Received: 13 January 2018 | Accepted: 25 August 2018

DOI: 10.1111/desc.12744

PAPER

WILEY Developmental Science

Laterality of the frontal aslant tract (FAT) explains externalizing behaviors through its association with executive function

Dea Garic[1] | Iris Broce[2] | Paulo Graziano[1] | Aaron Mattfeld[1] | Anthony Steven Dick[1]

[1]Department of Psychology, Florida International University, Miami, Florida

[2]Department of Radiology and Biomedical Imaging, University of California, San Francisco, San Francisco, California

Correspondence
Anthony Steven Dick, PhD, Associate Professor, Director, Cognitive Neuroscience Program and Graduate Certificate in Cognitive Neuroscience, Department of Psychology, Florida International University Modesto A. Maidique, Miami, FL.
Email:adick@fiu.edu

Funding information
National Institute of Mental Health, Grant/Award Number: R01MH112588 and R56MH108616; National Institute for Drug Abuse, Grant/Award Number: U01DA041156

Abstract

We investigated the development of a recently identified white matter pathway, the frontal aslant tract (FAT) and its association with executive function and externalizing behaviors in a sample of 129 neurotypical male and female human children ranging in age from 7 months to 19 years. We found that the FAT could be tracked in 92% of those children, and that the pathway showed age-related differences into adulthood. The change in white matter microstructure was very rapid until about 6 years, and then plateaued, only to show age-related increases again after the age of 11 years. In a subset of those children (5–18 years; n = 70), left laterality of the microstructural properties of the FAT was associated with greater attention problems as measured by the Child Behavior Checklist (CBCL). However, this relationship was fully mediated by higher executive dysfunction as measured by the Behavior Rating Inventory of Executive Function (BRIEF). This relationship was specific to the FAT—we found no relationship between laterality of a control pathway, or of the white matter of the brain in general, and attention and executive function. These findings suggest that the degree to which the developing brain favors a right lateralized structural dominance of the FAT is directly associated with executive function and attention. This novel finding provides a new potential structural biomarker to assess attention deficit hyperactivity disorder (ADHD) and associated executive dysfunction during development.

KEYWORDS

ADHD, attention, executive function, frontal aslant tract, inferior frontal gyrus, pre-supplementary motor area

1 | INTRODUCTION

It is critical to understand the etiology of children's externalizing behavior problems, including symptoms of attention-deficit/hyperactivity disorder (ADHD) such as inattention, hyperactivity, and impulsivity. These are the most common reason for early childhood mental health referrals (Keenan & Wakschlag, 2000; Thomas & Guskin, 2001) and can present early in development, occurring in 10%–25% of preschoolers (Carter, Briggs-Gowan, & Davis, 2004; Furniss, Beyer, & Guggenmos, 2006). Despite successful development of evidence-based treatments for such problems, early interventions have little impact on children's long-term academic and social impairment (Jensen et al., 2007; Molina et al., 2009, 2013; Sonuga-Barke et al., 2013). Researchers, clinicians, and patients are thus desperate for tangible progress in identifying biomarkers for treatment of mental illness in both adults and children. Identifiable biomarkers can serve as indicators of treatment response, as indicators of heterogeneity within broadly defined disorders, or as future targets of noninvasive brain stimulation treatments, and are necessary for applying precision medicine approaches to mental health treatment.

Here, we investigate a recently identified white matter fiber pathway, the frontal aslant tract (FAT), and attempt to define its functional relevance to executive function and externalizing behaviors—namely, attention problems—in a sample of typically developing children. The function of the FAT remains a matter of speculation, and its investigation in children has been minimal (Broce, Bernal, Altman, Tremblay, & Dick, 2015; Madsen et al., 2010). Based on the fiber pathway's putative connectivity joining the posterior inferior frontal gyrus (IFG) with the pre-supplementary and supplementary motor areas (pre-SMA and SMA, see Figure 1; Bozkurt et al., 2016; Catani et al., 2012; Kinoshita et al., 2012; Martino & De Lucas, 2014; Szmuda et al., 2017), investigators have focused on its involvement in speech and language function. For example, stimulation of the left FAT during awake surgery induces speech arrest (Fujii et al., 2015; Kinoshita et al., 2015; Vassal, Boutet, Lemaire, & Nuti, 2014), and the left FAT is associated with executive control of speech and language in other tasks (e.g., verbal fluency, stuttering; Basilakos et al., 2014; Broce et al., 2015; Catani et al., 2013; Kemerdere et al., 2016; Kinoshita et al., 2015; Kronfeld-Duenias, Amir, Ezrati-Vinacour, Civier, & Ben-Shachar, 2016; Mandelli et al., 2014; Sierpowska et al., 2015).

However, given the well-known laterality of function in the brain (Herve, Zago, Petit, Mazoyer, & Tzourio-Mazoyer, 2013; Toga & Thompson, 2003), the possibility remains that the function of the left FAT differs from its homolog on the right. Indeed, Aron, Robbins, and Poldrack (2014) suggested that the right posterior IFG, the pre-SMA, and the connections between those regions (i.e., via the FAT) are associated with inhibitory control in executive function tasks (Aron, Behrens, Smith, Frank, & Poldrack, 2007). This possibility is supported by fMRI, electrocorticography (ECoG), and diffusion-weighted imaging (DWI) data in adults (Swann et al., 2012). It is thus possible that while the left FAT might be associated with executive control of speech and language function (e.g., in the case of verbal fluency or speech initiation), the right FAT might be associated with executive control of action (e.g., inhibitory control of action). Consistent with this proposition, functional imaging data suggest that lateralization of these functions emerges during childhood (Everts et al., 2009; Holland et al., 2001). Furthermore, ADHD is associated with structural and functional abnormalities in the pre-SMA and right IFG regions connected by the FAT (Mostofsky, Cooper, Kates, Denckla, & Kaufmann, 2002; Rubia et al., 1999; Suskauer, Simmonds, Caffo, et al., 2008; Suskauer, Simmonds, Fotedar, et al., 2008). However, the direct contribution of the FAT to executive function, to attention, or to externalizing behaviors more broadly, during development has not been investigated.

We explored this issue in a DWI study of neurotypical children between the ages of 7 months and 19 years. We tracked the left and right FAT in these participants and related diffusion metrics of white matter microstructure to behavioral inventories of executive function, and attention. Based on the right-lateralized associations with IFG and pre-SMA function and executive function, we predicted that deviation from right lateralization of this pathway would be associated with poorer executive function, and increased instances of externalizing behaviors.

RESEARCH HIGHLIGHTS

- We tracked the recently identified frontal aslant tract (FAT) in 129 typically developing children using diffusion-weighted magnetic resonance imaging (DW-MRI).
- We found that reduced right laterality of the tract was associated with greater executive dysfunction, which predicted increased reports of attention problems.
- The findings suggest that the degree to which the developing brain favors right lateralized structure of the FAT is associated with executive function and attention.
- This novel finding provides a new potential structural biomarker to assess attention deficit hyperactivity disorder (ADHD) and associated executive dysfunction during development.

2 | MATERIALS AND METHODS

2.1 | Participants

In this study, we analyzed a publically available data set of neurotypical children from the Cincinnati MR Imaging of NeuroDevelopment (C-MIND) database, provided by the Pediatric Functional Neuroimaging

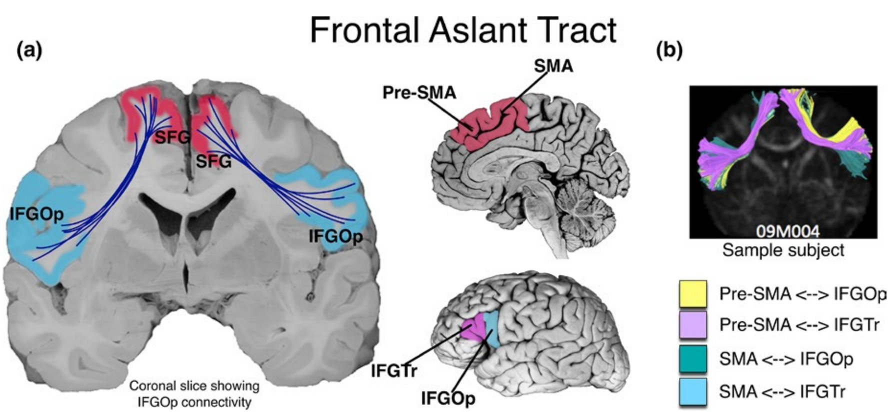


FIGURE 1 Illustration of the putative connectivity of the frontal aslant tract (FAT). (a) Connectivity of the tract is bilateral between the inferior frontal gyrus (*pars opercularis* (IFGOp) and *pars triangularis* (IFGTr) and the superior frontal gyrus (namely, pre-supplementary motor area (pre-SMA) and supplementary motor area (SMA)). (b) The pathway can be further differentiated into four parts connecting two parts of the IFG to the pre-SMA and SMA

Research Network (https://research.cchmc.org/c-mind/) and supported by a contract from the Eunice Kennedy Shriver National Institute of Child Health and Human Development (HHSN275200900018C). The data are available from CMIND by request, which facilitates validation of the results we report here. Participants in the database are full-term gestation, healthy, right-handed, native English speakers, without contraindication to MRI. By design, the C-MIND cohort is demographically diverse (38% nonwhite, 55% female, median household income $42,500), intended to reflect the US population.

We tracked the FAT in all available participants (n = 129; 70 females). The age range for the full sample was 7 months to 19 years (M = 8.8 years; SD = 5.0 years). From the full sample, 70 participants had behavioral data on all of the measures of interest, and also had the tracked fiber pathways of interest. Thus, the sample size for the mediation analysis we report below is n = 70. In this subset, the participants were equally split by gender (35 females), and ranged in age from 5 years to 18 years (M = 10.9 years; SD = 3.7 years). A wide range was represented on the measure of socioeconomic status, which was coded on a 10-point ordinal scale of household income ('0' = $0–$5,000 to '10' = Greater than $150,000; M = 5.1; SD = 2.6). In the subsample, all the children were typically developing and the sample was made up of 94% non-Hispanic/non-Latino participants. The study was approved by the Cincinnati Children's Hospital Medical Center Institutional Review Board. The Florida International University Institutional Review Board approved the data use agreement.

2.2 | Experimental design and statistical analysis

We employed analysis of a quasiexperimental design on a publicly available dataset consisting of DWI MRI scans, and parent/teacher report measures of executive function (i.e., the Behavior Rating Inventory of Executive Function; BRIEF) and externalizing behaviors (focusing on Attention Problems with the Child Behavior Checklist; CBCL). We conducted High Angular Resolution Diffusion Imaging (HARDI)-based analysis of the DWI data using a generalized q-sampling imaging (GQI) model-free reconstruction method (Yeh, Wedeen, & Tseng, 2010). We manually reconstructed the FAT in each hemisphere of each subject, defined on the original image space of the subject. We then explored the age-related differences in the pathway's microstructure, and calculated laterality of the pathway. Following that, we conducted a simple mediation analysis in which laterality of the FAT was entered as a predictor, executive function as measured by the BRIEF was entered as a mediator, and CBCL Attention Problems was entered as the outcome. The same analysis was conducted on the laterality of the whole-brain white matter, on the left and right FAT separately, and on a control pathway (the inferior longitudinal fasciculus; ILF). The details of these steps are presented below.

2.3 | MRI scans

Single-shell, 61 direction HARDI scans were created using a spin-echo, EPI method with intravoxel incoherent motion imaging (IVIM) gradients for diffusion weighting of the scans. They were acquired using a 32-channel head coil (SENSE factor of 3), which obtained 2 × 2 × 2 mm spatial resolution at b = 3,000 (EPI factor = 38, 1,752.6 Hz EPI bandwidth, 2 × 2.05 × 2 acquisition voxel; 2 × 2 × 2 reconstructed voxel; 112 × 109 acquisition matrix). The scan took under 12 min, with an average scan time of 11 min and 34 s. Seven b = 0 images were also acquired at intervals of eight images apart in the diffusion direction vector. These $b0$ images are used for coregistration and averaged to form the baseline for computation of the diffusion metrics of interest.

2.3.1 | HARDI postprocessing

The image quality of the HARDI data was assessed using DTIPrep (http://www.nitrc.org/projects/dtiprep), which discards volumes as a result of slice dropout artifacts, slice interlace artifacts, and/or excessive motion. The number of volumes remaining was included as a covariate in all subsequent analyses, which is important for mitigating the effects of motion on the reported findings (Lauzon et al., 2013; Roalf et al., 2016). All usable data were registered to the reference image (b = 0), using a rigid body mutual information algorithm and were eddy current corrected for distortion.

Using DSI Studio, we used the GQI model-free reconstruction method, which quantifies the density of diffusing water at different orientations (Yeh et al., 2010) to reconstruct the diffusion orientation distribution function (ODF), with a regularization parameter equal to 0.006 (Descoteaux, Angelino, Fitzgibbons, & Deriche, 2007). From this, we obtained normalized quantitative anisotropy (nQA). GQI reconstruction was preferred over the simpler diffusion-tensor model because it is empirically shown to more accurately resolve multiple fiber orientations within voxels (Daducci et al., 2014; Yeh, Verstynen, Wang, Fernandez-Miranda, & Tseng, 2013). In this HARDI data set we can take advantage of the large number of diffusion directions to conduct this reconstruction algorithm. The major advantage of GQI, in terms of the measurement of microstructural properties of the tissue, is the improved resolution of crossing/kissing fiber orientations. This is particularly important for an oblique fiber pathway like the FAT, which courses through white matter of the frontal lobe containing a number of laterally and longitudinally oriented fibers of proximal pathways (e.g., the superior longitudinal fasciculus or of the coronal radiation emanating from the rostrum of the corpus callosum).

In the GQI framework, QA is defined as the amount of anisotropic spins that diffuse along a fiber orientation, and it is given mathematically by:

$$QA = Z_0(\psi(\hat{a}) - iso(\psi))$$

where ψ is the spin distribution function (SDF) estimated using the generalized q-sampling imaging, $\hat{a}$ is the orientation of the fiber of interest, and $iso(\psi)$ is the isotropic background diffusion of the SDF. Z_0 is a scaling constant that scales free water diffusion to 1 (i.e., it is scaled to the maximum ODF of all voxels, typically found in cerebral spinal fluid).

QA can be defined for each peak in the SDF. Because deterministic tractography (which we use in this study) follows individual peaks across a streamline of voxels, we have focused on the first peak (QA_0). Unlike typical diffusion-tensor imaging (DTI) metrics such as FA, QA must be further normalized so that it can be compared across different participants. This normalized QA metric, nQA, was calculated according to the generalized *q*-sampling imaging method described above (Yeh et al., 2010), and essentially normalizes the maximum QA value to 1. GQI performs as well as other HARDI metrics, such as constrained super-resolved spherical deconvolution (CSD; Tournier, Calamante, & Connelly, 2007; Yeh et al., 2013) and better than standard DTI algorithms (Daducci et al., 2014; Yeh et al., 2013). To facilitate comparisons with prior work, we also reconstructed the FA metric using the standard diffusion-tensor algorithm.

In summary, we used the GQI reconstruction to map the streamlines, with deterministic tractography following the QA_0 at each voxel. We used the nQA_0 component in our analysis of the relation of white matter microstructure to behavior. To facilitate comparisons with prior literature, we report the DTI FA metric for assessment of age-related differences, and in mediation analyses that accompany the main analyses.

2.3.2 | Defining the should be tracts of interest

To define the FAT, we identified eight total regions of interest (ROIs) for each participant, four per hemisphere. In each hemisphere, we identified ROIs for two superior frontal gyri: the pre-SMA and SMA; and two inferior frontal gyri ROIs, the IFGOp, and the IFGTr.

We systematically identified the eight ROIs for each participant following the same sequence of steps, starting from identification of the brain's midline slice. From the midline slice, the anterior commissure was located, which represents the arbitrary dividing line between the pre-SMA and SMA ROIs (Kim et al., 2010; Vergani et al., 2014). The superior border for both ROIs is the top of the brain, and the inferior border is the cingulate gyrus. The pre-SMA ROI's anterior border is the anterior tip of the cingulate gyrus while the posterior border for the SMA is the precentral sulcus. Note that because of the callout above, IFGTr and IFGOp abbreviations can be used. (Duvernoy et al., 1999), and were defined by the semiautomated Freesurfer parcellation (Desikan et al., 2006). After semiautomated parcellation, all ROIs were visually inspected and edited to include the underlying white matter. Fiber tracking was terminated when the relative QA for the incoming direction dropped below a preset threshold (0.02–0.06, depending on the subject; Yeh et al., 2010) or exceeded a turning angle of 40°.

We also tracked the left and right ILF as a control, expecting this long association fiber pathway to have little association with attention problems or executive function (the pathway courses through the ventral temporal lobe as part of the ventral visual stream, has no parietal or frontal terminations or origins, and is typically associated with semantic processing and reading; Dick, Bernal, & Tremblay, 2014; Dick & Tremblay, 2012). To track the ILF we used an automated approach available as part of the DSI studio software. This approach applies an atlas-based ROI (from reconstruction of the Human Connectome Project group atlas) of both the left and right ILF.

2.3.3 | Calculation of laterality

We calculated FAT laterality (*L*) following the standard formula (Thiebaut de Schotten et al., 2011):

$$L = \frac{(\text{left} - \text{right})}{(\text{left} + \text{right})}$$

According to the laterality equation, positive values indicate greater left laterality. The HARDI metric nQA_0 was used as the main measure of interest.

2.4 | Behavioral measures

2.4.1 | Behavior Rating Inventory of Executive Function

The BRIEF (Gioia, Isquith, Guy, & Kenworthy, 2000) was used to assess executive function. The BRIEF is a parent- and teacher-report measure of executive function. It has eight subscales, which have been grouped, based on factor analysis of these scales, into two indices, the Metacognitive Index (MI) and the Behavioral Regulation Index (BRI). The BRI is comprised of the inhibit, shift, and emotional control subscales, and reflects the ability to set shift and control behavior through the administration of appropriate inhibitory control. The MI is comprised by the initiate, working memory, plan/organize, organization of materials, and monitor subscales. This index assesses the ability to initiate, plan, and organize behavior, and to apply and sustain appropriate working memory to control behavior (Gioia, Isquith, Retzlaff, & Espy, 2002). All eight subscales comprise a Global Executive Composite (GEC) score. The BRIEF has clinical utility for the diagnosis of ADHD (Isquith & Gioia, 2000). For example, McCandless and O'Laughlin (2007) found that the MI was sensitive to the diagnosis of ADHD, while the BRI was most sensitive to dissociating among subtypes of ADHD. The MI, BRI, and GEC composite scores were the focus of the present investigation.

2.4.2 | Child Behavior Checklist

The CBCL (Achenbach & Rescorla, 2000, 2001, 2003) was administered using either the preschool, school-age, or adult form (depending on the participant's age). We focused on the Attention Problems outcome scale, which has high reliability (r = 0.78 for the preschool form; r = 0.92 for the school-age form, with r = 0.70 and 0.60 for 12- and 24-month follow-up, respectively; r = 0.87 for the adult form). This scale is also highly associated with ADHD diagnosis (Biederman et al., 1993; Papachristou et al., 2016).

2.5 | Simple mediation analysis

We examined the relationships among the laterality of the FAT, executive function, and attention in typical individuals using a simple mediation model. This model was statistically analyzed in SPSS v23 within the PROCESS regression framework from Hayes (Hayes, 2013). We used Model 4 in the framework. Three mediation models were tested. In the first model, we tested whether the BRIEF GEC—which includes all subtests of the BRIEF—mediates the relation between laterality of the FAT and Attention Problems. Because some of the ratings on the BRIEF are directly related to items on the CBCL Attention Problems subscale (e.g., “Impulsive or acts without thinking”), we reran the same analysis replacing GEC with MI as a mediator, which mitigates that potential confound. Although not completely orthogonal, we also ran the analysis with BRI as the mediator. In the mediation analysis, the following covariates were included: gender, number of available HARDI volumes (to index movement), age (in days), whole-brain nQA (to control for general white matter microstructure), and household income (on a 10-point scale, to control for SES). Because these controls were included, raw scores were used for the outcome variables. In addition, to confirm whether the results we report were specific to the FAT, we also ran the same mediation model with laterality of the whole-brain white matter, and for laterality of the ILF, as the predictor of interest. Finally, to see if the pattern of results differs across hemispheres, the mediation analysis was run on the separate left and right FAT pathways.

3 | RESULTS

3.1 | Identification of the fiber tracts

Using the individually defined ROIs, we were able to track four subcomponents of the FAT, in the following percentage of participants from the full sample (n = 129; averaged across the hemispheres): IFGOp ↔ pre-SMA (92%); IFGTr ↔ pre-SMA (66%); IFGOp ↔ SMA (76%); IFGTr ↔ SMA (26%). However, the largest component defined the connections between the IFGOp and pre-SMA, and this was tracked in almost all participants for both hemispheres. This replicates the pattern of connectivity reported in adults (Bozkurt et al., 2016; Catani et al., 2012; Kinoshita et al., 2012; Martino & De Lucas, 2014; Szmuda et al., 2017). Furthermore, components overlap to a significant degree as they traverse the frontal white matter, and thus analysis of these components introduces a dependency in the results. Finally, the available literature suggests that the IFGOp and pre-SMA are most likely to be associated with executive function (Aron et al., 2007; Swann et al., 2012). Therefore, for analytic and conceptual simplicity, we focused on the IFGOp ↔ pre-SMA component for the age-related and mediation analyses described below.

3.2 | Age-related differences in fractional anisotropy

In Figure 2 we show the age-related differences in FA of the left (purple) and right FAT (in teal; IFGOp ↔ pre-SMA component), and

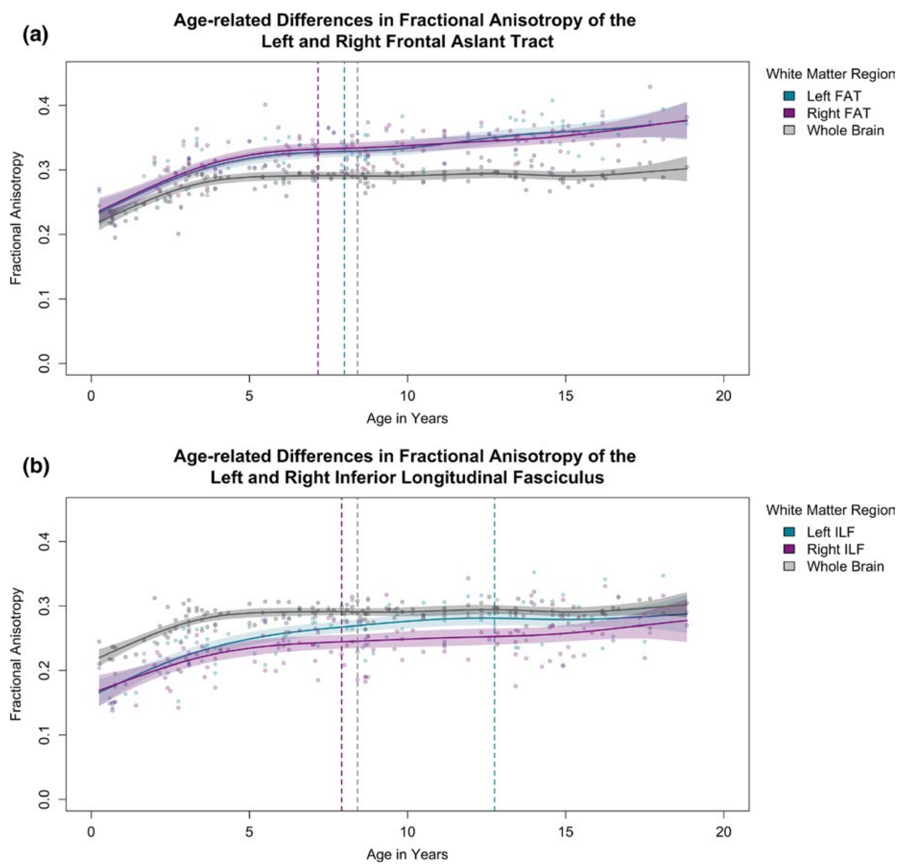


FIGURE 2 Top: Age-related differences in FA of the left (purple) and right FAT (in teal; IFGOp ↔ pre-SMA component). Bottom: Age-related differences in FA of the left (purple) and right ILF (in teal). These are mapped along with the general trend of white matter development in the whole brain (gray). Shading represents the 95% confidence intervals. Vertical hashed lines mark the first derivative, which indicates the asymptote of the curve and at what age this occurs

left (purple) and right ILF (in teal). These are mapped along with the general trend of white matter development in the whole brain (gray line). Shading represents the 95% confidence intervals.

Visual inspection of the scatter plots indicated that the data might be summarized by a nonlinear model. To accomplish this, we fit two models for each dependent measure. The first was a linear model of age and gender predicting FA. The second was a generalized additive model (GAM; R 3.4.3; package *gam*; Wood, 2006) with the same variables. Integrated smoothness estimation was applied (of the form *gam*(*dv~s*(*predictor*)). We computed Akaike information criterion (AIC) and Bayesian information criterion (BIC) values for each model. In addition, we computed the first derivative to identify the "peak" of the curve, in cases where the function was nonlinear.

There were no effects of gender in any of the models (smallest $p = 0.26$), so that variable was dropped. In addition, compared to the linear models, AIC and BIC fit indices were smaller for the nonlinear (i.e., GAM) models (Left FAT Linear: AIC = −512.8; BIC = −504.5; Nonlinear: AIC = −534.4; BIC = −517.7; Right FAT Linear: AIC = −509.1; BIC = −500.8; Nonlinear: AIC = −540.9; BIC = −524.3; Whole brain Linear: AIC = −635.2; BIC = −626.6; Nonlinear: AIC = −697.4; BIC = −680.2) Thus, the nonlinear models are reported here, and were significant for the left FAT ($F(4, 114) = 47.1$, $p < 0.001$), the right FAT ($F(4, 114) = 44.4$, $p < 0.001$), and the whole brain ($F(4, 124) = 36.89$, $p < 0.001$). We implemented the same procedure for the ILF. Left ILF Linear: AIC = −512.8; BIC = −504.5; Nonlinear: AIC = −534.4; BIC = −517.7; Right ILF Linear: AIC = −509.1; BIC = −500.8; Nonlinear: AIC = −540.9; BIC = −524.3; Left ILF nonlinear ($F(4, 114) = 47.1$, $p < 0.001$), right ILF nonlinear ($F(4, 114) = 44.4$, $p < 0.001$). We also calculated the first derivative of the curves to determine where an asymptote was reached following the early increase in FA in the first few years of life. For the FAT, inspection of the plot reveals that age-related differences in white matter appear rapidly over the first 6–7-years. However, while for the whole brain the differences in white matter plateau, for the FAT there is subsequent increase in FA after about age 11. For the ILF, a similar pattern was found, although the left ILF appeared to evidence small age-related differences until about age 13. In addition, unlike the FAT, the average ILF FA is less than that seen in the whole-brain average.

3.3 | Mediation analysis

The age-related differences in white matter suggest that age might be a potential "third variable" driving the association between white matter and behavior. Therefore, we first explored whether age was associated with the behavioral scores. It was not for BRIEF GEC or MI ($r = -0.16$ for BRIEF GEC, $t(68) = 1.31$, $p = 0.20$; $r = -0.14$ for BRIEF MI, $t(68) = 1.18$, $p = 0.24$) or for CBCL Attention Problems ($r = -0.10$, $t(68) = 0.80$, $p = 0.42$). However, there was a small correlation between age and BRIEF BRI scores ($r = -0.27$, $t(68) = 2.31$, $p = 0.03$). To mitigate this possible confound, we controlled for age and other covariates (sex, whole-brain white matter, movement in the scanner, and SES) in the analysis. With the exception of the relation between age and BRIEF BRI, no significant effects for the covariates were found, and the findings are reported with the covariates included in the model. This suggests that the mediation analysis speaks to individual differences in the measures of FAT white matter correlates that predict differences in executive function and externalizing behaviors.

Figure 3 and Table 1 show the results of the mediation analysis. Specifically, the results show that left laterality of the FAT predicted higher CBCL Attention Problems scores. It also predicted higher BRIEF scores. Thus, when considered in a mediation model, the relation between FAT laterality and Attention Problems was fully mediated by executive function as measured by the BRIEF. This finding held for the full executive function index of the BRIEF (i.e., GEC), and also for the MI and BRI considered separately. It also held when we entered as a predictor the FA measure instead of nQA (the 95% CI for the *ab* parameter covered zero for all models; $B = 42.4$ (10.2–80.5) for BRIEF GEC, $B = 32.8$ (6.32–69.7) for BRIEF MI, and $B = 32.9$ (7.4–68.6) for BRIEF BRI). Because higher scores on each of the outcome variables reflect greater executive function and attention problems, our analysis shows that greater left laterality predicts more executive dysfunction, and higher reports of attention problems, but the relation between laterality and attention is mediated by executive function.

This pattern of results was not apparent when we assessed laterality of the whole-brain white matter. Laterality of the whole-brain white matter did not predict CBCL Attention Problems ($B = 18.6$, $t(63) = 0.34$, $p = 0.73$, 95% CI = −89.8 to 126.9), nor did it predict BRIEF GEC ($B = 88.8$, $t(63) = 0.41$, $p = 0.68$, 95% CI = −343.5 to 521.1), BRIEF MI ($B = 27.1$, $t(63) = 0.86$, $p = 0.39$, 95% CI = −36.0 to 90.1), or BRIEF BRI ($B = 67.4$, $t(63) = 0.90$, $p = 0.37$, 95% CI = −81.6 to 216.3). There was no mediation effect (the 95% CI for the *ab* parameter covered zero for all models; $B = 15.6$ (−62.4 to 83.9) for BRIEF GEC, $B = 25.4$ (−44.2 to 78.7) for BRIEF MI, and $B = 29.8$ (−38.3 to 97.6) for BRIEF BRI).

We also assessed a control long association fiber pathway, the ILF, that we predicted would not be associated with our attention and executive function measures. Consistent with this prediction, laterality of the ILF white matter did not predict CBCL Attention Problems ($B = -2.63$, $t(62) = -0.20$, $p = 0.84$, 95% CI = −28.6 to 23.4), nor did it predict BRIEF GEC ($B = -46.7$, $t(62) = -0.91$, $p = 0.37$, 95% CI = −149.7 to 56.4), BRIEF MI ($B = -2.0$, $t(62) = -0.27$, $p = 0.79$, 95% CI = −17.1 to 13.1), or BRIEF BRI ($B = -25.0$, $t(62) = -1.42$, $p = 0.16$, 95% CI = −59.9 to 10.2). There was no mediation effect (the 95% CI for the *ab* parameter covered zero for all models; $B = -8.3$ (−25.4 to 7.2) for BRIEF GEC, $B = -1.9$ (−17.3 to 11.5) for BRIEF MI, and $B = 11.3$ (−28.9 to 3.7) for BRIEF BRI). These results suggest that the finding we report is specific to the FAT.

Finally, we examined whether each tract—left and right FAT—separately evidenced any relation to attention problems and executive function. The left FAT did not predict CBCL Attention Problems ($B = -17.5$, $t(63) = -0.40$, $p = 0.69$, 95% CI = −69.7 to 104.7), nor did it predict BRIEF GEC ($B = 243.1$, $t(63) = 1.43$, $p = 0.16$, 95% CI = −97.9 to 584.1), BRIEF MI ($B = 41.2$, $t(63) = 1.68$, $p = 0.10$, 95% CI = −8.0 to 90.3), or BRIEF BRI

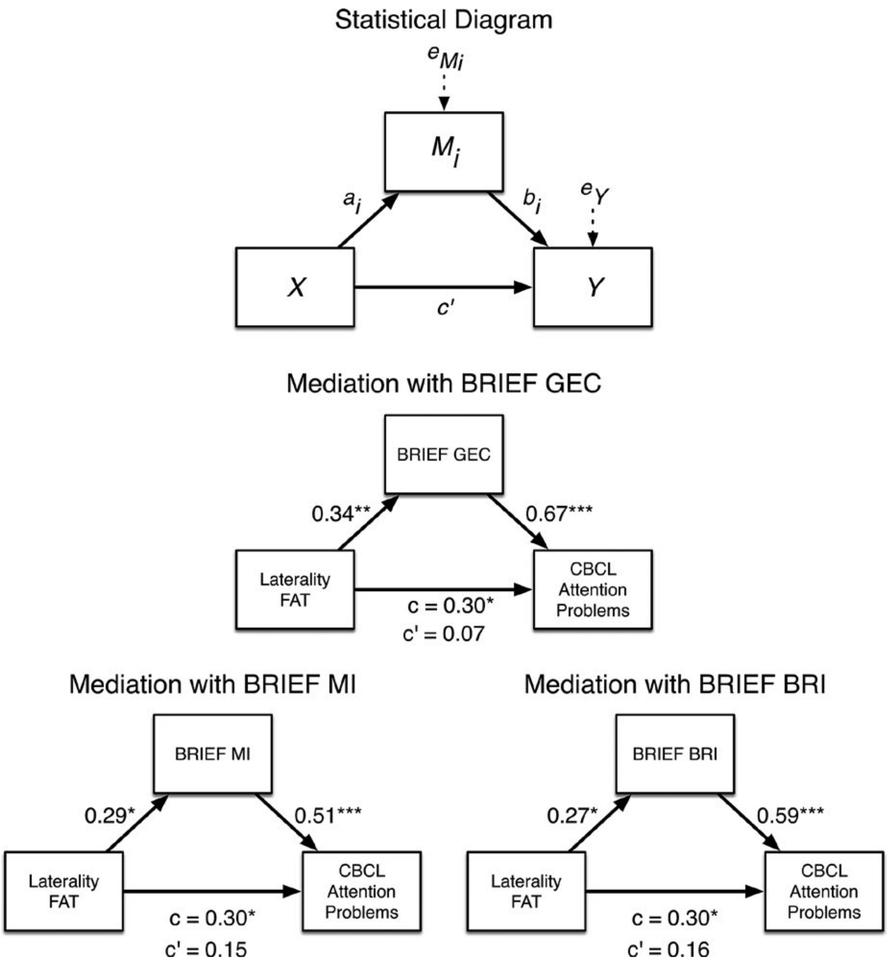


FIGURE 3 Mediation analysis showing greater left laterality of the FAT predicts more executive dysfunction on the BRIEF, and higher reports of attention problems on the CBCL. The statistical model is presented (top), and is tested with BRIEF GEC as the mediator (middle), BRIEF MI as the mediator (bottom left), and BRIEF BRI as the mediator (bottom right)

(B = 61.8, t(63) = 1.05, p = .30, 95% CI = −55.7 to 179.4). There was no mediation effect (the 95% CI for the *ab* parameter covered zero for all models; B = −8.3 (−25.4 to 7.2) for BRIEF GEC, B = 43.6 (−11.8 to 104.2) for BRIEF MI, and B = 27.8 (−14.0 to 84.8) for BRIEF BRI). In contrast, the right FAT did predict CBCL Attention Problems (B = −75.6, t(63) = −2.07, p = 0.04, 95% CI = −148.5 to −2.8), but it did not predict BRIEF GEC (B = −208.3, t(63) = 1.42, p = 0.16, 95% CI = −502.3 to 85.8), BRIEF MI (B = −18.1, t(63) = −0.84, p = 0.40, 95% CI = −61.2 to 25.0), or BRIEF BRI (B = −58.0, t(63) = 1.14, p = 0.26, 95% CI = −159.2 to 43.2). There was also no mediation effect (the 95% CI for the *ab* parameter covered zero for all models; B = −8.3 (−25.4 to 7.2) for BRIEF GEC, B = −35.4 (−101.6 to 12.4) for BRIEF MI, and B = −24.9 (−90.1 to 21.8) for BRIEF BRI).

4 | DISCUSSION

We investigated the development of the FAT and its association with executive function and externalizing behaviors in a sample of 129 children ranging in age from 7 months to 19 years. We found that the FAT could be tracked in over 90% of those children, and that the pathway showed age-related differences into adulthood. The change in white matter microstructure was very rapid until about 6 years, and then plateaued, only to show age-related increases again after the age of 11 years. In a subset of those children for whom behavioral data was available (5–18-years; n = 70), left laterality of the microstructural properties of the FAT predicted greater attention problems as measured by the CBCL. However, this relationship was fully mediated by higher executive dysfunction as measured by the BRIEF. This relationship was specific to the FAT—we found no relationship between laterality of the white matter of the brain in general and attention problems, or executive function. It was also specific to the laterality measure—although the right, but not left, FAT was associated with attention problems, this was not mediated by executive function. These findings suggest that the degree to which the developing brain favors a right lateralized structural dominance of the FAT is directly associated with developing executive function and attention. This novel finding provides a new potential structural biomarker for attention problems and associated executive dysfunction, which could lay the foundation for future exploration as a biological indicator of treatment response in developmental externalizing disorders, such as ADHD.

4.1 | The role of the frontal aslant tract in executive function

Our findings are consistent with current neurobiological models of executive function in adults. For example, several authors (Aron,

TABLE 1 Results of the mediation analyses for frontal aslant tract laterality predicting attention problems

Outcome	Predictor	*B* (β)	SE_{boot}	*t*	*p*-value	L 95% CI	U 95% CI	R^2 model
BRIEF GEC	Laterality FAT nQA	166.4 (0.34)	60.3	2.76	0.008**	45.8	287.00	0.15
CBCL Attention Problems	BRIEF GEC	0.17 (0.67)	0.02	7.1	0.000***	0.12	0.22	0.52
	Laterality FAT nQA	8.7 (0.07)	12.2	0.71	0.48	−15.7	33.0	
	Total effect (*c* path)	36.9 (0.30)	15.3	2.4	0.02*	6.3	67.5	
	Indirect effect (*ab*, or *c*–*c*′)	28.2 (0.23)	13.04	[a]	[a]	7.1	57.3	
BRIEF MI	Laterality FAT nQA	20.6 (0.29)	9.0	2.3	0.03*	2.7	38.5	0.13
CBCL Attention Problems	BRIEF MI	0.87 (0.51)	0.19	4.6	0.000***	0.49	1.24	0.35
	Laterality FAT nQA	19.0 (0.16)	14.0	1.4	0.17	−8.7	46.7	
	Total effect (*c* path)	36.9 (0.30)	15.3	2.4	0.02*	6.3	67.5	
	Indirect effect (*ab*, or *c*–*c*′)	17.9 (0.15)	11.4	[a]	[a]	1.1	44.7	
BRIEF BRI	Laterality FAT nQA	46.3 (0.27)	22.2	2.18	0.03*	3.9	88.7	0.15
CBCL Attention Problems	BRIEF BRI	0.42 (0.59)	0.08	5.5	0.000***	0.27	0.57	0.42
	Laterality FAT nQA	17.7 (0.14)	13.1	1.4	0.18	−8.6	43.9	
	Total effect (*c* path)	36.9 (0.30)	15.3	2.4	0.02*	6.3	67.5	
	Indirect effect (*ab*, or *c*–*c*′)	19.2 (0.16)	12.9	[a]	[a]	0.28	49.2	

Notes. All results control for age, gender, movement in the scanner, household income, and whole-brain normalized quantitative anisotropy.
[a]Presence of the indirect (*ab*) effect was determined by bootstrap (5,000 iterations) to account for possible asymmetry of the sampling distribution of *ab*. An effect was present if the confidence interval did not cover zero. L: Lower; U: Upper; CI: 95% confidence interval; BRIEF: Behavior Rating Inventory of Executive Function; CBCL: Child Behavior Checklist; GEC: Global Executive Composite; MI: Metacognitive Index; BRI: Behavioral Regulation Index; FAT: Frontal Aslant Tract.
$^*p < .05$; $^{**}p < .01$; $^{***}p < .001$.

Herz, Brown, Forstmann, & Zaghloul, 2016; Aron et al., 2007, 2014; Jahanshahi, Obeso, Rothwell, & Obeso, 2015; Wiecki & Frank, 2013) have proposed a model for stopping behavior—that is, countermanding an initiated response tendency via top–down executive control, recruited during Go/NoGo and stop-signal experimental paradigms. In these tasks, a prepotent response is initiated (a Go process) that must be over-ridden when a stop-signal occurs (the Stop process). These models propose that stopping requires the integrity of the right IFG and the pre-SMA, and that these regions form part of a cortico-basal ganglia "network for inhibition" (Jahanshahi et al., 2015).

In our study, we replicate the structural connection of the IFG and pre-SMA via the fibers of the FAT, and other research confirms the functional connectivity of these two regions (Duann, Ide, Luo, & Li, 2009). The establishment of this monosynaptic connection between the IFG and pre-SMA is important for exploring the distinct roles each region plays within this "network for inhibition" (Ridderinkhof, Ullsperger, Crone, & Nieuwenhuis, 2004). In the Wiecki/Frank computational model (Wiecki & Frank, 2013), the right IFG directly activates neurons of the subthalamic nucleus, which plays an explicit role in stopping motor behavior (Favre, Ballanger, Thobois, Broussolle, & Boulinguez, 2013; Jahanshahi, 2013; Obeso et al., 2014; Van Wouwe et al., 2017). However, others suggest that this connection may proceed via the pre-SMA (Aron et al., 2016). This is important to work out, and our results suggest that the connection between IFG and pre-SMA *is* an important structural component of this network. Furthermore, it may be that the modulation of subthalamic nucleus activity proceeds through this link. From this perspective, the right FAT is a pathway for inhibition. Indeed, higher FA in the white matter under the pre-SMA and right IFG is associated with better response inhibition in children (Madsen et al., 2010) and older adults (Coxon, Van Impe, Wenderoth, & Swinnen, 2012).

It is also possible, though, that the pathway does not play a role in inhibition, but rather in conflict detection. Thus, the pre-SMA may be critical for the detection of and resolution of conflicting action representations—the "winning" representation is reinforced, and the "losing" representation is suppressed (Nachev, Wydell, O'Neill, Husain, & Kennard, 2007). Indeed, Nachev et al. (2007) found that a patient with a focal lesion to the right pre-SMA was significantly impaired on a task requiring the resolution of conflict between competing action plans. This is consistent with fMRI task paradigms showing activation of right pre-SMA in situations in which a participant must choose to perform a new response in favor of an established response (Garavan, Ross, Kaufman, & Stein, 2003), and in single-unit recording of a human in which pre-SMA neurons appear to play a role in the selection and preparation of movements (Amador & Fried, 2004). The pre-SMA and its connections with the IFG appear to be important for these processes.

4.2 | The role of the frontal aslant tract in externalizing behaviors and attention

We also showed that microstructural properties of the FAT, as measured by DWI, are associated with increased reports of attention problems in children, a finding that was particularly apparent for the right FAT. The left FAT did not show this pattern. This is consistent with prior neuroimaging research in people with ADHD showing activation differences compared to neurotypical people in right IFG and pre-SMA during executive function tasks. For example, people with ADHD show hypoactivation of the right IFG during Go/NoGo and SST tasks (Rubia et al., 1999). Anatomic and functional differences in children with ADHD are also reported for the pre-SMA (Mostofsky et al., 2002; Suskauer, Simmonds, Caffo, et al., 2008; Suskauer, Simmonds, Fotedar, et al., 2008).

Thus, one interpretation of our results is that the FAT is involved in attention per se, and not necessarily inhibitory control or conflict detection. Indeed, one critique of the notion that the right IFG is associated with inhibition is that the typical experimental paradigms employed are assessing attentional processes (Chatham et al., 2012; Hampshire, Chamberlain, Monti, Duncan, & Owen, 2010). For example, Chatham and colleagues (Chatham et al., 2012) and Hampshire and colleagues (Erika-Florence, Leech, & Hampshire, 2014; Hampshire, 2015; Hampshire et al., 2010) have suggested that so-called "inhibitory control tasks" really tap into controlled context-monitoring processes, not inhibition. The authors further suggested that impairments in context-monitoring, supported by right IFG and associated circuits, might explain deficits seen in ADHD. They pointed to increased reaction time variability in SST paradigms in people with ADHD as support for such a contention (Castellanos, Sonuga-Barke, Milham, & Tannock, 2006), and suggest that treatments focusing on improving context-monitoring, rather than improving inhibitory control, might be more appropriately targeting the underlying deficit in ADHD. But these tasks confound context monitoring, conflict detection, and inhibitory control processes proposed to recruit the right IFG (Hampshire, 2015). Although some attempts have been made to tease these processes apart (Erika-Florence et al., 2014; Hampshire, 2015), there is still debate about whether right IFG is involved in attention more generally (Ridderinkhof et al., 2004), or more specifically inhibitory control (Aron et al., 2014).

It has also been proposed that a primary deficit in ADHD is in fact one of inhibitory control (Barkley, 1997; Neely et al., 2017; Schachar, Mota, Logan, Tannock, & Klim, 2000). However, inhibitory control and more broadly defined executive function deficits are not a universal feature of ADHD (Nigg, Willcutt, Doyle, & Sonuga-Barke, 2005), and in fact there may be executive function subtypes of ADHD, with an inhibitory control dysfunction profile describing only one of the subtypes (Roberts, Martel, & Nigg, 2017). These subtypes are defined at the behavioral level, and further progress in demarcating them may require the additional of data at other levels of analysis, such as at the neurobiological level. In this case, our findings suggest that delineation of the FAT in people with ADHD, and exploration of its functional relationship to executive function, might be important for understanding and dissociating ADHD subtypes. Indeed, our data reinforce the notion that attention problems associated with the FAT are explained by individual differences in executive function. There is a caveat here though—the mediation only held for the laterality measure. Although the right (but not left) FAT predicted attention, this particular association was not mediated by executive function. This raises an interesting possibility. That is, the degree to which functions best supported by a particular fiber pathway are co-opted by the contralateral pathway may predict dysfunction. Some evidence indicates this is the case for the FAT's involvement in stuttering. Thus, a recent study by Neef and colleagues (Neef et al., 2018) showed that stronger structural connectivity of the right, but not left, FAT is associated with worse stuttering. They interpreted this as indication of hyperactivity of the network involved in global response suppression, which disrupts fluent speech that typically relies strongly on left perisylvian networks, supported by the left FAT and associated perisylvian pathways. This proposal requires additional research, but it represents an interesting way of thinking about how fiber pathways that mirror each other across hemispheres might support sometimes complimentary and dissociable functions. A second caveat is worth noting as well. That is, our sample is a typical sample, and does not speak to whether there are subtypes that might be apparent in a clinical population. This would require further work in clinical populations, such as people diagnosed with ADHD.

4.3 | Subcomponents of the frontal aslant

Our analysis of the relation between the FAT and attention and executive function focused on one subcomponent of the tract, namely the component connecting the pre-SMA with the IFGOp. On the right hemisphere, the IFGOp is associated with inhibitory control (Aron et al., 2016; Herbet et al., 2015). However, the IFGTr also has efferent/afferent fibers coursing as part of the FAT. On the left hemisphere, this region is consistently associated with controlled lexical retrieval and selection, which is dissociated from the more posterior IFGOp associated with phonological selection and retrieval (Badre, Poldrack, Pare-Blagoev, Insler, & Wagner, 2005; Devlin, Matthews, & Rushworth, 2003; Gough, Nobre, & Devlin, 2005). Even on the right hemisphere, there appears to be some role for semantic selection for IFGTr. For example, transcranial magnetic stimulation (TMS) of the right IFGTr, but not IFGOp, improves semantic retrieval in a naming task in people with aphasia (Naeser et al., 2011).

SMA and pre-SMA also have different functional associations. The pre-SMA is especially thought to play a role in motor selection, as it does not make a direct connection to the primary motor cortex, the spinal cord, or the cranial nerve motor nuclei. Actual execution of movements is more associated with SMA and is dependent on and its direct connections with motor cortex (Dum & Strick, 1991; Lu, Preston, & Strick, 1994; Luppino, Matelli, Camarda, Gallese, & Rizzolatti, 1991). The pre-SMA thus seems to be involved in higher order selection, and conflict monitoring and resolution (Tremblay & Gracco, 2009, 2010). Differential connectivity of these medial frontal regions with the IFGTr and IFGOp may support somewhat complementary functions in the service of selecting among competing thoughts and actions. In the case of connections with IFGTr, this may be more important in situations involving *semantic* conflict. Connection with IFGOp may be associated with action selection and inhibitory control of actions more broadly. However, since the FAT is only a relatively recently identified fiber pathway, these proposals remain somewhat speculative and await further investigation.

4.4 | Limitations

One potential limitation of our study is the use of behavior report measures as a proxy for executive function and attention. This is a legitimate criticism, and the study should be in part viewed as a point of departure for future detailed investigations using laboratory paradigms. However, the behavioral ratings we used here have substantial construct validity and reliability (Achenbach & Rescorla, 2000, 2001, 2003; Gioia et al., 2000), and provide information that cannot necessarily be obtained from laboratory tasks. For example, Barkley and colleagues (Barkley & Fischer, 2011; Barkley & Murphy, 2010) found that ratings of executive function can sometimes be a better predictor of everyday impairment than laboratory tests of executive function. Rating scales are also effective with preschool children and perform as well as laboratory tasks, such as continuous performance tasks, at differentiating children with ADHD from typical children (Cak, Cengel Kultur, Gokler, Oktem, & Taskiran, 2017). Thus, while future research should incorporate laboratory tasks, it does not discount the utility of the results we report here.

CONCLUSIONS

The work we report here shows that the FAT develops in a protracted manner into late adolescence/early adulthood, and that right lateralization of the fiber pathway is significantly associated with executive function. This fits with the putative functional roles of the regions the pathway connects—the right IFG and right pre-SMA. These results suggest that the FAT should be explored more carefully in research on developing executive function, or dysfunction as occurs in externalizing disorders such as ADHD.

ACKNOWLEDGEMENTS

This work was supported by grants from the National Institutes of Mental Health (Grant R01MH112588 and R56MH108616 to P.G. and A.S.D.), and from the National Institute for Drug Abuse (U01DA041156; salary support to A.S.D.).

AUTHOR CONTRIBUTIONS

A.S.D., D.G., I.B., P.G., and A.M. designed research; D.G. and I.B. analyzed the diffusion data; A.S.D. conducted the statistical analysis; A.S.D. and D.G. wrote the paper, with input from P.G., I.B., and A.M.

CONFLICT OF INTEREST

None reported.

REFERENCES

Achenbach, T. M., & Rescorla, L. (2000). *Manual for the ASEBA preschool forms & profiles: An integrated system of multi-informant assessment*. Burlington, VT: ASEBA.

Achenbach, T. M., & Rescorla, L. (2001). *Manual for the ASEBA school-age forms & profiles: An integrated system of multi-informant assessment*. Burlington, VT: ASEBA.

Achenbach, T. M., & Rescorla, L. (2003). *Manual for the ASEBA adult forms & profiles: For ages 18–59: Adult self-report, adult behavior checklist*. Burlington, VT: ASEBA.

Amador, N., & Fried, I. (2004). Single-neuron activity in the human supplementary motor area underlying preparation for action. *Journal of Neurosurgery*, *100*(2), 250–259. https://doi.org/10.3171/jns.2004.100.2.0250

Aron, A. R., Behrens, T. E., Smith, S., Frank, M. J., & Poldrack, R. A. (2007). Triangulating a cognitive control network using diffusion-weighted magnetic resonance imaging (MRI) and functional MRI. *Journal of Neuroscience*, *27*(14), 3743–3752. https://doi.org/10.1523/JNEUROSCI.0519-07.2007

Aron, A. R., Herz, D. M., Brown, P., Forstmann, B. U., & Zaghloul, K. (2016). Frontosubthalamic circuits for control of action and cognition. *Journal of Neuroscience*, *36*(45), 11489–11495. https://doi.org/10.1523/JNEUROSCI.2348-16.2016

Aron, A. R., Robbins, T. W., & Poldrack, R. A. (2014). Inhibition and the right inferior frontal cortex: One decade on. *Trends in Cognitive Sciences*, *18*(4), 177–185. https://doi.org/10.1016/j.tics.2013.12.003

Badre, D., Poldrack, R. A., Pare-Blagoev, E. J., Insler, R. Z., & Wagner, A. D. (2005). Dissociable controlled retrieval and generalized selection mechanisms in ventrolateral prefrontal cortex. *Neuron*, *47*(6), 907–918. https://doi.org/10.1016/j.neuron.2005.07.023

Barkley, R. A. (1997). Behavioral inhibition, sustained attention, and executive functions: Constructing a unifying theory of ADHD. *Psychological Bulletin*, *121*(1), 65–94.

Barkley, R. A., & Fischer, M. (2011). Predicting impairment in major life activities and occupational functioning in hyperactive children as adults: Self-reported executive function (EF) deficits versus EF tests. *Developmental Neuropsychology*, *36*(2), 137–161. https://doi.org/10.1080/87565641.2010.549877

Barkley, R. A., & Murphy, K. R. (2010). Impairment in occupational functioning and adult ADHD: The predictive utility of executive function (EF) ratings versus EF tests. *Archives of Clinical Neuropsychology*, *25*(3), 157–173. https://doi.org/10.1093/arclin/acq014

Basilakos, A., Fillmore, P. T., Rorden, C., Guo, D., Bonilha, L., & Fridriksson, J. (2014). Regional white matter damage predicts speech fluency in chronic post-stroke aphasia. *Frontiers in Human Neuroscience*, *8*, 845. https://doi.org/10.3389/fnhum.2014.00845

Biederman, J., Faraone, S. V., Doyle, A., Lehman, B. K., Kraus, I., Perrin, J., & Tsuang, M. T. (1993). Convergence of the Child Behavior Checklist with structured interview-based psychiatric diagnoses of ADHD children with and without comorbidity. *Journal of Child Psychology and Psychiatry*, *34*(7), 1241–1251.

Bozkurt, B., Yagmurlu, K., Middlebrooks, E. H., Karadag, A., Ovalioglu, T. C., Jagadeesan, B., … Grande, A. W. (2016). Microsurgical and tractographic anatomy of the supplementary motor area complex in humans. *World Neurosurgery*, *95*, 99–107. https://doi.org/10.1016/j.wneu.2016.07.072

Broce, I., Bernal, B., Altman, N., Tremblay, P., & Dick, A. S. (2015). Fiber tracking of the frontal aslant tract and subcomponents of the arcuate fasciculus in 5-8-year-olds: Relation to speech and language function. *Brain and Language*, *149*, 66–76. https://doi.org/10.1016/j.bandl.2015.06.006

Cak, H. T., Cengel Kultur, S. E., Gokler, B., Oktem, F., & Taskiran, C. (2017). The behavior rating inventory of executive function and continuous performance test in preschoolers with attention deficit hyperactivity disorder. *Psychiatry Investigation*, *14*(3), 260–270. https://doi.org/10.4306/pi.2017.14.3.260

Carter, A. S., Briggs-Gowan, M. J., & Davis, N. O. (2004). Assessment of young children's social-emotional development and psychopathology: Recent advances and recommendations for practice. *Journal of Child Psychology and Psychiatry*, *45*(1), 109–134.

Castellanos, F. X., Sonuga-Barke, E. J., Milham, M. P., & Tannock, R. (2006). Characterizing cognition in ADHD: Beyond executive dysfunction. *Trends in Cognitive Sciences*, *10*(3), 117–123. https://doi.org/10.1016/j.tics.2006.01.011

Catani, M., Dell'acqua, F., Vergani, F., Malik, F., Hodge, H., Roy, P., … Thiebaut de Schotten, M. (2012). Short frontal lobe connections of the human brain. *Cortex*, *48*(2), 273–291. https://doi.org/10.1016/j.cortex.2011.12.001

Catani, M., Mesulam, M. M., Jakobsen, E., Malik, F., Martersteck, A., Wieneke, C., … Rogalski, E. (2013). A novel frontal pathway underlies verbal fluency in primary progressive aphasia. *Brain*, *136*(Pt 8), 2619–2628. https://doi.org/10.1093/brain/awt163

Chatham, C. H., Claus, E. D., Kim, A., Curran, T., Banich, M. T., & Munakata, Y. (2012). Cognitive control reflects context monitoring, not motoric stopping, in response inhibition. *PLoS ONE*, *7*(2), e31546. https://doi.org/10.1371/journal.pone.0031546

Coxon, J. P., Van Impe, A., Wenderoth, N., & Swinnen, S. P. (2012). Aging and inhibitory control of action: Cortico-subthalamic connection strength predicts stopping performance. *Journal of Neuroscience*, *32*(24), 8401–8412. https://doi.org/10.1523/JNEUROSCI.6360-11.2012

Daducci, A., Canales-Rodriguez, E. J., Descoteaux, M., Garyfallidis, E., Gur, Y., Lin, Y. C., … Thiran, J. P. (2014). Quantitative comparison of reconstruction methods for intra-voxel fiber recovery from diffusion MRI. *IEEE Transactions on Medical Imaging*, *33*(2), 384–399. https://doi.org/10.1109/TMI.2013.2285500

Descoteaux, M., Angelino, E., Fitzgibbons, S., & Deriche, R. (2007). Regularized, fast, and robust analytical Q-ball imaging. *Magnetic Resonance in Medicine*, *58*(3), 497–510. https://doi.org/10.1002/mrm.21277

Desikan, R. S., Segonne, F., Fischl, B., Quinn, B. T., Dickerson, B. C., Blacker, D., … Killiany, R. J. (2006). An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. *NeuroImage*, *31*(3), 968–980. https://doi.org/10.1016/j.neuroimage.2006.01.021

Devlin, J. T., Matthews, P. M., & Rushworth, M. F. (2003). Semantic processing in the left inferior prefrontal cortex: A combined functional magnetic resonance imaging and transcranial magnetic stimulation study. *Journal of Cognitive Neuroscience*, *15*(1), 71–84. https://doi.org/10.1162/089892903321107837

Dick, A. S., Bernal, B., & Tremblay, P. (2014). The language connectome: New pathways, new concepts. *Neuroscientist*, *20*(5), 453–467. https://doi.org/10.1177/1073858413513502

Dick, A. S., & Tremblay, P. (2012). Beyond the arcuate fasciculus: Consensus and controversy in the connectional anatomy of language. *Brain*, *135*(Pt 12), 3529–3550. https://doi.org/10.1093/brain/aws222

Duann, J. R., Ide, J. S., Luo, X., & Li, C. S. (2009). Functional connectivity delineates distinct roles of the inferior frontal cortex and pre-supplementary motor area in stop signal inhibition. *Journal of Neuroscience*, *29*(32), 10171–10179. https://doi.org/10.1523/JNEUROSCI.1300-09.2009

Dum, R. P., & Strick, P. L. (1991). The origin of corticospinal projections from the premotor areas in the frontal lobe. *Journal of Neuroscience*, *11*(3), 667–689.

Duvernoy, H. M., Bourgouin, P., Cabanis, E. A., Cattin, F., Guyot, J., Iba-Zizen, M. T., … Vannson, J. L. (1999). *The human brain: Surface, three-dimensional sectional anatomy with MRI, and blood supply*. New York, NY: Springer-Wien.

Erika-Florence, M., Leech, R., & Hampshire, A. (2014). A functional network perspective on response inhibition and attentional control. *Nature Communications*, *5*, 4073. https://doi.org/10.1038/ncomms5073

Everts, R., Lidzba, K., Wilke, M., Kiefer, C., Mordasini, M., Schroth, G., … Steinlin, M. (2009). Strengthening of laterality of verbal and visuospatial functions during childhood and adolescence. *Human Brain Mapping*, *30*(2), 473–483. https://doi.org/10.1002/hbm.20523

Favre, E., Ballanger, B., Thobois, S., Broussolle, E., & Boulinguez, P. (2013). Deep brain stimulation of the subthalamic nucleus, but not dopaminergic medication, improves proactive inhibitory control of movement initiation in Parkinson's disease. *Neurotherapeutics: The Journal of the American Society for Experimental NeuroTherapeutics*, *10*(1), 154–167. https://doi.org/10.1007/s13311-012-0166-1

Fujii, M., Maesawa, S., Motomura, K., Futamura, M., Hayashi, Y., Koba, I., & Wakabayashi, T. (2015). Intraoperative subcortical mapping of a language-associated deep frontal tract connecting the superior frontal gyrus to Broca's area in the dominant hemisphere of patients with glioma. *Journal of Neurosurgery*, *122*(6), 1390–1396. https://doi.org/10.3171/2014.10.JNS14945

Furniss, T., Beyer, T., & Guggenmos, J. (2006). Prevalence of behavioural and emotional problems among six-years-old preschool children. *Social Psychiatry and Psychiatric Epidemiology*, *41*(5), 394–399.

Garavan, H., Ross, T. J., Kaufman, J., & Stein, E. A. (2003). A midline dissociation between error-processing and response-conflict monitoring. *NeuroImage*, *20*(2), 1132–1139. https://doi.org/10.1016/S1053-8119(03)00334-3

Gioia, G. A., Isquith, P. K., Guy, S. C., & Kenworthy, L. (2000). *Behavior Rating Inventory of Executive Function*. Lutz, FL: Psychological Assessment Resources.

Gioia, G. A., Isquith, P. K., Retzlaff, P. D., & Espy, K. A. (2002). Confirmatory factor analysis of the Behavior Rating Inventory of Executive Function (BRIEF) in a clinical sample. *Child Neuropsychology*, *8*(4), 249–257. https://doi.org/DOI 10.1076/chin.8.4.249.13513

Gough, P. M., Nobre, A. C., & Devlin, J. T. (2005). Dissociating linguistic processes in the left inferior frontal cortex with transcranial magnetic stimulation. *Journal of Neuroscience*, *25*(35), 8010–8016. https://doi.org/10.1523/JNEUROSCI.2307-05.2005

Hampshire, A. (2015). Putting the brakes on inhibitory models of frontal lobe function. *NeuroImage*, *113*, 340–355. https://doi.org/10.1016/j.neuroimage.2015.03.053

Hampshire, A., Chamberlain, S. R., Monti, M. M., Duncan, J., & Owen, A. M. (2010). The role of the right inferior frontal gyrus: Inhibition and attentional control. *NeuroImage*, *50*(3), 1313–1319. https://doi.org/10.1016/j.neuroimage.2009.12.109

Hayes, A. F. (2013). *Introduction to mediation, moderation, and conditional process analysis: A regression-based approach*. New York, NY: The Guilford Press.

Herbet, G., Lafargue, G., Almairac, F., Moritz-Gasser, S., Bonnetblanc, F., & Duffau, H. (2015). Disrupting the right pars opercularis with electrical stimulation frees the song: Case report. *Journal of Neurosurgery*, *123*(6), 1401–1404. https://doi.org/10.3171/2014.12.JNS141829

Herve, P. Y., Zago, L., Petit, L., Mazoyer, B., & Tzourio-Mazoyer, N. (2013). Revisiting human hemispheric specialization with neuroimaging. *Trends in Cognitive Sciences*, *17*(2), 69–80. https://doi.org/10.1016/j.tics.2012.12.004

Holland, S. K., Plante, E., Weber Byars, A., Strawsburg, R. H., Schmithorst, V. J., & Ball, W. S. Jr (2001). Normal fMRI brain activation patterns in children performing a verb generation task. *NeuroImage*, *14*(4), 837–843. https://doi.org/10.1006/nimg.2001.0875

Isquith, P. K., & Gioia, G. A. (2000). BRIEF predictions of ADHD: Clinical utility of the Behavior Rating Inventory of Executive Function for detecting ADHD subtypes in children. *Archives of Clinical Neuropsychology*, *15*(8), 780–781. https://doi.org/Doi 10.1016/S0887-6177(00)80238-3

Jahanshahi, M. (2013). Effects of deep brain stimulation of the subthalamic nucleus on inhibitory and executive control over prepotent responses in Parkinson's disease. *Frontiers in Systems Neuroscience*, *7*, 118. https://doi.org/10.3389/fnsys.2013.00118

Jahanshahi, M., Obeso, I., Rothwell, J. C., & Obeso, J. A. (2015). A fronto-striato-subthalamic-pallidal network for goal-directed and habitual inhibition. *Nature Reviews Neuroscience*, *16*(12), 719–732. https://doi.org/10.1038/nrn4038

Jensen, P. S., Arnold, L. E., Swanson, J. M., Vitiello, B., Abikoff, H. B., Greenhill, L. L., ... Wells, K. C. (2007). 3-year follow-up of the NIMH MTA study. *Journal of the American Academy of Child & Adolescent Psychiatry*, *46*(8), 989–1002.

Keenan, K., & Wakschlag, L. S. (2000). More than the terrible twos: The nature and severity of behavior problems in clinic-referred preschool children. *Journal of Abnormal Child Psychology*, *28*(1), 33–46. https://doi.org/10.1023/A:1005118000977

Kemerdere, R., de Champfleur, N. M., Deverdun, J., Cochereau, J., Moritz-Gasser, S., Herbet, G., & Duffau, H. (2016). Role of the left frontal aslant tract in stuttering: A brain stimulation and tractographic study. *Journal of Neurology*, *263*(1), 157–167. https://doi.org/10.1007/s00415-015-7949-3

Kim, J. H., Lee, J. M., Jo, H. J., Kim, S. H., Lee, J. H., Kim, S. T., ... Saad, Z. S. (2010). Defining functional SMA and pre-SMA subregions in human MFC using resting state fMRI: Functional connectivity-based parcellation method. *NeuroImage*, *49*(3), 2375–2386. https://doi.org/10.1016/j.neuroimage.2009.10.016

Kinoshita, M., de Champfleur, N. M., Deverdun, J., Moritz-Gasser, S., Herbet, G., & Duffau, H. (2015). Role of fronto-striatal tract and frontal aslant tract in movement and speech: An axonal mapping study. *Brain Structure and Function*, *220*(6), 3399–3412. https://doi.org/10.1007/s00429-014-0863-0

Kinoshita, M., Shinohara, H., Hori, O., Ozaki, N., Ueda, F., Nakada, M., ... Hayashi, Y. (2012). Association fibers connecting the Broca center and the lateral superior frontal gyrus: A microsurgical and tractographic anatomy. *Journal of Neurosurgery*, *116*(2), 323–330. https://doi.org/10.3171/2011.10.JNS11434

Kronfeld-Duenias, V., Amir, O., Ezrati-Vinacour, R., Civier, O., & Ben-Shachar, M. (2016). The frontal aslant tract underlies speech fluency in persistent developmental stuttering. *Brain Structure and Function*, *221*(1), 365–381. https://doi.org/10.1007/s00429-014-0912-8

Lauzon, C. B., Asman, A. J., Esparza, M. L., Burns, S. S., Fan, Q., Gao, Y., ... Landman, B. A. (2013). Simultaneous analysis and quality assurance for diffusion tensor imaging. *PLoS ONE*, *8*(4), e61737. https://doi.org/10.1371/journal.pone.0061737

Lu, M. T., Preston, J. B., & Strick, P. L. (1994). Interconnections between the prefrontal cortex and the premotor areas in the frontal lobe. *The Journal of Comparative Neurology*, *341*(3), 375–392. https://doi.org/10.1002/cne.903410308

Luppino, G., Matelli, M., Camarda, R. M., Gallese, V., & Rizzolatti, G. (1991). Multiple representations of body movements in mesial area 6 and the adjacent cingulate cortex: An intracortical microstimulation study in the macaque monkey. *The Journal of Comparative Neurology*, *311*(4), 463–482. https://doi.org/10.1002/cne.903110403

Madsen, K. S., Baare, W. F., Vestergaard, M., Skimminge, A., Ejersbo, L. R., Ramsoy, T. Z., ... Jernigan, T. L. (2010). Response inhibition is associated with white matter microstructure in children. *Neuropsychologia*, *48*(4), 854–862. https://doi.org/10.1016/j.neuropsychologia.2009.11.001

Mandelli, M. L., Caverzasi, E., Binney, R. J., Henry, M. L., Lobach, I., Block, N., ... Gorno-Tempini, M. L. (2014). Frontal white matter tracts sustaining speech production in primary progressive aphasia. *Journal of Neuroscience*, *34*(29), 9754–9767. https://doi.org/10.1523/JNEUROSCI.3464-13.2014

Martino, J., & De Lucas, E. M. (2014). Subcortical anatomy of the lateral association fascicles of the brain: A review. *Clinical Anatomy*, *27*(4), 563–569. https://doi.org/10.1002/ca.22321

Molina, B. S., Hinshaw, S. P., Eugene Arnold, L., Swanson, J. M., Pelham, W. E., Hechtman, L., ... Abikoff, H. B. (2013). Adolescent substance use in the multimodal treatment study of attention-deficit/hyperactivity disorder (ADHD)(MTA) as a function of childhood ADHD, random assignment to childhood treatments, and subsequent medication. *Journal of the American Academy of Child & Adolescent Psychiatry*, *52*(3), 250–263.

Molina, B. S., Hinshaw, S. P., Swanson, J. M., Arnold, L. E., Vitiello, B., Jensen, P. S., ... Abikoff, H. B. (2009). The MTA at 8 years: Prospective follow-up of children treated for combined-type ADHD in a multisite study. *Journal of the American Academy of Child & Adolescent Psychiatry*, *48*(5), 484–500.

Mostofsky, S. H., Cooper, K. L., Kates, W. R., Denckla, M. B., & Kaufmann, W. E. (2002). Smaller prefrontal and premotor volumes in boys with attention-deficit/hyperactivity disorder. *Biological Psychiatry*, *52*(8), 785–794.

Nachev, P., Wydell, H., O'Neill, K., Husain, M., & Kennard, C. (2007). The role of the pre-supplementary motor area in the control of action. *NeuroImage*, *36*(Suppl 2), T155–T163. https://doi.org/10.1016/j.neuroimage.2007.03.034

Naeser, M. A., Martin, P. I., Theoret, H., Kobayashi, M., Fregni, F., Nicholas, M., ... Pascual-Leone, A. (2011). TMS suppression of right pars triangularis, but not pars opercularis, improves naming in aphasia. *Brain and Language*, *119*(3), 206–213. https://doi.org/10.1016/j.bandl.2011.07.005

Neef, N. E., Anwander, A., Butfering, C., Schmidt-Samoa, C., Friederici, A. D., Paulus, W., & Sommer, M. (2018). Structural connectivity of right frontal hyperactive areas scales with stuttering severity. *Brain*, *141*(1), 191–204. https://doi.org/10.1093/brain/awx316

Neely, K. A., Wang, P., Chennavasin, A. P., Samimy, S., Tucker, J., Merida, A., ... Huang-Pollock, C. (2017). Deficits in inhibitory force control in young adults with ADHD. *Neuropsychologia*, *99*, 172–178. https://doi.org/10.1016/j.neuropsychologia.2017.03.012

Nigg, J. T., Willcutt, E. G., Doyle, A. E., & Sonuga-Barke, E. J. (2005). Causal heterogeneity in attention-deficit/hyperactivity disorder: Do we need neuropsychologically impaired subtypes? *Biological Psychiatry*, *57*(11), 1224–1230. https://doi.org/10.1016/j.biopsych.2004.08.025

Obeso, I., Wilkinson, L., Casabona, E., Speekenbrink, M., Luisa Bringas, M., Alvarez, M., ... Jahanshahi, M. (2014). The subthalamic nucleus and inhibitory control: Impact of subthalamotomy in Parkinson's disease. *Brain*, *137*(Pt 5), 1470–1480. https://doi.org/10.1093/brain/awu058

Papachristou, E., Schulz, K., Newcorn, J., Bedard, A. C., Halperin, J. M., & Frangou, S. (2016). Comparative evaluation of child behavior checklist-derived scales in children clinically referred for emotional and behavioral dysregulation. *Frontiers in Psychiatry*, *7*, 146. https://doi.org/10.3389/fpsyt.2016.00146

Ridderinkhof, K. R., Ullsperger, M., Crone, E. A., & Nieuwenhuis, S. (2004). The role of the medial frontal cortex in cognitive control. *Science*, *306*(5695), 443–447. https://doi.org/10.1126/science.1100301

Roalf, D. R., Quarmley, M., Elliott, M. A., Satterthwaite, T. D., Vandekar, S. N., Ruparel, K., … Gur, R. E. (2016). The impact of quality assurance assessment on diffusion tensor imaging outcomes in a large-scale population-based cohort. *NeuroImage*, *125*, 903–919. https://doi.org/10.1016/j.neuroimage.2015.10.068

Roberts, B. A., Martel, M. M., & Nigg, J. T. (2017). Are there executive dysfunction subtypes within ADHD? *Journal of Attention Disorders*, *21*(4), 284–293. https://doi.org/10.1177/1087054713510349

Rubia, K., Overmeyer, S., Taylor, E., Brammer, M., Williams, S. C., Simmons, A., & Bullmore, E. T. (1999). Hypofrontality in attention deficit hyperactivity disorder during higher-order motor control: A study with functional MRI. *American Journal of Psychiatry*, *156*(6), 891–896. https://doi.org/10.1176/ajp.156.6.891

Schachar, R., Mota, V. L., Logan, G. D., Tannock, R., & Klim, P. (2000). Confirmation of an inhibitory control deficit in attention-deficit/hyperactivity disorder. *Journal of Abnormal Child Psychology*, *28*(3), 227–235.

Sierpowska, J., Gabarros, A., Fernandez-Coello, A., Camins, A., Castaner, S., Juncadella, M., … Rodriguez-Fornells, A. (2015). Morphological derivation overflow as a result of disruption of the left frontal aslant white matter tract. *Brain and Language*, *142*, 54–64. https://doi.org/10.1016/j.bandl.2015.01.005

Sonuga-Barke, E. J., Brandeis, D., Cortese, S., Daley, D., Ferrin, M., Holtmann, M., … Döpfner, M. (2013). Nonpharmacological interventions for ADHD: Systematic review and meta-analyses of randomized controlled trials of dietary and psychological treatments. *American Journal of Psychiatry*, *170*(3), 275–289.

Suskauer, S. J., Simmonds, D. J., Caffo, B. S., Denckla, M. B., Pekar, J. J., & Mostofsky, S. H. (2008). fMRI of intrasubject variability in ADHD: Anomalous premotor activity with prefrontal compensation. *Journal of the American Academy of Child and Adolescent Psychiatry*, *47*(10), 1141–1150. https://doi.org/10.1097/CHI.0b013e3181825b1f

Suskauer, S. J., Simmonds, D. J., Fotedar, S., Blankner, J. G., Pekar, J. J., Denckla, M. B., & Mostofsky, S. H. (2008). Functional magnetic resonance imaging evidence for abnormalities in response selection in attention deficit hyperactivity disorder: Differences in activation associated with response inhibition but not habitual motor response. *Journal of Cognitive Neuroscience*, *20*(3), 478–493. https://doi.org/10.1162/jocn.2008.20032

Swann, N. C., Cai, W., Conner, C. R., Pieters, T. A., Claffey, M. P., George, J. S., … Tandon, N. (2012). Roles for the pre-supplementary motor area and the right inferior frontal gyrus in stopping action: Electrophysiological responses and functional and structural connectivity. *NeuroImage*, *59*(3), 2860–2870. https://doi.org/10.1016/j.neuroimage.2011.09.049

Szmuda, T., Rogowska, M., Sloniewski, P., Abuhaimed, A., Szmuda, M., Springer, J., … Skorek, A. (2017). Frontal aslant tract projections to the inferior frontal gyrus. *Folia Morphol (Warsz)*, *76*, 574–581. https://doi.org/10.5603/FM.a2017.0039

Thomas, J. M., & Guskin, K. A. (2001). Disruptive behavior in young children: What does it mean? *Journal of the American Academy of Child and Adolescent Psychiatry*, *40*(1), 44–51. https://doi.org/10.1097/00004583-200101000-00015

Toga, A. W., & Thompson, P. M. (2003). Mapping brain asymmetry. *Nature Reviews Neuroscience*, *4*(1), 37–48. https://doi.org/10.1038/nrn1009

Tournier, J. D., Calamante, F., & Connelly, A. (2007). Robust determination of the fibre orientation distribution in diffusion MRI: Non-negativity constrained super-resolved spherical deconvolution. *NeuroImage*, *35*(4), 1459–1472. https://doi.org/10.1016/j.neuroimage.2007.02.016

Tremblay, P., & Gracco, V. L. (2009). Contribution of the pre-SMA to the production of words and non-speech oral motor gestures, as revealed by repetitive transcranial magnetic stimulation (rTMS). *Brain Research*, *1268*, 112–124. https://doi.org/10.1016/j.brainres.2009.02.076

Tremblay, P., & Gracco, V. L. (2010). On the selection of words and oral motor responses: Evidence of a response-independent fronto-parietal network. *Cortex*, *46*(1), 15–28. https://doi.org/10.1016/j.cortex.2009.03.003

Van Wouwe, N. C., Pallavaram, S., Phibbs, F. T., Martinez-Ramirez, D., Neimat, J. S., Dawant, B. M., … Wylie, S. A. (2017). Focused stimulation of dorsal subthalamic nucleus improves reactive inhibitory control of action impulses. *Neuropsychologia*, *99*, 37–47. https://doi.org/10.1016/j.neuropsychologia.2017.02.016

Vassal, F., Boutet, C., Lemaire, J. J., & Nuti, C. (2014). New insights into the functional significance of the frontal aslant tract: An anatomo-functional study using intraoperative electrical stimulations combined with diffusion tensor imaging-based fiber tracking. *British Journal of Neurosurgery*, *28*(5), 685–687. https://doi.org/10.3109/02688697.2014.889810

Vergani, F., Lacerda, L., Martino, J., Attems, J., Morris, C., Mitchell, P., … Dell'Acqua, F. (2014). White matter connections of the supplementary motor area in humans. *Journal of Neurology, Neurosurgery and Psychiatry*, *85*(12), 1377–1385. https://doi.org/10.1136/jnnp-2013-307492

Wiecki, T. V., & Frank, M. J. (2013). A computational model of inhibitory control in frontal cortex and basal ganglia. *Psychological Review*, *120*(2), 329–355. https://doi.org/10.1037/a0031542

Wood, S. (2006). *Generlized additive models: An introduction with R*. New York, NY: Chapman and Hall/CRC.

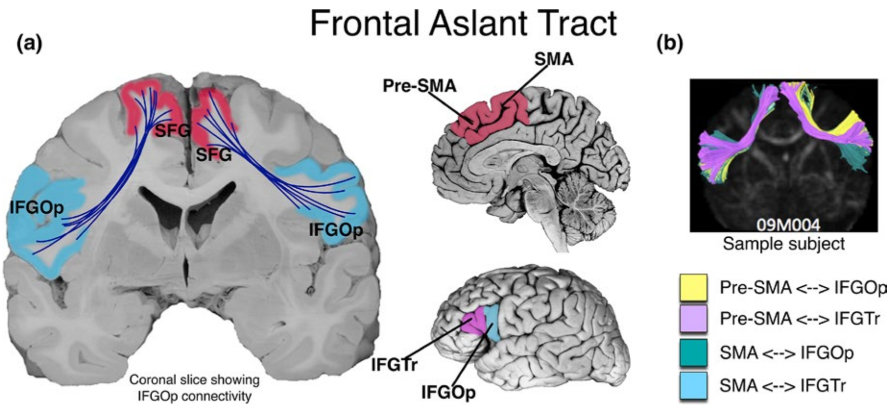
Yeh, F. C., Verstynen, T. D., Wang, Y., Fernandez-Miranda, J. C., & Tseng, W. Y. (2013). Deterministic diffusion fiber tracking improved by quantitative anisotropy. *PLoS ONE*, *8*(11), e80713. https://doi.org/10.1371/journal.pone.0080713

Yeh, F. C., Wedeen, V. J., & Tseng, W. Y. (2010). Generalized q-sampling imaging. *IEEE Transactions on Medical Imaging*, *29*(9), 1626–1635. https://doi.org/10.1109/TMI.2010.2045126

How to cite this article: Garic D, Broce I, Graziano P, Mattfeld A, Dick AS. Laterality of the frontal aslant tract (FAT) explains externalizing behaviors through its association with executive function. *Dev Sci.* 2018;e12744. https://doi.org/10.1111/desc.12744

Graphical Abstract

The contents of this page will be used as part of the graphical abstract of html only.
It will not be published as part of main article.



We investigated the development of a recently identified white matter pathway, the frontal aslant tract (FAT) and its association with executive function and externalizing behaviors in a sample of 129 neurotypical male and female human children ranging in age from 7 months to 19 years. We found that the FAT could be tracked in 92% of those children, and that the pathway showed age-related differences into adulthood. We also found that the degree of right lateralization of the tract predicted better executive function and fewer attention problems. These findings suggest that the degree to which the developing brain favors a right lateralized structural dominance of the FAT is directly associated with executive function and attention.