White matter pathways for prosodic structure building: A case study

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Abstract

The relevance of left dorsal and ventral fiber pathways for syntactic and semantic comprehension is well established, while pathways for prosody are little explored. The present study examined linguistic prosodic structure building in a patient whose right arcuate/superior longitudinal fascicles and posterior corpus callosum were transiently compromised by a vasogenic peritumoral edema. Compared to ten matched healthy controls, the patient's ability to detect irregular prosodic structure significantly improved between pre- and post-surgical assessment. This recovery was accompanied by an increase in average fractional anisotropy (FA) in right dorsal and posterior transcallosal fiber tracts. Neither general cognitive abilities nor (non-prosodic) syntactic comprehension nor FA in right ventral and left dorsal fiber tracts showed a similar pre-post increase. Together, these findings suggest a contribution of right dorsal and inter-hemispheric pathways to prosody perception, including the right-dorsal tracking and structuring of prosodic pitch contours that is transcallosally informed by concurrent syntactic information.

Keywords: language; prosody; voice; pitch; DTI; auditory pathways; arcuate fascicle; dorsal stream; corpus callosum

1. Introduction

White-matter fiber bundles connecting left fronto-temporal (and parietal) 'language areas' have become a centerpiece of modern language models (Friederici, 2011) and their divide into functionally specialized dorsal and ventral routes is largely undisputed (Hickok & Poeppel, 2007; Rauschecker & Scott, 2009). However, the established roles of left dorsal and ventral fiber tracts in speech production and semantic comprehension (Fridriksson et al., 2018; Kümmerer et al., 2013; Saur et al., 2008), as well as syntactic parsing (Friederici, 2012; Griffiths, Marslen-Wilson, Stamatakis, & Tyler, 2013; Wilson et al., 2011) ignore one important component of spoken language: Speech prosody, the rhythmic-melodic variations in speech that serve linguistic functions[1] (Cutler, Dahan, & Van Donselaar, 1997). The notable involvement of right-hemispheric fronto-temporal brain areas in linguistic prosodic processing (for reviews, see Baum & Pell, 1999; Belyk & Brown, 2014; Paulmann, 2016; Witteman, van Ijzendoorn, van de Velde, van Heuven, & Schiller, 2011) calls for reflection upon the contribution of right-hemispheric (Sammler, Grosbras, Anwander, Bestelmeyer, & Belin, 2015) as well as inter-hemispheric pathways to natural language comprehension (Friederici & Alter, 2004). Here, we present a case study that lends evidence for the functional *necessity* of right dorsal and transcallosal pathways in linguistic prosodic structure building.

Speakers naturally vary prosodic features such as intonation and rhythm in their utterances to package information into meaningful units and to accentuate thematically relevant words (Cole, 2015; Cutler et al., 1997; Wagner & Watson, 2010). Indeed, we do well in relying on prosodic cues in ambiguous sentences like "Wave at the girl with the hat." to understand at which girl we should wave and in which way (Lehiste, 1973; Snedeker & Trueswell, 2003). This example is one of many to illustrate how the prosodic structure of an utterance, i.e., its organization into smaller phonological or intonational phrases (Selkirk, 1996), can assist language comprehension: The systematic alignment of prosodic phrase boundaries with syntactic and semantic structure (Cooper & Paccia-Cooper, 1980; Selkirk, 1984; Watson & Gibson, 2004) allows listeners to use prosody in their syntactic and semantic interpretation, and *vice versa* (Buxó-Lugo & Watson, 2016; Cole, Mo, & Baek, 2010). Changes in pitch contour, pre-boundary lengthening and pauses are amongst the most important acoustic cues that signal prosodic boundaries (Ladd, 2008; Pierrehumbert & Hirshberg, 1990) and constrain parsing possibilities.

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[1] Prosody also conveys paralinguistic information about speakers' emotions, attitudes, and intentions (Hellbernd & Sammler, 2016; Scherer, 1986) which will not be addressed in the present study.

The tracking of these cues has often been associated with the right hemisphere, in line with cue-dependent models of auditory speech perception (Friederici & Alter, 2004; McGettigan & Scott, 2012; Poeppel, 2003; Zatorre, Belin, & Penhune, 2002). These models argue for a relative processing benefit of right auditory cortices for pitch and spectral information (Jamison, Watkins, Bishop, & Matthews, 2006; Johnsrude, Penhune, & Zatorre, 2000; Obleser, Eisner, & Kotz, 2008; Schönwiesner, Rübsamen, & von Cramon, 2005; Zatorre et al., 2002) that unfolds over extended timescales (Giraud et al., 2007; Poeppel, 2003). As a consequence, the right hemisphere may optimally track suprasegmental prosodic features and complement left-hemispheric syntactic and semantic processes, as proposed in the *Dynamic Dual Pathway Model* of Friederici and Alter (2004). In keeping with this hemispheric division of labor, fMRI and dichotic listening studies reported predominant right fronto-temporal activations (Kyong et al., 2014; Meyer, Alter, Friederici, Lohmann, & von Cramon, 2002; Meyer, Steinhauer, Alter, Friederici, & von Cramon, 2004; Plante, Creusere, & Sabin, 2002) and a left ear advantage (i.e., right hemisphere involvement; Blumstein & Cooper, 1974; Shipley-Brown, Dingwall, Berlin, Yeni-Komshian, & Gordon-Salant, 1988) when listening to filtered or degraded speech with high demands on prosodic processing. Likewise, explicit attention to prosodic pitch contours in statements and questions (compared to processing of phonemes and lexical meaning) induced right-lateralized activity in fronto-temporal regions (Kreitewolf, Friederici, & von Kriegstein, 2014; Sammler et al., 2015). The right-lateralization of prosody is less clear-cut in studies with natural language material (e.g., Perkins, Baran, & Gandour, 1996; Tang, Hamilton, & Chang, 2017), prosody production (Kellmeyer et al., 2013; Peschke, Ziegler, Eisenberger, & Baumgaertner, 2012), and tasks that go beyond the processing of low-level acoustic-prosodic cues such as pitch contour (for reviews showing bilateral involvement, see Baum & Pell, 1999; Belyk & Brown, 2014; Paulmann, 2016; Witteman et al., 2011). This indicates the inevitable interaction of prosodic information with concurrent syntactic (den Ouden, Dickey, Anderson, & Christianson, 2016) or lexical-semantic processes (Domahs, Klein, Huber, & Domahs, 2013; Gandour et al., 2004; van Lancker, 1980) that are hard to separate during natural language comprehension.

The present study focuses on sentence-level prosodic structure building, i.e., the gradual emergence of a (hierarchical) representation of prosodic constituency that aligns with syntactic structure. As outlined above and implied by previous psycholinguistic research, the prosodic parser most likely draws both on acoustic markers for prosodic boundaries (Ladd, 2008; Pierrehumbert & Hirshberg, 1990; Snedeker & Trueswell, 2003) as well as concurrent syntactic structure (Buxó-Lugo & Watson, 2016; Cole et al., 2010) to build prosodic representations. At the neural level, this implies involvement of both right-hemispheric fronto-temporal networks that track relevant prosodic features over time as well as inter-hemispheric exchange to map syntactic and prosodic structure onto each other (Friederici & Alter, 2004).

This assumption naturally raises the question *how* information is transferred between relevant brain areas. Syntactic structure building in the left hemisphere is known to involve ventral fronto-temporal connections via the inferior fronto-occipital (IFOF) and uncinate fascicles (UF) for simple syntactic parsing, while dorsal connections via the arcuate and superior longitudinal fascicles (AF/SLF) support parsing of complex syntactic structures (Friederici, 2012; Griffiths et al., 2013) (for reviews, see Friederici, 2011; Gierhan, 2013b). Correspondingly, damage to left dorsal fiber tracts (Meyer, Cunitz, Obleser, & Friederici, 2014; Wilson et al., 2011) or their developmental immaturity (Skeide, Brauer, & Friederici, 2016) coincide with reduced comprehension of syntactically complex sentences.

Recently, we demonstrated a similar multi-pathway architecture in the right hemisphere for the perception of prosodic pitch contours in statements and questions (Sammler et al., 2015). This finding was remarkable because the relevance of right-hemispheric and particularly right *dorsal* tracts in speech and language has been questioned until very recently (Hickok, 2012). Indeed, direct right dorsal fronto-temporal connections were often found to be anatomically weaker than their left-hemispheric counterparts (Fernández-Miranda et al., 2015; Glasser & Rilling, 2008; Parker et al., 2005; Powell et al., 2006; Thiebaut de Schotten, Ffytche, et al., 2011) and have been studied nearly exclusively in the context of atypical language lateralization (Duffau, Leroy, & Gatignol, 2008; Vassal, Le Bars, Moritz-Gasser, Menjot, & Duffau, 2010), e.g., during aphasia rehabilitation (Forkel et al., 2014; Schlaug, Marchina, & Norton, 2009). What has remained unexplored so far is the potential contribution of right dorsal tracts to the processing of suprasegmental prosodic information in speech. Our data on statement and question discrimination lend initial evidence for that, albeit only for single words (Sammler et al., 2015; for converging evidence in emotional prosody perception, see Frühholz, Gschwind, & Grandjean, 2015; Glasser & Rilling, 2008). It seems plausible, though, that the capacity of (right) AF/SLF and temporal-premotor loops to constantly monitor sound and pitch (Guenther & Vladusich, 2012; Houde & Chang, 2015; Zarate, 2013) may benefit the acoustic detection of prosodic boundaries in sentences. A yet bolder proposal that awaits testing is the potential involvement of right dorsal fronto-temporal tracts in more advanced prosodic structuring, beyond basic pitch tracking (Bornkessel-Schlesewsky & Schlesewsky, 2013).

The interaction between the lateralized syntax and prosody streams requires a dynamic exchange between the two hemispheres (Friederici & Alter, 2004; Steinmann & Mulert, 2012). Several studies suggest that syntax-prosody alignment hinges particularly on the cross-talk between the temporal lobes via commissural fibers that cross through the posterior third of the corpus callosum (CC; Friederici, von Cramon, & Kotz, 2007; Sammler, Kotz, Eckstein, Ott, & Friederici, 2010; for the anatomy of CC, see Hofer & Frahm, 2006; Huang et al., 2005). Accordingly, patients with permanent lesions in the posterior CC no longer processed prosodic (or syntactic) irregularities that were only detectable if the syntactic (or prosodic) context was taken into account (Friederici et al., 2007; Sammler et al., 2010). The present study extends these findings to a new case with temporary dysfunctions of relevant white matter tracts.

We report the case of a patient in whom right dorsal and transcallosal connectivity were transiently compromised due to a vasogenic peritumoral edema, allowing assessment of potential prosodic deficits and their recovery in the same individual. Vasogenic edemas are extracellular edemas; other than cytotoxic edemas they infiltrate white matter, not cell bodies (Stokum, Gerzanich, & Simard, 2016), i.e., leave the neurons largely intact if the edema is medically treated to induce its reabsorption. Nevertheless, vasogenic edemas can compromise function in that they compress tissue and disturb information flow along the infiltrated white matter tracts. While the underlying neurophysiological mechanisms are still not fully understood, resulting physical or cognitive deficits are typically alleviated over the course of edema reabsorption (e.g., Bizzi et al., 2012). We capitalized on this phenomenon to probe the involvement of right dorsal and inter-hemispheric tracts in prosody perception in a patient with vasogenic edema infiltrating right AF/SLF and the posterior corpus callosum.

One important consideration for our investigation is that vasogenic edemas are seen around brain tumors. Our patient was diagnosed with a benign convexity meningioma (grade I) in the right parietal region. This type of meningioma is a slow-growing tumor on the surface of the brain, i.e., not invading grey matter. In line with a slow growth rate, symptoms typically have an insidious onset such as slowly evolving headache, suggestive of increased intracranial pressure, or a protracted history of partial seizures (Rockhill, Mrugala, & Chamberlain, 2007). Complete excision of the meningioma is often curative. Slow growth allows for functional compensation; among intracranial tumors, meningiomas are the ones with the highest incidental discovery rate, and can remain neurologically and cognitively asymptomatic, especially if located in the right hemisphere (Nishizaki, Ozaki, Kwak, & Ito, 1999). Overall, the long-term course of meningioma with potential for compensation make it likely that post-surgical reversal of pre-surgical deficits in our patient are due to edema absorption, i.e., relief from edema-induced compression and recovery of white matter tracts, rather than removal of the tumor.

The present study combined pre- and post-surgical diffusion-weighted neuroimaging with behavioral assessment of linguistic prosody perception in a male patient with a right parietal edema infiltrating AF/SLF and the posterior corpus callosum. Specifically, we assessed the patient's ability to detect prosodic phrase boundaries that mismatched syntactic phrase structure (Eckstein & Friederici, 2006), requiring both right-hemispheric prosodic contour processing as well as syntax-prosody alignment across both hemispheres. To rule out general left-hemispheric syntax processing deficits, a non-prosodic control task was designed that tested comprehension of sentences with canonical and non-canonical syntactic structure (Gierhan, 2013a). The patient's performance was compared with performance of ten matched healthy controls (HC) that were tested twice at the same interval as the patient, to control for learning effects. General cognitive functioning was assessed with a standard neuropsychological test battery. If right dorsal and/or transcallosal pathways are essential for prosodic structure building and vasogenic edemas compromise white matter function, the patient's prosody perception should (i) be deficient in the pre-surgical but normal in the post-surgical session compared to HC, should (ii) increase more strongly between pre- and postsurgical session than in HC (who could show learning effects), and should (iii) increase more strongly than in the non-prosodic syntax task and neuropsychological tests.

2. Materials and methods

2.1. Participants

Our patient (male, 43 years, right-handed) presented for assessment of two generalized epileptic seizures at the neurosurgical department of the University Hospital Leipzig. A computer tomography (CT) of the brain revealed a vasogenic edema (37393 mm^3) surrounding a benign convexity meningioma (25519 mm^3) in the right parietal lobe (Figure 1A; see also Supplementary Figure 1). The edema was immediately admitted to treatment with glucocorticoids/dexamethasone (Meixensberger & Jaeger, 2005; 48 mg intravenous on the day of diagnosis, then 3 x 8 mg daily up until surgery). Such a treatment leads to the continuous absorption of the edema within a period of 2-3 weeks, usually associated with a considerable functional recovery that illustrates that the edema causes transient deficits beyond those caused by the tumor. Twenty-one days after diagnosis, the tumor was microsurgically resected. We tested the patient on day 2 and acquired MR images on day 3 after beginning of medication, i.e., when the edema still compromised the dorsal fiber tracts. The second acquisition was 110 days after neurosurgical resection of the tumor and full absorption of the edema (i.e., 134 days after the first session). Ten healthy male control participants (HC) matched in age (mean ± *SEM*: 42 ± 0.6 years), years of school education (10.2 ± 0.2 years), and handedness were tested and re-tested with a mean interval of 145 ± 12 days between sessions to account for potential learning effects in a test-retest setup. Neither the patient, nor the controls were musicians; none of the controls reported hearing deficits as verified with a MAICO MA 33 audiometer (MAICO Diagnostics GmbH, Berlin, Germany). The patient displayed slightly lower hearing on the left than the right ear (125 Hz: left 17.5 / right 32.5 dB HL; 250 Hz: 20.0 / 37.5 dB HL; 1000 Hz: 25.0 / 45.0 dB HL; 4000 Hz: 17.5 / 55 dB HL). This was accounted for by adjusting the volume of the experimental stimuli to well audible level. All participants gave written informed consent. The study was approved by the ethics committee of the University of Leipzig (017-10-180112009).

2.2. MRI data acquisition

Anatomical and diffusion MRI data were obtained pre- and post-surgically in the patient and once for seven of the HC. Three HC were not scanned due to MR incompatibility. Data were acquired with a 32-channel head coil in a 3 Tesla TIM TRIO scanner (Siemens Healthineers, Erlangen, Germany) at the Max Planck Institute for Human Cognitive and Brain Sciences, Leipzig, Germany. High-resolution T_1-weighted anatomical datasets (1 × 1 × 1 mm^3 voxel size) were acquired using a 3D magnetization-prepared rapid gradient echo (MPRAGE) sequence (repetition time TR = 1300 ms, echo time TE = 3.46 ms, 176 sagittal slices, field of view FOV = 240 × 256 mm^2, flip angle = 10°). The diffusion-weighted data sets were acquired with a twice-refocused spin-echo EPI sequence (TR = 12.9 s, TE = 100 ms, 88 axial slices without gap, FOV = 220 × 220 mm^2, flip angle = 90°, GRAPPA acceleration factor 2) with a voxel size of 1.72 × 1.72 × 1.7 mm^3. Diffusion-weighting was isotropically distributed along 60 diffusion-encoding gradient directions with a b-value of 1000 s/mm^2. Acquisition of diffusion-weighted images was interspersed with seven images without diffusion-weighting (b0), one at the beginning of the sequence and one after each block of 10 diffusion-weighted images, serving as anatomical reference for offline motion correction. Total duration of both MRI scans was about 25 minutes.

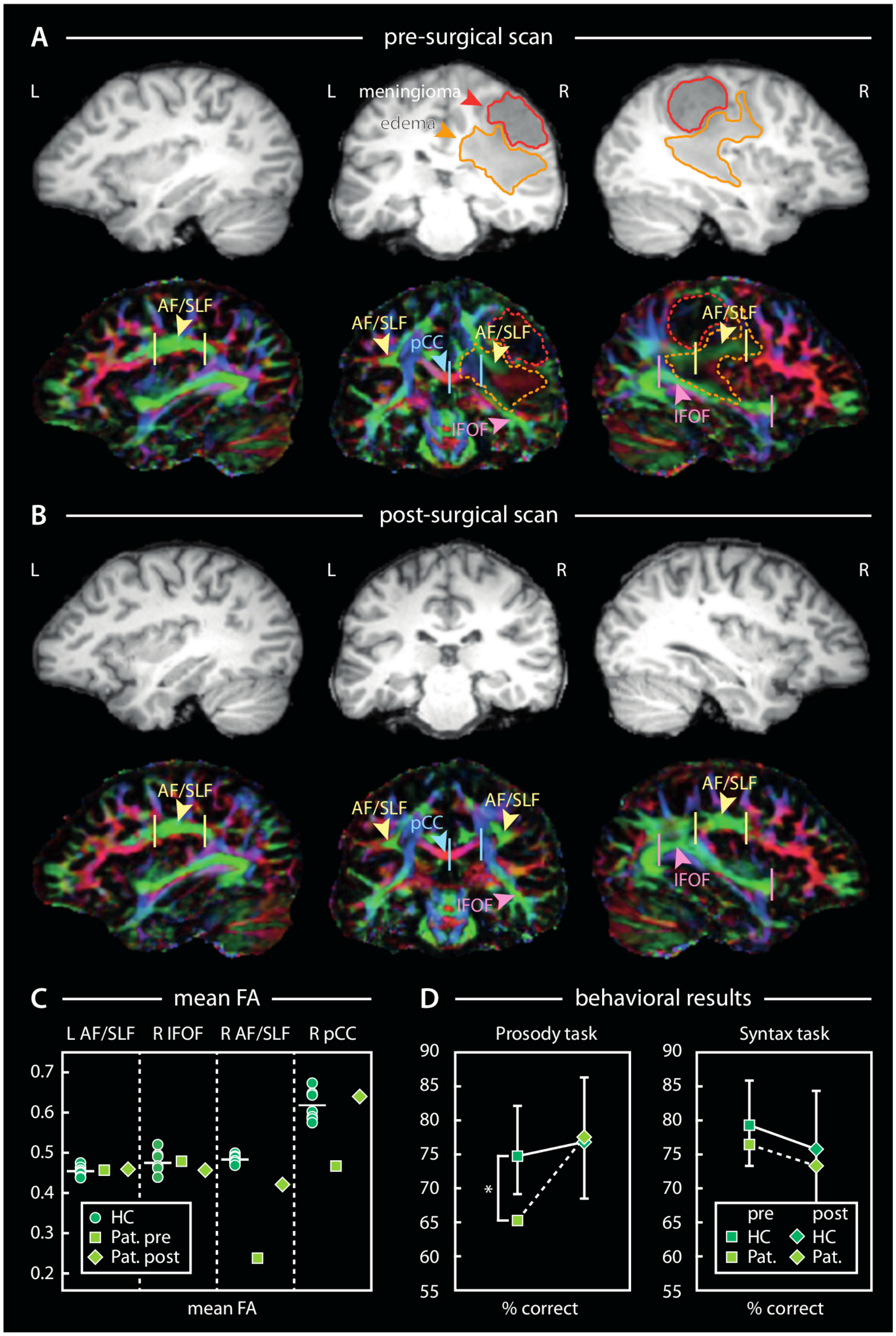

Figure 1. Pre- and post-surgical results. **(A)** Pre-surgical anatomical (grey) and directionally colored diffusion MR FA-images of the patient. The peritumoral edema (orange) infiltrated right dorsal fronto-temporal/parietal pathways leading to lower fractional anisotropy (FA; dark green) in right compared to left AF/SLF (white arrows). The meningioma (red) did not invade but displaced brain tissue as can be seen in the position of the corpus

callosum (CC). White bars indicate borders for extraction of mean FA in AF/SLF as depicted in (C). Edema and tumor were manually segmented with itk-SNAP 3.2 (http://www.itksnap.org/pmwiki/pmwiki.php). **(B)** Post-surgically, the edema was fully reabsorbed and the tumor resected, allowing for a recovery of tissue properties (measured by FA) in right AF/SLF (higher green saturation than in (A)). **(C)** Pre-surgically low FA in right AF/SLF and posterior CC (pCC) of the patient (green square) approached mean FA values of HC (green circles) in the post-surgical session (green diamond), while left AF/SLF as well as right IFOF showed similar FA values as in HC across both sessions. Horizontal lines indicate mean FA of HC. **(D)** Behavioral results in the prosody and syntax task. Plots show pre- and post-surgical performance of the patient (dashed line) compared to the 1st and 2nd test session of ten matched healthy controls (solid line). Error bars indicate bootstrapped 95% confidence intervals.

2.3. Behavioral assessment

2.3.1. Prosody task

Participants were presented with 96 German sentences spoken by a female native speaker. Half of the sentences contained a prosodic irregularity in that pitch contour signaled sentence closure before all obligatory syntactic elements had occurred (Figure 2). All sentences consisted of a matrix clause including a proper name (*'Steffen'*) and a verb (*'sieht'/'sees'*), and a subordinate clause including a complementizer (*'dass'/'that'*), a noun phrase (*'der Lehrer'/'the teacher'*), a prepositional phrase (*'beim Tadel'/'during-the reproval'*), and a verb (*'schmunzelt'/'smiles'*). Sentences were rendered prosodically irregular by inserting a prosodic boundary tone with falling pitch contour on the penultimate noun (i.e., *'Tadel'*) by means of cross splicing (for details on stimulus preparation and acoustic properties, see Eckstein & Friederici, 2006). This acoustic manipulation induced a mismatch between syntactic and prosodic structure: Syntax predicted sentence continuation beyond the noun given that at least the obligatory verb (*'smiles'*) was still to follow. As a consequence, the noun's falling prosodic contour violated syntax-driven expectancies of prosodic form (auditory examples are provided as Supplementary Material). Prosodically regular and irregular sentences were presented with equal probability across the experiment in pseudo-random order with no more than three consecutive trials of the same type. Sentences had an average (± *SEM*) duration of 3368 ± 19 ms and were presented binaurally at a comfortable volume via loudspeakers (Eltax HT-1; Eltax, Aulum, Denmark) in a silent room using Presentation 12.2. (Neurobehavioral Systems, Inc., Albany, Canada). Participants were asked to judge the prosodic regularity of the sentences by pressing one of two buttons. The experiment started with ten practice trials (with feedback) to acquaint participants with the task and lasted approximately 15 minutes.

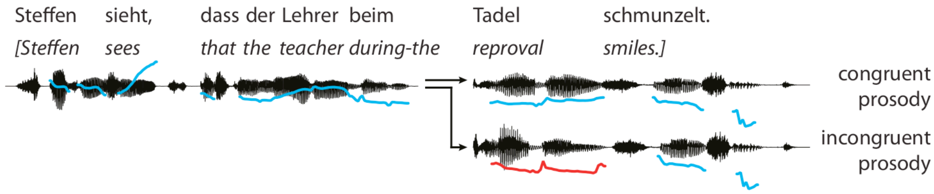

Figure 2. Stimulus examples of the prosody task. The penultimate word of German sentences (here: 'Tadel') was rendered prosodically incongruent (falling instead of rising pitch contour) by means of cross-splicing (Eckstein & Friederici, 2006).

2.3.2. Syntax task

To ensure that putative deficits in detecting prosodic irregularities are not due to a general deficit in processing syntactic information, a non-prosodic sentence comprehension task was adapted from Gierhan (2013a) that is known to involve left (not right) dorsal fiber tracts (Friederici & Gierhan, 2013). Participants were presented with 90 sentences with canonical and non-canonical syntactic structure spoken by a female native speaker of German. Sentences were composed of a pronoun (*'Dann'/'Then'*), a verb (*'grüßt'/'greets'*), an animate subject (*'der Soldat'/'the soldier'*), and an animate object (*'den Major'/'the major'*). Half of the sentences presented the subject first, followed by the object (S-O sentences, e.g., *'Dann grüßt der$_{[S]}$ Soldat$_{[S]}$ den$_{[O]}$ Major$_{[O]}$.'/'Then greets the$_{[S]}$ soldier$_{[S]}$ the$_{[O]}$ major$_{[O]}$.'*). The other half presented the object before the subject (O-S sentences, e.g., *'Dann grüßt den$_{[O]}$ Major$_{[O]}$ der$_{[S]}$ Soldat$_{[S]}$.'/'Then greets the$_{[O]}$ major$_{[O]}$ the$_{[S]}$ soldier$_{[S]}$.'*), which is a legal construction in German. (Note that in both examples, it is the soldier who greets the major.) Sentences were spoken with neutral, non-accentuated prosody (auditory examples are provided as Supplementary Material). After each sentence, participants were asked a comprehension question (spoken by the same female speaker) of the sort 'who did what to whom' to assess their syntactic processing. These questions required either a 'yes' response (50%), or a 'no' response because it reversed subject and object (25%; e.g., it was asked whether the major greets the soldier), or introduced a new action or protagonist (25%; e.g., it was asked whether the soldier blames the major; for examples, see Table 1). Sentences had an average (± *SEM*) duration of 2619 ± 12 ms and were presented in the same way as stimuli in the prosody task. The experiment started with six practice trials (with feedback) and lasted approximately 15 minutes.

Table 1. Stimulus examples of the syntax task (with literal translations).

(1) Example S-O sentence (subject-first)
Dann grüßt der$_{[S]}$ Soldat$_{[S]}$ den$_{[O]}$ Major$_{[O]}$.
Then greets the$_{[S]}$ *soldier*$_{[S]}$ *the*$_{[O]}$ *major*$_{[O]}$.
(2) Example O-S sentence (object-first)
Dann grüßt den$_{[O]}$ Major$_{[O]}$ der$_{[S]}$ Soldat$_{[S]}$.
Then greets the$_{[O]}$ *major*$_{[O]}$ *the*$_{[S]}$ *soldier*$_{[S]}$.
(3) Examples of questions that require a 'yes' response
Grüßt der$_{[S]}$ Soldat$_{[S]}$ den$_{[O]}$ Major$_{[O]}$? / Grüßt den$_{[O]}$ Major$_{[O]}$ der$_{[S]}$ Soldat$_{[S]}$?
Greets the$_{[S]}$ *soldier*$_{[S]}$ *the*$_{[O]}$ *major*$_{[O]}$? / *Greets the*$_{[O]}$ *major*$_{[O]}$ *the*$_{[S]}$ *soldier*$_{[S]}$?
(4) Examples of questions that require a 'no' response
Grüßt der$_{[S]}$ Major$_{[S]}$ den$_{[O]}$ Soldat$_{[O]}$? / Rügt der$_{[S]}$ Soldat$_{[S]}$ den$_{[O]}$ Major$_{[O]}$?
Greets the$_{[S]}$ *major*$_{[S]}$ *the*$_{[O]}$ *soldier*$_{[O]}$? / *Blames the*$_{[S]}$ *soldier*$_{[S]}$ *the*$_{[O]}$ *major*$_{[O]}$?

S: subject, O: object.

2.3.3. Neuropsychological assessment – General cognitive functioning

Furthermore, to ensure that the results in the prosody task were not due to general cognitive deficits, we applied a brief battery of standard neuropsychological tests. This battery assessed the ability to store and rehearse verbal and spatial contents using the digit-span and block-span test of the Wechsler Memory Scale (WMS-R; Wechsler, 1987), the ability to focus attention using the d2 test that requires speeded detection of target symbols amongst distractors (Brickenkamp, 1994), and visuo-spatial reasoning using the third subtest of the Leistungsprüfsystem (LPS-3) that requires identification of rule violations in series of symbols (Horn, 1983). At the outset as well as post-surgically, the patient's performance was within normal average-low to above-average range relative to the age matched normative samples provided by the standard neuropsychological tests (pre-/post-surgical percentile rank of forward digit-span: 35/35; backward digit-span: not assessed; forward block-span: 93/32; backward block-span: 23/23; LPS-3: 69/93; d2: 34/54; standard diagnostic cutoffs of normal average performance: 16-84).

2.4. Data analysis

2.4.1. Diffusion MRI data

Diffusion MRI data were analyzed using LIPSIA (Max Planck Institute for Human Cognitive and Brain Sciences, Leipzig, Germany), and FSL (FMRIB, University of Oxford, UK, www.fmrib.ox.ac.uk/fsl). First, T_1-weighted structural scans were reoriented to the sagittal intercommissural plane and the brain was segmented in LIPSIA. A trimmed brain mask was created by shrinking the inner skull surface by 7 mm to later reduce noisy endpoints of streamlines. Then, motion correction parameters for the 60 diffusion-weighted images were computed based on the 7 (b0) reference images distributed over the entire sequence using rigid-body transformations implemented in FSL. Interpolated motion correction parameters were combined with a global registration to the T_1-anatomy and applied to all 60 volumes that were resampled to an isotropic resolution of 1.7 mm. The gradient direction for each volume was corrected using the rotation parameters. Finally, the diffusion tensor, the three eigenvectors, and the fractional anisotropy (FA) value were computed for each voxel.

The diffusion tensor image was used for full-brain deterministic fiber tracking using an in-house implementation of the tensor deflection algorithm (Lazar et al., 2003) in all voxels of the trimmed brain mask. Together with a lowered FA threshold of 0.075, this algorithm allowed for robust tracking in areas of low anisotropy (i.e., the edema) while excluding the tumor area and the ventricles. Lowering the FA threshold without any additional processing might, however, introduce false positive connections. To eliminate spurious streamlines while retaining the bundles of interest, tracking was performed in an adapted two-step approach. First, right AF/SLF and posterior CC were selected from the full-brain tracking using inclusion and exclusion masks. The volume of the extracted bundle was computed by selecting all voxels that were crossed by at least two streamlines. In this way, spurious single streamlines were excluded. Inclusion masks for right AF/SLF were placed in the temporal lobe near the temporo-parietal junction and in the posterior frontal lobe (Catani, Jones, & Ffytche, 2005; Mori, 2007). Streamlines crossing the extreme capsule and the thalamus were excluded. Inclusion masks for posterior CC were placed in isthmus and splenium of the CC and right posterior temporal lobe. Streamlines reaching parietal or occipital lobe were excluded. Masks were individually adapted for every participant. In the second step, the extracted bundle volume was dilated by 1 mm and streamline tracking was performed again, restricted to this volume. Then, the same inclusion and exclusion masks as described above were applied again and the final bundle was extracted.

The same procedure was applied to define left AF/SLF and right IFOF, as contralateral dorsal and ipsilateral ventral control tracts, respectively. Masks for left AF/SLF were analogous to those used in the right hemisphere. Inclusion masks for the right IFOF were placed in right IFG and right angular gyrus (Makris & Pandya, 2009). Streamlines targeting areas dorsal of angular gyrus or crossing right AF/SLF or the corpus callosum were excluded.

To assess recovery of FA, mean FA values of right AF/SLF and posterior CC were extracted from pre- and post-surgical scans, limited to the central horizontal parts of the extracted bundle volumes, i.e., deep white matter (see borders in Figure 1A and B) where tractography is most robust and reproducible and FA values are less affected by partial volume effects than in the fanning ends of the bundle. To demonstrate general test/re-test stability of FA (compare green squares and diamonds in Figure 1C), mean FA values of left AF/SLF and right IFOF were extracted in the same way, also excluding the fanning ends of the tract. The IFOF runs ventral of the edema but it was made sure that the chosen segment fully covered the extent of the edema along its y-dimension. The patient's FA values were statistically compared to those of the HC by means of bootstrapped confidence intervals (see section 2.4.2).

2.4.2. Behavioral data

Prosody perception and syntax processing abilities were quantified as %correct responses. Cognitive abilities were compared based on raw test scores (Table 2; raw scores rather than percentile ranks were used for statistical comparison to preserve original distribution and differences between scale units; Thorndike & Thorndike-Christ, 2013). Change scores were calculated for each test by subtracting pre-surgical (1^{st} session) from post-surgical (2^{nd} session) performance measures. To specifically compare performance changes in the two matched language tasks—prosody vs. syntax—the difference between the two change scores ($[Prosody_{post} – Prosody_{pre}] – [Syntax_{post} – Syntax_{pre}]$) was calculated. For statistical comparison of patient's and HC's data, we chose a non-parametric bootstrapping approach as in Meyer et al. (2014) to account for the limited number of HC and the resulting violations of the sphericity assumption (Mauchly, 1940). We generated two-tailed 95% confidence intervals (CIs) based on 10000 random draws from the values of HC (Efron, 1979) as implemented in MATLAB (The MathWorks, Inc., Natick, MA, USA). Patient's scores were considered significantly different from those of HC when they were outside these bootstrapped CIs. HC's performance in 1^{st} and 2^{nd} session was compared by means of two-tailed *t*-tests for paired samples.

3. Results

3.1. Anatomy and diffusion MRI data

Post-surgically, the tumor was fully resected with no remaining cavity, and the edema was entirely reabsorbed (Figure 1B; see also Supplementary Figure 2). As shown in Figure 1C and Table 2, the patient's right AF/SLF showed significantly reduced mean FA in the pre-surgical session (green square; M = 0.238) compared to HC (green circles; $M \pm SD$ = 0.481 ± 0.010) that recovered to near-normal values after surgery (green diamond; M = 0.421), although it remained below HC's mean FA values. Similarly, the patient's posterior CC connecting the temporal lobes showed significantly reduced pre-surgical FA (M = 0.470) compared to HC ($M \pm SD$ = 0.619 ± 0.178) that fully recovered after surgery (M = 0.643). In turn, the patient's left AF/SLF showed nearly identical FA values in the pre- (M = 0.457) and post-surgical session (M = 0.459), both not significantly different from mean FA in HC ($M \pm SD$ = 0.454 ± 0.013). Likewise, the patient's right IFOF showed stable FA values in the pre- (M = 0.478) and post-surgical scan (M = 0.454) that were both within the bounds of HC's bootstrapped CI ($M \pm SD$ = 0.472 ± 0.029; for statistical values, see Table 2).

Table 2. Statistical comparison of fractional anisotropy in patient and healthy controls.

Fiber tract	Healthy Controls		95% CI		Patient		
	M	*SEM*	Lower	Upper	Pre	Post	Change
Right AF/SLF	0.481	0.010	0.476	0.491	**0.238**	**0.421**	+ 0.183
Posterior CC	0.619	0.178	0.596	0.648	**0.470**	0.643	+ 0.173
Left AF/SLF	0.454	0.013	0.446	0.464	0.457	0.459	+ 0.002
Right IFOF	0.472	0.029	0.453	0.494	0.478	0.454	- 0.024

AF/SLF: arcuate/superior longitudinal fascicle, CC: corpus callosum, IFOF: inferior fronto-occipital fascicle. Bold values represent significant lower fractional anisotropy in patient than healthy controls.

3.2. Behavioral data

In the **prosody task**, our patient showed a performance increase from pre- to post-surgical session (+12.50%) that was significantly stronger than the nominal performance change in HC ($M \pm SD$ = 2.08% ± 2.33%; see Figure 1D and Table 3 for statistical details). Pre-surgically, the patient showed significantly lower performance (65.63%) than HC ($M \pm SD$ = 75.11% ± 3.91%), whereas his performance reached normal levels in the post-surgical session (78.13%; HC: $M \pm SD$ = 77.19% ± 5.41%). HC performed equally well across the two sessions (paired samples t-test: $t(9) = -0.89$, $p > .395$).

In the non-prosodic **syntax task**, our patient showed stable performance across sessions (pre: 76.67%; post: 73.3%), similar to HC (1^{st}: $M \pm SD$ = 79.22% ± 3.36%; 2^{nd}: 75.33% ± 4.99%). Performance did not differ between patient and HC, neither pre- nor post-surgically nor in terms of performance change over time (see Table 3 for CI's). HC showed no performance differences between the two sessions ($t(9) = 1.29$, $p > .229$; see Figure 1D).

The comparison of the **change scores between the two tasks** revealed that the patient's pre-post-surgical performance gain was stronger (by 15.84%) in the prosody than in the syntax task, which was significantly more than in HC (CI: 0.15% – 12.99%). Note that this result cannot be due to general differences in task difficulty or ceiling and floor effects. HC's results confirmed that the two tasks were perfectly matched in difficulty (no significant main effect of TASK in a repeated-measures ANOVA with factors TASK and SESSION: $F(1,9) = 0.07$, $p > .791$) and were well above chance level (one-sample *t*-tests against 50% per session and task: *t*'s > 5.02, *p*'s < .002) and well below ceiling (one-sample *t*-tests against 100% per session and task: *t*'s < -4.21, *p*'s < .003).

Likewise, the patient's performance gain in the prosody task cannot be explained by a putative recovery of **general cognitive functions**. In none of the cognitive tasks, our patient showed a pattern of pre-surgical deficit and post-surgical recovery (as observed in the prosody task). In the span tests, the patient showed perfectly *stable* (forward digit-span, backward block-span) or post-surgically *decreased* (instead of increased) performance (forward block-span). In the attention task (d2), patient's performance increased over time, however, to a similar extent as in HC ($t(9) = -7.64$, $p < .001$), i.e., denoting a general learning effect rather than recovery. Overall, in both the attention task and the span tests, our patient scored mostly slightly below HC, constantly across both sessions, making it unlikely that these abilities contributed to performance recovery in the prosody test. Only exception was the spatial-reasoning task (LPS-3). Here, the patient showed a pre-post-surgical performance increase that was significantly stronger than in HC, although his pre-surgical performance did not significantly differ from HC's scores. This finding is compatible with right dorsal pathway involvement in spatial relational reasoning (Krawczyk, 2012; Shokri-Kojori, Motes, Rypma, & Krawczyk, 2012; Watson & Chatterjee, 2012).

Table 3. Statistical comparison of behavioral results of patient and healthy controls in the two sessions.

Test	Healthy Controls		95% CI		Patient	
	M	*SEM*	Lower	Upper	Score	Direction
Critical tests (% correct)						
Prosody perception						
1st session	75.11	3.91	68.23	82.82	**65.63**	**–**
2nd session	77.19	5.41	67.25	87.12	78.13	=
difference (2nd – 1st session)	2.08	2.33	-2.61	6.04	**12.50**	**+**
Syntax processing						
1st session	79.22	3.36	73.33	85.67	76.67	=
2nd session	75.33	4.99	66.17	84.45	73.33	=
difference (2nd – 1st session)	-3.89	3.01	-9.17	2.22	-3.34	=
General cognitive functions (raw scores)						
d2 concentration performance						
1st session	175.20	10.30	158.00	196.20	**141**	**–**
2nd session	197.50	10.40	178.50	217.00	**163**	**–**
difference (2nd – 1st session)	22.30	2.92	17.60	28.60	22	=
Digit span forward						
1st session	8.10	0.48	7.10	8.90	**7**	**–**
2nd session	8.10	0.60	7.00	9.30	7	=
difference (2nd – 1st session)	0.00	0.49	-1.00	0.80	0	=
Block span backward						
1st session	8.40	0.58	7.20	9.40	**7**	**–**
2nd session	9.60	0.67	8.10	10.60	**7**	**–**
difference (2nd – 1st session)	1.20	0.53	0.40	2.40	**0**	**–**
Block span forward						
1st session	8.60	0.37	8.00	9.50	**12**	**+**
2nd session	9.30	0.37	8.60	9.90	**8**	**–**
difference (2nd – 1st session)	0.70	0.37	0.10	1.50	**-4**	**–**
LPS-3						
1st session	27.50	1.92	21.80	30.00	23	=
2nd session	29.90	1.22	27.40	32.00	30	=
difference (2nd – 1st session)	2.40	1.38	0.10	5.50	**7**	**+**

Bold values represent significant differences between patient and healthy controls. Symbols indicate whether patient's performance (change) was higher (+), similar to (=) or lower than (–) in controls.

4. Discussion

Following the hypotheses that right dorsal (Sammler et al., 2015) and posterior transcallosal fiber tracts (Friederici et al., 2007; Sammler et al., 2010) support prosodic structure building, and that vasogenic edemas can induce reversible deficits when infiltrating white matter tracts (Bizzi et al., 2012; Gierhan et al., 2012), we tested an edema patient on his abilities to process linguistic prosody, both before and after edema treatment and neurosurgery. Before treatment, i.e., when the edema was infiltrating and compressing right AF/SLF and posterior CC, the patient presented deficits in recognizing irregular prosody that mismatched syntactic structure. Reabsorption of the edema and resection of the benign meningioma were associated with a reversal of these deficits. This behavioral recovery was accompanied by increased average FA values in right AF/SLF and posterior CC, while FA was constant in left AF/SLF and right IFOF. Neither short term and working memory nor syntactic comprehension exhibited a similar pre-to-post-surgical performance gain. Consequently, the reversal of the prosodic deficit cannot be due to a nonspecific recovery of cognitive or verbal abilities. Rather, the findings invite the discussion of *causal* involvement of right dorsal and posterior transcallosal fiber tracts in the processing of prosodic structure.

What remains to be resolved is exactly *how* these pathways may contribute to the processing of prosodic information. In cognitive terms, it seems plausible to think of prosodic structure building as a hierarchical multi-step process with information passing through consecutive stages of basic acoustic analyses, higher-level auditory grouping and integration with syntactic and semantic information (for similar multi-step models of emotional prosody, see Brück, Kreifelts, & Wildgruber, 2011; Kotz & Paulmann, 2011; Schirmer & Kotz, 2006; Wildgruber, Ackermann, Kreifelts, & Ethofer, 2006). Intra- and inter-hemispheric pathways secure rapid and bidirectional information exchange within and between these stages represented in distributed neural networks. Although the present study cannot dissociate the functions supported by right dorsal and transcallosal pathways (because both of them were infiltrated by the edema), models of auditory, speech and language processing (Bornkessel-Schlesewsky, Schlesewsky, Small, & Rauschecker, 2015; Friederici, 2011; Friederici & Alter, 2004; Hickok & Poeppel, 2007; Rauschecker & Scott, 2009) may lend a basis to start reflecting upon possible mechanisms, as will be done in the remainder of the text. Three capacities should be considered: (i) the time-sensitive tracking of prosodic features and (ii) their grouping into higher order structures, and (iii) the integration of syntactic and prosodic information.

4.1. Right dorsal pathways – time-sensitive tracking and structuring of prosodic features

The decision upon a sentence's prosodic form and regularity, as in the present study, requires processing of auditory-prosodic cues, e.g., the recognition of pitch contours as either rising (here:

regular) or falling (irregular). This requirement may tap into the capacity of dorsal pathways to **track auditory information**—including pitch—over time. In its accepted role to map sound to articulation (Hickok & Poeppel, 2007; Saur et al., 2008), dorsal pathways are typically assumed to host auditory-motor loops that continuously monitor the sound and pitch of one's own vocalizations during speech production (Guenther & Vladusich, 2012; Hickok, 2012; Houde & Chang, 2015; Zarate, 2013). The same auditory-motor system in reversed processing mode has been proposed to serve speech perception (Hickok, Houde, & Rong, 2011; Rauschecker, 2011), including perception of prosodic contour (Sammler et al., 2015) and discrimination of vocal pitch (D'Ausilio, Bufalari, Salmas, Busan, & Fadiga, 2011). Altogether, it seems that **dorsal connections between auditory temporal and (pre)motor areas** could provide a basic computational building block necessary to track prosodic pitch contours over time, that may have been temporarily disrupted in our patient.

From a higher-order linguistic point of view, successful **parsing of prosodic structure** involves the segmentation of sentence-level prosodic information into constituent elements, e.g., intonational phrases (Nespor & Vogel, 1986; Selkirk, 1984). This requirement resonates with recent proposals that the dorsal stream may identify basic prosodic units (e.g., prosodic words) and combine them into successively larger linguistic chunks over time (e.g., intonational phrases; Bornkessel-Schlesewsky & Schlesewsky, 2013). Right AF/SLF involvement in the structuring of auditory pitch information in music (Loui, Alsop, & Schlaug, 2009; Peretz, 2016)(but see Chen et al., 2015) may provide cross-domain support for this idea. To date, only little is known about the neuroanatomical bases of sentence-level prosodic structure building. However, several findings are compatible with fronto-temporal information exchange during prosodic phrasing (Geiser, Zaehle, Jancke, & Meyer, 2008; Ischebeck, Friederici, & Alter, 2008; Strelnikov, Vorobyev, Chernigovskaya, & Medvedev, 2006)(but see den Ouden et al., 2016). Whether or not the fronto-temporal information exchange happens via a **dorsal posterior temporal to inferior frontal pathway**, as possibly suggested by our patient's performance, is an interesting topic for future research.

Irrespective of whether dorsal white matter tracts constitute building blocks for basic pitch monitoring or advanced prosodic structuring (or both in interaction), their computational characteristics may be described in terms of internal (forward) models that serve to **predict forthcoming sensory events** (here: the to-be-perceived pitch contour) on the basis of previous input (Bornkessel-Schlesewsky & Schlesewsky, 2013; Rauschecker, 2011). Notably, these predictions are likely to arise from both prosodic and non-prosodic priors—including continuity of pitch contour and prosodic phrase but also syntactic structure, as will be discussed in the following.

4.2. Posterior transcallosal pathways – syntax-prosody interface

Syntactic structure guides prosodic parsing (Buxó-Lugo & Watson, 2016; Cole et al., 2010; Cutler et al., 1997) and *vice versa* (Lehiste, 1973; Snedeker & Trueswell, 2003) and the posterior corpus callosum has been proposed as the relevant interface (Friederici et al., 2007; Sammler et al., 2010). The present task drew on this interface by violating prosodic expectancies that were established through syntactic structure (see *Methods*). The patient's sentence-level syntactic processing was arguably intact in both sessions as indicated by his unimpaired performance in the non-prosodic syntax task. Yet, online syntactic processes may have no longer triggered the build-up of prosodic expectancies because of the temporary disruption of the necessary crosstalk between syntax and prosody processing streams. This transient deficit would mark a further case for the relevance of the posterior CC for information exchange between the temporal lobes in syntax-prosody alignment.

Taken together, our patient's performance pattern may be interpreted as temporary deficit in tracking and/or predicting prosodic contour at lower and/or higher linguistic levels. Although we cannot isolate the relative contribution of intra- and inter-hemispheric fiber tracts in the present case, both the capacity of dorsal pathways to **process auditory-prosodic information in a time-sensitive manner** (Bornkessel-Schlesewsky & Schlesewsky, 2013; Frühholz & Grandjean, 2013; Kreiner & Eviatar, 2014; Rauschecker, 2011) and the role of transcallosal pathways in **interfacing prosody and syntax** may satisfy crucial requirements for prosodic parsing: the analysis *how* prosodic information evolves over time and relative to concurrent syntactic information.

4.2. Focality of edema-induced disruptions

Vasogenic edemas are extracellular edemas; they spread along white matter tracts and are assumed to temporarily disturb information flow along these tracts (Bizzi et al., 2012; Gierhan et al., 2012). It is, however, difficult to reliably estimate the extent of the affected region. First, the edema invaded the posterior CC as well as several dorsal sub-pathways, including those supporting visuo-spatial attention and relational integration (Krawczyk, 2012; Shokri-Kojori et al., 2012; C. E. Watson & Chatterjee, 2012) such as right SLF III (Thiebaut de Schotten, Dell'Acqua, et al., 2011). The latter may account for the patient's post-surgical performance increase in visuo-spatial reasoning. A second obvious concern is that space-occupying edemas may compromise not only fiber tracts but may also reduce functionality of surrounding grey matter through compression, i.e., of right parietal areas in the present study. Prevailing models of prosody perception do not typically include the parietal lobe (Brück et al., 2011; Friederici & Alter, 2004; Schirmer & Kotz, 2006; Wildgruber et al., 2006; Wildgruber, Ethofer, Grandjean, & Kreifelts, 2009; Witteman, Van Heuven, & Schiller, 2012); nevertheless, right inferior parietal activations (BA 40/7) have been occasionally reported in prosody studies (Belyk & Brown, 2014; Merrill et al., 2012) and were proposed to reflect rehearsal-based working memory processes for prosodic pitch contours (Kreitewolf et al., 2014; Perrone-Bertolotti et al., 2013). The present study cannot discriminate between neural mass effects and changes in white matter conductivity. Yet, it is notable that the recovery of prosodic deficits was accompanied by increased average FA values in those tracts that had passed through the edema before surgery. This relationship between recovered diffusivity values and recovered cognitive functions makes it likely that white matter connectivity contributed to the behavioral effects. The potential contribution of IPL to the observed effects can be probed in future studies with healthy participants by means of transcranial magnetic stimulation.

5. Conclusion

In summary, the present case study provides new insights into right dorsal and posterior transcallosal pathway functions in auditory language comprehension by demonstrating that temporary edema-induced dysfunction of right AF/SLF and posterior CC perturbs sentence-level prosody perception. The sensitivity of dorsal pathways to temporal dynamics of auditory information may constitute the decisive computational feature that provides the dorsal pathways with the capacity to track, predict and/or evaluate prosodic contour over time. Future research should look into potential divisions of labor between different dorsal sub-pathways and their interaction. Assuming functional parallels to left dorsal pathways, posterior temporal to premotor connections might be particularly suited to track pitch over time by virtue of the time-sensitivity of the motor system (Houde & Chang, 2015; Rauschecker, 2011). Posterior temporal to inferior frontal connections, in turn, might be involved in prosodic structure building by virtue of the combinatorial capacities of IFG (Friederici, 2011; Koelsch, 2005) and a linkage with non-prosodic syntactic information provided by the left hemisphere via the posterior corpus callosum (Friederici et al., 2007; Sammler et al., 2010).

6. Statement of Significance

Dorsal and ventral pathways in the left hemisphere play established roles in syntactic parsing and semantic comprehension, while pathways for linguistic prosody perception remain little explored. The present single case lesion study suggests a causal role of right dorsal pathways in prosodic structure building that further depends on the integrity of the posterior corpus callosum to interact with concurrent syntactic information.

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7. Supplementary Material

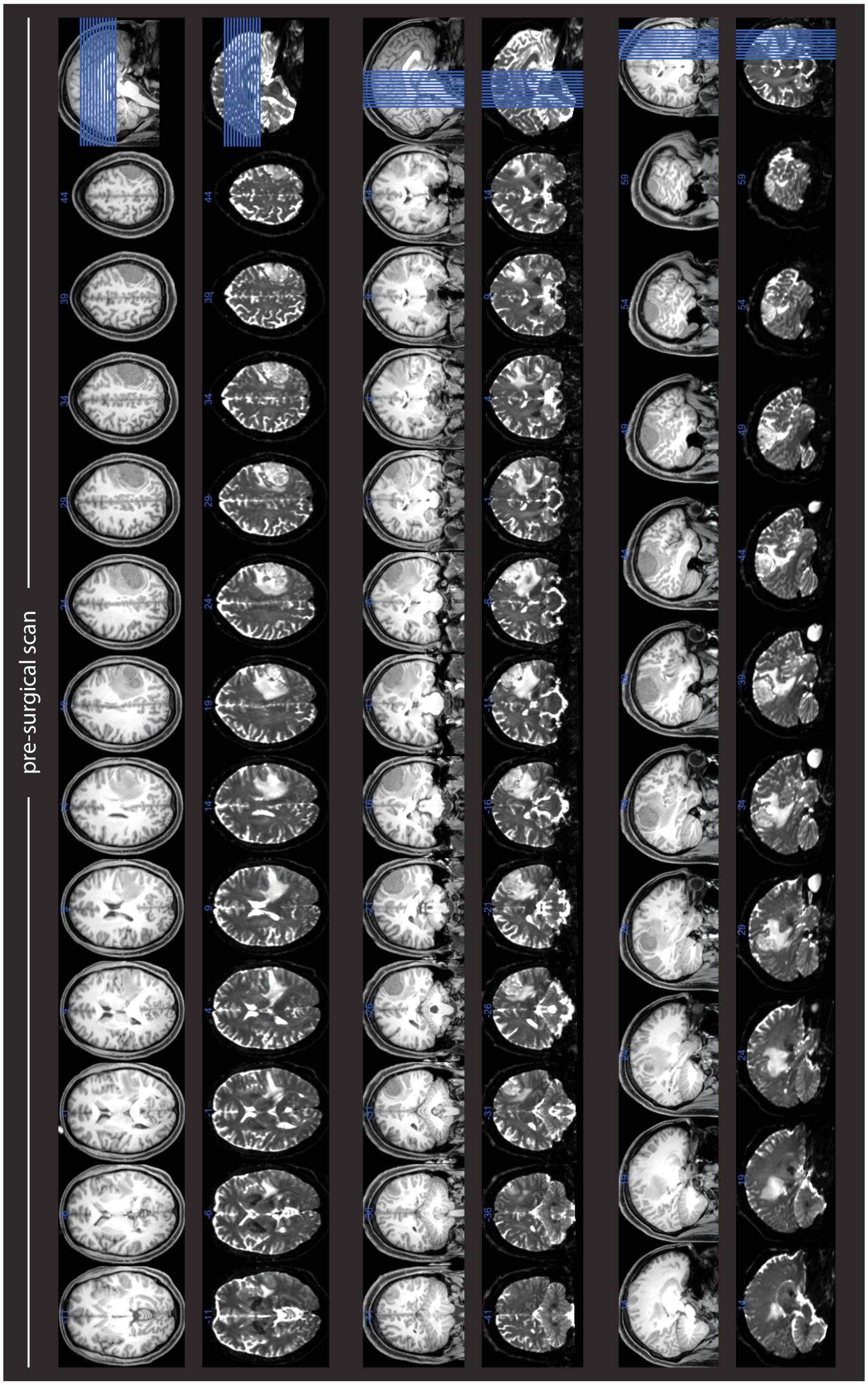
Sound 1. Stimulus example of the prosody task with congruent prosody.

Sound 2. Stimulus example of the prosody task with incongruent prosody.

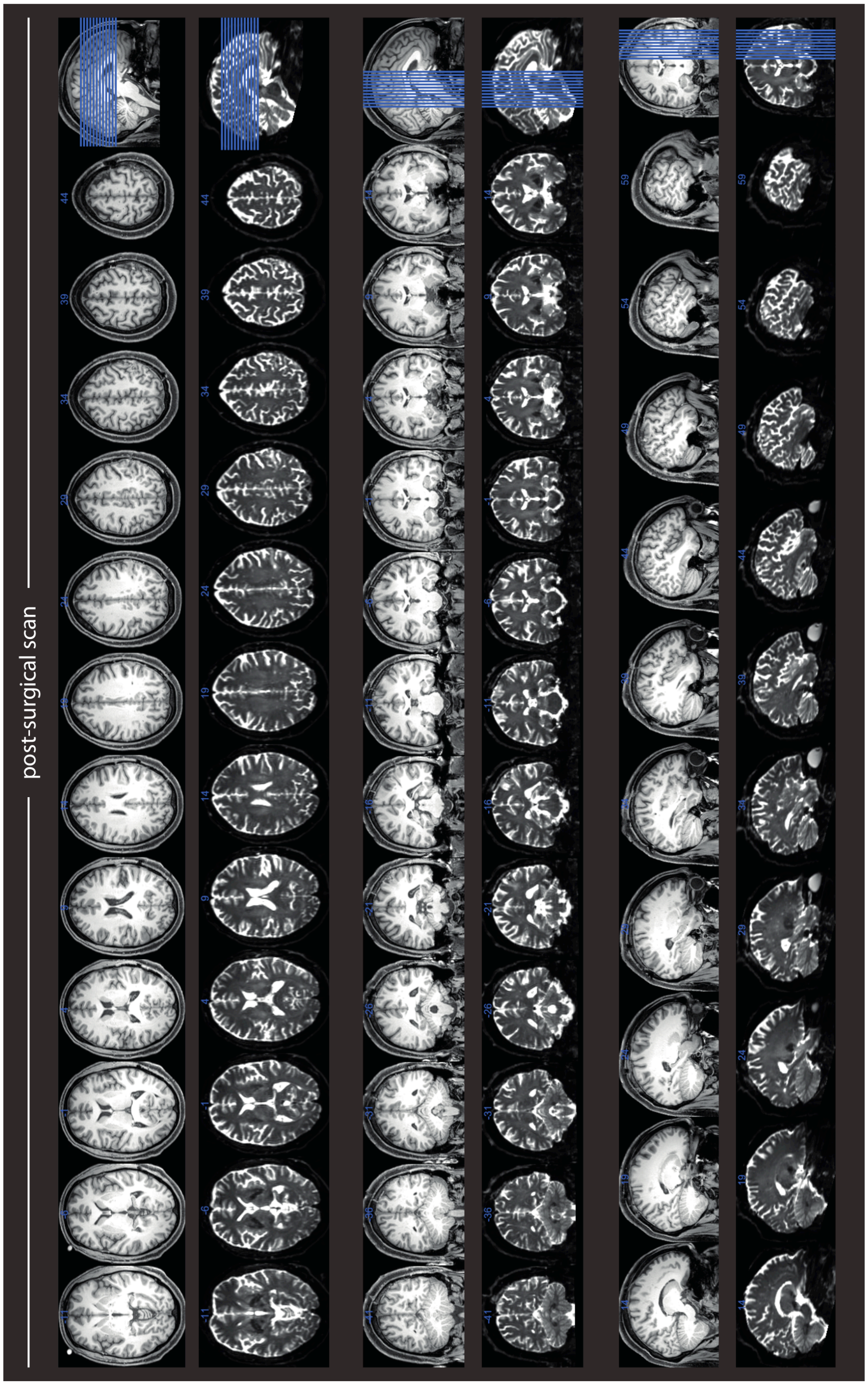
Sound 3. Stimulus example of the syntax task with S-O structure.

Sound 4. Stimulus example of the syntax task with O-S structure.

Sound 5. Example of a comprehension question in the syntax task.



Supplementary Figure 1. Multi-slice view of pre-surgical scans. Depicted are axial, coronal and sagittal views of T_1-weighted anatomical images for good visibility of the tumor (dark gray in upper lines) as well as the corresponding b0 images for good visibility of the edema (bright shadow in lower lines).



Supplementary Figure 2. Multi-slice view of post-surgical scans. Depicted are axial, coronal and sagittal views of T_1-weighted (upper lines) and b0 images (lower lines) to illustrate the precision of tumor resection and complete edema reabsorption.