Separate lanes for math and reading in the white matter highways of the human brain

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Keywords

Reading, math, language, network, connectome, anatomy, functional MR, diffusion MR

Abstract

Math and reading involve distributed brain networks and learning disabilities associated with these skills have a high rate of co-occurrence. However, it is unknown what are shared vs. dissociated white matter substrates of math and reading networks. Here we address this question using an innovative, multimodal approach applying functional MRI, diffusion MRI, and quantitative MRI to define these networks and evaluate structural properties of their fascicles. Results reveal that the superior longitudinal (SLF) and arcuate (AF) fascicles are shared between math and reading networks. Strikingly, within these fascicles, reading- and math-related tracts are segregated into parallel sub-bundles and show structural differences related to myelination. These novel findings: (i) open a new avenue of research enabling linkage of sub-bundles within fascicles to behavior and (ii) may explain both isolated and comorbid cases of math and reading disabilities, which may be associated with white matter abnormalities within sub-bundles or entire fascicles, respectively.

Math and reading are essential for functioning in modern society. We are not born with these skills, but rather acquire them through extensive learning, typically in childhood. While math and reading are distinct tasks, they utilize several overlapping cognitive processes, including encoding of visual stimuli, verbalization, as well as working memory[1]. There is also a surprisingly high rate of co-morbidity between math and reading disabilities: 17%-66% of children affected by dyscalculia, a math learning disability, also suffer from dyslexia, a reading learning disability (for review see[2]). A large body of research has examined both the cortical regions and the white matter connections of the reading network[3,4]. However, the cortical network[5] and, specifically, the white matter connections of the math network are not well understood. Further, presently it is unknown which white matter connections are shared or dissociated across reading and math networks.

Investigations on the white matter tracts crucial for reading have discovered several key white matter fascicles including: (i) The arcuate fasciculus (AF), which connects the frontal and temporal cortices. Diffusion MRI (dMRI) measurements show that fractional anisotropy (FA) in the left AF correlates with phonological awareness in both typical[6] and impaired[7,8] readers and that dyslexics have reduced FA in the left AF[7,9]. (ii) The inferior fronto-occipital fasciculus (IFOF), which connects the frontal and occipital cortices. Children with dyslexia show a reduced leftward asymmetry of the IFOF[10] and FA of this tract is linked to orthographic processing skill[7,11]. (iii) The inferior longitudinal fasciculus (ILF), which connects the occipital lobe with the anterior tip of the temporal lobe. Lesions to the ILF can lead to pure alexia[12], and atypical development of FA in the ILF is associated with poor reading proficiency[13] as well as dyslexia[8]. (iv) The vertical occipital fasciculus (VOF), which connects the occipital and parietal cortices[14] and is thought to relay top-down signals from the intraparietal sulcus (IPS) to ventral occipito-temporal cortex during reading[15]. Interestingly, these four fascicles intersect with the visual word form area (VWFA)[16,17], a region in the occipito-temporal sulcus (OTS) that responds preferentially to words over other stimuli. The VWFA is thought to process visually presented words[18,19] and is causally involved in word recognition, as lesioning it produces dyslexia[20].

To date, it is unknown if these fascicles, which are important for reading, are also associated with mathematical processing. This fundamental gap in knowledge is due to three main reasons: First, substantially more neuroscience research has been done on the neural bases of reading[3,4] than the neural bases of math[5]. Second, most prior studies have evaluated either the neural bases of math[21–25] or the neural bases reading[16,18,26–31], but not both systems in the same individuals (for an exception see [32]). Third, to our knowledge, no study has examined the relationship between gray and white matter substrates of the math network. That is, it is unknown which fascicles intersect with cortical regions involved in mathematical processing. In contrast, a few previous studies have examined which white matter fascicles connect to a key cortical region of the reading network, namely the VWFA[16,17]. Thus, the goal of this study is twofold: (1) identify and quantify the white matter fascicles of the brain network involved in mathematical processing and (2) determine which aspects of this white matter are unique to the math network, and which are shared with the reading network.

To fill these gaps in knowledge we applied an innovative, multimodal approach, in which we collected function MRI (fMRI), diffusion MRI (dMRI), and quantitative MRI (qMRI) data from the same 14 participants. The goal of the fMRI experiment was to identify in each participant's brain the cortical regions that are involved in reading or mathematical processing, as in our prior study[33]. Using dMRI data and modern tractography methods that account for crossing fibers[34–36], we generated a whole-brain white matter connectome in each participant. Using automatic fascicle quantification[37] (AFQ) we identified in each subject's connectome 12 major white matter fascicles, bilaterally. We then determined the functionally-defined white matter tracts (fWMT) of each the math and reading network by intersecting these 12 fascicles with the cortical regions involved in math or reading as identified by fMRI, in each subject. Together, this allowed us to determine (1) what are the white matter fascicles of the math and reading networks (2) which fascicles are network unique and which are shared between math and reading, and (3) whether white matter tracts associated with math and reading are physically intertwined or segregated within a fascicle. Finally, we measured the proton relaxation time[38–40] (T_1) of fWMT of the math and reading networks using qMRI. As T_1 in the white matter is correlated with myelination[41] and T_1 changes with development and varies across fascicles[42], qMRI data provides a unique opportunity to test if there are differences in structural white matter characteristics across the reading and math networks.

The multimodal approach outlined above enabled us to determine for the first time what are the shared and segregated white matter fascicles of the math and reading networks, as well as measure their structural properties. This advancement broadens our understanding of the brain substrates of fundamental skills learned by children world-wide. This, in turn, may provide a key stepping stone for understanding how childhood education may shape the brain.

Results

Neighboring gray matter regions process math and reading

We first used fMRI to define gray matter regions that are involved in math and reading tasks in each participant. In the fMRI experiment, participants performed a reading task, a math task, and a color memory task on the same visual stimuli (number-letter morphs, **Fig. 1a**). In each trial, subjects viewed a cue indicating the task ("Read" /"Add"/"Color"), then viewed four number-letter morph stimuli that were presented sequentially, and at end of the trial gave a task-relevant 2-alternative-forced choice answer. In the math (adding) task, subjects summed up the presented stimuli and indicated which of the numbers is the correct sum. In the reading task, they were instructed to read the word and indicate which of the 2 words they had read, and in the color task they were instructed to attend to the color of the stimuli and indicate which of 2 colors had been used for one of the presented characters. Crucially, these tasks were performed on the same visual input and were matched in their working memory load and the amount of verbalization they elicit. Regions involved in math were defined by higher responses during the math task than the reading and color tasks, while regions involved in reading were defined by higher responses during the reading task than the math and color tasks (as in our prior study[33]). Crucially, all regions were defined in individual subjects' native anatomical space and without spatial smoothing, as both group averaging and spatial smoothing may introduce artificial overlap between regions[43].

We found consistently stronger responses during the reading task compared to math and color tasks in four anatomical expanses (**Fig. 1b-green, Supplementary Fig. 1-2**): (i) A region in the occipito-temporal sulcus (OTS) (left hemisphere: N=12, size ±SE: 506±140 mm^3; right hemisphere: N=9, size ±SE: 90±34 mm^3). Activations in the OTS were frequently divided into two distinct subregions and likely correspond to the visual word form areas (VWFA1 and VWFA2[18,19]). Here, we took their union as a single functional region of interest (fROI), as we are interested in determining the large-scale white matter networks associated with reading and math. (ii) A region in the superior temporal sulcus (STS), which extended into the middle temporal sulcus (left hemisphere: N=14, size ±SE: 842±258 mm^3; right hemisphere: N=12, size ±SE: 399±153 mm^3). (iii) A region in the supramarginal gyrus (SMG) (left hemisphere: N=14, size ±SE: 511±204 mm^3; right hemisphere: N=14, size ±SE: 84±30 mm^3). (iv) A region in the inferior frontal gyrus (IFG), which likely corresponds to "Broca's Area" (left hemisphere: N=14, size ±SE: 1484±351 mm^3; right hemisphere: N=14, size ±SE: 606±144 mm^3). Activations in the IFG spanned 2-3 clusters and here we took their union. Activations during reading were substantially smaller and less frequent in the right hemisphere than the left hemisphere, thus we report further analyses only for the left hemisphere.

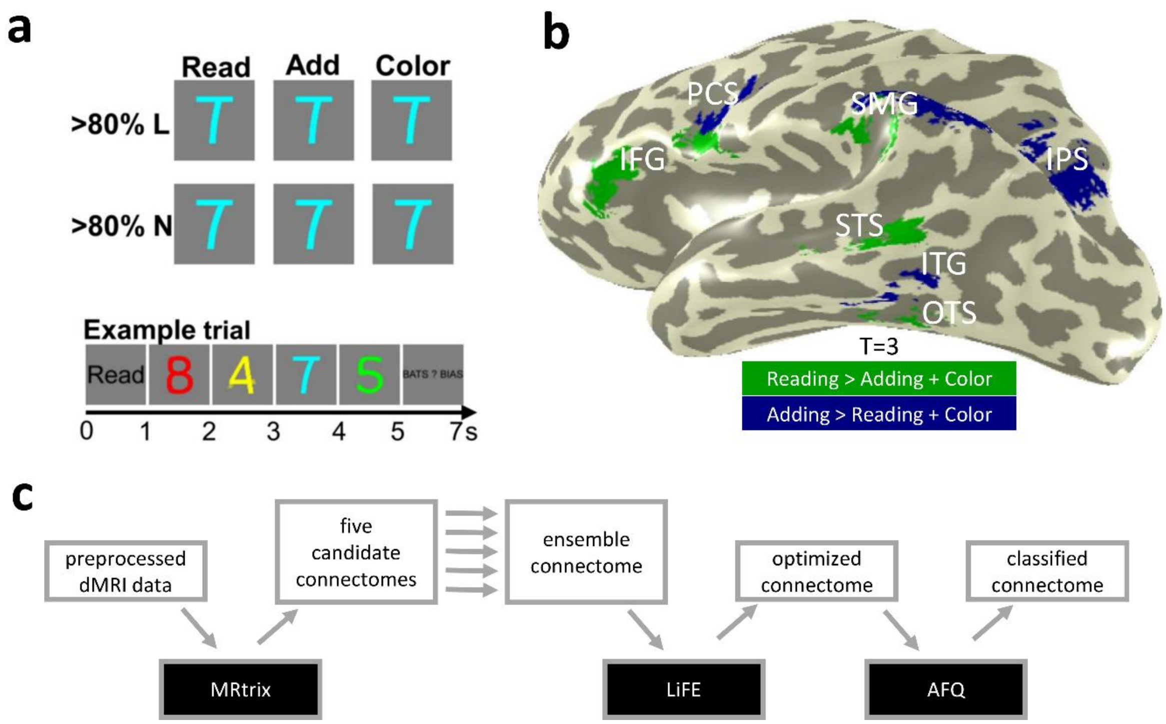

Figure 1. Overview of the Experimental Methodology. (a) FMRI experiment used to define math- and reading-related regions. Subjects viewed morphs between numbers and letters, containing either >80% letter (<20% number) or >80% number (<20% letter) information. At the beginning of each trial, a cue ("Read"/"Add"/"Color") indicated which task should be performed, then 4 stimuli of the same morph type appeared for 1 sec each, followed by an answer screen presented for 2 seconds. Subjects indicated their answer with a button press. Identical stimuli were presented across tasks. Trial structure is shown at the bottom. **(b)** Gray matter regions used to identify the math and reading networks. Reading- (green) and math- (blue) related regions were defined based on higher responses in the reading task or the math task, respectively, than the other tasks (T≥3). *Abbreviations:* IFG=inferior frontal gyrus, PCS=precentral sulcus, SMG=supramarginal gyrus, STS=superior temporal sulcus, ITG=inferior temporal gyrus, OTS=occipito-temporal sulcus, IPS=intraparietal sulcus. **(c)** DMRI processing pipeline. DMRI data was preprocessed to correct for motion and Eddy currents. Tractography was done with constrained spherical deconvolution (CSD) and probabilistic fiber tracking using the MRtrix software. We generated 5 candidate connectomes with different curvatures (0.5,1,2,4). These candidate connectomes were then concatenated into one large ensemble connectome. Linear fascicle evaluation (LiFE) was used to optimize the concatenated connectome. Tracts that did not make a substantial contribution to predicting the diffusion data were removed. The resulting optimized connectome was analyzed by automated fascicle quantification (AFQ) to extract 12 well-established fascicles in each hemisphere.

We also identified four bilateral regions that responded more strongly during the adding than reading or color tasks (**Fig. 1b-blue, Supplementary Fig. 1-2**): (i) A region in the inferior temporal gyrus (ITG; left hemisphere: N=13, size ±SE: 539±165 mm^3; right hemisphere: N=13, size ±SE: 475±92 mm^3), which is consistent with prior studies[33,44]. (ii) A region in the intra-parietal sulcus (IPS; left hemisphere: N=13, size ±SE: 948±234 mm^3; right hemisphere: N=12, size ±SE: 1042±181 mm^3), which is in line with previous research showing IPS involvement in numerosity processing[21,23]. (iii) A region in the SMG (left hemisphere: N=14, size ±SE: 749±217 mm^3; right hemisphere: N=14, size ±SE: 818±119 mm^3). (iv) A region in the inferior part of the precentral sulcus (PCS; left hemisphere: N=12, size ±SE: 617±158 mm^3; right hemisphere: N=14, size ±SE: 401±79 mm^3). This region is anatomically proximal to the inferior frontal junction (IFJ), which has been implicated in visual object-based attention[45].

Interestingly, gray matter regions involved in reading and math were often neighboring. In the prefrontal cortex, the reading-related IFG is proximal, but inferior to the math-related PCS. Likewise, in the SMG the reading-related fROI was proximal, but inferior to the math-related fROI. In the temporal cortex, math-related ITG is in between two reading-related fROIs, centered on the STS and OTS. In the IPS we found only a math-related fROI.

The SLF and the AF contribute to math and reading networks

After establishing which cortical regions are activated during math and reading tasks, we determined which fascicles are associated with each of these fROIs (**Fig. 2**). For this, we identified 12 well-established fascicles of the brain bilaterally in each participant using AFQ. Next, we intersected each participant's classified white matter connectome with each of the eight fROIs to determine the functionally-defined white matter tracts (fWMT) associated with reading or math. To summarize the fascicles connecting to each reading and math related region across subjects, we quantified for each fROI the percentage of the fWMT associated with each of the 12 fascicles identified by AFQ. We will refer to this relative contribution of each fascicle as "connectivity weight". Results reveal two main findings.

First, across participants, six fascicles contain almost all fWMT of each fROI (sum of their connectivity weights is close to 100%). These fascicles are: inferior fronto-occipital fasciculus (IFOF), inferior longitudinal fasciculus (ILF), superior longitudinal fasciculus (SLF), arcuate fasciculus (AF), posterior AF (pAF), and vertical occipital fasciculus (VOF). In Figure 2, the left panels show the fWMT of math and reading fROIs in a representative subject; the middle panels show the connectivity weight of these fascicles across subjects; the right panel provide a schematic illustration of the same data, depicting the general anatomical layout. Supplementary Figure 3 shows the same analyses for the right hemisphere math related fROIs. Four out of these six fascicles: SLF, AF, pAF, and VOF form the backbone of the math and reading networks. For at least one fROI in each network, these fascicles contain >10% of all fWMT.

Second, we found that anatomically neighboring math and reading fROIs in the prefrontal cortex and SMG connect to the same fascicles with a comparable weight. That is, they show a relatively similar connectivity fingerprint. Both the reading fROI in the IFG and math fROI in the PCS illustrate substantial connectivity to the SLF (connection weight > 59%), which connects the frontal and parietal lobes. Further, each of the IFG and PCS fROIs are also connected with the AF (connection weight >26%), which connects the fontal and temporal lobes, and these frontal fROIs show no substantial connections to other fascicles (**Fig. 2**, first row). Both reading and math fROIs in the SMG are also strongly connected to the SLF (weight >80%), are weakly connected to the pAF (>16%), which connects the parietal and temporal lobes, and show no substantial connections to other fascicles (**Fig.**

2, second row). In comparison, reading and math fROIs in the temporal cortex and IPS showed more differentiated connections across networks. For example, while the reading fROI in the OTS showed above 10% connection weight with the AF, pAF, and VOF, a nearby math fROI in the ITG showed above 10% connection weight for the former two, but not the latter (**Fig. 2**, third row).

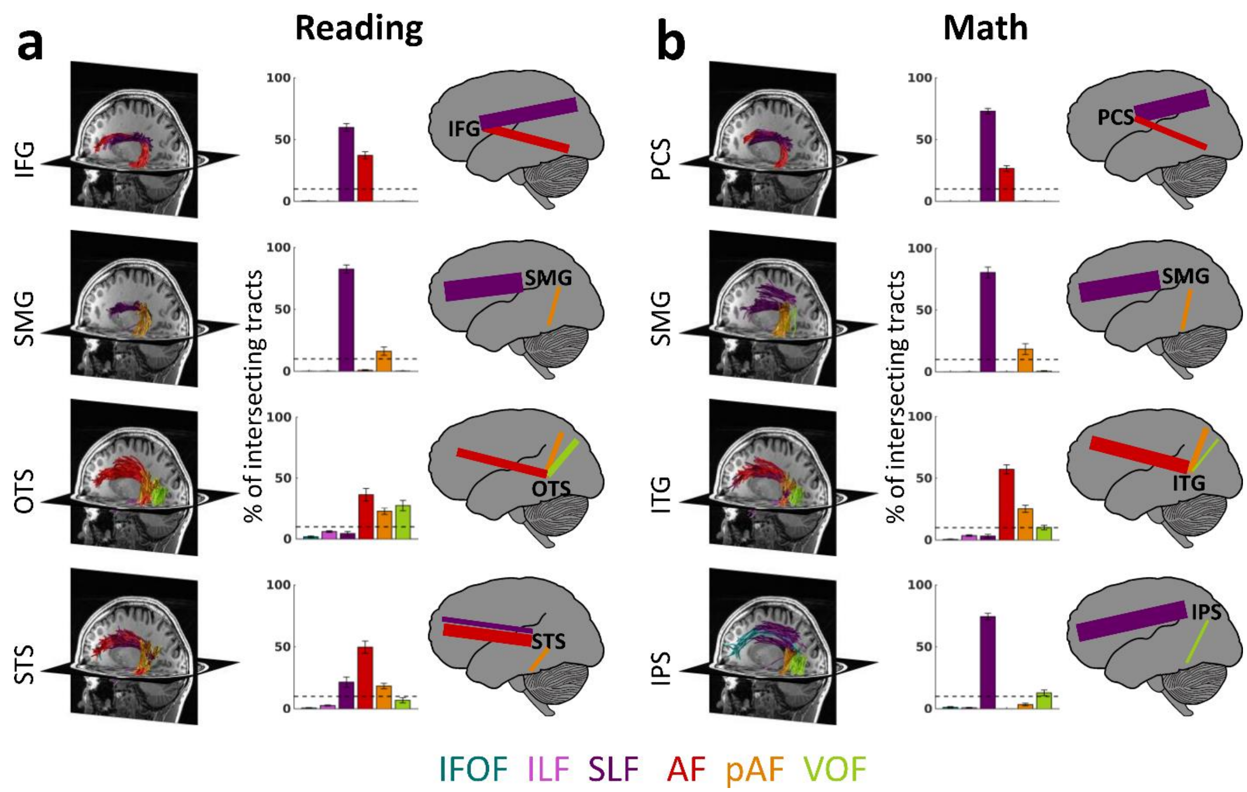

Figure 2. Functionally-defined white matter tracts (fWMT) of reading and math related regions. (a) Six fascicles (see legend at the bottom) contain close to 100% of all fWMT of the fROIs identified in the reading task. **(b)** The same six fascicles also contain close to 100% of all fWMT of the fROIs identified in the math task. In **(a, b)**: *Left:* fWMT for each fROI in a representative subject's left hemisphere. The same subject is displayed in all panels; Fascicle are color coded in accordance with the legend at the bottom. *Middle*: Bar graphs showing what percentage of the fWMT is associated with each of the six fascicles. The graph shows the mean across subjects ± SEM. *Dashed horizontal line*: Line is placed at 10%, which was the cut-off used for schematics in the right columns. *Right:* Schematic illustration of the fascicles associated with each fROI. The thickness of the lines is derived from the bar graph, showing the relative weight of each fascicle. *Abbreviations*: IFG=inferior frontal gyrus, PCS=precentral sulcus, SMG=supramarginal gyrus, STS=superior temporal sulcus, ITG=inferior temporal gyrus, OTS=occipito-temporal sulcus, IPS=intraparietal sulcus, IFOF=inferior fronto-occipital fasciculus, ILF=inferior longitudinal fasciculus, SLF=superior longitudinal fasciculus, AF=arcuate fasciculus, pAF=posterior arcuate fasciculus, VOF=vertical occipital fasciculus.

To determine the fWMT of the math and reading networks, rather than of isolated fROIs, we next evaluated within-network connections. Thus, we identified fWMT that connect between pairs of fROIs within each network (**Fig. 3a,e** shows a representative subject). We quantified the pairwise connections relative to the total fWMT of these fROIs using the dice coefficient (DC[46]), and evaluated if it was significantly greater than chance level (**Fig. 3b,f**). The DC indicates the proportion of fWMT shared between two fROIs relative to the total fWMT of these fROIs. We also evaluated which fascicles the fWMT connecting pairs of regions are associated with (**Fig. 3c,g**). Supplementary Figure 4 shows the same analyses for the right hemisphere math network.

In the reading network we find significantly (to determine significance we used the Bonferroni adjusted threshold of $p<0.008$) above chance DC (**Fig. 3a,b**) between: (i) the OTS and the STS (paired t-test: $p=0.0003$, $t(11)=5.30$), (ii) the OTS and the IFG (paired t-test: $p=0.002$, $t(11)=3.98$), (iii) the STS and the IFG (paired t-test: $p<0.0001$, $t(13)=5.89$), and (iv) the SMG and the IFG (paired t-test: $p=0.0004$, $t(13)=4.78$). The frontal-parietal (SMG-IFG) and frontal-temporal connections (STS-IFG; OTS-IFG) of the reading network are supported by the SLF and the AF, respectively (**Fig. 3c**). In the math network, we find significantly (to determine significance we used the Bonferroni adjusted threshold of $p<0.008$) above chance DC (**Fig. 3e,f**) between (i) the ITG and the PCS (paired t-test: $p<0.0001$, $t(11)=6.21$, **Fig. 3f**) supported by the AF (**Fig. 3g**), and (ii) between the SMG and the PCS (paired t-test: $p=0.0003$, $t(11)=5.26$, **Fig. 3f**), through the SLF (**Fig. 3g**). We summarize the pairwise connections and their predominant contributing fascicle in a schematic of within-network connections (**Fig. 3d,h**). Overall, these analyses suggest that both math and reading networks illustrate significant within-network connectivity, and the AF and the SLF emerge as key fascicles in both networks.

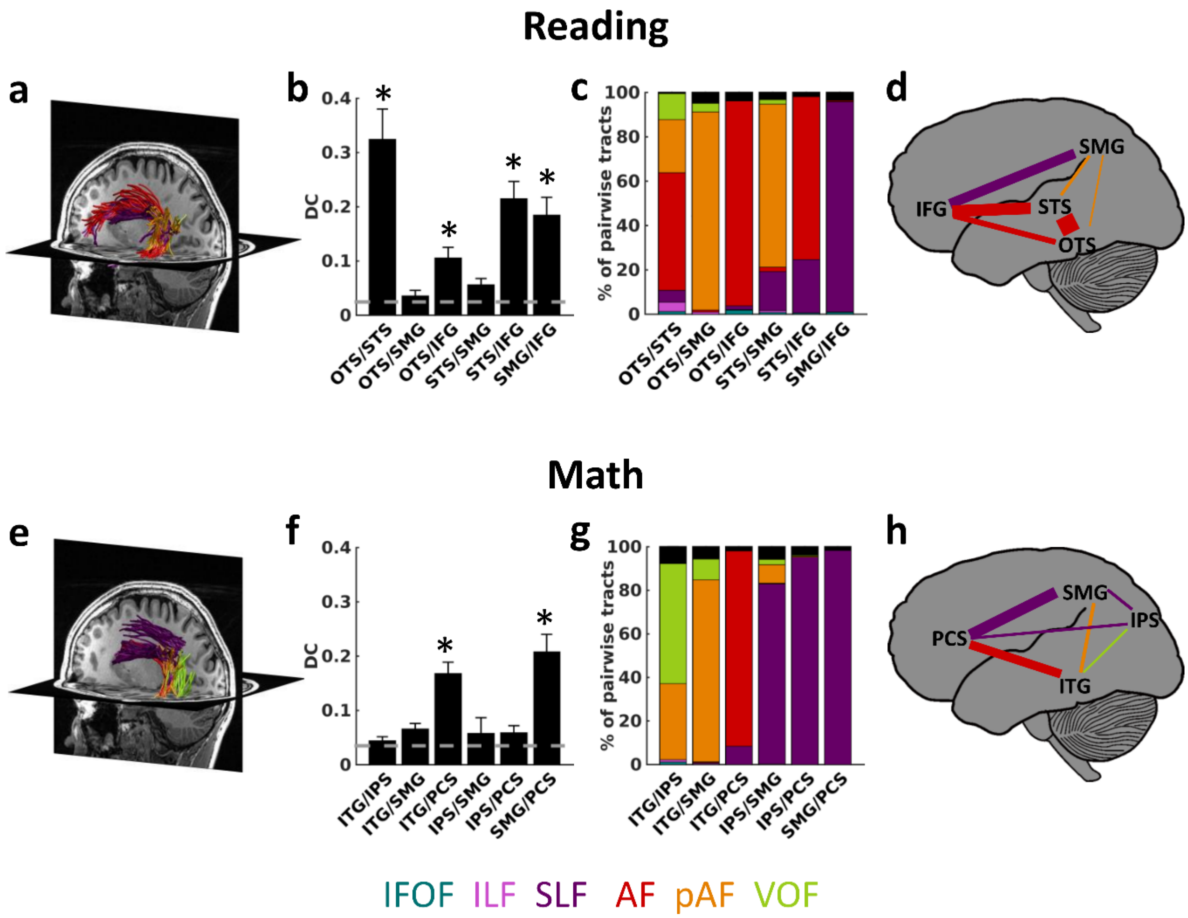

Figure 3. Pairwise fWMT within the reading (a-d) and math (e-f) networks. (a,e): Pairwise white matter connections in a representative subject's left hemisphere. **(b,f)**: Dice coefficient (DC) of pairwise within-network connections, mean across subjects ± SEM. The DC quantifies the overlap in the fWMT of both fROIs: a DC of 1 indicates that all tracts that intersect with the first fROI also intersect with the second fROI, while a DC of 0 indicates no shared tracts. X-labels indicate the fROI pairing. *Dashed line:* Chance level DC estimated from the average connections of each network to out of network fROIs in ventral temporal cortex that were activated maximally during the color task. *: DC is significantly higher than chance, $p<0.008$ (significance level was Bonferroni adjusted). **(c,g)**: The relative contribution of six fascicle (see legend at the bottom) to the overall pairwise connections. X-labels indicate the fROI pairing. **(d,h)**: Schematic illustration of the pairwise connections in the reading and math networks. *Line thickness* is scaled proportionally to the DC; *color* indicates the fascicle with the highest relative contribution to pairwise connections. *Abbreviations:* IFG=inferior frontal gyrus, PCS=precentral sulcus, SMG=supramarginal gyrus, STS=superior temporal sulcus, ITG=inferior temporal gyrus, OTS=occipito-temporal sulcus, IPS=intraparietal sulcus, IFOF=inferior fronto-occipital fasciculus, ILF=inferior longitudinal fasciculus, SLF=superior longitudinal fasciculus, AF=arcuate fasciculus, pAF=posterior arcuate fasciculus, VOF=vertical occipital fasciculus.

Reading and math tracts are segregated within SLF and AF

Our data show that the SLF and the AF are important fascicles of both the math and the reading networks. However, both the SLF and AF are large and contain many tracts. This raises the question of whether the entire fascicles are part of both networks or, alternatively, if sub-bundles within these fascicles relay tracts of the reading network, or the math network, respectively.

We tested these hypotheses by visualizing and quantifying within the SLF tracts connecting the IFG and SMG in the reading network as well as the PCS and SMG in the math network, and examined if they are spatially intertwined or segregated in each subject. Similarly, in the AF, we visualized and compared tracts connecting the PCS and the ITG in the math network and the IFG and STS in the reading network. Across subjects, and in both the SLF and the AF, tracts were segregated by network: fWMT of the math network (blue in **Fig. 4a,d**; **Supplementary Fig. 5-6**) were consistently superior to fWMT of the reading network (green in **Fig. 4a,d**; **Supplementary Fig. 5-6**). Interestingly, this superior to inferior organization mirrors the spatial layout of neighboring math and reading fROIs on the cortical surface (**Fig. 1b**).

To validate and quantify this segregation, we first sectioned the SLF and AF to 30 (which is the default in AFQ) equal-sized bins, referred to as nodes, in each subject and then conducted two additional analyses:

(1) We measured the distribution of distances (Euclidean distance in mm) between individual tracts from the core tract (mean tract) of the network they belong to vs. the core tract of the other network. We reasoned that if tracts of the math and reading networks are segregated, distances to the within-network core tract should be smaller than to the between-network core tract. In contrast, if the tracts are intertwined, distances should not be significantly different. Results show that individual tracts are significantly closer to the within-network core tract, compared to the core tract of the other

network in both the SLF (two-sample Kolmogorov-Smirnov test on distance distributions: $p<0.0001$; paired t-test on mean distance across tract: $p<0.0001$, $t(11)=6.86$) and the AF (two-sample Kolmogorov-Smirnov test on distance distributions: $p<0.0001$; paired t-test on mean distance across tract: $p<0.0001$, $t(11)= 10.44$) (**Fig. 4c,f**).

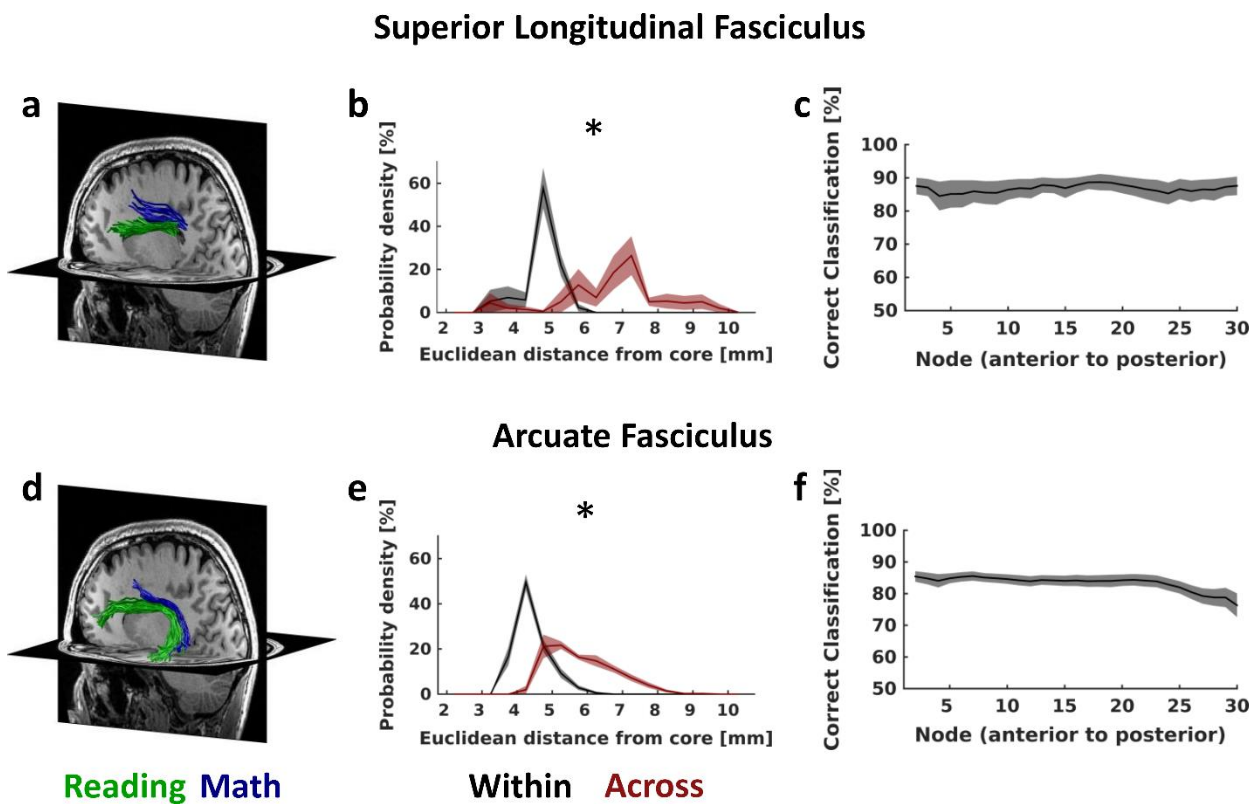

Figure 4. Pairwise connections within the reading and the math networks are segregated and parallel in the SLF and the AF. (a-c): SLF tracts connecting IFG and SMG in the reading network and PCS and SMG in the math network. **(d-f)**: AF tracts connecting the IFG and STS in the reading network and the PCS and ITG in the math network. **(a,d)**: Math (blue) and reading (green) tracts of the SLF and AF in a representative individual subject showing the spatial segregation of these tracts. **(b,e)**: Euclidean distance in mm (derived from x,y,z coordinates) of all tracts relative to the core (mean) tract, within-network (black) and across-network (maroon). The distance was calculated across all tracts; the plot shows the mean across all nodes of 12 subjects ±SEM. * Distributions differ significantly, $p<0.05$. **(c,f)**: Performance of a SVM classifying math and reading tracts within the SLF and AF based on their spatial location. Data show mean classification accuracy across nodes in 12 subjects ±SEM. *Abbreviations:* IFG=inferior frontal gyrus, PCS=precentral sulcus, SMG=supramarginal gyrus, STS=superior temporal sulcus, ITG=inferior temporal gyrus, AF=arcuate fasciculus, SLF=superior longitudinal fasciculus.

(2) Next, we used an independent classifier approach to evaluate if reading- and math-related fWMTs are spatially segregated at the entire length of the fascicle or only in a restricted region. We reasoned that if they are segregated at each node, a classifier should be able to determine if tracts belong to either the math or reading network solely based on their spatial location within the fascicle. To test this prediction, at each node, we trained a support vector machine (SVM) classifier with a 2^{nd} degree polynomial kernel to distinguish math tracts from reading tracts based on their location (training: x,y,z coordinates of all tracts in a node). Then, we tested how well the SVM classifies new data based on tract coordinates at the neighboring more posterior node. Across subjects and nodes, classification of tracts as being either associated with reading or math was greater than 75% correct in both the SLF and the AF (**Fig. 4-b,e**). The average classification across the fascicle was significantly higher than the 50% chance level (SLF: $p<0.0001$, $t(11)=12.41$; AF: $p<0.0001$, $t(11)=18.88$).

These analyses show that tracts associated with math and reading remain segregated, and largely parallel to each other within the SLF and the AF; within these fascicles tracts of the math network are located superior to tracts of the reading network.

Reading tracts show faster T_1 than math tracts

As our data indicate spatial segregation between tracts associated with reading and math, within the SLF and AF, we next asked if there are also structural differences between reading and math fWMT within these fascicles. Using qMRI we measured T_1 of reading and math fWMT, as T_1 is inversely correlated with myelination (lower T_1 is associated with higher myelin content, we also tested macromolecular tissue volume fraction (MTV), which yielded comparable results (**Supplementary Fig. 7**)).

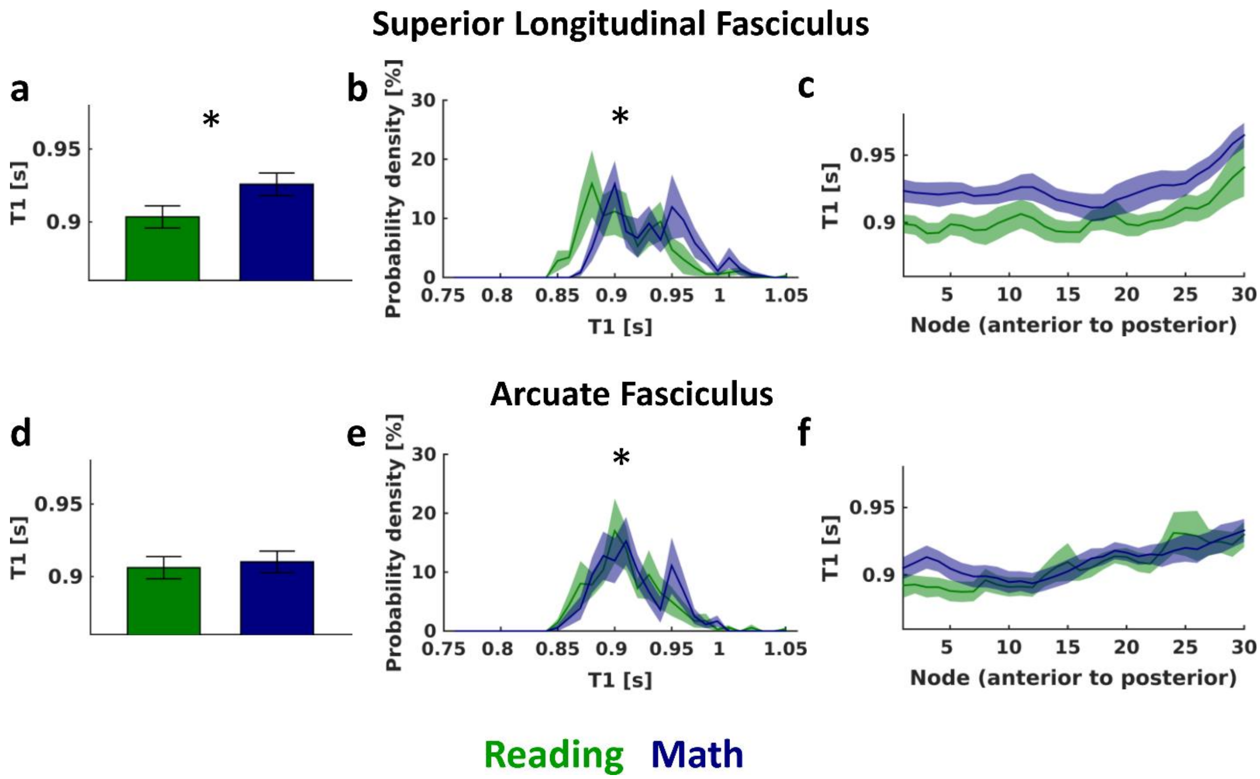

Figure 5. Tracts associated with reading show faster proton relaxation time (T_1) than those associated with math in the SLF and the anterior section of the AF. (a-c): T_1 measurements for SLF tracts connecting IFG and SMG in the reading network (green) and PCS and SMG in the math network (blue). **(d-f)**: T_1 measurements for AF tracts connecting the IFG and STS in the reading network (green) and the PCS and ITG in the math network (blue). **(a,d)**: Average T_1 for reading- and math-related tracts in the SLF and the AF. Bar graph shows mean across 12 subjects ± SEM. *: T_1 for math and reading related tracts differs significantly, $p<0.05$. **(b,e)**: Distribution of T_1 values across all tracts. Distributions were calculated within each subject and node; the plot shows the mean across all nodes of 12 subjects ± SEM. *: Distributions differ significantly, $p<0.05$. **(c,f)**: Average T_1 for reading- and math-related tracts along the SLF and the AF. Line graph shows mean across subjects ± SEM. *Abbreviations:* IFG=inferior frontal gyrus, PCS=precentral sulcus, SMG=supramarginal gyrus, STS=superior temporal sulcus, ITG=inferior temporal gyrus, SLF=superior longitudinal fasciculus, AF=arcuate fasciculus.

We first measured the average T_1 of math and reading tracts across the length of the fascicles (**Fig. 5a,d**). In the SLF, but not in the AF, average T_1 was significantly lower in reading tracts than in math tracts (SLF: p=0.006, t (11)=3.39; AF: p=0.11, t(11)=1.72). Since the SLF and AF are long fascicles, we also tested for local difference across the tracts. For this, we segmented each tract to 30 nodes in each subject and then measured T_1 along the tracts. Examination of the distributions of T_1 values across the nodes of these tracts showed lower T_1 in the fMWTs of the reading network compared to the math network in both the SLF (two-sample Kolmogorov-Smirnov test: $p<0.0001$) and the AF (two-sample Kolmogorov-Smirnov test: $p<0.03$, **Fig. 5b,e**). Examination of the spatial distribution of T_1 values along the tracts revealed differences across the SLF and AF (**Fig. 5c,f**). In the SLF, T_1 in fWMT of the reading network was consistently lower than in fWMT of the math network, throughout the entire length of the SLF. However, in the AF, T_1 of fWMT of the reading network was lower than T_1 of fWMT of the math network only towards the anterior end of the fascicle. The faster T_1 found along the SLF and the anterior section of the AF for tracts associated with reading, suggests that these tracts are more heavily myelinated then those associated with math.

Discussion

In the current study, we addressed a fundamental gap in knowledge in human brain function: what are the shared and dissociated white matter substrates of math and reading, the two most essential skills every child is expected to acquire in school. Our multimodal data revealed three key findings. First, neighboring gray matter regions in the math and reading networks show similar white matter connectivity. Second, the AF and SLF are important for within network connectivity in both reading and math networks. Third, within the SLF and the anterior AF, tracts associated with math and reading are segregated, and show significant structural differences. Our data thereby opens a new avenue of research focused on understanding how subdivisions of fascicles contribute to human behavior.

Our study made several significant innovations compared to prior studies that investigated white matter in reading and math. First, spherical deconvolution methods (CSD) have rarely been used to investigate tracts associated with reading[10,47] and math[25]. This innovation is crucial as the commonly applied tensor-based tracking methods are unable to resolve white matter tracts close to the gray matter. Therefore, tensor-based methods do not allow examining which white matter tracts connect to which gray matter regions. Second, we report, for the first time, the white matter fascicles associated with several distinct cortical regions involved in math and reading measured within the same individuals. This produced a more precise and comprehensive understanding of the white matter associated with functional regions of both the math and reading networks. After all, prior studies have either examined white matter[5,25] or gray matter regions[5,24] in isolation or have focused only on determining the white matter connections of one region in the reading network, the VWFA[16,17]. In contrast, here we not only investigated the white matter tracts associated with multiple regions in each network, but also determined which fascicles connect between regions. Third, this is the first study to apply qMRI to elucidate structural properties of fascicles involved in math and reading. Prior investigations of white matter tracts of math and reading reported FA, mean or directional diffusivity of these tracts. While these metrics provide valuable characterization of white matter and its development[42], the relation of these metrics to the underlying microstructure is complex and not well understood[48,49]. In contrast T_1 of the white matter is directly correlated with myelin content[41], thereby providing important insights about a fundamental structural component of these tracts. Fourth, by designing an experiment that uses identical stimuli for three different tasks, which are matched in their working memory load and the amount of verbalization they elicit, we were able to distil cortical regions that are specifically involved in math or reading, while controlling for stimulus differences as well as general cognitive demands.

Importantly, our innovations and data provide direct functional and structural evidence for the triple-code-model (TCM) of numerical processing[50], the most influential model in mathematical cognition. In brief, the TCM posits that there are three representations of numbers in the brain: (i) a visual representation, (ii) a magnitude (often referred to as a numerosity) representation, and (iii) a verbal representation. Our data provides strong empirical evidence supporting the TCM, as we find a likely neural correlate of each of these representations; we find activations (i) centered on the ITG, which is thought to be involved in transforming visual information to a number quantity[33,51–53], (ii) the IPS, which is thought to be involved in evaluating and manipulating number magnitude[21,23], and (iii) the SMG, which is thought to be involved in both phonological processing[54] and mathematical fact retrieval[5]. Critically, for the first time, we also identified the white matter fascicles that support this predicted network. Our data show that SLF and AF are key fascicles, supporting fronto-parietal (PCS to IPS) and fronto-temporal (PCS to ITG) connections, respectively. Additionally, we found that the VOF and pAF are the main fascicles connecting temporal (ITG) to parietal (IPS) regions (**Fig. 3**). It should be noted though, that the fascicles of the math network reported here do not contain the entire white matter of the math network, for two reasons. First, in addition to the within-network connections described here, the cortical regions activated during math likely also connect to regions outside the math network. Second, there are likely additional white matter tracts associated with each region outside of long-range fascicles (e.g. shorter tracts, U-fibers), which have not been considered here.

By investigating both math and reading within the same participants, we found that cortical regions preferentially activated during math or reading are often neighboring (**Fig. 1b**). This neighboring relationship was observed in (i) the frontal cortex (reading centered on IFG and math on PCS), (ii) the lateral occipito-temporal cortex (reading centered on OTS, STS and math on ITG), and (iii) the SMG. Interestingly, gray matter regions involved in math were found to generally be located superior to regions involved in reading, which mirrors the superior-to-inferior arrangement of tracts associated with math and reading, respectively, in the AF and SLF. Further, as prior research suggests that white matter development precedes and predicts the location of functional regions involved in reading, such as the VWFA[55], our data highlights the possibility that long range white matter fascicles may also determine the locations of cortical regions involved in math. Future developmental research could test this hypothesis.

Our study yields several novel insights on the fascicles of the reading and math networks. First, our data shows that the SLF and AF are shared across the math and reading networks. Second, even as the SLF and AF are key fascicles for both tasks, they each contain separate sub-bundles for reading or math. Specifically, analogous to separate lanes on a highway, parallel and segregated tracts within these fascicles are part of either the reading or the math network (**Fig. 4, Supplementary Fig. 3-4**). Third, strikingly, we found structural differences within math and reading sub-bundles in the anterior AF and SLF. That is, T_1 was shorter for reading than math tracts.

These findings are important for three main reasons. First, they simultaneously explain the occurrence of both comorbid and isolated cases of math and reading learning disabilities. Specifically, structural abnormalities that transcend the entire AF or SLF could underlie the comorbidity of these disorders, while structural abnormalities localized to either the superior or the inferior section of these fascicles could underly cases where math or reading deficits occur in isolation. Second, our data shows that, even though math and reading involve several shared cognitive processes, such as the encoding of visual stimuli and cognitive control[1], they are processed largely in parallel. This, in turn, suggests that improvements in one skill may not translate to the other skill, unless this improvement is linked to broad changes that transcend entire fascicles. Third, the faster T_1 of the reading tracts than the math tracts within the SLF and anterior AF suggests more substantial myelination of the former than the latter (**Fig. 5**). Notably, as reading is practiced more frequently and intensely than math during childhood[56], and myelination is dependent on neural activity[57], our findings raise the intriguing possibility that the amount of learning and its resultant neural activity may affect the myelination of specific white matter tracts within fascicles.

This last finding makes an interesting prediction for the link between white matter properties and math and reading skills: While the properties of the inferior section of the SLF and the anterior AF should predict reading performance, the superior section should predict math performance. That is, if myelination improves transmission of information across distributed networks, then T_1 of the inferior portion of the SLF and anterior AF should predict reading ability, and T_1 of the superior portions of these fascicles, math ability. Accordingly, atypical myelination of these tracts within the superior and inferior portion of the SLF and anterior AF during development may also be correlated with math or reading disabilities, respectively. Further, if neural activity promotes myelination, then people with intense practice in one of these tasks, such as expert mathematicians (e.g.[53]), will show lower T_1 in the respective tracts compared to lay people. These predictions will be particularly relevant for studies evaluating the efficacy of interventions aimed at improving math and reading skills (e.g.[27,58,59]).

Crucially, the structural differences within the SLF and anterior AF observed in the current study have implications beyond math and reading. While, structural differences within large tracts have recently been shown in the optic radiation, where an anterior sub-bundle that includes Meyer's loop defined from anatomical landmarks showed higher T_1 than the entire optic radiation[60], the present study is the first to reveal such structural differences between functionally-defined tracts within a fascicle. Our data thus encourages a novel research direction that links quantitative properties of functionally-defined sub-bundles to human behavior. That is, we believe that understanding the relationship between white matter properties and brain functions (not only in reading and math[8–10,23,5], but in a broad range of functions including face processing[61], working memory[62], and attention[63]) may be improved if white matter is defined more precisely, by intersecting it with the specific cortical regions that support each function.

In conclusion, our data shows striking functional and structural segregation of mathematical processing and reading in the human brain. These findings have implications for understanding the neural underpinning of math and reading learning disabilities as well as the link between white matter properties and human behavior more broadly.

Methods

Participants

14 volunteers (6 female, mean age ±SE: 28±2 years) were recruited from Stanford University and surrounding areas and participated in two experimental sessions. Subjects gave their informed written consent and the Stanford Internal Review Board on Human Subjects Research approved all procedures.

Functional MRI of math and reading related regions

Data acquisition and preprocessing

Anatomical MRI: A whole-brain, anatomical volume was acquired, once for each participant, using a T1-weighted BRAVO pulse sequence (resolution: 1mm x 1 mm x 1 mm, TI=450 ms, flip angle: 12°, 1 NEX, FoV: 240 mm). The anatomical volume was segmented into gray and white matter using FreeSurfer (http://surfer.nmr.mgh.harvard.edu/), with manual corrections using ITKGray (http://web.stanford.edu/group/vista/cgi-bin/wiki/index.php/ItkGray). From this segmentation, each participant's cortical surface was reconstructed.

Functional MRI: fMRI data was collected at the Center for Cognitive and Neurobiological Imaging at Stanford University, using a GE 3 tesla Signa Scanner with a 32-channel head coil. We acquired 48 slices covering the occipitotemporal and most of the frontal cortex using a T2*-sensitive gradient echo sequence (resolution: 2.4 mm x 2.4 mm x 2.4 mm, TR: 1000 ms, TE: 30 ms, FoV: 192 mm, flip angle: 62°, multiplexing factor of 3).

The functional data was analyzed using the mrVista toolbox (http://github.com/vistalab) for Matlab, as in previous work[33]. In short, the data was motion-corrected within and between scans and then aligned to the anatomical volume. No smoothing was applied. The time course of each voxel was high-pass filtered with a 1/20 Hz cutoff and converted to percentage signal change. A design matrix of the experimental conditions was created and convolved with the hemodynamic response function (HRF) implemented in SPM (http://www.fil.ion.ucl.ac.uk/spm) to generate predictors for each experimental condition. Response coefficients (betas) were estimated for each voxel and each predictor using a general linear model (GLM).

Stimuli and design

In the fMRI experiment, we presented well-controlled character-like stimuli, which could be used for a reading task, a math task, and a color memory task (**Fig. 1a**). These stimuli allowed us to define both math- and reading-related brain regions within the same experiment, while keeping the visual input constant. Details on the experimental design can be found in a previous study[33]. In brief, at the beginning of each trial, subjects were presented with a cue ("Add", "Read", or "Color"), indicating which task they should perform. In the adding task, participants were asked to sum the values of the stimuli and to indicate the correct sum. In the reading task, subjects were instructed to read the word in their head, and to indicate which word had been presented. Finally, in the color task, participants were asked to memorize the color of the stimuli and to indicate which color was shown during the trial. After the cue, 4 images were shown sequentially, followed by an answer screen. Each image was a morph of a number and a letter. All images in a trial were either number morphs (N, >80% number + <20% letter) or letter morphs (L, >80% letter + <20% number), i.e. stimuli that mostly contained information from one category, but held just enough evidence from the other category to be recognizable as both letters and numbers. The same stimuli appeared in all tasks. The answer screen was presented for 2 seconds and showed the correct answer as well as one incorrect answer at counterbalanced locations left and right of fixation. Participants performed 6 runs, each lasting six minutes, and the task order was randomized across runs and participants. Prior to the experiment, subjects were given training to ensure that they could perform the task with at least 80% accuracy.

Functionally defined gray matter regions

Reading- and math-related gray matter regions were defined in each participant's cortical surface using both functional and anatomical criteria. The resulting functional regions of interest (fROIs) were labeled according to their anatomical location. Reading-related fROIs consist of voxels that showed higher responses in the reading than the math and the color task ($T \geq 3$, voxel level), while math-related fROIs contain voxels which showed higher responses in the math than the reading and the color task ($T \geq 3$, voxel level). Here we report data from regions that showed a reliable preference across participants. In other words, while in a given individual there may be additional voxels that respond preferentially during reading or during math, here we focus on the most robust activations.

In addition to math- and reading-related regions, we also defined fROIs involved in color memory, which were used to determine a chance level for pairwise connections in the math and reading networks. Color-preferring voxels were identified in the medial aspect of the fusiform gyrus and showed significantly higher responses during the color task than the other two tasks ($T \geq 3$, voxel level). These voxels were frequently divided into three distinct subregions (likely corresponding to color patches Ac, Cc, and Pc[64]). Given that these regions are proximal, and we needed to dilate the white matter to intersect with them, here we took the union of these color patches (left hemisphere: N=13, size ±SE: 225±60 mm^3; right hemisphere: N=13, size ±SE: 234±71 mm^3).

Diffusion MRI of the math and reading networks

Data acquisition and preprocessing

Diffusion-weighted MRI (dMRI) data was collected in the same participants during a different day, at the same facility and with the same 32-channel head-coil. DMRI was acquired using a dual-spin echo sequence in 96 different directions, 8 non-diffusion-weighted (b=0) images were collected, 60 slices provided full head coverage (resolution: 2 mm × 2 mm × 2 mm, TR: 8000 ms, TE: 93.6 ms, FoV: 220 mm, flip angle: 90°, b0: 2000 s mm^{-2}).

DMRI data was preprocessed using the mrDiffusion toolbox (http://github.com/vistalab) for Matlab, as in previous work[65]. In short, dMRI data was registered to the average of the non-diffusion weighted images, corrected for eddy-currents and motion, and then aligned to the corresponding high-resolution anatomical brain volume. Tensors were fit to each voxel using a least-squares algorithm that removes outliers[66].

Ensemble tractography

Tractography was performed on the preprocessed dMRI data and consisted of 4 main steps: We (1) created multiple whole brain connectomes that varied in their allowed curvature, (2) concatenated these candidate connectomes into one large ensemble connectome, (3) optimized the ensemble connectome, and (4) automatically labelled major fascicles in the ensemble connectome (**Fig. 1c**).

1) Candidate connectome generation: We used MRtrix[36] (version 0.2.12, http://www.mrtrix.org/) to generate 5 candidate connectomes which varied in the allowed minimum radius of curvature (0.25, 0.5, 1, 2 and 4). The goal of this approach was to generate candidate connectomes with tracts with different degrees of curviness, rather than limiting the connectome to one particular set of parameters[35]. For each connectome, we used probabilistic fiber tracking and constrained-spherical deconvolution[67] with the following parameters: up to 8 spherical harmonics (lmax=8), step size: 0.2 mm, minimum length: 10 mm, maximum length: 200 mm, fiber orientation distribution amplitude stopping criterion: 0.1, vector specifying the initial direction: 20°. The white matter mask from the FreeSurfer segmentation was used as a seed mask, and seed voxels were randomly chosen to produce individual streamlines. Each candidate connectome consisted of 200,000 streamlines.
2) The 5 candidate connectomes were concatenated into one ensemble connectome containing a total of 1,000,000 streamlines using custom Matlab code available in the Fascicle Analysis Toolbox (FAT) (https://github.com/zhenzonglei/fat).
3) To remove redundant tracts from the ensemble connectome and to reduce type 1 error, we optimized the connectome using Linear Fascicle Evaluation[34] (LiFE; https://github.com/brain-life/encode). In brief, LiFE uses the connectome to build a model of the dMRI data and then tests how well this model predicts the data. Tracts which make no contribution to the prediction (i.e. those with zero weights) are considered to be false-alarms and removed from the connectome. This procedure produces an optimized connectome with the smallest number of tracts that best explain the diffusion data.

4) We used Automated Fiber-Tract Quantification[37] (AFQ, https://github.com/yeatmanlab/AFQ) to segment the optimized connectome into 12 well-established major fascicles, bilaterally. We conducted all subsequent analyses on these long-range connections, as we were interested in identifying large-scale, whole-brain networks supporting reading and math. Of the 12 investigated fascicles, 6 were associated with math or reading and subjected to further analyses: the inferior fronto-occipital fasciculus (IFOF), the inferior longitudinal fasciculus (ILF), the superior longitudinal fasciculus (SLF), the arcuate fasciculus (AF), the posterior arcuate fasciculus (pAF), and the vertical occipital fasciculus (VOF[14,68,69]).

Functionally-defined white matter tracts

In the current study, we investigated white matter tracts that support math and/or reading. To identify these tracts, we intersected 12 major fascicles with math- and reading-related fROIs, which yielded functionally-defined white matter tracts (fWMT). First, we dilated the endpoints of all tracts by a radius of 7 mm. This dilation was necessary to ensure that tracts within the investigated fascicles reach into the gray matter. Following this, we restricted the fascicles to include only tracts whose endpoints intersected with the gray matter fROIs. We then visualized the reading- (**Fig. 2a**) and math- (**Fig. 2b, Supplementary Fig. 3**) related fWMT in individual subjects (**Fig. 2a,b-left** shows a representative subjects). In all plots, tracts are color-coded by the fascicle they belong to, outliers whose maximum Gaussian distance from the core of the fascicle exceeded 2.5 standard deviations were removed, and the plots are thresholded at a maximum of 75 tracts per fascicle to enable clearer visualization. We also quantified what proportion of all fWMT of each region is contained in each fascicle (**Fig. 2a,b-middle**). Finally, we created a schematic representation of the fascicles each fROI connects to, where the width of the line represents the proportion of the total fWMT occupied by that fascicle, and the color and approximate directions of the line corresponds to the fascicles spatial arrangement (**Fig. 2a,b-right**).

Next, we restricted our fWMT further, to include only tracts that connect to at least two fROIs in either the math or the reading networks. This allowed us to isolate within-network connections from outside-network connections. For both reading (**Fig. 3a-d**) and math (**Fig. 3e-h, Supplementary Fig. 4**), we first visualized all pairwise fWMT in each individual subject, color coded by the fascicle they belong to (**Fig. 3-a,e** show a representative subject). Next, we quantified the pairwise connections using the dice coefficient (DC[46]; **Fig. 3-b,f**): $\mathrm{DC} = \frac{2(\mathrm{A} \cap \mathrm{B})}{A+B}$, where A is all tracts that connect to one region, B is all tracts that connect to the second region, and A∩B is those tracts that connect to both regions. The dice coefficient (DC) quantifies the similarity of two samples; a DC of 1 indicates complete overlap (i.e. each tract that connects to one region, also connects to the other region), while a DC of 0 indicates that there are no tracts that connect to both regions. We also calculated the DC for pairwise fWMT between each the math and the reading network to ventral regions activated during the color memory task (pairwise connections with the OTS were not included, due to its close anatomical proximity with fROIs involved in processing color). The average DCs of these pairwise connections were used as chance level DCs for each network, given that we expected connections to color-related regions to be irrelevant for participants' math and reading skills. In addition, we also evaluated what percentage of the pairwise connections belong to each fascicle (**Fig. 3-c,g**). Finally, we created a schematic representation of these pairwise connections, where the width of the line is determined from the DC and the color of the lines indicate which fascicle contributed most strongly to this connection (**Fig. 3-d,h**).

Quantification of segregation within fascicles

For those fascicles that contributed to significant pairwise connections in both the math and the reading network, we finally asked the question whether fWMT within these fascicles are segregated by network. Specifically, we evaluated if, within the SLF, tracts connecting the SMG to the IFG in the reading network are intertwined with tracts connecting the SMG to the PCS in the math network (**Fig. 4a-c**, tracts that connect to all 4 fROIs were excluded). Further, we evaluated if, within the AF, tracts connecting the STS and the IFG are intertwined with tracts connecting the ITG and the PCS (**Fig. 4d-f**, tracts that connect to all 4 fROIs were excluded). First, we visualized pairwise connections of the math and reading network within each fascicle, in each individual subject, to visually inspect their spatial layout (**Fig. 4-a,d** and **Supplementary Fig. 5-6**). Then, we resampled each tract in each subject to 30 equally spaced nodes (i.e. locations) between the way-point ROIs used by AFQ to define the fascicle. This procedure ensured that we have the same number of measurements per subject, even though the absolute length of the fascicles may vary across subjects. Finally, we quantified the segregation of fWMT of each network within each fascicle using two complimentary approaches: (1) we measured the distance of each tract from the core tract of all pairwise connections within each network, as well as, the core tract of the other network, and tested whether the former is lower than the latter and (2) we used an independent classifier to test if, across nodes, fWMT can be identified as being part of the reading or the math network based on their anatomical location.

(1) *Distance to core tract within and across networks*: We first calculated the core (mean) tract of the pairwise connections within the AF and SLF, separately for math and reading-related fWMT, using AFQ. Next, we measured, within each subject and at each node, how far away (Euclidian distance in mm, derived from x,y,z coordinates) each tract is from the core tract within its network and the core tract of the other network (**Fig. 4-c,f**). We

expected tracts to be closer to the core tract of their own network if math- and reading-related fWMT are segregated within the fascicle, but equal distant from both core tracts if math- and reading-related fWMT are intertwined within the fascicle.

(2) *Classification:* We also tested if, across the length of the fascicle, we can classify tracts as "math" or "reading" based on their anatomical location. At each node and within each subject, the coordinates of all math and reading related tracts were used to train a support vector machine (SVM) classifier with a 2nd degree polynomial kernel. The SVM from each node was used to classify tracts at the next (posterior) node as either "math" or "reading" (**Fig. 4-d,e**). We expected the classifier to perform at chance (50% accuracy) if math and reading related tracts are intertwined, but significantly above chance if math and reading tracts are spatially segregated across the lengths of the fascicle.

Quantitative MRI of math- and reading-related tracts

Data acquisition and preprocessing

Quantitative MRI (qMRI[38]) data was collected within the same session and with the same head coil as the dMRI data. T_1 relaxation times were measured from four spoiled gradient echo images with flip angles of 4°, 10°, 20° and 30° (TR: 14 ms, TE: 2.4 ms). The resolution of these images was later resampled from 0.8x0.8x1.0 mm^3 to 1mm isotropic voxels. We also collected four additional spin echo inversion recovery (SEIR) scans with an echo planar imaging read-out, a slab inversion pulse and spectral spatial fat suppression (TR: 3 s, resolution: 2 mm x 2 mm x 4 mm, 4 echo time set to minimum full, 2x acceleration, inversion times: 50, 400, 1200, and 2400 ms). The purpose of these SEIRs was to remove field inhomogeneities.

Both the spoiled gradient echo and the SEIR scans were processed using the mrQ software package (https://github.com/mezera/mrQ) for Matlab to estimate the proton relaxation time (T_1) and macromolecular tissue volume (MTV) in each voxel, as in previous studies[38,70]. In brief, the mrQ analysis pipeline corrects for RF coil bias using the SEIRs scans, which produces accurate proton density (PD) and T_1 fits across the brain. MrQ also produces maps of MTV, by calculating the fraction of a voxel that is non-water. T_1 and MTV maps of each subject were co-registered to the same anatomical whole brain volume as dMRI and fMRI data.

Comparison of T_1 for math and reading tracts

We used the T_1 maps to evaluate tissue properties of tracts belonging to the math or to the reading network (**Fig. 5**; MTV data is presented in **Supplementary Fig. 7**). We focused on tracts within those fascicles that showed significant pairwise connections between regions of both networks. In particular, within the SLF, we compared tracts connecting the SMG to the IFG in the reading network with tracts connecting the SMG to the PCS in the math network (**Fig. 5a-c**, tracts that connect to all 4 fROIs were excluded). Further, within the AF, we compared tracts connecting the STS and the IFG in the reading network with tracts connecting the ITG and the PCS in the math network (**Fig. 5d-f**, tracts that connect to all 4 fROIs were excluded). We first evaluated the mean T_1 values of each tract in each subject and tested if there are between-network differences (**Fig. 5-a,d**). Then, we resampled the tract to 30 equally-spaced nodes. We evaluated the distribution of T_1 values, using data from all nodes and subjects, and tested if the distribution varies between math and reading tracts (**Fig. 5-b,e**). Finally, we visualized the T_1 of math and reading tracts across the different nodes, to determine if T_1 differences are homogenous across the length of the tract (**Fig. 5-c,f**).

Statistics

We used paired t-tests to evaluate if DCs or decoding accuracies differed significantly from chance. We also used paired t-test to evaluate if there are T_1 differences between math and reading related tracts. When more than one t-test was conducted at the same time, the statistical threshold was Bonferroni-adjusted to account for multiple comparisons. When comparing distribution, for example distribution of T_1 values, we used the non-parametric two-sample Kolmogorov-Smirnov test to test for statistically significant differences.

Data availability

The data generated in this study will be made available upon reasonable request.

Code availability

The fMRI and qMRI data were analyzed using the open source mrVista software (available in GitHub: http://github.com/vistalab). and mrQ software (available in GitHub: https://github.com/mezera/mrQ) packages, respectively. The dMRI data were also analyzed using open source software, including MRtrix[36] (http://www.mrtrix.org/), LiFE[34] (https://github.com/brain-life/encode) and AFQ[37] (https://github.com/yeatmanlab/AFQ). We make the entire pipeline freely available in the Fascicle Analysis Toolbox (FAT) (https://github.com/zhenzonglei/fat).

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Acknowledgements

This research was supported by the National Institute of Health (NIH; 1R01EY02391501A1), by the Deutsche Forschungsgemeinschaft (DFG; GR 4850/1-1) and by an Innovation Grant from the Stanford Center for Cognitive and Neurobiological Imaging (CNI). The authors would like to thank Brianna Jeska for her help with the data collection.

Author Contribution

MG collected the data. ZZ developed the FAT toolbox used for diffusion and quantitative data analyses. MG and KGS analyzed the data and wrote the manuscript.

Competing Interests

The authors declare no competing interests.

Materials and Correspondence

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Figure Legends

Figure 1. Overview of the Experimental Methodology. (a) FMRI experiment used to define math- and reading-related regions. Subjects viewed morphs between numbers and letters, containing either >80% letter (<20% number) or >80% number (<20% letter) information. At the beginning of each trial, a cue ("Read"/"Add"/"Color") indicated which task should be performed, then 4 stimuli of the same morph type appeared for 1 sec each, followed by an answer screen presented for 2 seconds. Subjects indicated their answer with a button press. Identical stimuli were presented across tasks. Trial structure is shown at the bottom. **(b)** Gray matter regions used to identify the math and reading networks. Reading- (green) and math- (blue) related regions were defined based on higher responses in the reading task or the math task, respectively, than the other tasks ($T \geq 3$). *Abbreviations:* IFG=inferior frontal gyrus, PCS=precentral sulcus, SMG=supramarginal gyrus, STS=superior temporal sulcus, ITG=inferior temporal gyrus, OTS=occipito-temporal sulcus, IPS=intraparietal sulcus. **(c)** DMRI processing pipeline. DMRI data was preprocessed to correct for motion and Eddy currents. Tractography was done with constrained spherical deconvolution (CSD) and probabilistic fiber tracking using the MRtrix software. We generated 5 candidate connectomes with different curvatures (0.5,1,2,4). These candidate connectomes were then concatenated into one large ensemble connectome. Linear fascicle evaluation (LiFE) was used to optimize the concatenated connectome. Tracts that did not make a substantial contribution to predicting the diffusion data were removed. The resulting optimized connectome was analyzed by automated fascicle quantification (AFQ) to extract 12 well-established fascicles in each hemisphere.

Figure 2. Functionally-defined white matter tracts (fWMT) of reading and math related regions. (a) Six fascicles (see legend at the bottom) contain close to 100% of all fWMT of the fROIs identified in the reading task. **(b)** The same six fascicles also contain close to 100% of all fWMT of the fROIs identified in the math task. In **(a, b)**: *Left:* fWMT for each fROI in a representative subject's left hemisphere. The same subject is displayed in all panels; Fascicle are color coded in accordance with the legend at the bottom. *Middle*: Bar graphs showing what percentage of the fWMT is associated with each of the six fascicles. The graph shows the mean across subjects ± SEM. *Dashed horizontal line*: Line is placed at 10%, which was the cut-off used for schematics in the right columns. *Right:* Schematic illustration of the fascicles associated with each fROI. The thickness of the lines is derived from the bar graph, showing the relative weight of each fascicle. *Abbreviations*: IFG=inferior frontal gyrus, PCS=precentral sulcus, SMG=supramarginal gyrus, STS=superior temporal sulcus, ITG=inferior temporal gyrus, OTS=occipito-temporal sulcus, IPS=intraparietal sulcus, IFOF=inferior fronto-occipital fasciculus, ILF=inferior longitudinal fasciculus, SLF=superior longitudinal fasciculus, AF=arcuate fasciculus, pAF=posterior arcuate fasciculus, VOF=vertical occipital fasciculus.

Figure 3. Pairwise fWMT within the reading (a-d) and math (e-f) networks. (a,e): Pairwise white matter connections in a representative subject's left hemisphere. **(b,f)**: Dice coefficient (DC) of pairwise within-network connections, mean across subjects ± SEM. The DC quantifies the overlap in the fWMT of both fROIs: a DC of 1 indicates that all tracts that intersect with the first fROI also intersect with the second fROI, while a DC of 0 indicates no shared tracts. X-labels indicate the fROI pairing. *Dashed line:* Chance level DC estimated from the average connections of each network to out of network fROIs in ventral temporal cortex that were activated maximally during the

color task. *: DC is significantly higher than chance, $p<0.008$ (significance level was Bonferroni adjusted). **(c,g)**: The relative contribution of six fascicle (see legend at the bottom) to the overall pairwise connections. X-labels indicate the fROI pairing. **(d,h)**: Schematic illustration of the pairwise connections in the reading and math networks. *Line thickness* is scaled proportionally to the DC; *color* indicates the fascicle with the highest relative contribution to pairwise connections. *Abbreviations:* IFG=inferior frontal gyrus, PCS=precentral sulcus, SMG=supramarginal gyrus, STS=superior temporal sulcus, ITG=inferior temporal gyrus, OTS=occipito-temporal sulcus, IPS=intraparietal sulcus, IFOF=inferior fronto-occipital fasciculus, ILF=inferior longitudinal fasciculus, SLF=superior longitudinal fasciculus, AF=arcuate fasciculus, pAF=posterior arcuate fasciculus, VOF=vertical occipital fasciculus.

Figure 4. Pairwise connections within the reading and the math networks are segregated and parallel in the SLF and the AF. (a-c): SLF tracts connecting IFG and SMG in the reading network and PCS and SMG in the math network. **(d-f)**: AF tracts connecting the IFG and STS in the reading network and the PCS and ITG in the math network. **(a,d)**: Math (blue) and reading (green) tracts of the SLF and AF in a representative individual subject showing the spatial segregation of these tracts. **(b,e)**: Euclidean distance in mm (derived from x,y,z coordinates) of all tracts relative to the core (mean) tract, within-network (black) and across-network (maroon). The distance was calculated across all tracts; the plot shows the mean across all nodes of 12 subjects ±SEM. * Distributions differ significantly, $p<0.05$. **(c,f)**: Performance of a SVM classifying math and reading tracts within the SLF and AF based on their spatial location. Data show mean classification accuracy across nodes in 12 subjects ±SEM. *Abbreviations:* IFG=inferior frontal gyrus, PCS=precentral sulcus, SMG=supramarginal gyrus, STS=superior temporal sulcus, ITG=inferior temporal gyrus, AF=arcuate fasciculus, SLF=superior longitudinal fasciculus.

Figure 5. Tracts associated with reading show faster proton relaxation time (T_1) than those associated with math in the SLF and the anterior section of the AF. (a-c): T_1 measurements for SLF tracts connecting IFG and SMG in the reading network (green) and PCS and SMG in the math network (blue). **(d-f)**: T_1 measurements for AF tracts connecting the IFG and STS in the reading network (green) and the PCS and ITG in the math network (blue). **(a,d)**: Average T_1 for reading- and math-related tracts in the SLF and the AF. Bar graph shows mean across 12 subjects ± SEM. *: T_1 for math and reading related tracts differs significantly, $p<0.05$. **(b,e)**: Distribution of T_1 values across all tracts. Distributions were calculated within each subject and node; the plot shows the mean across all nodes of 12 subjects ± SEM. *: Distributions differ significantly, $p<0.05$. **(c,f)**: Average T_1 for reading- and math-related tracts along the SLF and the AF. Line graph shows mean across subjects ± SEM. *Abbreviations:* IFG=inferior frontal gyrus, PCS=precentral sulcus, SMG=supramarginal gyrus, STS=superior temporal sulcus, ITG=inferior temporal gyrus, SLF=superior longitudinal fasciculus, AF=arcuate fasciculus.