White matter association tracts underlying language and theory of mind: An investigation of 809 brains from the Human Connectome Project

Leo R. Zekelman[a,b,1,*], Fan Zhang[c,1], Nikos Makris[e,f], Jianzhong He[c,l], Yuqian Chen[c,d], Tengfei Xue[c,d], Daniela Liera[g], Daniel L. Drane[h,i,j], Yogesh Rathi[c,k], Alexandra J. Golby[a,c], Lauren J. O'Donnell[c]

[a]Department of Neurosurgery, Brigham and Women's Hospital, Harvard Medical School, Boston, USA

[b]Speech and Hearing Bioscience and Technology, Harvard Medical School, Boston, USA

[c]Department of Radiology, Brigham and Women's Hospital, Harvard Medical School, Boston, USA

[d]School of Computer Science, University of Sydney, NSW, Australia

[e]Department of Anatomy and Neurobiology, Boston University School of Medicine, Boston, USA

[f]Center for Morphometric Analysis, Department of Psychiatry and Neurology, A. Martinos Center for Biomedical Imaging, Massachusetts General Hospital and Psychiatric Neuroimaging Laboratory, Brigham and Women's Hospital, Harvard Medical School, Boston, USA

[g]Harvard College, Cambridge, MA, USA

[h]Department of Neurology, Emory University School of Medicine, Atlanta, GA, USA

[i]Department of Pediatrics, Emory University School of Medicine, Atlanta, GA, USA

[j]Department of Neurology, University of Washington School of Medicine, Seattle, WA, US

[*]Corresponding author at: Department of Neurosurgery, Brigham and Women's Hospital, Harvard Medical School, Boston, USA. zekelman@g.harvard.edu (L.R. Zekelman).
[1]Both the authors contributed equally to this work.

Author Manuscript

[k]Psychiatry Neuroimaging Laboratory, Department of Psychiatry, Brigham and Women's Hospital, Harvard Medical School, Boston, USA

[l]Institution of Information Processing and Automation, Zhejiang University of Technology, Hangzhou, China

Abstract

Language and theory of mind (ToM) are the cognitive capacities that allow for the successful interpretation and expression of meaning. While functional MRI investigations are able to consistently localize language and ToM to specific cortical regions, diffusion MRI investigations point to an inconsistent and sometimes overlapping set of white matter tracts associated with these two cognitive domains. To further examine the white matter tracts that may underlie these domains, we use a two-tensor tractography method to investigate the white matter microstructure of 809 participants from the Human Connectome Project. 20 association white matter tracts (10 in each hemisphere) are uniquely identified by leveraging a neuroanatomist-curated automated white matter tract atlas. The fractional anisotropy (FA), mean diffusivity (MD), and number of streamlines (NoS) are measured for each white matter tract. Performance on neuropsychological assessments of semantic memory (NIH Toolbox Picture Vocabulary Test, TPVT) and emotion perception (Penn Emotion Recognition Test, PERT) are used to measure critical subcomponents of the language and ToM networks, respectively. Regression models are constructed to examine how structural measurements of left and right white matter tracts influence performance across these two assessments. We find that semantic memory performance is influenced by the number of streamlines of the left superior longitudinal fasciculus III (SLF-III), and emotion perception performance is influenced by the number of streamlines of the right SLF-III. Additionally, we find that performance on both semantic memory & emotion perception is influenced by the FA of the left arcuate fasciculus (AF). The results point to multiple, overlapping white matter tracts that underlie the cognitive domains of language and ToM. Results are discussed in terms of hemispheric dominance and concordance with prior investigations.

Keywords

1. Introduction

The expansion of the association cortex, supported by long-range white matter fibers within each cerebral hemisphere, has been hypothesized to give rise to the high-level cognition that allows us to process the complexity of our surrounding world (Buckner and Krienen, 2013). Situated within the association cortex are two cognitive capacities, language and theory of mind (ToM), that contribute to successful communication by means of understanding the words, beliefs, and emotional states of others (Braga et al., 2020; DiNicola et al., 2020). Diffusion magnetic resonance imaging (dMRI), which estimates the cellular microstructure through measuring the random diffusion of water molecules in the brain, can be used to noninvasively map the white matter connections (i.e., fiber tracts) (Basser et al., 2000;

Basser and Pierpaoli, 1996). Quantitative dMRI measures can also be used to investigate the relationship between the microstructure of the white matter tracts and measures of language and ToM function (Forkel and Catani, 2019; Wang et al., 2018).

Unlike task-based and resting-state functional MRI (fMRI) investigations which are able to consistently localize and differentiate language and ToM networks in the cortex (Braga et al., 2020; Carrington and Bailey, 2009; DiNicola et al., 2020; Dodell-Feder et al., 2011; Fedorenko et al., 2010; Hertrich et al., 2020), dMRI investigations have revealed numerous and sometimes conflicting white matter tracts to be associated with these functions. For example, the *right* inferior occipital frontal fasciculus (IOFF, also called IFOF) has been linked to improved performance on language assessments in healthy controls (Houston et al., 2019), while studies of glioma patients provide evidence for the role of the *left* IOFF in language processing (Almairac et al., 2015). Likewise, there have been contradictory findings regarding the relationship between measures of the right uncinate fasciculus (UF) and assessments of facial emotion processing (see Coad et al., 2020, for an investigation of 42 subjects, and Unger et al., 2016, for an investigation of 28 subjects). Reviews that discuss the white matter tracts and their relationship to language or ToM have suggested that the variability of results may be related to the effects of disease, limitations in sample sizes, and differences in dMRI methods and atlas-based approaches (Dick and Tremblay, 2012; Forkel et al., 2020; Gierhan, 2013; Wang et al., 2018; Wang and Olson, 2018). While language and ToM are both social tools that together enable successful communication, the majority of existing dMRI studies have focused their investigations on subcomponents of the language network (Houston et al., 2019) *or* the ToM network (Unger et al., 2016). Few white matter tract studies and reviews have examined both language and ToM function together (Forkel et al., 2020; Grosse Wiesmann et al., 2017). Results from such investigations indicate that the same tracts (e.g. the arcuate fasciculus (AF)) may support both language and ToM networks. Finally, we note that recent lesion analysis studies and cognitive stimulation mapping results also point to more broadly distributed cortical regions and additional white matter tracts involved in supporting these functions (Drane and Pedersen, 2019; Yamada et al., 2021) than reflected by the classical models (i.e., language models that connect Wernicke's to Broca's area via the AF Geschwind, 1970 and ToM models that include the right temporal parietal junction as a critical hub Saxe and Wexler, 2005).

To address the limitations and expand upon findings from previous studies, the present study investigates 20 white matter tracts in a large dataset of 809 healthy brains from Human Connectome Project (HCP) (Van Essen et al., 2013) using a machine learning approach to consistently extract the white matter tracts from individual subjects (Zhang et al., 2018b). The long-range intra-hemispheric white matter tract connections examined in this study include the left and right arcuate fasciculus (AF), cingulum bundle (CB), extreme capsule (EmC), inferior longitudinal fasciculus (ILF), inferior occipito-frontal fasciculus (IOFF), middle longitudinal fasciculus (MdLF), superior longitudinal fasciculi I, II, III (SLF-I, SLF-II, SLF-III), and uncinate fasciculus (UF) (Zhang et al., 2018b). Furthering our understanding of how language and ToM are organized in the brain, we investigate how the white matter association tract microstructure in both hemispheres influences performance on the NIH Toolbox Picture Vocabulary Test (TPVT; Gershon et al., 2014 and the Penn Emotion Recognition Test (PERT; Carter et al., 2009). To our knowledge, this is the first

study to use a dataset of this size to examine how the microstructure of the white matter tracts relates to cognitive and socio-emotional function. Furthermore, we believe it is the first to investigate the white matter tracts underlying a subcomponent of language and a subcomponent of ToM in the same study, using common methods and healthy adult participants.

The following sections of this paper describe the Human Connectome Project (HCP) dataset, the identification of the white matter association tracts using machine learning (Zhang et al., 2018b), and a description of the multiple linear regression statistical analyses performed. We find the microstructure of multiple white matter tracts in both the left and right hemispheres significantly influences performance on TPVT, a language-related assessment of semantic memory, and PERT, a ToM-related assessment of emotion perception. Our results suggest that multiple white matter tracts support the distributed language and ToM networks. Finally, we conclude with a discussion of the results in terms of their hemispheric dominance and concordance with prior investigations.

2. Methods

Fig. 1 provides an overall conceptual representation of the methodology used to examine how behavior relates to microstructural measures of the white matter tracts. We focused on two types of brain data included in the HCP dataset, namely dMRI data and neuropsychological data. From the dMRI data, we generated whole brain tractography for each participant, and we identified each individual's unique white matter tracts using a neuroanatomical atlas. Then, we measured microstructural measures from each tract. Linear regression statistical models were created with the microstructural measures as independent variables and the neuropsychological behavioral measures (TPVT and PERT) as dependent variables. Finally, the white matter tracts whose microstructure significantly influenced each behavioral measure were visualized. The following paragraphs of this section describe each of these steps in greater detail.

2.1. Study dataset

This study utilized dMRI data and neuropsychological assessment data from the HCP, a large multimodal dataset composed of 1206 healthy young adults (Van Essen et al., 2013). Written informed consent, including consent to share de-identified data, was obtained from each participant and approved by the Washington University Institutional Review Board. Permission to use this data was obtained from HCP and the protocol was approved by the Mass General Brigham Institutional Review Board.

The dMRI data was collected for a subset of 1065 participants. From the 1065 subjects, 100 participants with dMRI data were excluded from this analysis because they were used to develop the white matter atlas employed in this project (for details see Zhang et al., 2018b). Furthermore, to control for the genetic family structure inherent to this dataset, 154 monozygotic twin siblings were excluded due to their nearly identical genetics. Two subjects without PERT scores were also excluded. The final study dataset thus included 809 participants, 382 male participants and 427 female participants. Ages ranged from 22 years to 36 years, with a mean age of 28.6 years. 710 participants demonstrated a preference

of right-handedness, scoring at least 40 on a scale ranging from −100 to 100 denoting exclusively left-handedness to exclusively right-handedness (Oldfield, 1971; Schachter et al., 1987). (See Supplementary Fig. 1 depicting the distribution of participant handedness.)

Scores from two computerized neuropsychological assessments were investigated, TPVT and PERT. TPVT is a measure of single word semantic memory (Gershon et al., 2013) and PERT is a measure of facial emotion perception (Carter et al., 2009). Although TPVT and PERT directly measure very narrow subcomponents of cognition, there is evidence to suggest that these subcomponents relate to the more general and broadly distributed brain networks of language and theory of mind (ToM) (Fedorenko et al., 2010; Hawco et al., 2017). While these studies suggest a relationship between the abilities tested by these assessments and the broader language and ToM cognitive networks in the brain, we note this is an open area of research. (See reviews on the relationship between language and memory (Martin and Slevc, 2012; Van Dyke, 2012) and the overlap between emotion perception and ToM (Mitchell and Phillips, 2015).

To briefly summarize the TPVT assessment, participants heard a word and were presented with four pictures on a screen (Gershon et al., 2014). Using computer adaptive testing, participants were instructed to click on the picture that captured the meaning of the presented word. A maximum of 25 pictures were presented, and responses were scored using item response theory (Gershon et al., 2014). We used the unadjusted TPVT scores that were normed without taking into account effects of age and gender (Slotkin et al., 2012). This allowed us to control for effects of age and sex demongraphics unique to our participant sample. Higher TPVT scores reflect a better vocabulary ability, while lower scores reflect poorer performance. The mean unadjusted TPVT score in the study population was 117.12 points (Fig. 2*, left panel*).

Likewise, to briefly summarize the PERT assessment, participants viewed 40 different faces balanced for gender, age, ethnicity and emotional category (Carter et al., 2009). Participants were asked to identify the emotion elicited by that facial expression. Participants chose from five possible emotional expressions – angry, fearful, happy, sad and neutral (see Carter et al., 2009 for a more detailed explanation of the task). PERT scores were calculated from the number of correct responses out of a maximum score of 40. PERT scores in the study population demonstrated a slight left skew, with 13 participants scoring the maximum possible score of 40 points and a mean score of *35.59* points (Fig. 2, *right panel*).

2.2. Tractography, white matter tract identification, and diffusion measure extraction

The investigated dMRI data comes from the HCP minimally pre-processed dataset (Glasser et al., 2013). The HCP dMRI data were acquired using three shells ($b = 1000$, 2000 and 3000 s/mm^2), TE/TR = 89.5/5520 ms, and an isotropic voxel size of 1.25 mm^3 (Van Essen et al., 2013). For each subject, the $b = 3000$ shell of 90 gradient directions and all $b = 0$ scans were extracted (for similar methods see also Zhang et al., 2018b). This single shell was chosen to reduce computation time and memory use given our large sample size, while providing the highest angular resolution for tractography (Descoteaux et al., 2007; Ning et al., 2015).

Whole brain tractography was computed by applying a two-tensor Unscented Kalman Filter (UKF) method (Malcolm et al., 2010; Reddy and Rathi, 2016) to each subject's preprocessed dMRI data, as implemented in the *ukftractography* package (https:// github.com/pnlbwh/ ukftractography). This step produced approximately 700k streamlines per subject on average. A two-tensor model was chosen to account for the many crossing fibers (Farquharson et al., 2013; Vos et al., 2013) found in the architecturally complex white matter association tracts. In this method, the first tensor is associated with the fiber tract that is being traced, while the second tensor captures the fibers that cross through that tract. UKF tractography is highly consistent across ages, health conditions and image acquisitions (Zhang et al., 2018b) and has enabled many studies of tract microstructure (Hamoda et al., 2019; Olszewski et al., 2017; Zhang et al., 2018a). Visual and quantitative quality control of the tractography was performed using a quality control tool in the *whitematteranalysis* (WMA) software package (https://github.com/SlicerDMRI/whitematteranalysis).

For each subject, we identified white matter association tracts using a robust machine learning approach that has been shown to consistently identify white matter tracts across the full human lifespan, across health conditions including brain tumors, and across different image acquisitions (Zhang et al., 2018b). Furthermore, the method has high test-retest reproducibility (Zhang et al., 2019) and has been employed in multiple recent studies (Gong et al., 2018; Irimia et al., 2020; Kochsiek et al., 2021; Levitt et al., 2021). This method is implemented in the WMA package, which uses a well-established fiber clustering pipeline (O'Donnell et al., 2012; O'Donnell and Westin, 2007) in conjunction with an anatomical white matter tract atlas (Zhang et al., 2018b). This neuroanatomist-curated white matter tract atlas was trained using tractography data from a separate subset of 100 HCP participants. The atlas contains 58 unique white matter tracts, including 20 white matter association tracts that connect intrahemispheric cortical regions. We applied the WMA package to parcellate each participant's whole brain tractography into separate tracts that correspond with the atlas tracts. To achieve this, first a tractography-based registration was performed to align the subject's tractography data into the atlas space (O'Donnell et al., 2012). Then, a fiber spectral embedding was conducted to compute the similarity of fibers between the subject and the atlas, followed by the assignment of each fiber of the subject to the corresponding atlas tract (O'Donnell and Westin, 2007; Zhang et al., 2018b). This produced a total of 58 identified white matter tracts per subject, including the 20 white matter association tracts under study.

All of the long-range ipsilateral association white matter tracts in the atlas were investigated. This anatomical set of tracts consists of the left and right arcuate fasciculus (AF), cingulum bundle (CB), extreme capsule (EmC), inferior longitudinal fasciculus (ILF), inferior occipito-frontal fasciculus (IOFF), middle longitudinal fasciculus (MdLF), superior longitudinal fasciculi I, II and III (SLF-I, SLF-II, SLF-III), and uncinate fasciculus (UF) (Schmahmann and Pandya, 2006). The long-range association tracts were selected for this investigation because of their well documented relationship to behavior (Schmahmann et al., 2008) and their complete mapping in our atlas (Zhang et al., 2018b). Fig. 3 provides lateral views of these 20 white matter tracts. (See Supplementary Figs. 2 and 4 for additional visualizations of these tracts.) None of the white matter association tracts were excluded from this investigation because there is evidence to suggest that each of the white matter

association tracts belonging to either the left or right hemisphere may be involved in subcomponents of language and/or ToM (Almairac et al., 2015; Blom-Smink et al., 2020; Del Tufo et al., 2019; Fujie et al., 2008; Geschwind, 1970; Grosse Wiesmann et al., 2017; Herbet et al., 2014; Herbet et al., 2015; Houston et al., 2019; Luo et al., 2020; Makris and Pandya, 2009; Mandonnet et al., 2007; Nakajima et al., 2018; Pawełczyk et al., 2020; Philippi et al., 2009; Salvan et al., 2017; Saur et al., 2008; Thomas et al., 2008; Wang et al., 2013; Wilson et al., 2011). Therefore, as to not preclude finding a possible microstructural influence on assessments of language and ToM subcomponents, all the long-range association tracts in both hemispheres were investigated.

For each individual's white matter tracts, three white matter tract measurements were calculated: the fractional anisotropy of the first tensor (FA), the mean diffusivity of the first tensor (MD), and the number of streamlines (NoS) within each tract. Mean FA, MD, and NoS were chosen for their common use in diffusion imaging studies, including those of language and ToM (Forkel and Catani, 2019; Wang et al., 2018). FA indexes how far a tensor is from a sphere to quantify the diffusion anisotropy of the water molecules. Very elongated tensors have a high FA value of 1, while spherical tensors have a low FA value of 0 (O'Donnell and Westin, 2011). MD indexes the average magnitude of water diffusion (O'Donnell and Westin, 2011). The NoS is popularly used to detect differences in structural connectivity (Sotiropoulos and Zalesky, 2019). Note, NoS is sometimes termed "number of fibers." However, the term "fibers" does not refer to the number of axonal projections, but rather the number of reconstructed streamlines (Jones et al., 2013). Additionally, we note that these measures are all sensitive to a variety of tissue properties including the myelination, axonal density, cell membranes, and microtubules (Beaulieu, 2009; Jones et al., 2013). In this sense, each measure reflects multiple aspects of the tract microstructure and not a specific microscopic anatomical property.

2.3. Statistical analyses and white matter tract visualizations

All statistical models were computed using R statistical software (R Core Team, 2020). Multiple linear regression was used to examine the influence of tract measures on assessment scores on TPVT and PERT. For each of the three tract measures (i.e. FA, MD, and NoS), a total of 20 models were created. Half of these models had PERT as the dependent variable and the other half had TPVT as the dependent variable. For each assessment, 10 models were created for each of the 10 bilateral white matter tracts, so that each regression model had two tract measures (left and right tracts) as independent variables. Following the technique of a previous study (Unger et al., 2016), both a left tract and a right tract were included in each model to account for their fairly symmetrical structure across hemispheres (see SupplementaryFig. 3 for plots (Phillips, 2017) depicting each tract's laterality). Age and sex were included as covariates, as previous studies have demonstrated their association with white matter structure (Charlton et al., 2009; Houston et al., 2019; Ingalhalikar et al., 2014; Lebel et al., 2012; Slater et al., 2019; van Hemmen et al., 2017). For each of the three tract measures investigated, we corrected for the multiple comparisons (i.e., across 20 behavioral regression models). *P*-values associated with each model and independent variable were adjusted using the false discovery rate (FDR) (Benjamini and Hochberg, 1995). Standardized beta coefficients were computed for each of the independent

variables using the "lm.beta" package in R (Behrendt, 2014). Effect plots were created using the "effects" package in R (Fox and Weisberg, 2018a, 2018b). All brain visualizations were created in 3D Slicer, a platform for medical image informatics (www.slicer.org) via SlicerDMRI, a module to map the white matter connections (http://dmri.slicer.org) (Norton et al., 2017; Zhang et al., 2020). White matter tracts whose measures significantly influenced performance on PERT or TPVT are depicted in visualizations. In addition, to assist understanding of the tract results in relation to the cortical regions involved, we aligned the white matter tract atlas to the standard MNI space where a Freesurfer cerebral cortical parcellation is made available (https://identifiers.org/neurovault.image:23262) (Desikan et al., 2006; Fischl et al., 2004). Then, for each tract under study, we provide a visualization of a cortical surface heatmap, where the values indicate the number of steamline endpoints closest to each surface point.

3. Results

Table 1 summarizes the results from the computed multiple regression analyses. Each model was computed with either TPVT or PERT as the dependent variable. The independent variables included in each model are microstructure measures of the left and right white matter tracts, along with age and gender as covariates. In Table 1, we include the models with tract measures that significantly influenced performance after correcting for multiple comparisons. For each model, we present the overall R^2 and F values. For the independent variables from each model, we provide the p-value, standardized beta coefficient and t-value. Significant independent variables are noted with asterisks.

Visualizing the asterisked white matter tracts of Table 1, *Fig. 4* depicts the tracts with microstructure that significantly influenced TPVT and PERT performance. The leftmost columns depict the tracts with microstructure that influence TPVT, and the rightmost columns depict tracts with microstructure that influence PERT. Each row in the top and bottom panels displays a different microstructure tract measure (i.e., NoS, FA and MD). In the top panel, white matter tracts are colored according to p-value; light yellow tracts have microstructure that significantly influence TPVT or PERT performance with the lowest p-values, while orange and red tracts have the highest p-values. In the bottom panel, white matter tracts that significantly influence these two assessments are colored according to standardized beta coefficient; light colored tracts have microstructure with the greatest effect, while darker colored tracts have microstructure with the least effect on these assessments.

We examine the SLF-III more closely because the microstructure of the *left* SLF-III influenced performance on TPVT, while the microstructure of the *right* SLF-III influenced performance on PERT. Conversely, the microstructure of the *left* AF influenced performance on both TPVT and PERT. Fig. 5 depicts effect plots visualizing the partial slope of the tract microstructure measure when the other independent variables (i.e., a measure of the opposite hemisphere tract, age, and sex) are held fixed. Tract microstructure measures examined are the NoS of the SLF-III and FA of the AF.

To help visualize how the AF and SLF-III relate to the broader language and ToM networks, the cortical regions these tracts connect are depicted in Fig. 6 (see Supplementary Fig. 4 for visualizations of additional tracts). The AF broadly connects the temporal regions (including the superior, middle and inferior temporal cortices) with frontal regions (including caudal middle frontal, rostral middle frontal, pars opercularis, and precentral cortices). The SLF-III forms major connections between parietal regions (including supramarginal and inferior parietal cortices) and prefrontal regions (including the pars opercularis).

4. Discussion

This study used dMRI tractography of bilateral association tracts to investigate the relationship between tract microstructure and subcomponents of language and theory of mind (ToM). In a large sample of healthy subjects, we found that multiple dMRI tract measures significantly influence performance on assessments of language and ToM subcomponents (i.e. semantic memory and emotion perception). These results demonstrate a significant relationship between white matter structure and cognitive function, and this work lends support to the concept that multiple white matter tracts contribute to the broad networks of language and ToM.

Although significant, the results indicate that the structural measures investigated only weakly influence cognitive function in healthy adults, as less than 10% of the variability in the cognitive measures can be explained by any one model (the R^2 values in Table 1 are less than 0.1). This is in line with a body of recent work that uses neuroimaging measures to examine behavior in the HCP dataset (Sina Mansour et al., 2021; Tian et al., 2020). For example, one recent study used a novel, high-resolution structural connectivity map of the entire brain to predict an overall "cognition" score that was derived using 109 behavioral assessments from the HCP. The resulting explained variance was well under 0.1 (Sina Mansour et al., 2021). Overall, prediction of phenotype data (such as neuropsychological behavioral measures) using neuroimage and connectome information is an open challenge (Finn and Rosenberg, 2021), with novel machine learning methods under investigation for improvement of prediction accuracy (W. Gong et al., 2021).

4.1. Opposing hemispheric dominance

Our results are relevant to the lateralization and hemispheric dominance of language and ToM. fMRI evidence points to language lateralized to the left hemisphere (Bradshaw et al., 2017) and ToM lateralized to the right hemisphere (Saxe and Wexler, 2005). In this sense we expect to find similar results regarding their hemispheric dominance in dMRI studies. However, existing dMRI studies of healthy subjects have provided contradictory results. For example, better performance on language-related assessments has been associated with the white matter tracts in the non-dominant hemisphere (Houston et al., 2019). Similarly, better performance on ToM-related assessments has been associated with the white matter tracts in both hemispheres (Cabinio et al., 2015; Unger et al., 2016). These results have been explained as recruitment of the additional hemisphere resulting in better performance on language and ToM assessments. However, such results are contrasted by evidence gathered from investigations of the white matter tracts in various patient populations. In investigations

of patient populations, language deficits are linked to abnormalities of the left hemisphere white matter (Griffis et al., 2017; Luo et al., 2020; Sierpowska et al., 2019) and ToM deficits are found to arise from abnormalities of the right hemisphere white matter (Díez-Cirarda et al., 2015; Meletti et al., 2009; Philippi et al., 2009; Weed et al., 2010). The findings from this present study add support to the understanding that the language network is typically rooted in the left hemisphere, and ToM is situated in the right hemisphere. As depicted in Fig. 4, the majority of the white matter tracts with microstructure that influenced semantic memory performance were in the *left* hemisphere, while the majority of the white matter tracts with microstructure that influenced emotion perception were in the *right* hemisphere. Additionally, our results imply that neither of these subcomponents of language and ToM is completely lateralized to a single hemisphere. We found the microstructure of the left AF influenced emotion perception performance, and the microstructure of right MdLF and right UF influenced semantic memory performance. This finding agrees with previous investigations that have found that the language and ToM networks are oppositely lateralized but distributed across both hemispheres in neurotypical individuals (Dufour et al., 2013; Fedorenko et al., 2010; Jouravlev et al., 2020). However, as Supplementary Fig. 1 demonstrates we have included participants with preferences for left and mixed handedness. This population is known to have higher rates of atypical functional laterality compared to the right-handed population (Szaflarski et al., 2002), which may have influenced our findings.

While many of the white matter tracts studied here have been heavily investigated in terms of language and ToM (e.g., AF, SLF-III, SLF-II, IOFF, UF, ILF (Chang et al., 2015; Coad et al., 2020; Dick and Tremblay, 2012; Liégeois et al., 2013; Wang et al., 2018), we will briefly discuss some of the white matter tracts that are less often investigated, including the MdLF and the EmC. The MdLF and EmC are two parallel running white matter tracts that have only recently been delineated using diffusion MRI (Makris, 1999; Makris et al., 2009; Makris and Pandya, 2009). Studies have linked both the MdLF and EmC to aspects of language. More specifically, the MdLF has been associated with semantic deficits and EmC have been found to play a role in language learning (Lopez-Barroso et al., 2011; Luo et al., 2020; Wang et al., 2013). Our results support previous work suggesting that the MdLF and EmC are both involved in language processing, as we found the MdLF and EmC microstructure significantly influenced an important subcomponent of language function, semantic memory. More specifically, we found the NoS of the right MdLF and FA of the left EmC to significantly influence semantic memory performance. It should be specified that the MdLF was traced involving the inferior and superior parietal lobules (IPL and SPL) as well as the superior temporal gyrus and temporal pole. Therefore, one may expect it to be associated with not only language function but also visual spatial processing, which may explain the rightward laterality (Makris et al., 2013; Makris et al., 2017; Wang et al., 2013).

Our results may also shed light on the role of the AF and SLF-III in the broader networks of language and ToM. Many studies have tied the lateralization of the left AF to lateralization of language (Allendorfer et al., 2016; Barrick et al., 2007; Paldino et al., 2016; Sreedharan et al., 2015; Takaya et al., 2015). While our results support the role of the left AF's involvement in semantic memory, our results additionally indicate that the microstructure of the left AF also influences emotion perception performance (see Fig. 5, *bottom panel)*.

While the role of the left AF in the ToM network is less noted in the literature, this study is not the first to observe a relationship between the AF and ToM-related assessments. A study on glioma patients found a relationship between the right AF and the ToM network (Herbet et al., 2014), while a study on developing children found a relationship between both right and left AF and ToM performance (Grosse Wiesmann et al., 2017). Our findings and previous research bring into question how the left AF may be involved in right ToM lateralization.

Additionally, our results point to the SLF-III playing a role in the functional lateralization of language and ToM. We found the NoS of the *left* SLF-III significantly influences semantic memory performance and the NoS of the *right* SLF-III significantly influences emotion perception performance (see Fig. 5, top panel). That is, the microstructure of the SLF-III in the left hemisphere related to a left-lateralized language network and the microstructure of the SLF-III in the right hemisphere related to a right-lateralized ToM network. Previous work has suggested the interactions mediated by the SLF-III may be a prerequisite for gestural communication that "presages" linguistic communication (Petrides and Pandya, 2002; Schmahmann and Pandya, 2006) and has been hypothesized to be involved in articulatory aspects of language (Nikos Makris et al., 2005). In addition, in the monkey, there is evidence that the frontal regions that receive input from the SLF-III contain "mirror neurons" (Rizzolatti et al., 1996, 1999; Schmahmann and Pandya, 2006), which may interplay with the ToM network (Schulte-Rüther et al., 2007). More recently, the SLF-III has been considered to contribute to a variety of functions beyond but including semantic processing and mirror neuron related functions (e.g. action observation and ToM) (Parlatini et al., 2017). An interesting direction for future research will be to further investigate the role the SLF-III may play in language and ToM lateralization. Additionally, future studies may investigate the role additional white matter tracts, (e.g., thalamo-cortical projection tracts) play in lateralization and hemispheric dominance of language, ToM, and their subcomponents.

4.2. Relationship of AF and SLF-III to cortical regions

As discussed above, our results may shed light on the role of the AF and SLF-III in the broader networks of language and ToM. Here we discuss the cortical regions that are connected by the AF and SLF-III (as visualized in Fig. 6), with regards to their functional roles in the broader language and ToM networks. First, we note that the regional connections made by the AF and SLF-III in our atlas are in line with previous research describing the AF connecting frontal and temporal regions (Catani and Thiebaut de Schotten, 2008; Makris et al., 2005; Rilling et al., 2008), and the SLF-III connecting parietal and frontal regions (Barbeau et al., 2020; Makris et al., 2005). It is important to note that both the precise cortical terminations of the tracts (Yeh, 2020), and the functional regions associated with language and ToM (Braga et al., 2020; DiNicola et al., 2020; Fedorenko et al., 2010; Ojemann, 1979; Saxe, 2006) vary across individuals.

The left hemisphere regions that are connected by the left AF and left SLF-III are more frequently associated with language-related processes than ToM-related processes. Regions in the left superior, middle and inferior temporal cortices, where many streamlines of the left

AF terminate, have been associated with various language and language-related processes including the encoding of speech sounds, thought processes, and comprehension (Binder, 2017; Corina et al., 2010; Dronkers et al., 2004; Turken and Dronkers, 2011; Wensing et al., 2017; Yi et al., 2019). The left frontal regions (and in particular, the left pars opercularis), which receive many terminations from both the left AF and left SLF-III, have also been associated with various language and speech functions (Long et al., 2016; Rogalsky et al., 2008). Finally, the left parietal regions, such as the supramarginal and inferior parietal cortices, which receive terminations from the left SLF-III, have been associated with semantic processing (Gilmore et al., 2021; Numssen et al., 2021). The left frontal and temporal connections of the left AF are less frequently discussed in the ToM literature, although some reports have investigated left frontal regions (Marchetti et al., 2015; Rowe et al., 2001).

The right hemisphere regions that are connected via the right SLF-III are frequently associated with ToM-related processes in the literature. The right parietal regions in which the streamlines from the right SLF-III terminate (sometimes termed the right temporal parietal junction (rTPJ)) are associated with ToM, social cognitive, and emotional processes (Lettieri et al., 2019; Numssen et al., 2021; Schurz et al., 2014). The right inferior frontal regions where the SLF-III streamlines terminate are inconsistently associated with ToM processes, perhaps due to fMRI paradigmatic constraints (Hartwright et al., 2016; Samson et al., 2015; Schurz and Tholen, 2016).

4.3. Microstructural measures and interpretation

The tract microstructure measure that is best able to capture different aspects of cognition is an open area of research. This study investigated 3 measures (FA, MD and NoS) commonly utilized in diffusion MRI research (Forkel and Catani, 2019). Overall, in this study, NoS was the tract measure that most consistently influenced performance on both TPVT and PERT (Table 1). The NoS of 7 tracts influenced performance on TPVT, and the NoS in 2 tracts influenced performance on PERT. The FA of four tracts (left ILF, left AF, left EmC and left SLF-II) significantly influenced performance on TPVT. The FA of only one tract, the left AF, significantly influenced PERT. MD was the least influential tract measure, with only the MD of the left SLF-II influencing performance on TPVT.

How strongly each of these microstructural measures influence subcomponents of language and ToM (i.e. as measured through TPVT and PERT) may relate to the inherent sensitivity of these microstructural measures. The least influential of the investigated measures, MD, is nearly constant in healthy brain parenchyma (Pierpaoli et al., 1996), though it is somewhat reduced in regions of complex fiber architecture (Vos et al., 2012). FA, which was the second most influential of the investigated measures, is highly sensitive to local differences in fiber architecture (e.g. fiber crossings) (Pierpaoli et al., 1996). Finally, NoS, which was found to be the most influential measure in this study, is an indirect measure of tissue microstructure that is especially sensitive to starting and stopping anisotropy thresholds used to begin and terminate fiber tracking. There is not a direct relationship between NoS and the number of biological axons (Jones et al., 2013), though it is a popular and widely used measure to quantify the connectivity strength (Zhang et al., 2021). In stark contrast

to real biological axons, streamlines *do not* have an associated volume; streamlines are by definition one-dimensional and thus, infinitesimally thin (Smith et al., 2020). NoS must therefore be interpreted with caution (Jones et al., 2013). However, as a measure of the connectivity between cortical regions, the NoS and related measures are highly sensitive to brain changes in health and disease (Fornito et al., 2015; Griffa et al., 2013).

Given the hemispheric lateralization of language and ToM in the human brain, it is also possible that the influence of each of these microstructural measures on subcomponents of language and ToM relates to their degree of lateralization across hemispheres. The lateralization of the white matter fiber tracts has been studied using many different measures (such as NoS, FA and tract volume) (Bain et al., 2019; Catani et al., 2007; Lebel and Beaulieu, 2009; Maffei et al., 2019; Thiebaut de Schotten et al., 2011). To assess sensitivity to brain lateralization in our study, we measured the lateralization of each of the investigated measures (see Supplementary Fig. 3). We found the greatest degree of lateralization in NoS and the least amount of lateralization in MD. Others have found more variable degrees of lateralization in NoS, FA, and volume of the association white matter tracts (Thiebaut de Schotten et al., 2011).

It is important to note that the white matter measures investigated in this paper are correlated. This is expected, as MD and FA are not mutually mathematically orthogonal measures (Ennis and Kindlmann, 2006), and the NoS is affected by seeding thresholds determined by FA. Despite these well-known correlations, MD and FA are almost always studied together because they provide insight into different properties of the diffusion tensor (the magnitude of diffusivity and the "shape" of the tensor) (O'Donnell and Westin, 2011). In addition, the study of NoS is very popular as it provides a proxy of "connection strength" (Zhang et al., 2021). Interestingly, we found that the correlation between measures varied across tracts and across hemispheres (see Supplementary Fig.5).

4.4. Limitations and future work

It is important to note several limitations of this study. While our study is able to take advantage of an unusually large sample size, we are limited to the neuropsychological measures included in the HCP. Despite the limited sensitivity of PERT (see slight ceiling effect and limited range of scores in Fig. 2), we were able to find 3 tract measures that significantly influenced PERT performance and 12 that influenced TPVT. While it is possible that there are fewer long-range white matter association tracts underlying emotion perception compared to semantic memory, we suspect that with a more sensitive measure (e.g., PERT correct response reaction times), we may find more tracts with microstructure that influence ToM performance. An additional limitation of this study is that we have violated the assumption of independent observations by including dizygotic twins and siblings in our analysis. Future investigations may better take into account family structure by, for example, using multi-level block permutation (Winkler et al., 2015).

Moreover, TPVT and PERT are only two subcomponent measures of highly studied and complicated domains of cognition. The extent to which we can associate TPVT and PERT with high-level naturalistic language and ToM is an open area of investigation (Chen et al., 2019; Oakley et al., 2016). However, multiple neuroimaging studies have used TPVT and

PERT-like assessments to understand the broader networks of language and ToM (Chen et al., 2019; Hawco et al., 2017; Jáni and Kašpárek, 2018; Mier et al., 2010; Palmer et al., 2020). In addition, awake intraoperative neurosurgical mapping of language and ToM have utilized similar assessments in the operating room in an effort to preserve the cognition of their patients. Object naming assessments have been utilized to map language since the times of Penfield (Penfield and Roberts, 1959), and more recently facial emotion recognition tasks, such as Reading the Mind in the Eyes, have been used to intraoperatively map ToM (Herbet et al., 2015). In contrast to the majority of tasks used in intraoperative neurosurgical cognitive mapping that require *spontaneously generated* responses (e.g., confrontation naming tasks), TPVT and PERT only require *matching* words to their corresponding picture (Drane et al., 2021).

Although we have included participants who demonstrate a preference for left-handedness and ambidexterity, our participant sample predominantly has a preference for right-handedness (see Supplementary Fig. 1). In this sense, our findings most strongly reflect a right-handed population and should be interpreted with caution when applied to left-handed and ambidextrous populations. While there has been documentation of left handers demonstrating reduced functional lateralization in verbal and facial processing tasks compared to right-handed individuals (Johnstone et al., 2021), differences in the white matter are less clearly documented. Some have found increased FA of the white matter when comparing the microstructure of left-handed to right-handed adults (McKay et al., 2017), while other investigators have found no difference in the white matter microstructure between left- and right-handed children (López-Vicente et al., 2021).

We highlight the continued need for large neuroimaging samples and methods to consistently analyze them. Small sample sizes are known to be particularly problematic for neuroimaging and psychology studies because they produce unreliable results (Button et al., 2013; Maxwell et al., 2015). Our study is able to surmount these challenges by employing a machine-learning approach to consistently identify the white matter tracts in hundreds of individual brains. This allows us to investigate how each individual's unique tract microstructure relates to individual measures of behavior. It is important that future studies investigate the reproducibility of these results using likewise large datasets, especially those with diverse demographics and unrelated participants. In lieu of other comparably large datasets, we have leveraged the current dataset to examine the statistical significance of these results. We implemented a bootstrap subsampling technique to examine the distribution of the p-value statistics calculated for each tract (see Supplementary Fig.6). The results of this bootstrap experiment support the most significant findings from the main experiment; all white matter tracts that had bootstrap p-value confidence intervals below the alpha threshold ($\alpha = 0.05$) were also significant in the main experiment shown in Table 1 and visualized in Fig. 4. However, we note that some tracts did not have confidence intervals that fell entirely below the alpha threshold, despite their significance in the main experiment. This suggests additional experiments on the association white matter tracts are warranted to better understand the contribution that tract microstructure may have on TPVT and PERT.

Finally, for simplicity we have investigated only the popular MD, FA, and NoS measures here. In addition to these measures, many more measures can be computed and studied

using dMRI data (Jensen et al., 2005; Pasternak et al., 2009; Zhang et al., 2012). Future investigations can examine how additional measures (e.g., neurite orientation dispersion and density indices, kurtosis, axial diffusivity, radial diffusivity, tract volume) relate to measures of language and ToM. Future work may also include alternative approaches that perform dimensionality reduction of the number of dMRI measures (Ceschin et al., 2015; Chamberland et al., 2019; Geeraert et al., 2020), especially if more than three measures are of interest.

Finally, we note that this investigation has only focused on healthy subjects. As such, the interpretation of our findings is limited to the tract microstructure that is associated with *improved* performance and does not reveal the tracts or tract microstructure that may be *essential* for healthy performance. To further understand how the white matter tracts support cognition, future studies can investigate how the microstructure of these tracts differs in patient populations with known language and ToM deficits, including patients with autism spectrum disorder (Bennett et al., 2013), specific language impairment (Nilsson and de Lopez, 2016), schizophrenia (Gavilán Ibáñez and García-Albea Ristol, 2013), temporal lobe epilepsy (Giovagnoli et al., 2011; Kaestner et al., 2020), and glioma (Antonsson et al., 2018; Nakajima et al., 2018). Additionally, further studies may investigate how the microstructure of these tracts changes over the course of development and evolution. Previous studies have theorized about the intertwined relationship between language and ToM, with suggestive evidence pointing to their developmental and evolutionary influence on each other (Bergelson and Swingley, 2012; de Villiers and de Villiers, 2014; Givón and Malle, 2002; Marchman and Fernald, 2008; Miller, 2006; Ruba and Repacholi, 2019). Our findings in this study support the idea that semantic memory and emotion recognition are influenced by shared and distinct neural resources in healthy young adults.

5. Conclusion

This study maps language and ToM subcomponents in the white matter association tracts using noninvasive measures and an exceptionally large sample size ($n = 809$). We demonstrate that the white matter microstructure is able to influence performance on assessments of semantic memory and emotion perception, two critical subcomponents of the language and ToM networks. Our results suggest that multiple, overlapping white matter tracts underlie the cognitive domains of language and ToM. As this study demonstrates, cognition is not only situated within the association cortex but is also reflected in the microstructure of the underlying white matter association tracts.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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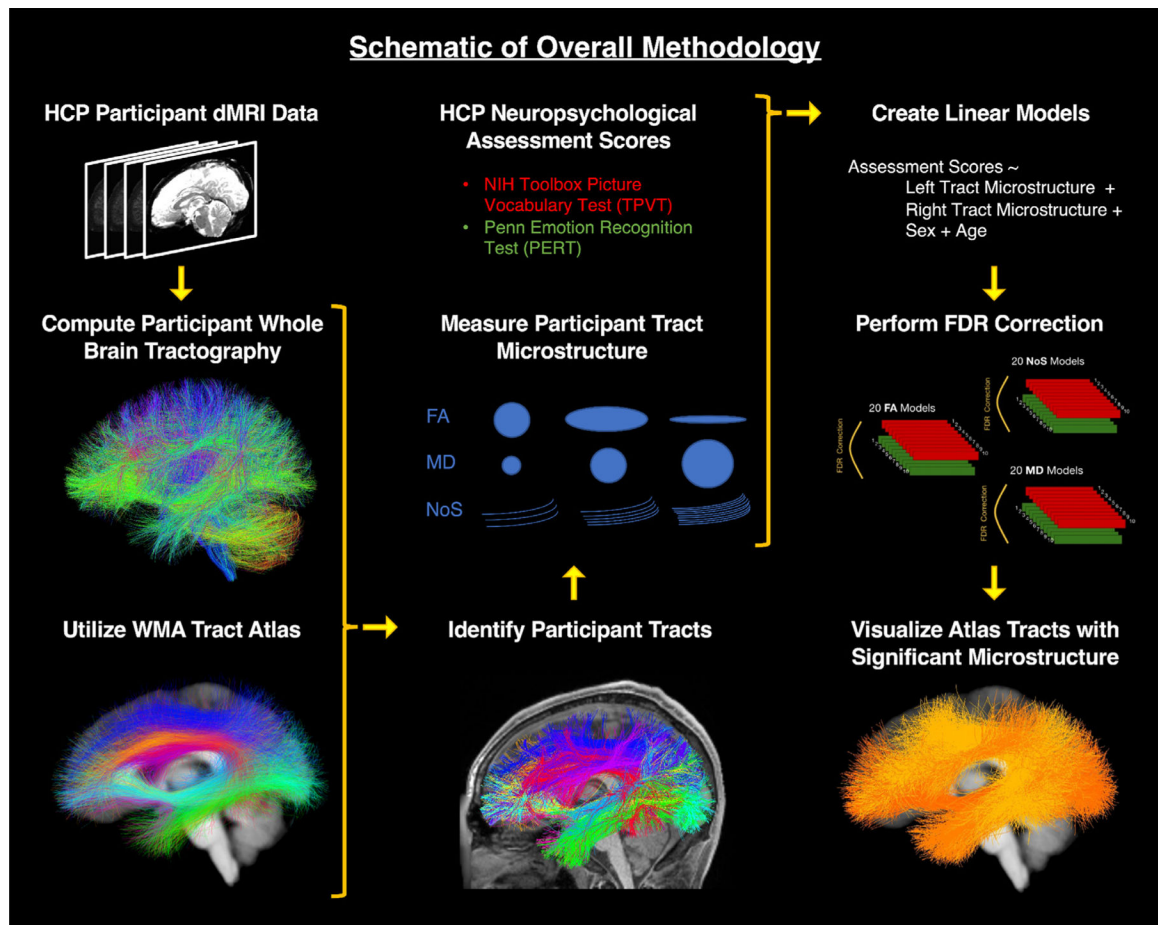
Fig. 1.
Schematic of overall methodology. First, dMRI data and neuropsychological assessment scores (TPVT and PERT) were obtained from the HCP. Whole brain tractography was computed using individual dMRI data from 809 participants. Next, using the whole brain tractography, we identified each association tract included in the atlas. From the identified tracts, three microstructural measures (FA, MD and NoS) were computed. These microstructural measures were then used as independent variables in linear regression models, which had either TPVT or PERT as a dependent variable. The linear models were corrected for multiple comparisons using the FDR method. Finally, white matter tracts with microstructural measures that significantly influenced performance on neuropsychological behavioral assessments were visualized. HCP: Human Connectome Project, WMA: White Matter Analysis, FA: fractional anisotropy, MD: mean diffusivity, NoS: number of streamlines.
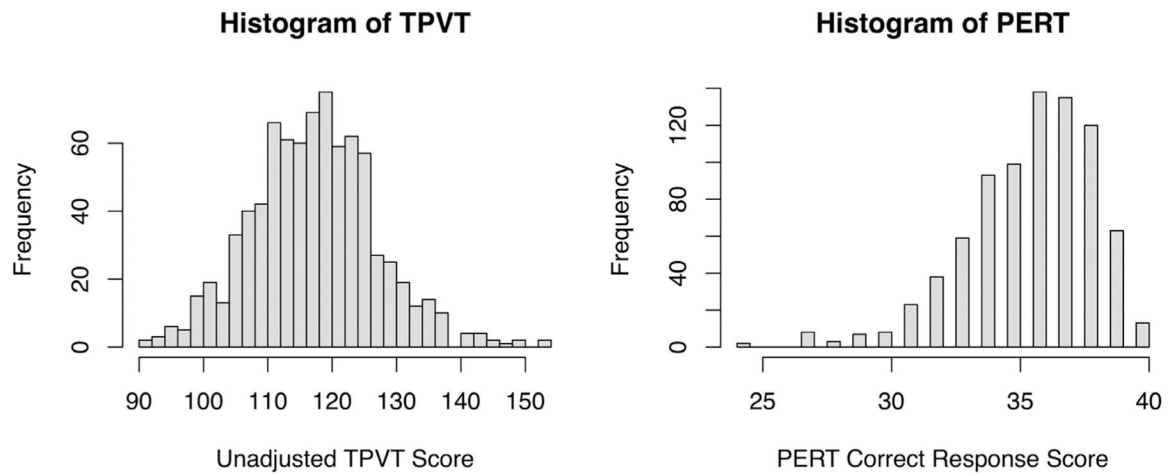
Fig. 2.
Histograms of TPVT and PERT. Left: Histogram of TPVT scores, minimum score = 90.69, maximum score = 153.09, mean of scores = 117.12. Right: Histogram of PERT scores, minimum score = 24, maximum score = 40, mean of scores = 35.59
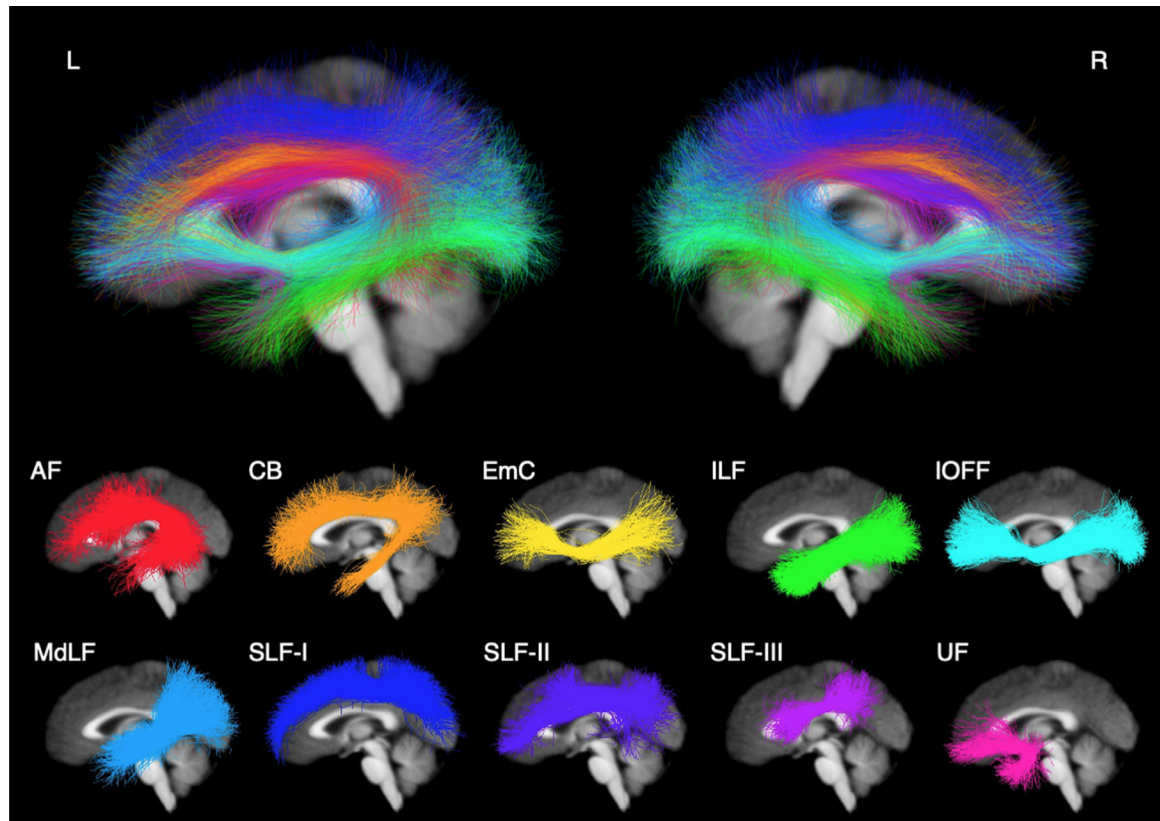
Fig. 3.
The 20 white matter association tracts. Tracts are positioned in front of an HCP population mean T1 mid-sagittal slice. Top panel: Lateral views of the 10 left and 10 right hemisphere tracts. Bottom panel: Each individual left hemisphere tract depicted unaccompanied by other tracts. Tracts visualized do not belong to a single brain, but rather represent the anatomical structure and variability found in the atlas's 100 subjects. Different colors signify different white matter association tracts. L: left; R: right; AF: arcuate fasciculus; CB: cingulum bundle; EmC: extreme capsule; ILF: inferior longitudinal fasciculus; IOFF: inferior occipital fasciculus; MdLF: middle longitudinal fasciculus; SLF-I,II,III: superior longitudinal fasciculus I, II, III; UF: uncinate fasciculus.
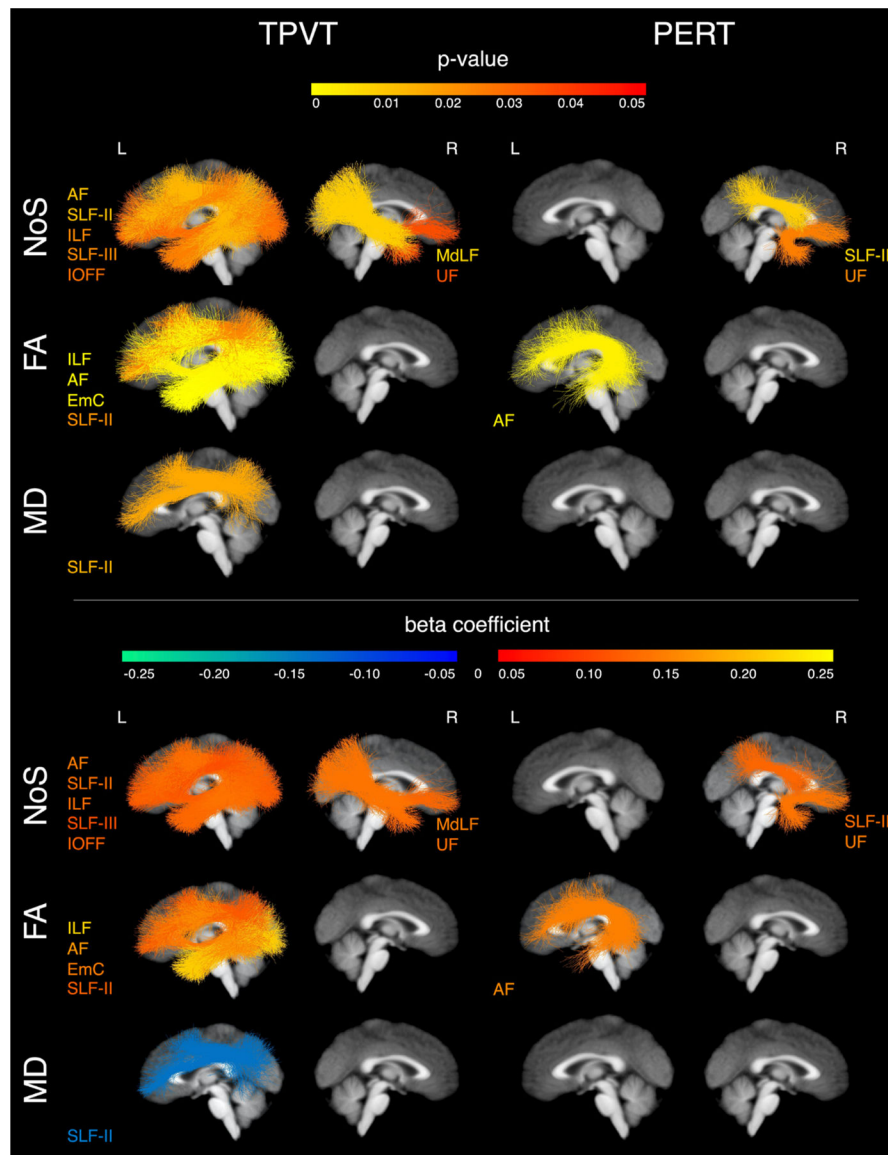
Fig. 4.
Visualization of the association white matter tracts with microstructure that significantly influences performance on PERT or TPVT. Top panel: Tracts are colored according to their FDR-corrected *p*-value. Bottom panel: Tracts are colored according to their standardized beta coefficient. L: left hemisphere, R: right hemisphere, NoS: Number of Streamlines, FA: fractional anisotropy, MD: mean diffusivity; TPVT: Toolbox Picture Vocabulary Test; PERT: Penn Emotion Recognition Test.
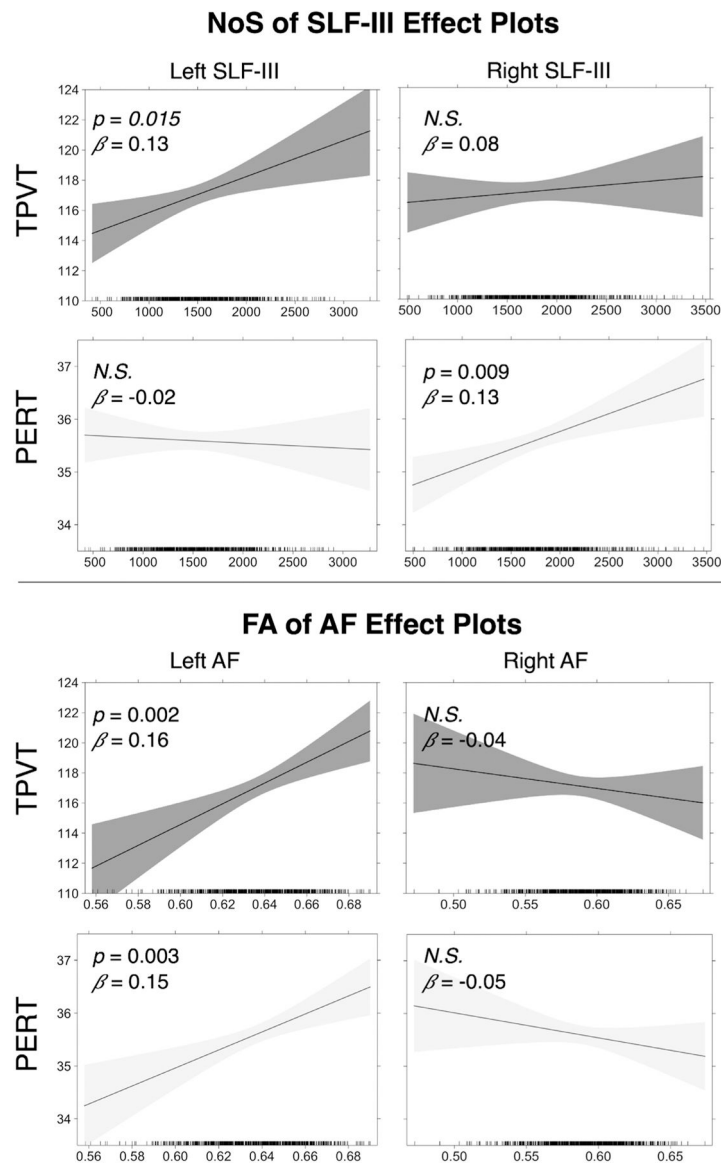
Fig. 5.
SLF-III and AF Effect Plots. Plots depict the effect of the NoS of the SLF-III (top panel) and FA of the AF (bottom panel) in both the left and right hemisphere on TPVT and PERT performance. The shaded region signifies the confidence band for the fitted values computed from the regression model (dark gray: TPVT, light gray: PERT). Tick marks at the bottom of each plot visualize the distribution of FA values and NoS. *P*-values and beta coefficients are reported for each plot. N.S.: not significant.
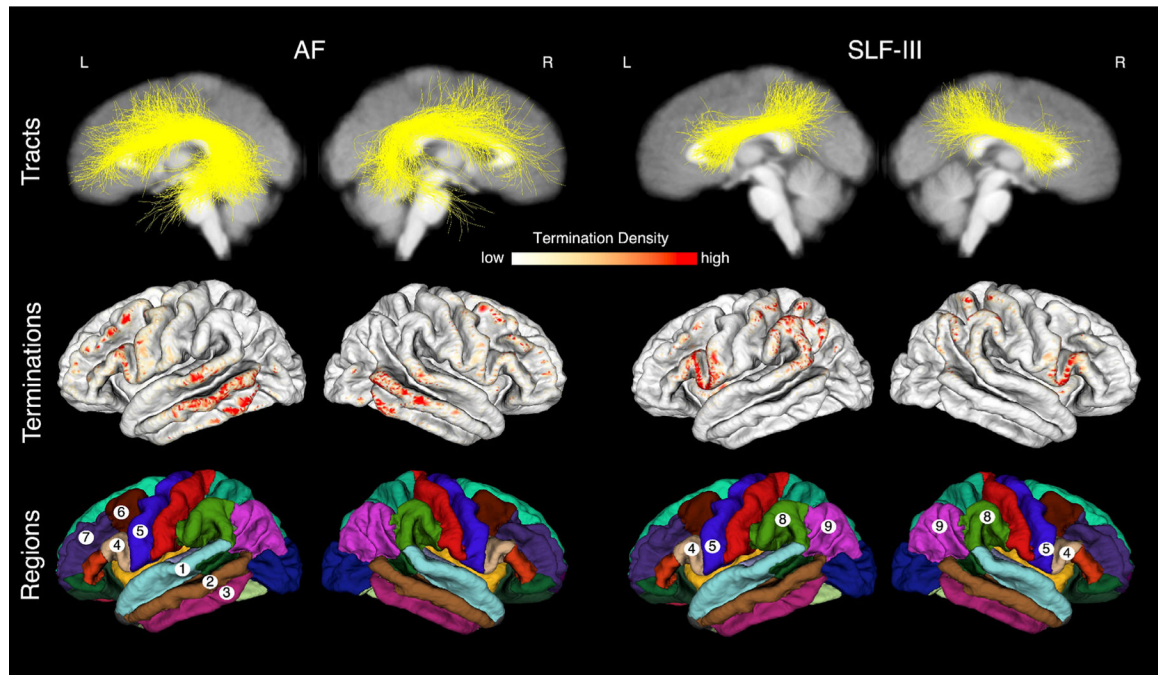
Fig. 6.
The AF and SLF-III are depicted in relation to the cortical regions they connect (see Supplementary Fig. 4 for additional tracts and their connected regions). The first row depicts the atlas white matter tracts (yellow) superimposed over the mid-sagittal slice of the atlas population mean T2w image from left and right lateral views. The second row depicts a cortical surface heat map of the tract termination points; darker red regions indicate a higher density of termination points, while lighter yellow regions indicate lower density of termination points. For ease of interpretation, the third row depicts the cortical regions colored according to the freesurfer color scheme. Regions with a high density of connections in either the AF or SLF-III are numbered. 1: superior temporal, 2: middle temporal cortex, 3: inferior temporal, 4: pars opercularis, 5: precentral, 6: caudal middle frontal, 7: rostral middle frontal, 8: supramarginal, 9: inferior parietal, L: left, R: right, AF: Arcuate Fasciculus, SLF-III: Superior Longitudinal Fasciculus III.

Table 1

Summary of regression models in which the white matter microstructure significantly influenced TPVT or PERT performance. Regression models are ordered by F-statistic. Only the significant ($p < 0.05$) models after FDR correction are reported. F-statistic degrees of freedom are 4 and 804. β denotes the standardized beta coefficients.

	Number of Streamlines				
	P	**β**	**t**	**R^2**	**F**
TPVT				0.07	16.16
left ILF [*]	0.025	0.13	2.81		
right ILF	0.057	0.11	2.45		
age [***]	<0.001	0.13	3.81		
sex	0.117	0.06	1.57		
TPVT				0.06	12.72
left SLF-II [*]	0.015	0.13	3.19		
right SLF-II	0.156	0.08	1.93		
age [***]	<0.001	0.13	3.84		
sex	0.050	0.07	2.01		
TPVT				0.05	10.60
left UF	0.786	0.03	0.72		
right UF [*]	0.035	0.13	2.71		
age [***]	<0.001	0.14	3.96		
sex	0.074	0.07	1.81		
TPVT				0.05	10.05
left MdLF	0.976	− 0.01	− 0.34		
right MdLF [**]	0.009	0.14	3.48		
age [***]	<0.001	0.13	3.74		
sex [*]	0.017	0.11	3.10		
TPVT				0.04	9.08
left AF [*]	0.014	0.14	3.41		
right AF	0.235	− 0.07	− 1.62		
age [***]	<0.001	0.14	3.85		
sex [*]	0.017	0.11	2.99		
TPVT				0.04	9.03
left IOFF [*]	0.029	0.12	2.69		
right IOFF	0.780	0.02	0.44		
age [***]	<0.001	0.14	3.84		
sex [*]	0.044	0.08	2.14		
TPVT				0.04	9.02
left SLF-III [*]	0.025	0.11	2.82		

Number of Streamlines					
	P	**β**	**t**	**R²**	**F**
right SLF-III	0.631	0.03	0.75		
age ***	<0.001	0.14	4.08		
sex *	0.028	0.10	2.62		
PERT				0.02	3.93
left SLF-III	0.953	− 0.02	− 0.43		
right SLF-III **	0.009	0.13	3.32		
age	0.497	− 0.10	− 2.59		
sex *	0.028	− 0.02	− 0.68		
PERT				0.02	3.12
left UF	0.169	− 0.09	− 1.89		
right UF *	0.025	0.14	2.91		
age	0.492	− 0.09	− 2.28		
sex *	0.039	− 0.03	− 0.73		

Fractional Anisotropy					
	P	**β**	**t**	**R²**	**F**
TPVT				0.07	14.93
left ILF ***	<0.001	0.21	4.78		
right ILF	0.919	− 0.02	− 0.46		
age ***	<0.001	0.15	4.18		
sex ***	<0.001	0.15	4.18		
TPVT				0.05	10.24
left AF **	0.002	0.16	3.76		
right AF	0.668	− 0.04	− 0.92		
age ***	<0.001	0.14	4.06		
sex ***	<0.001	0.13	3.74		
TPVT				0.04	9.07
left EmC **	0.004	0.14	3.40		
right EmC	0.508	− 0.07	− 1.78		
age ***	<0.001	0.14	4.09		
sex **	0.001	0.13	3.63		
TPVT				0.04	8.93
left SLF-II *	0.024	0.12	2.76		
right SLF-II	0.955	0.00	− 0.08		
age ***	<0.001	0.14	4.03		
sex **	0.002	0.12	3.33		
PERT				0.02	4.26
left AF **	0.003	0.15	3.50		

| Number of Streamlines | | | | |
	P	**β**	**t**	**R²**	**F**
right AF	0.668	− 0.05	− 1.27		
age	0.531	− 0.07	− 1.95		
sex	0.061	− 0.03	− 0.76		

| Mean Diffusivity | | | | |
	P	**β**	**t**	**R²**	**F**
TPVT				0.04	8.97
left SLF-II *	0.017	− 0.14	− 3.35		
right SLF-II	0.374	0.07	1.60		
age ***	<0.001	0.15	4.30		
sex **	0.003	0.12	3.30		

Significant codes are *** for $p < 0.001$, ** for $p < 0.01$, and * for $p < 0.05$ (after controlling for multiple comparisons). FA: fractional anisotropy, MD: mean diffusivity, NoS: number of streamlines, TPVT: Toolbox Picture Vocabulary Test, PERT: Penn Emotion Recognition Test.