The Role of Ventral Fibre Pathway in Language Production in Health and Disease

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While neuroimaging research on language production has traditionally focused primarily on grey matter, several recent studies highlight the involvement of ventral and dorsal white matter pathways. The exact functional role of these pathways is a debated issue. The ventral pathway has been suggested to underlie top-down control in language production, but the functional roles of each specific white matter tract within this pathway, like the inferior fronto-occipital fasciculus (IFOF), the inferior longitudinal fasciculus (ILF), and the uncinate fasciculus (UF), have not yet been elucidated. To investigate the involvement of these tracts in top-down control, 16 patients with primary progressive aphasia (PPA), an acquired language deficit due to neurodegenerative disease, and 22 age-matched healthy controls performed a picture-word interference task. The task elicited an interference effect, which served as a behavioural measure of the participants' top-down interference control. Furthermore, the microstructural integrity of the IFOF, the ILF, and the UF was calculated as a neuroanatomical measure with diffusion tensor magnetic resonance imaging (MRI) and tractography, based on Fractional Anisotropy (FA) and Mean Diffusivity (MD) values. A linear mixed-effects model revealed that patients were more susceptible to the interference effect in reaction time compared to controls. Moreover, the integrity of all three tracts was altered in patients compared to controls. Importantly, the integrity of the IFOF was not associated with the interference effect in reaction times or accuracy. The integrity of the ILF was associated with the interference effect in reaction times, but not accuracy. The integrity of the UF was associated with the interference effect in both reaction times and accuracy. These results indicate that patients with PPA manifest impaired top-down control processes in language production and that these processes are mediated by the microstructural properties of the inferior longitudinal fasciculus and uncinate fasciculus in both patients with PPA and healthy individuals.

Keywords: language production, ventral pathway, top-down control, tractography, primary progressive aphasia

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In its early beginnings, research on the neuroanatomy of language was restricted to one specific region, Broca's area, which was thought to be the centre of language production (Broca, 1861). It was not long until another area involved in language processing, located in the posterior part of the superior temporal gyrus, was discovered and found to be necessary for speech comprehension (Wernicke, 1874). Wernicke suggested that these areas are directly connected and damage to this connection would lead to a specific speech deficit, which he called conduction aphasia. Post-mortem dissections by Dejerine and Dejerine-Klumpke (1895) confirmed the existence of this connection and the fibre pathway was named arcuate fasciculus. This fibre pathway starts in the superior and middle temporal gyrus and arches around the Sylvian fissure to terminate in the posterior part of the inferior frontal gyrus (Catani, Jones, & ffytche, 2005; Geschwind, 1970; Glasser & Rilling, 2008). It is this tract that lies at the centre of the dorsal pathway of language processing. Historically, less attention has been paid in research to a ventral pathway of processing, which consists of a number of fibre tracts that run under the Sylvian fissure from posterior temporal to anterior temporal and frontal areas (Hickok & Poeppel, 2007; Rauschecker & Scott, 2009). The work reported in this thesis aimed to contribute to a better understanding of the role of these ventral fibre tracts in language, in particular, language production.

The dorsal-ventral pathway distinction originates from the visual processing domain, indicating two information processing streams that differ in anatomy (occipitoparietal vs. occipitotemporal), and function ('how', spatial relation vs. 'what', object recognition) (Ungerleider & Haxby, 1994). This analogy has since been extended to auditory processing (Kaas & Hackett, 1999; Rauschecker & Tian, 2000), and language in particular (Hickok & Poeppel, 2004; Hickok & Peoppel, 2007; Wise, 2003). In these theories, it is generally agreed upon that the dorsal pathway is responsible for mapping sound representations (e.g., phonemes or words) to motor representations (e.g., articulatory movements) and the ventral pathway for mapping sound to meaning (e.g., concepts) representations. Evidence supporting this dual-stream processing of language comes from a study in which participants performed an overt repetition task and a listening task (Saur et al., 2008). Results of this study showed that performance in the repetition task was associated with the dorsal stream and performance in the listening task with the ventral stream. Therefore, the authors concluded that the dorsal stream was necessary for sublexical repetition of speech and the ventral stream for comprehension. More research on the distinction between the two pathways confirms the involvement of the dorsal pathway in repetition (Fridriksson et al., 2010) and the involvement of the ventral pathway in comprehension (Harvey, Wei, Ellmore, Hamilton, & Schnur, 2013; Scott, Blank, Rosen, & Wise, 2000). These were all studies on repetition of meaningless speech or speech comprehension. However, no agreement exists on the involvement of these pathways in production of meaningful speech.

This anatomical pathway of language production (i.e., mapping meaning onto speech output representations) has been an issue of debate. Analysis of data from both healthy participants as well as patients with aphasia has yielded two different views on the issue, namely the dorsal production view and the ventral production view. The dorsal production view entails that mapping meaning onto speech output happens primarily through the arcuate fasciculus. This view has been implemented in the WEAVER++/ARC computational model (Roelofs, 2014). This model suggests the ventral pathway to have an indirect role in language production, namely a role in top-down executive control. Importantly, the model successfully accounts for research from stroke patients where damage to the arcuate fasciculus, but not to the uncinate fasciculus or extreme capsule (components of the ventral pathway), predicts impairment in language production (Marchina et al., 2011; Wang, Marchina, Norton, Wan, & Schlaug, 2013). However, this view has potentially been challenged by a study from Wilson et al. (2011), who found no effects of damage of the arcuate fasciculus on picture naming in patients of different subtypes of primary progressive aphasia (PPA). This is a neurodegenerative disease that primarily affects language processing and will be discussed in more detail below, as this patient group is of direct relevance to the current study. In the ventral production view, it is assumed that mapping meaning onto speech output primarily happens through the ventral pathway. This pathway includes the white matter tracts of the inferior fronto-occipital fasciculus (IFOF), inferior longitudinal fasciculus (ILF), uncinate fasciculus (UF), extreme capsule (EmC) and the recently described middle longitudinal fasciculus (MdLF). The ventral production view has also been implemented computationally in the Lichtheim 2 model (Ueno, Saito, Rogers, & Lambon Ralph, 2011). This model successfully simulates several findings in the aphasia literature but seems to be challenged by the finding that damage to the arcuate fasciculus, but not the uncinate fasciculus or extreme capsule, predicts impairment in language production (Marchina et al., 2011; Wang et al., 2013).

In order to measure if white matter tracts are involved in certain tasks or processes, diffusion tensor imaging (DTI) and tractography are often used. DTI is a magnetic resonance imaging (MRI) sequence that maps the diffusion of water molecules in the brain and tractography is used to visually represent 3D images of white matter tracts with a high spatial resolution (Alexander, Lee, Lazar, & Field, 2007). These techniques allow us to measure microstructural integrity of specific white matter tracts in vivo as a proxy for anatomical connectivity. The two most used indicators of microstructural integrity are fractional anisotropy (FA), the strength of diffusivity along a particular direction, and mean diffusivity (MD), the total amount of diffusion in a volume of brain tissue. Typically, higher FA and lower MD values indicate stronger connectivity. Consequently, lower FA and higher MD values could indicate a neurodegenerative disorder. Multiple patient studies using these techniques provide support for the dorsal/phonological and ventral/lexical-semantic distinction. Studies on white matter damage in the different subtypes of PPA found lower FA and higher MD in the UF and ILF in patients of the semantic variant. Interestingly, these patients showed very poor performance on a naming task compared to other subtypes and controls (Agosta et al., 2013; Galantucci et al., 2011). Two studies with stroke patients showed that the occurrence of semantic paraphasias in a picture naming task was strongly associated with loss of integrity in the left IFOF, UF and ILF (Han et al., 2013; McKinnon et al., 2018). A semantic paraphasia occurs when a participant names a word that is semantically related to the target (e.g., tiger instead of lion).

In intraoperative studies on awake patients undergoing brain surgery, direct electrical stimulation to a specific site can disrupt a particular cognitive function. This methodology has been used to investigate the regions involved in language production and has provided much knowledge on the involvement of the ventral pathway. Studies by Duffau and colleagues show that stimulation of the IFOF induced semantic paraphasias in picture naming. Importantly, stimulation of the UF, ILF and MdLF did not induce these naming disturbances (De Witt Hamer, Moritz-Gasser, Gatignol, & Duffau, 2011; Duffau et al., 2005; Duffau, Gatignol, Moritz-Gasser, & Mandonnet, 2009; Duffau, Herbet, & Moritz-Gasser, 2013; Mandonnet, Nouet, Gatignol, Capelle, & Duffau, 2007). The authors propose that there is a direct route of semantic processing that consists of the IFOF and an indirect route that consists of the UF, ILF and possibly the MdLF.

In most of the previously mentioned research, a picture naming task was used to assess the language production performance of participants. However, naming a picture constitutes of many linguistic as well as non-linguistic processes. Therefore, it is difficult to determine whether the ventral pathway is involved in mapping meaning to motor representations, which relate to processes in speech, or in more domain-general control processing. From language comprehension studies, it is known that the ventral pathway is involved in semantic control (Harvey et al., 2013; Whitney, Kirk, O'Sullivan, Lambon Ralph, & Jefferies, 2011). However, a different task than simple picture naming is necessary to investigate this for language production. The picture-word interference task proves to be a valid way to study interference and control processing in language production (Glaser & Düngelhoff, 1984).

In the picture-word interference paradigm, participants are instructed to name a picture with superimposed letter strings that could induce different effects. For example, for a picture of a dog, the superimposed text could be neutral (e.g., a string of letters, XXX), semantically related (e.g., cat), unrelated (e.g., banana) or the word of the picture itself (dog). Experiments with this paradigm show that unrelated words vs. a string of letters (lexical interference) and related vs. unrelated words (semantic interference) induce slower reaction times. These mean reaction times in turn predict the inhibitory control of the participant (Shao, Roelofs, & Meyer, 2012). Multiple picture-word interference studies have shown the ventral pathway to be associated with top-down control. For instance, in an intraoperative picture-word interference experiment, stimulation of the ventral pathway induced semantic paraphasias, causing the participants to name semantically related words instead of the target (Ries et al., 2019). In a picture-word interference experiment with patients with lesions in the left prefrontal cortex, a lexical interference effect was found (Piai, Ries, & Swick, 2015). Furthermore, a semantic interference effect was found in the prefrontal cortex in an fMRI experiment (de Zubicaray, Wilson, McMahon, & Muthiah, 2001). Importantly, the prefrontal cortex is a termination site for the ventral pathway (Catani & Thiebaut de Schotten, 2008; Forkel et al., 2014; Sarubbo, De Benedictis, Maldonado, Basso, & Duffau, 2013). This could indicate that the ventral pathway is involved in the top-down resolution of these interference effects.

As previously mentioned, the dorsal and ventral production views describe different views on which pathway is involved language production. Hence these views differ in the function of the ventral pathway in language production. In the dorsal view, it is only involved in top-down cognitive control and in the ventral view, it is involved in mapping meaning to speech output. It makes sense to hypothesize that top-down control processes are involved in language production, because word planning in language production requires attention (Roelofs & Piai, 2011). The fact that the lateral prefrontal cortex is associated with executive function and control (Petrides, 2005) makes a good case to consider that IFOF is involved in control processes in language, supporting the dorsal production view.

More research on the ventral pathway and its role in top-down control comes from non-linguistic pathologies that show a clear deficit in inhibition and interference control. For obsessive-compulsive disorder (OCD), lower FA values were consistently found in bilateral IFOF and also correlated with symptom severity and neuropsychological performance (Garibotto et al., 2010; Li et al., 2014; Peng et al., 2012). Interestingly, OCD patients show decreased response inhibition and Stroop task performance (Abramovitch, McCormack, Brunner, Johnson, & Wofford, 2019; Gruner & Pittenger, 2017; Shin, Lee, Kim, & Kwon, 2014). Moreover, schizophrenia patients show consistently lower FA in left IFOF and ILF, with severity of disorder being related to IFOF and disorganised factor to ILF integrity (Cheung et al., 2008; Epstein et al., 2014; Koch et al., 2010; Rigucci et al., 2013; Yao et al., 2013). In this disorder, a deficit in selective attention and inhibitory processes and an increased interference effect in the Stroop task are found as well (Boucart, Mobarek, Cuervo, & Danion, 1999; Henik & Salo, 2004; Westerhausen, Kompus, & Hugdahl, 2011). Also, for attention hyperactivity deficit disorder (ADHD), one study found lower FA in left ILF and higher MD in left IFOF, with attentional performance negatively related to MD in left ILF (Konrad et al., 2012). For adults with ADHD that were more inattentive, lower FA values were found in bilateral IFOF and left UF (Shaw et al., 2015). In a meta-analysis, ADHD patients of all age groups showed lower interference control than healthy controls (Lansbergen, Kenemans, & Van Engeland, 2007). This multidisciplinary research shows that the ventral pathway, and the IFOF in particular, is involved in top-down control. The question remains, however, if this is also the case in language production.

Comparing a patient group with language deficits and altered tract integrity to a healthy population enables the investigation of white matter tracts and their involvement in language production in health and disease. This comparison is possible with patients of primary progressive aphasia (PPA), as it is a neurodegenerative disease characterised by speech and language deficits and relatively spared other cognitive domains (Mesulam, 1982). This makes the comparison between healthy controls and patients with PPA of different subtypes suitable to investigate certain questions about language production. Moreover, the picture-word interference effect has not been investigated in patients with PPA. Therefore, the current study provides a novel approach by investigating top-down control in language production in patients with PPA. The three subtypes of PPA can be described by the differences in their main deficits. Logopenic PPA is characterised by deficits in word retrieval and sentence repetition, nonfluent (or agrammatic) PPA by agrammatism and effortful, slow speech, and semantic PPA (or semantic dementia) by deficits in naming and single-word comprehension (Gorno-Tempini et al., 2011). Interestingly, significant differences in white matter integrity have been found in patients with PPA and identified even in the different subtypes. Damage of the UF and ILF has been found to be different in patients with PPA and controls (D’Anna et al., 2016). Moreover, a study on the white matter damage in the subtypes of PPA shows that the behavioural symptoms converge with the areas in which tracts are damaged (Galantucci et al., 2011). In the nonfluent variant, changes in DTI metrics were mostly found in dorsal tracts. In the semantic variant, these changes were found in the UF and ILF. Lastly, for the logopenic variant, no difference in metrics of entire tracts was observed, but FA and diffusivity changes were found in the left temporoparietal region of the dorsal pathway. The possibility to measure differences in white matter structure in PPA and its subtypes combined with isolated language deficits make PPA a relevant disorder to measure language production and white matter changes.

Aim and approach

From the existing literature and research on language production and white matter pathways, several questions remain unresolved, which we aim to answer. First, the current study investigates whether the ventral white matter pathway is involved in meaning-to-motor mapping or top-down control in language production. This will provide evidence for either the dorsal or the ventral production view. Secondly, a picture-word interference task performed by patients with PPA and age-matched healthy controls with a regular naming and interference condition will allow us to assess the amount of top-down control. With this task, we will be able to investigate if patients with PPA have damaged top-down interference control in language processing behaviourally, which is not known from the literature. Because of their language processing deficits, we expect patients with PPA to perform worse than controls. Lastly, research is inconclusive about which specific tracts in the ventral pathway could underlie language production. Intraoperative studies are effective in showing a causal relationship, but the methods have a low spatial sampling. Therefore, the present study will use DTI and probabilistic tractography to measure the microstructural differences in the three main tracts in the ventral pathway, namely the IFOF, ILF and UF. Finally, with this approach, we will be able to determine which specific tracts underlie top-down interference control in language processing in healthy individuals and patients with PPA. We expect to see a correlation between tract integrity and top-down control in the IFOF and UF but not ILF in both groups because of the literature on top-down control and the fact that these tracts connect frontal (control) and temporal (semantic) areas. This study will deepen the understanding of the neurobiology of language and control. The findings on patients with PPA, their interference control, and the involvement of the ventral pathway could also aid in the diagnosis of PPA.

Method

Participants

Sixteen patients with PPA (mean age = 70.0, eight females) were recruited from multiple hospitals in the Netherlands, including Radboud University Medical Centre (Nijmegen), Erasmus Medical Centre (Rotterdam) and Jeroen Bosch Hospital ('s-Hertogenbosch). Clinical diagnoses were established based on extensive assessment, including neuropsychological testing and neurological tests. These tests consisted of neuroimaging and, when available, liquor diagnostics. Among the patients with PPA were six of the logopenic variant, two of the non-fluent variant, and eight of the semantic variant (semantic dementia). Twenty-two controls (mean age = 67.1, seven females) participated. Their age was not significantly different from that of the patients. All participants were right-handed and native Dutch speakers. All patients were tested with the approval of the local ethics committee (CMO Arnhem-Nijmegen, CMO 2016-2340, NL56842.091.16) and healthy controls were tested with the approval of the local ethics committee (CMO Arnhem-Nijmegen) under the general ethics approval ("Imaging Human Cognition", CMO 2014/288). All participants gave their written consent before participation.

Task and materials

A picture-word interference task was used to measure the participants' top-down control processes recruited to resolve the interference in the task. Twelve pictures divided over two semantic categories (animals and fruit) were used as stimuli. On each picture, words were superimposed as distractors. In the neutral condition, a number of X's was superimposed on the picture. In the incongruent condition, the distractor words were picture names from the same semantic category as the picture (e.g., a picture of a banana with the word kiwi printed on top). In Figure 1, an example trial is shown. All the distractor words were part of the response set of the experiment. Both conditions consisted of 60 items, with the incongruent condition including each picture with all other picture names of the same category as distractor words. Stimuli were randomised with the following constraints: stimulus cannot be shown twice in a row, distractor cannot be shown twice in a row, a maximum of four items of the same category can be shown in a row. Each participant received a different order of stimuli.

Procedure

Stimuli were presented in six blocks of twenty items using Presentation software (http://nbs.neurobs.com). The pictures appeared in the centre of a screen with a white background for 4000 ms. In-between trials, a blank screen was presented for 1000 ms. Responses were recorded for the purpose of determining accuracy and response time.

First, participants completed twelve practice trials, after which they were allowed to ask clarification questions about the experiment. The instruction for the experiment was to name the picture as fast as possible and ignore the superimposed word.

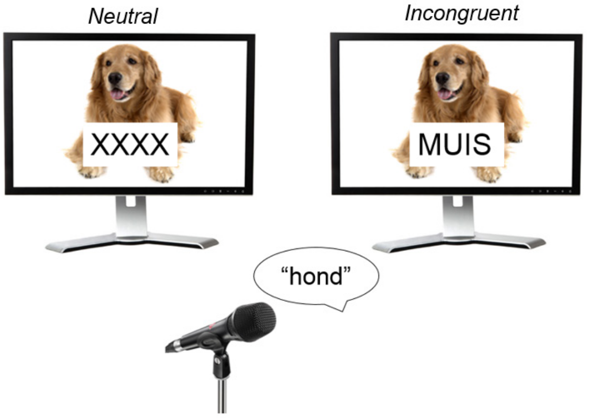

Figure 1. Example of a trial in the two conditions of the picture-word interference task.

Image acquisition

Structural and diffusion-weighted images were acquired in a single session from all participants using a Siemens Prisma Fit 3T scanner and a 32-channel head coil at the Donders Centre for Cognitive Neuroimaging, Nijmegen.

Diffusion weighted images were acquired with a simultaneous-multislice diffusion-weighted Echo Planar Imaging (EPI) sequence. Acquisition parameters were the following: multiband factor = 3; TR (repetition time) = 2282 ms; TE (echo time) = 71.2 ms; in-plane acceleration factor = 2; voxel size = 2×2×2 mm3; 9 unweighted scans; b-values = 1250 and 2500 s/mm2; 100 diffusion-encoding gradient directions in multiple shells for both b-values; Taq (total acquisition time) = 8 min 29 s.

Anatomical scans were acquired for accurate localization of anatomical structures in the tractography procedure, using the MP2Rage sequence (Marques et al., 2010). The following parameters were used: 176 slices; voxel size = 1×1×1 mm^3; TR = 6000 ms; TE = 2.34 ms; Taq = 7 min 32 s.

DTI analysis

Preprocessing

Diffusion MR images were realigned and corrected for eddy-current induced distortion with SPM12 (Penny, Friston, Ashburner, Kiebel, & Nichols, 2006). Furthermore, brain extraction and correction for artefacts resulting from head/cardiac motion was performed with the PATCH algorithm (Zwiers, 2010). The diffusion tensor model was fitted at each voxel with weighted least-squares regression in DTIFIT from the FMRIB Diffusion Toolbox (FDT) to produce maps of DTI measures such as FA and MD, as well as the eigenvectors and eigenvalues.

Tractography

To model for crossing fibres, the distribution of diffusion parameters was estimated with a multi-shell generalised ball-and-sticks model at each voxel using BedpostX (Jbabdi, Sotiropoulos, Savio, Grana, & Behrens, 2012). We only included the tracts in the left hemisphere because of the strong lateralisation of the language system in the brain. For reconstructing the UF and ILF tracts, TRActs Constrained by UnderLying Anatomy (TRACULA) from Freesurfer was used, which is an automated global probabilistic tractography method (Yendiki et al., 2011). It uses prior anatomical information about the tracts derived from training subjects of which 18 white matter tracts were manually labelled. The output represents a probabilistic distribution of the reconstruction of each tract, of which we used the reconstruction of the UF and ILF. The tractography algorithm of TRACULA with its inclusion of prior anatomical information fits the research question at hand very well since we are looking for known tracts. The IFOF was not included in the tracts that are defined in TRACULA. Therefore, probabilistic tractography was performed with Probtrackx for this tract (Behrens et al., 2003; Behrens, Johansen-Berg, Jbabdi, Rushworth, &Woolrich, 2007). In this algorithm, the probability distribution of streamlines is estimated, starting from the seed mask and ending in a termination mask, not having been rejected by exclusion masks. All seeds were drawn in native diffusion space to maximise anatomical accuracy for each participant. For the IFOF, two seeds were drawn, one localised in the frontal and one in the occipital lobe. The frontal seed was defined as a rectangle over the entire left hemisphere on the coronal slice a few slices anteriorly to the corpus callosum. The occipital seed was defined as a rectangle over the left cerebrum on the coronal slice approximately five slices posteriorly to the curve of the arcuate fasciculus. Exclusion masks were added to constrain the fibre tracking to the relevant tract and to prevent the algorithm from including neighbouring tracts. After creating the masks, fibre tracking was performed with 10000 streamline samples initiated from all voxels within the seed mask, a curvature threshold of 0.2 and a step length of 0.5 mm. The output of fibre tracking, a probability distribution of the reconstruction of the tract, was then normalised by log transforming and dividing by the maximum value. This was done to control for the size of the seed mask. Tracking was done in two directions, from seed to waypoint mask and the other way around. After that, the average of the two connectivity maps was calculated. This was done because the tracking procedure favours voxels close to the seed mask. The distributions were then thresholded to exclude spurious connections and noise. The connectivity maps can be seen in Figure 2.

For all three tracts, a mask was created from the connectivity map and used to derive the FA and MD from these images.

Statistical analysis

Analyses were performed on both reaction times (RT) and accuracy of the recorded responses. RTs were manually assessed using Praat software (Boersma & Weenink, 2019). For the RT analyses, the median RT of responses was used because very long RTs are expected for the patients with severe language impairment, and the median is more robust to outliers and a skewed distribution than the mean. Responses that were defined as errors included hesitations, semantic and phonological paraphasias, naming the distractor word and no response. Accurate responses where the target word was preceded by an article or when the RT was otherwise not reliable were not included in the RT analysis.

Statistical analyses were performed with R version 3.5.0 (R Core Team, 2016), using the lme4 package for its linear mixed-effects models (Bates et al., 2019).

To test for behavioural differences in RT and accuracy between patients and controls as well as between conditions, two linear mixed-effects models were used. For both models, group (controls, patients), condition (incongruent, neutral), and interaction between group and condition were fixed effects. A main effect of condition served as a measure of the interference effect. Random effects of condition by participant and a random intercept for item were also included.

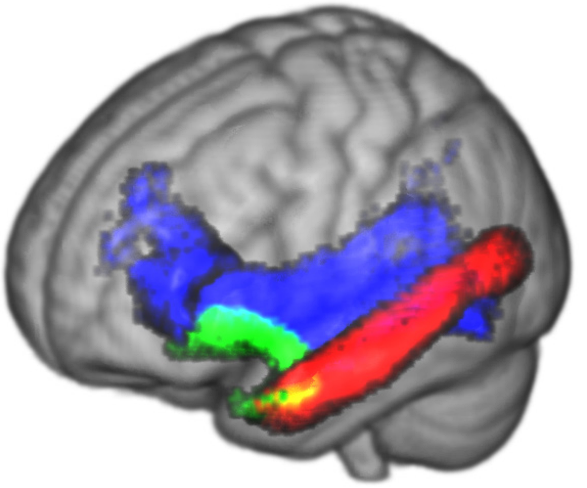

Figure 2. Tractography results of all three ventral tracts. The tracts represent the mean tracts of all participants. Green indicates the UF. Blue indicates the IFOF. Red indicates the ILF. The results are displayed on a 3D 2 mm3 template in the Montreal Neurological Institute standard space.

Furthermore, the differences in FA and MD of all three tracts were analysed between controls and patients. FA is the most widely used measure in DTI research and is shown to be altered in neurodegenerative diseases (Galantucci et al., 2011). We felt it was important to include MD as well, as it reflects additional information about white matter properties over the information that merely FA can show (Alexander et al., 2011; Alexander, Lee, Lazar, & Field, 2007). These analyses were performed with Kruskal-Wallis tests, which do not assume normality. This test was chosen because of our small sample size and the fact that the dependent variables (FA and MD) are not normally distributed.

To assess whether the differences in RT and accuracy between conditions are influenced by the integrity of the three ventral tracts, linear mixed-effects models were used. However, FA and MD of each white matter tract turned out to be very collinear (Spearman's $\varrho < -0.6$ for all tracts). In many cases, the best way to control for high collinearity would be to simply remove one of the collinear variables from the analysis. Yet, we believe that the two measures provide important complementary information about the biological properties of the white matter. Therefore, we decided to perform a principal component analysis (PCA) using the psych package in R (Revelle, 2019). In a model with variables that may be correlated, a PCA is able to produce the underlying component that accounts for the largest amount of variability in the model. A PCA with two factors was performed on the FA and MD of each tract and the first component of the analysis, the one which explains the most variance, was used as a comprehensive measure of white matter integrity.

The PCAs showed that for all tracts two components explain 100% of the variance in FA and MD. Component 1 (C1) explained 83% in the IFOF, 78% in the UF, and 88% in the ILF and component 2 (C2) explained the other 17% in the IFOF, 22% in the UF, and 12% in the ILF. The loadings of the dependent variables for C1 were 0.91 for FA and -0.91 for MD in the IFOF, 0.88 for FA and -0.88 for MD in the UF, and 0.94 for FA and -0.94 for MD in the ILF. For C2, the loadings were 0.41 for both FA and MD in the IFOF, 0.47 in the UF, and 0.35 in the ILF. Because of the negative relationship between FA and MD and the fact that C1 accounts for a very large part of the variance, this component was used for the following linear mixed-effects models for all tracts.

For the linear mixed-effects models, C1, condition and the interaction between C1 and condition were included as fixed effects. A random intercept for participant was also included.

To measure goodness of fit, we compared these models with an ANOVA to the same models without fixed effects. Lastly, additional linear-mixed effects models with the same variables and effects were used on a subset of the data, indexing the specific groups. This was done to investigate the effect of integrity of the tracts on the interference effect for the two groups separately.

Results

Interference effect

In the picture-word interference task, patients with PPA responded slower than controls (β = 0.37, SE = 7.4 x 10-2, t[36] = 4.97, p < .001, Fig. 3A). Moreover, all participants responded slower in the incongruent condition compared to the neutral condition (i.e., the interference effect) (β = 0.14, SE = 1.9 x 10-2, t[30] = 7.07, p < .001). There was also an interaction of group and condition (β = 0.11, SE = 3.1 x 10-2, t[33] = 3.66, p < .001, Fig. 3B).

Regarding the accuracy rates, patients also made more errors than controls (β = -3.58, SE = 0.60, z = -5.94, p < .001, Fig. 3C). More errors were made in the incongruent condition than in the neutral condition for all participants (β = -1.61, SE = 0.53, z = -3.01, p = .003). However, there was no interaction of group and condition for accuracy rates (β = 0.77, SE = 0.54, z = 1.41, p = .16, Fig. 3D).

White matter integrity

Patients with PPA showed a highly decreased FA compared to controls for the UF (χ^2[1, N = 38] = 872.42, p < .001), IFOF (χ^2[1, N = 38] = 371.10, p < .001), and ILF (χ^2[1, N = 38] = 2327.40, p < .001). Likewise, patients with PPA showed a highly increased MD compared to controls for the UF (χ^2[1, N = 38] = 872.80, p < .001), IFOF (χ^2[1, N = 38] = 635.14, p < .001), and ILF (χ^2[1, N = 38] = 1077.90, p < .001). Figure 4 shows the differences between groups for all tracts.

White matter integrity and interference effect

IFOF

For the IFOF, the linear mixed-effects model did not show a main effect of tract integrity on RT (β = -9.6 x 10-2, SE = 5.0 x 10-2, t[32] = -1.90, p = .07). There was also no significant interaction between condition and tract integrity on RT (β = -1.0 x 10-2,

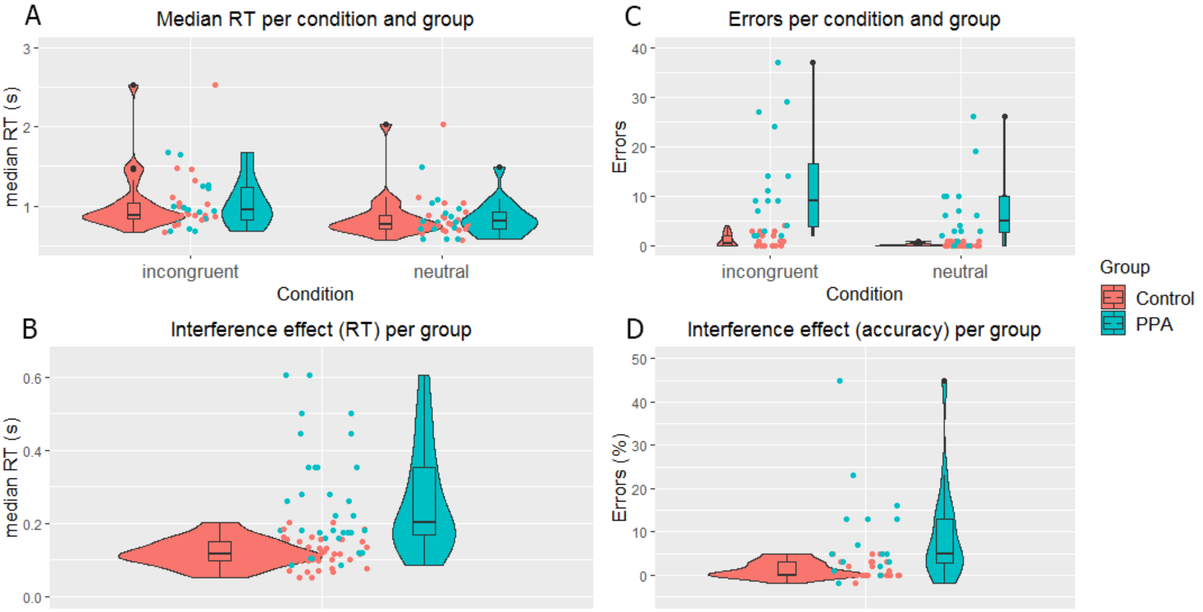

Figure 3. Behavioural results of the picture-word interference task. A. Median reaction times for each condition and group. B. Interference effect in reaction time for each group. C. Error rates for each condition and group. D. Interference effect in error percentage for each group.

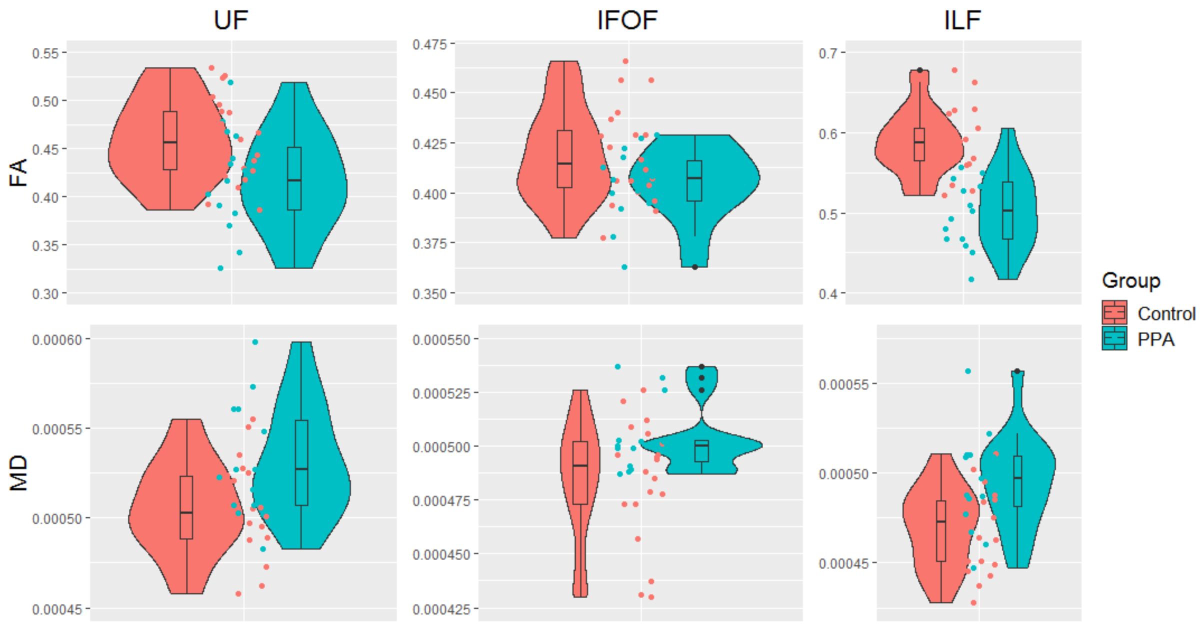

Figure 4. Differences in white matter integrity between patients of PPA and healthy controls. Top row: Differences in FA values. Bottom row: Differences in MD values. Left column: Differences in UF metrics. Middle column: Differences in IFOF metrics. Right column: Differences in ILF metrics.

SE = 8.0 x 10-3, t[3750] = -1.19, p = .23, Fig. 5AB). The generalised linear mixed-effects model also did not show a main effect of tract integrity on accuracy rates (β = 0.49, SE = 0.37, z = 1.35, p = .18). There was also no significant interaction between condition and tract integrity on accuracy rates (β = 0.11, SE = 0.19, z = 0.59, p = .56, Fig. 5CD). Figure 6 displays the relationships between tract integrity of all three tracts as measured by FA and MD and performance in the two conditions.

These results show that the integrity of the IFOF is not associated with performance in picture naming or the interference effect for both RT and accuracy.

UF

For the UF, the linear mixed-effects model did not show a main effect of tract integrity on RT (β = -9.6 x 10-2, SE = 5.3 x 10-2, t[33] = -1.81, p = .08). There was, however, a significant interaction between condition and tract integrity on RT (β = -2.0 x 10-2, SE = 9.0 x 10-3, t[3813] = -2.28, p = 2.3 x 10-2, Fig. 5AB). The generalised linear mixed-effects model showed a main effect of tract integrity on accuracy rates (β = 1.00, SE = 0.34, z = 2.91, p = .004). Moreover, there was a significant interaction between condition and tract integrity on accuracy rates (β = -0.31, SE = 0.15, z = -2.00, p = .046, Fig. 5CD).

So, the tract integrity of the UF is associated with performance in picture naming in accuracy rates, but not in RT. Furthermore, for both accuracy and RT the integrity of the UF is associated with the interference effect.

ILF

For the ILF, the linear mixed-effects model showed a main effect of tract integrity on RT (β = -0.14, SE = 4.6 x 10-2, t[35] = -3.07, p = .004). There was also a significant interaction between condition and tract integrity on RT (β = -3.4 x 10-2, SE = 8.4 x 10-3, t[4039] = -4.09, p < .001, Fig. 5AB). The generalised linear mixed-effects model also showed a main effect of tract integrity on accuracy rates (β = 1.27, SE = 0.32, z = 3.94, p < .001). However, there was no significant interaction between condition and tract integrity on accuracy rates (β = -0.20, SE = 0.18, z = -1.10, p = .27, Fig. 5CD).

This means that for both RT and accuracy the integrity of the ILF was associated with performance in picture naming. Furthermore, for RT but not for accuracy the integrity of the ILF was associated with the interference effect.

Model fit

The ANOVAs for the linear mixed-effects models for RT (χ^2 [3, N = 2] = 407.74, p < .001) and accuracy (χ^2 [3, N = 2] = 56.93, p < .001) and IFOF integrity, RT (χ^2 [3, N = 2] = 395.31, p < .001) and accuracy (χ^2 [3, N = 2] = 56.05, p < .001) and UF integrity, and RT (χ^2 [3, N = 2] = 442.15, p < .001) and accuracy (χ^2 [3, N = 2] = 64.65, p < .001)

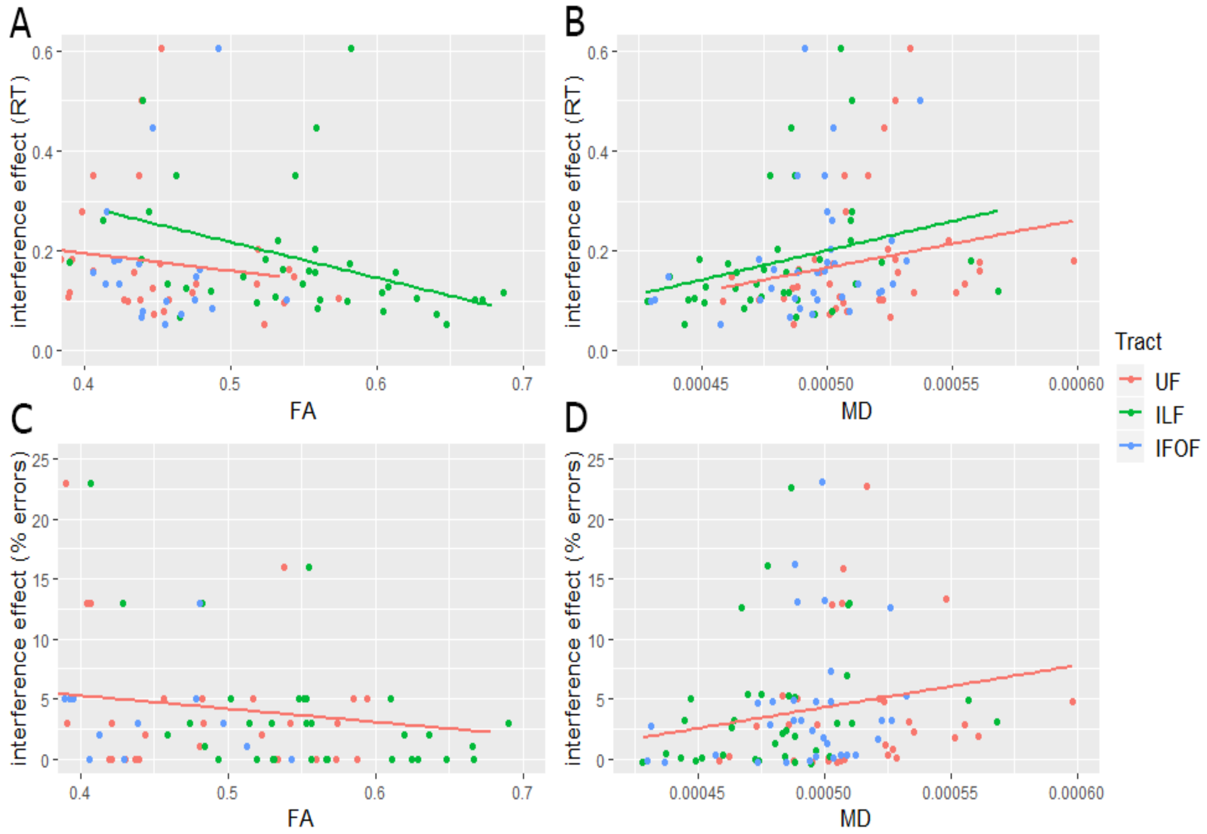

Figure 5. Relationship between tract integrity and the interference effect for all three ventral tracts. A. Relationship between fractional anisotropy (FA) and reaction time (RT). B. Relationship between mean diffusivity (MD) and reaction time (RT). C. Relationship between fractional anisotropy (FA) and error rates. D. Relationship between mean diffusivity (MD) and error rates. Regression lines show significant associations between tract integrity (as measured by the first component of the performed PCA) and the interference effect. Non-significant associations are not displayed as regression lines.

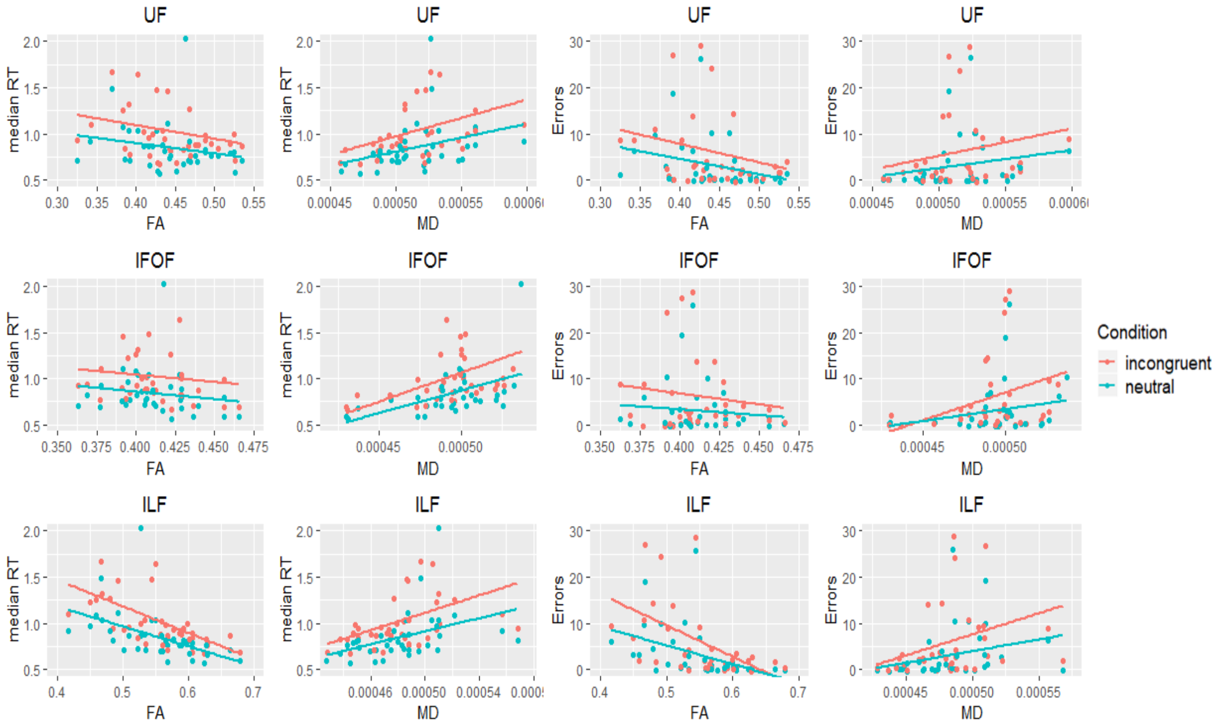

Figure 6. Relationships between tract integrity and performance in both conditions of the picture-word interference task. Left six panels: Results for median RT. Right six panels: Results for error rates.

and ILF integrity all showed that the fixed effects are justified and explain more of the variance in the data.

White matter integrity and interference effect within groups

From the separate analyses of the effect of tract integrity on the interference effect within the patient and control groups, almost all of them did not show an effect. The integrity of the IFOF in controls was related to picture naming in RT (β = -5.1 x 10-2, SE = 1.9 x 10-2, t[18] = -2.64, p = .02). Moreover, the integrity of the UF in controls was related to the interference effect in RT (β = 1.7 x 10-2, SE = 7.9 x 10-3, t[2580] = 2.21, p = .03). All other analyses did not show an effect.

Discussion

This study is the first to investigate the interference effect in a picture-word inference task in patients with PPA as a proxy for top-down control. Moreover, it is novel in linking this interference effect to the integrity of white matter tracts. The effect of tract integrity on top-down control was also assessed within the two groups, patients with PPA and healthy individuals.

Our results show that patients with PPA respond slower and less accurately than healthy controls in both conditions of the picture-word interference task. Moreover, the interference effect (i.e., difference in performance between the two conditions) is larger in patients with PPA than in healthy controls. In the comparison of integrity of the ventral white matter tracts between groups, we find that the integrity of all three tracts is lower in patients with PPA than in controls. Our results also show that the UF and ILF, but not the IFOF, are associated with picture naming and the interference effect in the whole sample. When these effects are investigated within groups, the relationship between integrity of the IFOF and picture naming in RT and the integrity of the UF and the interference effect in RT are observed only for controls.

Our finding that patients with PPA are slower and make more errors in picture naming is in line with the PPA pathology. This goes for the logopenic and semantic variant in particular, showing deficits in naming (Gorno-Tempini et al., 2011). The interference effect of the picture-word interference task is also corroborated (Glaser & Düngelhoff, 1984). All participants responded slower and made more errors in the incongruent condition than in the neutral condition. A novel finding from this study is the fact that the interference effect was larger in patients with PPA than in healthy controls. Inhibitory control in patients with PPA has not been studied in an experiment with a specific task manipulation before. In the Stroop task, patients with semantic dementia have been found to perform worse in one study, while another study only found these effects for nonfluent PPA, and not semantic dementia (Desgranges et al., 2007; Heidler-Gary et al., 2007). Interestingly, lack of inhibitory control can be seen in the disinhibition in behaviour in the behavioural variant of frontotemporal dementia (Brun et al., 1994). The other subtypes of frontotemporal dementia are the three PPA variants (Chare et al., 2014). Symptoms of the behavioural variant can often be seen in patients with PPA when their disorder has progressed into a later stage, particularly in semantic dementia. This suggests that the degeneration of the frontotemporal network results in impairment in inhibitory control in both language and behaviour.

The comparison of the integrity of the ventral tracts between patients with PPA and healthy controls showed that for patients with PPA in all three tracts the FA was decreased and the MD increased. These results are in line with previous findings on the altered integrity of the ILF and the UF in subtypes of PPA (Agosta et al., 2013; Galantucci et al., 2011). A new finding of this study is the degeneration of the IFOF in patients with PPA, which is seen in both FA and MD values.

No association was found between the integrity of the IFOF and picture naming or the interference effect. This is surprising, as the IFOF has been implicated to play a role in picture naming (Han et al., 2013; Harvey & Schnur, 2015). Furthermore, several studies have found an association between semantic control and the IFOF (Harvey & Schnur, 2015; Nugiel, Alm, & Olson, 2016). Our findings are also different from the findings obtained by Duffau and colleagues using electrostimulation during intraoperative surgery, who found consistent involvement of the IFOF in picture naming (Duffau et al., 2005; Duffau et al., 2009; Moritz-Gasser, Herbet, & Duffau, 2013). A limitation of these awake studies, however, is that their anatomical precision is not optimal due to "brain shifting" after tumour removal (Bello et al., 2010). Additionally, the white matter fibres of IFOF and ILF run closely next to each other through the occipital and up until the anterior temporal lobe (Catani & Thiebaut de Schotten, 2008). Therefore, this method may not be ideal to delineate them accurately. To that end, tractography is a more reliable method. However, as discussed later, we had to use the Probtrackx rather than the TRACULA algorithm for the IFOF, which makes use of different methods and types of information to reconstruct white matter tracts. This presumably reduced the quality of the tractography for the IFOF, which may explain the absence of a correlation with picture naming.

For the UF (using TRACULA), we find an association between the tract integrity and picture naming for accuracy but not for RT across conditions. This is consistent with some studies, linking the UF to processing semantics and specific semantic categories in picture naming (Han et al., 2013; Papagno et al., 2011). These effects could reflect the process of mapping semantic to motor representations, as held by the ventral production view and computationally implemented in the Lichtheim 2 model (Ueno et al., 2011). However, other studies that use a simple picture naming task, such as the Boston Naming Test, do not find an effect of the integrity of the UF on picture naming (Marchina et al., 2011; Wang et al., 2013). This is different from our findings, but our task includes superimposed letter strings in both conditions. In both of these conditions, top-down control is recruited, although more in the incongruent condition than in the neutral condition. No top-down control is necessary in simple picture naming. Therefore, this difference in naming paradigm (i.e., picture-word interference vs. plain picture naming) could explain why we obtained an effect for the UF (i.e., top-down control was required in our study) and others did not (where top-down control was required less or not at all). If the UF maps meaning onto articulation in picture naming (as the ventral pathway view maintains), then the difference between our results and those of Marchina et al. (2011) and Wang et al. (2013) remain unexplained. However, if the UF underpins top-down control in picture naming, then the difference in results is readily explained (i.e., the difference is due to differential requirement of top-down control).

Supporting the view that the UF mediates top-down control in picture naming is our finding that the integrity of the UF is associated with the magnitude of the interference effect for both accuracy and RT. This finding provides direct evidence that the UF is involved in top-down control rather than meaning-to-motor mapping. This is in line with the WEAVER++/ARC model of Roelofs (2014) and the literature on the ventral pathway connecting the left inferior frontal gyrus as a source of top-down control on semantic information within the anterior temporal lobe (Badre, Poldrack, Pare-Blagoev, Insler, & Wagner, 2005; Badre & Wagner, 2007; Barredo, Verstynen, & Badre, 2016; Bedny, McGill, & Thompson-Schill, 2008; Novick, Trueswell, & Thompson-Schill, 2010; Roelofs, 2014; Thompson-Schill, D'Esposito, Aguirre, & Farah, 1997). These findings are also in line with research showing involvement of the arcuate fasciculus but not of the ventral tracts in simple picture naming (Marchina et al., 2011; Wang et al., 2013). As indicated, the picture-word interference task requires top-down control and relies on the contribution of the ventral tracts, while simple picture naming, investigated by Marchina et al. and Wang et al., does not. Summarizing, our findings provide a strong case for the dorsal production view, where meaning-to-motor mapping happens through the dorsal pathway, while top-down influences are relayed by the ventral pathway, most likely the UF.

A strong association of the integrity of the ILF can be seen in picture naming for accuracy and RT. This tract has been described as being part of the ventral visual stream (Ungerleider & Haxby, 1994). Lesions in the tract are associated with impairments in visual object recognition (Shinoura et al., 2010). Anatomically, this makes sense, as the ILF connects visual (occipital) areas with conceptual (ATL) areas. Therefore, decreased integrity of the ILF can lead to impaired picture recognition, which could lead to slower or incorrect responses. Apart from object recognition, the ILF has also been proposed as a central tract in lexical retrieval in picture naming by Herbet et al. (2016). However, the ILF is strongly connected with the medial temporal gyrus (MTG) through U-shaped fibres along the tract and the MTG is a crucial area for lexical retrieval in picture naming (Catani, Jones, Donato, & Ffytche, 2003; Indefrey & Levelt, 2004). Therefore, the effects of the ILF ascribed by Herbet et al. (2016) to lexical retrieval processes actually originate from a later process in picture naming, namely lexical retrieval mediated by the MTG. Herbet et al. used phonological cueing in their picture naming task. If a patient could not name a picture (e.g., a poodle), a phonological cue was given (e.g., the initial phoneme /p/), which helped retrieving the picture name. According to Herbet et al., this cueing effect demonstrates that the ILF mediates lexical retrieval. However, if damage to the ILF leads to poor object recognition (e.g., it is unclear for the patient whether the object is a poodle or a horse), the retrieval of the picture name mediated by the MTG may be helped by a phonological cue (i.e., /p/). Thus, there is no need to assume that the ILF is directly underpinning word retrieval, as Herbet et al. do, but problems in object recognition due to low integrity of the ILF may propagate into the later stage of word retrieval, mediated by the MTG.

A surprising finding of our study is that the interference effect is associated with the integrity of the ILF in RT, but not in accuracy. While the study by Nugiel et al. (2016) relates the ILF to semantic control with a verb generation task, previous research generally does not provide much support for the idea that the ILF is involved in top-down control in language production. Considering the areas the ILF connects to and the type of information it passes on, one would not assume the ILF to be involved in control processes. What might cause this effect is the possibility that the integrity of the ILF could impair object recognition and in turn affect lexical retrieval, which is more difficult in the incongruent than in the neutral condition of the picture-word interference task. It is important to note that the research on the functional role of the ILF is very limited. Thus, by putting these findings into perspective, future studies on lesions, neurodegeneration, and tractography of the ILF will be able to tell us more about the role of the ILF in top-down control.

Differences between healthy and degenerated white matter tracts in the ventral pathway and their influence on picture naming and interference effect were also assessed. Only for the healthy controls an association was found between the integrity of the IFOF and picture naming in RT, and integrity of the UF and the interference effect in RT. The effect of the integrity of the IFOF on picture naming was not seen in the analysis of the whole sample, but in fact corresponds more closely with previous research (Han et al., 2013; Harvey & Schnur, 2015). The effect of the integrity of the UF on the interference effect was also seen in the analysis on the whole sample and here, it is corroborated for healthy individuals, but not for patients with PPA. No other relationship between integrity of the ventral tracts and interference effect in RT or accuracy was found within groups. This may indicate that for the patients with PPA, the integrity of the tracts is degenerated to such a degree that on average the tract integrity is too low compared to healthy controls to show a linear relationship with interference effect for the whole sample.

The current study has its limitations. An evident limitation of this study is that different tractography programs and algorithms were used for the delineation of the tracts. For the delineation of the IFOF, Probtrackx was used, and for the UF and ILF, TRACULA was used. This was done because TRACULA does not include the IFOF in their atlas and therefore it cannot be reconstructed with this program. An inherent difference between the two tractography algorithms is that the former is local and the latter is global. Local tractography fits the pathway from the seed to the waypoint mask one step at a time using the local diffusion orientation. Global tractography fits the entire pathway at once using the diffusion orientation of all of the voxels along the pathway length. Moreover, TRACULA uses prior anatomical knowledge from an atlas, while Probtrackx does not use prior information. For TRACULA, this results in tracts that are much more constrained to their probable location compared to the more error-prone algorithm of Probtrackx. While thresholding and multiple subject-specific exclusion masks were used to limit the differences in tract reconstruction, the connectivity maps of the IFOF look very different from those of the other tracts. Therefore, the results of the IFOF in this study have to be regarded more as exploratory than conclusive. A second limitation of the study is the fact that the sample size of the PPA subtypes withheld us from analysing differences between them. Such analyses have previously been done for the UF and ILF, where the integrity of the UF in semantic dementia is seen to be altered (Agosta et al., 2013; Galantucci et al., 2011). PPA subtypes show atrophy and microstructural degeneration in different areas of the brain (Gorno-Tempini et al., 2004). Thus, it can be expected that subtypes with atrophy in brain areas related to top-down control perform worse on the picture-word interference task and show decreased integrity in tracts located in these areas. Therefore, an analysis on the integrity of the three ventral tracts in all three PPA subtypes and how this relates to the interference effect would have been an informative addition to this study. Lastly, our conclusions of the influence of tract integrity on top-down control for the whole sample should be interpreted with some caution. The data of the whole sample are not normally distributed, because they contain data of both patients and controls and these two groups have a different distribution. As a result, the relationship between tract integrity and interference effect is not a straightforward linear relationship driven by a normal distribution, but rather by the differences between the patients and the healthy controls. The variance of the patients is much larger than the variance of the controls, which skews the regression (black line in Fig. 7) slightly towards the patient data (blue dots in Fig. 7). Thus, one could say that a lower integrity leads to a higher interference effect, but not in the form of a simple linear relationship. Rather, it shows that white matter degeneration is related to a high interference effect and healthy white matter is not.

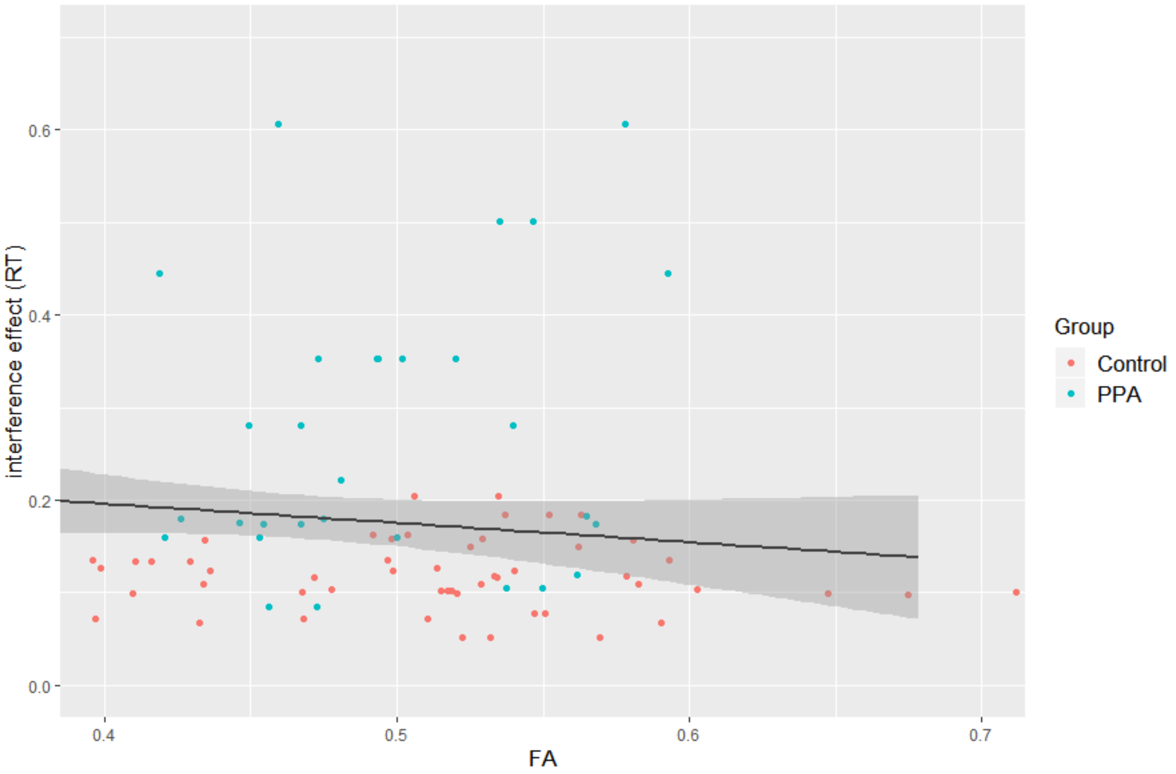

Figure 7. Variance of data between groups shown for the relationship between interference effect in RT and FA.

Conclusion

The impairment in top-down control of semantic information in patients with PPA is established in this study and could be integrated or added to diagnostic practices. Future work could investigate the top-down control of non-linguistic information in this patient group, as patients with PPA also show impairments in non-linguistic domains such as memory, despite language being their main deficit (Eikelboom et al., 2018). Top-down control in healthy language production is also a topic that calls for further investigation, since it has been linked to the ability to speak coherently in healthy aging (Hoffman, Loginova, & Russell, 2018). Finally, we have shown that damage to ventral white matter tracts, specifically the UF and ILF, affects top-down control in language production. These findings are in line with the dorsal production view. Yet, research on the function of white matter tracts in linguistic processes is in its infancy. Language research with MRI methods has historically focused on grey matter and fMRI. Only recently, with the development of tractography, white matter tracts have been linked to language function. More research on the involvement of white matter in linguistic processes in health and disease will provide meaningful insights on the neurobiology of language.

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