patients (Auriat et al., 2015; Lindenberg et al., 2012) and for selected white matter regions in traumatic brain injury (Sidaros et al.,

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Table 2 – Comparisons between left and right hemisphere white matter tracts for the aphasia group.

	FA		MD		AD		RD	
	t	p	t	p	t	p	t	p
AF left – AF right	−7.422	<.001	6.039	<.001	5.567	<.001	6.188	<.001
SLF left – SLF right	−9.942	<.001	6.115	<.001	5.415	<.001	6.417	<.001
IFOF left – IFOF right	−6.678	<.001	5.139	<.001	4.428	<.001	5.405	<.001
ILF left – ILF right	−7.516	<.001	5.167	<.001	3.858	<.001	5.595	<.001
UF left – UF right	−5.782	<.001	4.358	<.001	3.975	<.001	4.489	<.001
CST left – CST right	−6.468	<.001	5.820	<.001	5.464	<.001	5.862	<.001

Table 3 – Partial correlation coefficients of DTI indices for major tracts with subtest language scores while taking age, time post onset and lesion size into account.

		Comprehension of single words (nouns and verbs)	Comprehension of sentences and commands	Naming (nouns and verbs)	Sentence construction
AF left	FA	.336 ($p = .052$)	.33 ($p = .057$)	.503 ($p = .002$)*	.442 ($p = .009$)*
	MD	−.077 ($p = .665$)	−.041 ($p = .818$)	−.425 ($p = .012$)	−.164 ($p = .353$)
	AD	−.004 ($p = .98$)	.046 ($p = .797$)	−.351 ($p = .042$)	−.061 ($p = .732$)
	RD	−.107 ($p = .547$)	−.078 ($p = .662$)	−.45 ($p = .008$)*	−.206 ($p = .242$)
SLF left	FA	.014 ($p = .939$)	.017 ($p = .923$)	.263 ($p = .133$)	.232 ($p = .187$)
	MD	.216 ($p = .22$)	.259 ($p = .139$)	−.188 ($p = .287$)	.022 ($p = .903$)
	AD	.254 ($p = .148$)	.306 ($p = .079$)	−.148 ($p = .404$)	.083 ($p = .64$)
	RD	.197 ($p = .264$)	.236 ($p = .179$)	−.205 ($p = .245$)	−.006 ($p = .971$)
IFOF left	FA	.504 ($p = .002$)*	.247 ($p = .159$)	.344 ($p = .046$)	.331 ($p = .056$)
	MD	−.361 ($p = .036$)	−.072 ($p = .686$)	−.287 ($p = .1$)	−.306 ($p = .079$)
	AD	−.335 ($p = .052$)	−.058 ($p = .745$)	−.264 ($p = .131$)	−.287 ($p = .1$)
	RD	−.37 ($p = .031$)	−.078 ($p = .663$)	−.295 ($p = .09$)	−.313 ($p = .072$)
ILF left	FA	.524 ($p = .001$)**	.431 ($p = .011$)	.354 ($p = .04$)	.307 ($p = .077$)
	MD	−.389 ($p = .023$)	−.239 ($p = .174$)	−.302 ($p = .083$)	−.206 ($p = .243$)
	AD	−.354 ($p = .04$)	−.198 ($p = .262$)	−.289 ($p = .098$)	−.173 ($p = .326$)
	RD	−.399 ($p = .019$)	−.253 ($p = .149$)	−.303 ($p = .081$)	−.217 ($p = .218$)
UF left	FA	.12 ($p = .5$)	−.134 ($p = .449$)	.082 ($p = .644$)	.134 ($p = .451$)
	MD	−.056 ($p = .754$)	.211 ($p = .232$)	−.014 ($p = .936$)	−.1 ($p = .575$)
	AD	−.042 ($p = .814$)	.221 ($p = .208$)	.013 ($p = .944$)	−.08 ($p = .653$)
	RD	−.061 ($p = .73$)	.206 ($p = .243$)	−.025 ($p = .886$)	−.108 ($p = .545$)
CST left	FA	−.118 ($p = .505$)	−.009 ($p = .959$)	−.01 ($p = .957$)	.055 ($p = .759$)
	MD	.008 ($p = .965$)	−.038 ($p = .829$)	−.214 ($p = .225$)	−.273 ($p = .118$)
	AD	−.022 ($p = .903$)	−.022 ($p = .902$)	−.261 ($p = .136$)	−.297 ($p = .088$)
	RD	.018 ($p = .92$)	−.043 ($p = .81$)	−.189 ($p = .284$)	−.255 ($p = .146$)
CC body	FA	.006 ($p = .975$)	.146 ($p = .411$)	.201 ($p = .256$)	.104 ($p = .558$)
	MD	.157 ($p = .374$)	.098 ($p = .582$)	−.065 ($p = .715$)	.078 ($p = .66$)
	AD	.245 ($p = .163$)	.236 ($p = .179$)	.032 ($p = .859$)	.185 ($p = .294$)
	RD	.121 ($p = .496$)	.045 ($p = .802$)	−.098 ($p = .58$)	.037 ($p = .837$)
CC genu	FA	.105 ($p = .553$)	.096 ($p = .59$)	.089 ($p = .615$)	−.001 ($p = .997$)
	MD	−.041 ($p = .817$)	−.051 ($p = .775$)	−.092 ($p = .607$)	.004 ($p = .983$)
	AD	.05 ($p = .779$)	.024 ($p = .894$)	−.015 ($p = .933$)	.064 ($p = .719$)
	RD	−.071 ($p = .69$)	−.075 ($p = .675$)	−.114 ($p = .52$)	−.017 ($p = .924$)
CC splenium	FA	.3 ($p = .084$)	.288 ($p = .098$)	.425 ($p = .012$)	.273 ($p = .118$)
	MD	−.212 ($p = .23$)	−.134 ($p = .449$)	−.399 ($p = .019$)	−.286 ($p = .102$)
	AD	−.065 ($p = .714$)	.011 ($p = .952$)	−.21 ($p = .232$)	−.177 ($p = .316$)
	RD	−.246 ($p = .162$)	−.173 ($p = .327$)	−.434 ($p = .01$)*	−.301 ($p = .083$)

Note. Significant correlations are marked: ** $p \leq .001$; * $p < .01$.

2008). To the best of our knowledge, RD and AD indices have not yet been investigated in stroke patients in relation to language processing.

Additionally, in the aphasia group, all tracts in the left hemisphere had significantly lower mean FA values and significantly higher MD, RD, AD values compared to patients' own tracts in the intact right hemisphere. No significant inter-hemispheric differences in DTI metrics were found for the control group, except for differences in the ILF, with significantly higher FA values in the right hemisphere, possibly indicating a rightward asymmetry for this tract, that has previously been demonstrated in healthy controls (Michel Thiebaut de Schotten et al., 2011). Overall, our findings support and further extend previous DTI studies that demonstrated an overall decrease of FA in selected left hemisphere tracts in chronic stroke patients (Breier et al., 2008; Kim & Jang,

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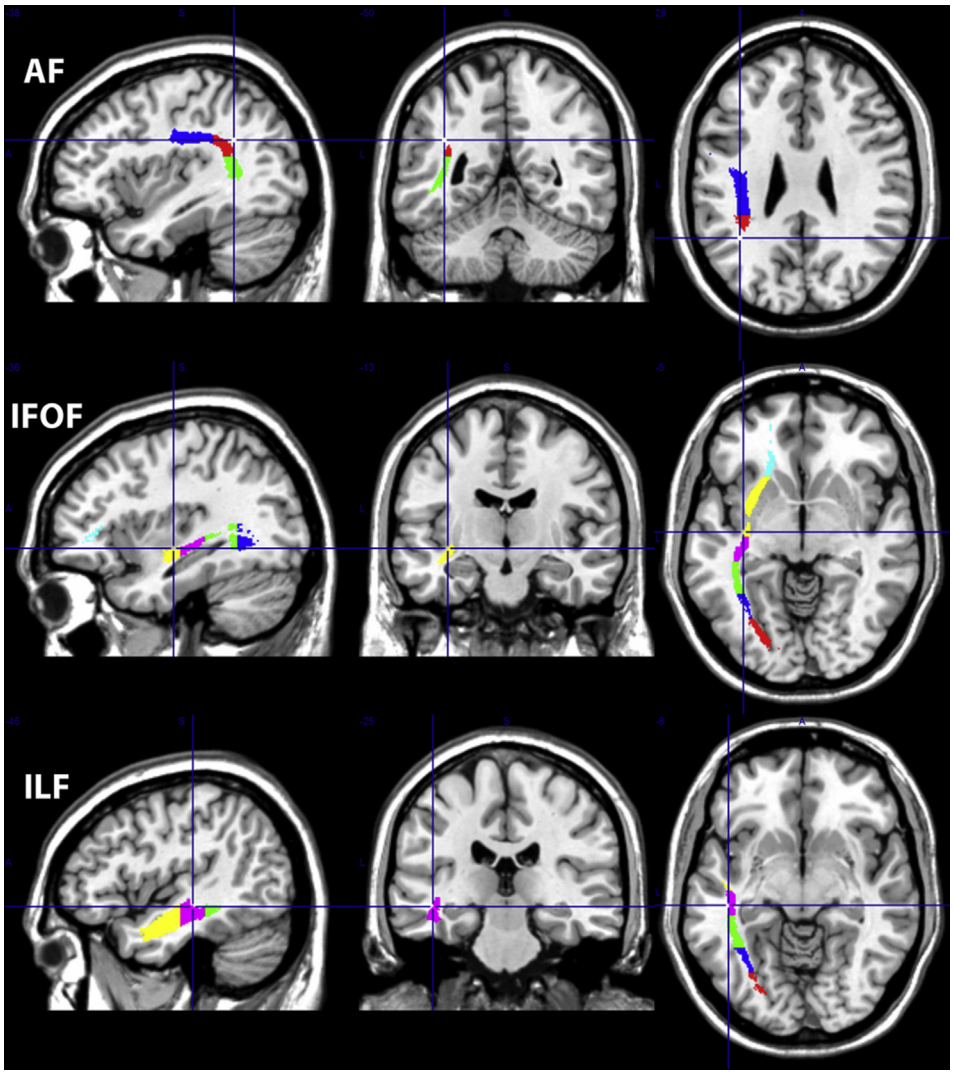

Fig. 4 – Segmentation of AF, IFOF and ILF in the left hemisphere. See Table 4 for MNI coordinates of tract segments.

2013) and in primary progressive aphasia (Agosta et al., 2013, 2010; Catani et al., 2013; Grossman et al., 2013).

While the predominant loss of fiber integrity was observed in the lesioned hemisphere, small but systematic intergroup differences in FA, MD, RD and AD were also observed for AF, ILF and IFOF in the right hemisphere. These findings are somewhat surprising given that only individuals with left hemisphere stroke were included in the study. Potentially, changes in microstructure in white matter tracts in the non-lesioned hemisphere could reflect effects of distal degeneration or diffuse white matter damage and general age-related atrophy that are more characteristic of the stroke group. Supporting the distal degeneration hypothesis is the presence of a significant relationship between FA of CC and of the right ILF and IFOF identified in a post-hoc correlational analyses (the correlations between CC and the right AF were marginally significant). Also, previous research on healthy aging has documented systematic changes in all diffusion indices with age (Bennett & Madden, 2014; Bennett, Madden, & Vaidya, 2010). Furthermore, usually with age more pronounced differences in RD rather than AD are observed (Bennett & Madden, 2014), as was the case in our study with right hemisphere tracts demonstrating greater differences from the control group specifically in RD. While there were no significant differences in age between our two groups, the aphasia group did have a wider age range and included older individuals compared to the control group. Partially supporting this age-related explanation are positive significant post-hoc correlations between age and DTI indices observed for major right hemisphere tracts in the aphasia group. The relationship between age and DTI indices was not significant for the control group, nor for left hemisphere tracts in the aphasia group, where a possible influence of age was probably overridden by the prominent effect of stroke on neural integrity. No previous studies have systematically investigated differences in DTI indices of white matter tracts in the non-lesioned hemisphere between stroke and control groups. To the best of our knowledge, only Kim and Jang (2013) reported a trend of decreased FA and increased MD values for the right AF in individuals with aphasia compared to the control group. Potentially, the DTI metrics of white matter in the non-lesioned hemisphere could serve as an important prognostic

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Table 4 – Anatomical segmentation of AF, IFOF and ILF in the left hemisphere and partial correlations between FA metrics for tract segments and language measures.

Tract	Anatomical landmarks	Color coding in Fig. 4	Includes MNI coordinates	Comprehension of single words (nouns and verbs)	Comprehension of sentences and commands	Naming (nouns and verbs)	Sentence construction
AF	Anterior dorsal portion	Blue	X +[a] Y [−36 ∞] Z +	−.104 (p = .558)	−.085 (p = .631)	.215 (p = .222)	.167 (p = .346)
	Middle (parietal) portion	Red	X + Y [∞ −36] Z [18 ∞]	.310 (p = .074)	.291 (p = .095)	.415* (p = .015)	.374* (p = .029)
	Inferior ventral (temporal) portion	Green	X + Y + Z [∞ 18]	.644** (p < .001)	.642** (p < .001)	.528** (p = .001)	.508** (p = .002)
IFOF	Most anterior (frontal) segment	Turquoise	X + Y [21 ∞] Z +	.103 (p = .563)	−.099 (p = .576)	−.027 (p = .878)	.016 (p = .929)
	Anterior segment	Yellow	X + Y [−16 21] Z +	.235 (p = .181)	−.032 (p = .857)	.172 (p = .331)	.232 (p = .186)
	Anterior-middle segment	Violet	X + Y [−31 −16] Z +	.588** (p < .001)	.391* (p = .022)	.452* (p = .007)	.473* (p = .005)
	Middle segment	Green	X + Y [−51 −31] Z +	.459** (p = .006)	.386* (p = .024)	.26 (p = .138)	.205 (p = .245)
	Posterior segment	Blue	X + Y [−66 −51] Z+	.348* (p = .043)	.359* (p = .037)	.237 (p = .177)	.199 (p = .258)
	Most posterior segment	Red	X + Y [∞ −66] Z +	.355* (p = .039)	.401* (p = .019)	.232 (p = .188)	.132 (p = .455)
ILF	Anterior segment	Yellow	X + Y [−16 ∞] Z +	.087 (p = .623)	−.06 (p = .737)	.123 (p = .489)	.186 (p = .291)
	Anterior-middle segment	Violet	X + Y [−31 −16] Z +	.54** (p = .001)	.468* (p = .005)	.262 (p = .135)	.363* (p = .035)
	Middle segment	Green	X + Y [−51 −31] Z +	.523* (p = .002)	.439* (p = .009)	.349* (p = .043)	.266 (p = .128)
	Posterior segment	Blue	X + Y [−66 −51] Z +	.417* (p = .014)	.432* (p = .011)	.25 (p = .153)	.186 (p = .292)
	Most posterior segment	Red	X + Y [∞ −66] Z +	.383* (p = .025)	.402* (p = .019)	.189 (p = .284)	.098 (p = .58)

Note. Significant correlations are marked: ** $p \leq .001$; * $p < .05$.
[a] '+' indicates that all coordinates along this axis were taken into account.

factor, indicating microstructural potency of non-lesioned areas and a possible substrate for compensatory language rerouting (Forkel, Thiebaut de Schotten, Dell'Acqua, et al., 2014). Future research is needed to determine the source and the prognostic value of the altered white matter in the contralesional hemisphere.

4.2. *Relationship between white matter integrity and language measures*

Language comprehension was found to be related to the integrity of the left IFOF and left ILF, while language production was related to integrity of the left AF, as indicated via positive significant correlations between respective language measures and FA and a consistent negative trend for other DTI indices. At first approximation, such a functional distribution is consistent with dorsal-ventral models of language processing (Bornkessel-Schlesewsky et al., 2015; Kümmerer et al., 2013; Poeppel et al., 2012; Saur et al., 2008), that postulate that dorsal tracts are predominantly involved in phonological processing and language production (i.e., mapping of sound to articulation), while ventral tracts are responsible for lexical-semantic processing and comprehension (i.e., mapping of sound to meaning). We found no contribution of the UF to language processing. This is consistent with most DTI studies in aphasia that also fail to find a relationship between this tract and language processing (Breier et al., 2008; Marchina et al., 2011; Rosso et al., 2015). By examining the AF component of the SLF separately, we clearly demonstrated its distinctive role in language processing. The remaining parts of the SLF were not related to language processing. Altogether, by providing more fine-grained information on tract integrity, DTI metrics offer insights on functional roles of fiber pathways that cannot be grasped from a more gross analysis based on categorical lesion data.

In our study no significant relationship between DTI indices of tracts in the non-lesioned right hemisphere and language processing was observed, thus distal changes in tract microstructure were not directly related to comprehension and production language deficits in aphasia. These findings at first might seem contrary to that obtained by Forkel et al. (2014), who found anatomical predictors of recovery in the right hemisphere. Forkel and colleagues discovered that the *volume* of the long segment of the right AF in acute patients predicted recovery. Our study did not measure tract volume, as our participants were already in the chronic stage of their illness, and we were not predicting recovery. On the other hand, the Forkel study found no significant effects in their FA analysis. In this sense, our results are compatible, as both studies found no significant FA differences in the AF of the right hemisphere.

It should be acknowledged that the extent to which language deficits are directly a result of white or grey matter involvement cannot be definitively determined here, as only lesion size (but not location) was used as a covariate in the correlational analyses. However, additional evidence warrants the strong link between tract integrity and language processing. First, the observed relationships cannot be simply a result of a lesion in the left hemisphere, as for instance our control tract – the CST – along with the UF and CC all showed

altered indices of white matter integrity, but none were related to language processing. Second, several individuals in our aphasia group had lesions only in the white matter tracts, sparing critical cortical areas completely, and still demonstrated language deficits consistent with the group findings. An example of one such case can be seen in Figure B of the Appendix. Third, by segmenting each tract into short subsections, we aimed to isolate the effects to smaller units of white matter that might avoid grey matter involvement. In the future, one way to approach this problem would be to use damage to an array of cortical areas as covariates in regression analyses; however, this would require an even larger group than participated in the present study (Bates et al., 2003).

4.3. *Relationship of language measures to individual tract segments*

In the current study in order to pinpoint the functional contribution of fiber pathways to language, different segments of the tracts were considered separately for the first time, as they may play a differential role in language processing. Overall, it is an oversimplification to regard fasciculi as indivisible entities: white matter tracts consist of both long and short fibers that transmit information between distant and adjacent regions, respectively, and are likely to have at least partly distinctive functionality. Previously, investigation of small tract segments in relation to language processing has never been attempted. While the work of Catani et al. (2005) and Forkel et al. (2014) refer to different branches of the AF with different regions of origin and termination, the present study segmented each fiber bundle into smaller, adjacent sections.

Different segments of the left AF, IFOF, and ILF were differentially related to language production and comprehension in aphasia. FA measurements of the inferior ventral (temporal) portion of the AF were significantly related to both comprehension and production equally at the word and sentence level. Thus, the role of the AF in language comprehension was also experimentally demonstrated in this DTI study in stroke-related aphasia. Further along the tract, the integrity of the middle (parietal) portion of the AF was related exclusively to production at the word and sentence level. Overall, this pattern is consistent with previous research and further expands our knowledge about the functional segregation of the AF. Previous DTI studies demonstrated a critical role of the AF in determining aphasia severity (Breier et al., 2008; Rosso et al., 2015). Lesion symptom mapping studies have also shown the importance of the AF both in supporting speech production (Bates et al., 2003) and its temporal portion in sustaining lexical-semantic integration (Dronkers et al., 2004). Catani et al. (2005), based on tractography data in healthy participants and reanalysis of aphasia case studies, hypothesized that the indirect branch of the AF connecting temporal and parietal regions might support auditory comprehension. In a tract-lesion overlap study, Marchina et al. (2011) demonstrated that AF lesion load significantly predicted rate, informativeness, and overall efficiency of speech as well as naming ability. Contrary to previous findings (Fridriksson et al., 2013) no significant relationship between the anterior segment of the AF and language processing was found in the present study. Possibly this divergence is due to the fact that we did not specifically test repetition or speech fluency in our study.

FA indices for the middle and posterior segments of both the IFOF and ILF were strongly related to language comprehension at the word and sentence level. A particularly robust relationship with language comprehension was observed for the portion of the tract underneath the middle and inferior portions of the left temporal lobe, an area known to be critical for language processing, particularly language comprehension (Bates et al., 2003; Dronkers et al., 2004; Kümmerer et al., 2013; Turken & Dronkers, 2011; see also; Bajada et al., 2015). This might possibly be due to a disconnection between dorsal and ventral pathways (Rosso et al., 2015), although the exact mechanisms of how the dorsal and ventral processing streams might interact remains to be determined (Cloutman, 2013). More anterior portions of the IFOF and ILF, that lie closer to the insular lobe, were also moderately associated with language production, reflecting contribution of these tracts in naming and sentence generation. No clear functional dissociation between the ILF and IFOF was obtained in our study.

Overall, when functional significance of tract segments, rather than whole tracts, were considered, a much more complex picture emerged and the clear juxtaposition of production versus comprehension and their segregation along dorsal and ventral streams as proposed in several previous studies (Kümmerer et al., 2013; Saur et al., 2008) becomes less feasible. Our investigation of small segments within temporal tracts brings together previously conflicting findings regarding the role ILF and IFOF in comprehension (Dronkers et al., 2004; Kümmerer et al., 2013; Turken & Dronkers, 2011) and naming (Bello et al., 2008; Mandonnet et al., 2007). Thus, our data point to the insufficiency of determining functional relevance of the whole tract, as different parts seem to play distinctive roles. Future investigations with large groups of individuals with aphasia will need to determine which segments play a decisive role in different language functions.

4.4. *Conclusions*

We undertook the first broad examination of major white matter tracts in post-stroke aphasia using all basic DTI indices of tract microstructure. Differential roles of small tract segments were also explored in the present investigation. Our findings emphasize the potential importance of fiber pathways in supporting different language functions (Dick et al., 2014; Poeppel et al., 2012), and in line with Turken and Dronkers (2011) point to the importance of temporal lobe tracts in language processing, particularly comprehension. As for the dorsal tracts, our data support an exclusive role of the AF in language processing, particularly in language production (per Dronkers et al., 2007). Results also corroborate previous findings in aphasia that the integrity of white matter regions in the left dominant hemisphere, strategically located at the crossroads between ventral and dorsal streams, is highly associated with the severity of language impairment (Rosso et al., 2015). Finally, our findings highlight the need to examine individual small tract segments, as opposed to assuming equipotentiality within each white matter tract, in the quest to accurately delineate the functional roles of fiber pathways.

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Supplementary data

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