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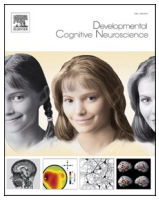

Age-related, multivariate associations between white matter microstructure and behavioral performance in three executive function domains

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ABSTRACT

The executive function (EF) domains of working memory (WM), response inhibition (RI), and set shifting (SS) show maturational gains and are linked to neuroimaging-measured brain changes. This study explored ways in which maturation-linked differences in EF abilities are systematically associated with white matter microstructural differences from adolescence into young adulthood. Diffusion tensor imaging (DTI) and nine neurocognitive tests were collected from 120 healthy subjects ages 12–24. Analyses across the white matter skeleton were performed, focusing on fractional anisotropy (FA). Data were 'fused' using a multivariate technique (CCA+jICA), producing four independent components (ICs) depicting white matter FA values that covaried with test performance. Correlations between age and IC loading coefficients identified three EF-DTI profiles that may change developmentally. In one, SS performance was linked to greater reliance on the FA of ventral brain tracts, and less on dorsal tracts with age. In another, white matter microstructure was related to a pattern of strong WM and weak SS that became more pronounced with age. A final IC revealed that younger individuals with low RI and high WM/SS skills typically matured out of this cognitive imbalance, underscored by white matter changes with age. These novel multivariate results begin to emphasize the complexity of brain structure-cognition relationships in adolescents and young adults.

1. Background

Although there are many different cognitive abilities described as "executive" in nature, a subset of them has been usefully categorized into three generally-accepted domains – response inhibition, working memory, and set shifting that despite some inter-correlation still are generally discete (Miyake et al., 2000). Developmental studies of these three domains have found that adult-like levels of ability typically are reached after age 15 or so. In studies of response inhibition, rapid improvements have been noted after preschool (Garon et al., 2008; Klenberg et al., 2001; Zelazo et al., 2003; Carlson, 2005; Best and Miller, 2010), followed by a plateau in early adolescence. Working memory shows a developmental profile that is somewhat more linear (Best and Miller, 2010). Across several working memory tasks examined, Gathercole et al. (2004) found linear gains from ages 4–14, leveling between the ages of 14 and 15. In the set shifting domain, Luciana and Nelson (1998) studied the development of performance on the Intra-Extra Dimensional Set Shift task and found that as age approached young adulthood, there was a steady increase in participants who completed all nine stages of the task. Similarly, Huizinga et al. (2006) reported that shift costs for 7- and 11- year olds were significantly greater than those of 15-year-olds, who did not differ from young adults.

Despite this seeming performance plateau at mid-adolescence, careful research has found that there are subtle, protracted, strategy- and complexity- related improvements within each domain after mid-adolescence that indicate these EF domains continue to develop and be refined into early adulthood. For example, while the early gains in response inhibition are characterized by the attainment of rule formation abilities, faster reaction time, and better overall accuracy, nuanced improvements that continue to emerge during adolescence (Best and Miller, 2010) include observations that young adults slow their responses after committing an error to prevent further mistakes (Hogan et al., 2005). Although working memory capacity itself does not appreciably increase after around age 15, there are continued

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improvements in the ability to handle increased executive demands on working memory tasks (Luciana et al., 2005; Conklin et al., 2007). For example, Geier et al. (2009) administered a visuospatial working memory task (oculomotor delayed response task) to 13 children, 15 adolescents, and 18 adults (all free of psychiatric/developmental conditions) and noted that behavioral precision was only present in adults, indicated by corrective saccades following memory-guided saccades (also see Luna et al., 2004). For set shifting, Davidson et al. (2006) found that accuracy "costs" to rapidly switch mental sets diminished until early adolescence, but reaction time-based shift costs continued to increase until adulthood. Adults also seemed to learn to slow down responses on shift trials to ensure they were responding correctly, as seen in response inhibition tasks (Hogan et al., 2005). There has yet to be a consensus characterizing protracted developmental nuances in EF beyond peaks in overall capacity.

These extended trajectories in EF maturation parallel robustly documented normative brain changes that also continue into early adulthood. Although many researchers have focused on changes to frontal lobe brain activity and neural network connectivity as measured by fMRI metrics of functional connectivity (Durston et al., 2006; Casey et al., 1997; Stevens et al., 2009), neurodevelopmentally-characteristic changes in white matter structure also occur throughout adolescence. There is compelling evidence that these changes do not stop at the end of adolescence. Instead, white matter microstructure appears to go through an optimization period where increasing myelination lasts well into young adult years. Bava et al. (2010) collected diffusion MRI (dMRI) data on 22 17-year-olds, and then again 16 months later. Using a diffusion tensor imaging (DTI) model, this longitudinal study supported the notion of continued microstructural white matter change during late adolescence, as well as overall correlations between white matter change and cognitive performance. Lebel et al. (2012) modeled the evolution of 12 white matter tracts in 403 healthy volunteers across the lifespan, reporting an overall inverted U-shaped trajectory peaking at age 37. Asato et al. (2010) discussed the cognitive implications of white matter change. They found that areas that continued to mature through adolescence were more localized in association and projection fibers in frontal pathways. Specifically, portions of the uncinate fasciculus (UF), superior longitudinal fasciculus (SLF), anterior thalamic radiations (ATRs), corona radiata, genu of the internal capsule, and the posterior portion of the corpus callosum all showed immaturity during adolescence compared to later ages. Those authors posit that protracted development in these fibers connecting the PFC and subcortical regions may relate to improvements in top-down behavioral and cognitive control.

To our knowledge only one review exists that summarizes the findings from studies of white matter microstructure and executive function development across adolescence (Goddings et al., 2021). This review recapitulates the field's current understanding of white matter's relationship to adolescent EF development, organized by the three EF domains. Overall, the lack of firm conclusions on how white matter relates to the development of EF represents a notable gap in the literature. For response inhibition, better inhibitory performance has been consistently associated with higher fractional anisotropy (FA) measurements in frontal lobe white matter. But there have been notable inconsistencies across DTI studies in which specific tracts are associated with inhibition ability, and which of these associations are developmental in nature (Madsen et al., 2010; Treit et al., 2014; Fjell et al., 2012). Working memory-DTI developmental studies have been few and likewise inconsistent. Similar to the inconsistencies within response inhibition literature, researchers have been unable to reach consensus on specific tracts that predict mature, adult levels of working memory ability. For example, while one cross-sectional study found developmental associations only between visuospatial working memory and FA (Krogsrud et al., 2018), another found relationships between manipulation of information within working memory and FA (Bathelt et al., 2018). Finally, white matter correlates of set shifting domain abilities have been least studied using DTI methods. Although two studies (Seghete et al., 2013; Treit et al., 2014) showed positive associations between set shifting maturation and DTI-measured FA, the specific tracts differed across studies. Neither study had large samples optimal for detecting developmental differences. Overall, Goddings and colleagues' (2021) review suggests that relationships between white matter and EF development exist and are quantifiable. However, the mixed and inconsistent findings should prompt pause and concern about the direction of this inquiry. Investigators so far have not been able to establish one-to-one relationships between specific tract development and specific EF skill development. The ongoing failure to isolate a single, replicable DTI-EF association prompts fresh consideration of what alternative types of relationships might exist between white matter development and EF maturation from adolescence into adulthood.

In this study, we turned away from seeking one-to-one associations between specific tracts and EF tests to instead investigate whether broad profiles of microstructural white matter differences measured across early adolescence to young adulthood might better account for changes in the overall relationships between response inhibition, working memory, and set shifting task performance across adolescent development. In other words, this study shifted from using univariate analysis methods to multivariate methods to learn if normative adolescent EF maturation might depend on complex, brain-wide changes in many white matter tracts. Such a multivariate analysis may be able to better account for the subtle complexities in these brain-behavior relationships that might drive inconsistent findings across prior studies. Further, a multivariate approach may be better aligned with current theoretical frameworks of adolescent brain development that favor distributed circuit perspectives on brain changes throughout adolescence (Casey et al., 2008; Somerville et al., 2011; Casey, 2015; Casey et al., 2016). These frameworks suggest it might be more useful to think about *patterns* in white matter development across distributed systems in conjunction with cognitive development when considering changes in whole-brain anatomical connectivity. Thus, this project will address the hole in the literature regarding how white matter tract FA may underlie protracted EF development. Neurotypical participants ages 12–24 in this study underwent DTI scans and performed a computerized battery of nine executive function tests, with three tasks assessing each EF domain. EF and DTI data were examined for complex multivariate associations using canonical correlation analysis + joint independent components analysis (CCA + jICA) (Sui et al., 2010). This multivariate analysis technique ensured we would characterize relationships between DTI and EF features if any exist. Again, our overarching hypothesis was not focused on specific EF/DTI links. We instead predicted that older individuals who typically are better at EF tasks would express complex profiles of DTI-EF associations differently from younger individuals. However, we also thought it most likely that any multivariate relationships between white matter and EF abilities would show elements of the results summarized in the Goddings et al. (2021) review. For example, despite prior studies' inconsistent findings we expected to see at least some evidence for higher frontal lobe tract FA associated with better response inhibition ability, higher fronto-parietal and occipito-temporal FA associated with better working memory, and a link between FA and set shifting abilities even in the absence of no clear prior findings for set shifting (Goddings et al., 2021).

2. Methods

2.1. Participants

Participants included 120 healthy adolescents and young adults age 12–24 recruited from the Hartford County, CT area ($M = 18.48$, $SD = 3.70$). This was part of an NIH-funded study (R01 MH081969) of neurodevelopment. They were balanced by gender (59 female), and there were ten participants in each yearly age group. IQ estimates were obtained using the WASI-II, and participants were included in the study if

their IQ estimate was 80 or above ($M = 108.04$, $SD = 12.21$). They also completed the WRAT-IV word reading test to ensure they had at least a sixth-grade reading level.

2.2. Clinical and cognitive assessment

Following informed consent (and parental consent plus assent, where applicable), potential participants were evaluated to ensure they were free of Axis-I psychiatric disorders. The KSADS-PL (Kaufman et al., 1997) was used for those under age 18, and the SCID (First et al., 1996) was used for those 18 and older. The presence of any psychiatric illness resulted in exclusion from the study. Questionnaires were administered for demographic information and exploratory analyses, and examined alcohol and other substance use, and family psychiatric history. Participants lastly completed a battery of three cognitive tasks within each domain of executive function. For working memory, tasks included Letter-Number Sequencing, Digit Span, and Spatial Span subtests of the WISC-IV (Wechsler, 2003). Response inhibition tasks consisted of the Conners CPT-II (Conners, 2005), Stop-Signal Reaction Time Task (SSRT) (Logan et al., 1997), and the antisaccade task (Luna and Sweeney, 2004). Set shifting tasks included the CANTAB IE/ED task (Robbins et al., 1998), Local/Global task (Miyake et al., 2000), and the Meiran Visuospatial Shift task (Meiran, 1996). Task descriptions can be found in the supplementary materials.

2.3. Structural MRI

All neuroimaging was conducted using a Siemens 3 T Allegra. T1- and T2- weighted images were acquired from all participants to ensure lack of structural pathology. The T1-weighted scan was a 3D MPRAGE pulse sequence with the following imaging parameters: TR/TE/TI= 2300/2.74/900 ms, flip angle= 8°, FOV= 176 × 256 mm, Matrix= 176 × 256 × 176, Voxel size= 1 × 1 × 1 mm, Pixel bandwidth= 190 Hz, Total scan time= 7:09 min. The T2-weighted scan was a single slab 3D variable flip angle turbo spin-echo: TR/TE= 2500/355msec, Echo train length= 209, FOV= 208 × 256 mm, Slab thickness= 176 mm, Matrix = 176 × 208 × 256, Voxel size = 1 × 1 × 1 mm, Pixel bandwidth= 675 Hz, Total scan time = 7:24 min. The DTI scans were single shot spin echo EPI sequences (TR/TE=6300/85msec, FOV=220 mm, 32 directions, 45 slices with 1.7 ×1.7 ×3.0 mm^3 resolution. Three sequences were acquired over approximately 11 min and later combined in data preparation.

2.4. Data processing

The DTI sequences for each participant were concatenated then preprocessed for analysis along with the T1-weighted scan using TractoFlow 2.21 (Theaud et al., 2020). TractoFlow automatizes FSL-based brain extraction (Smith, 2002), MRtrix3 denoising (Veraart et al., 2016), FSL Eddy current correction (Andersson and Sotiropoulos, 2016) with slicewise outlier detection of signal loss from movement and correction, and ANT-based N4 bias correction (Tustison et al., 2010) steps of DTI processing to produce controlled, reproducible results. The resulting DTI metric images were cropped, normalized to a mean value of 1000, and resampled to 1 mm isotropic resolution. FSL's TBSS then was used to construct white matter skeletons for each participant, normalized to the FMRIB58_FA_1mm template (Smith et al., 2006). Skeletonized fractional anisotropy (FA) maps were analyzed for this study. TBSS was chosen because it represents the central white matter tracts common to the sample, is an improvement on misregistration error across participants compared to other voxel-based approaches, typically has high reliability, and would facilitate future replication through its ease of use (Bach et al., 2014). TBSS represented much of the most valuable information about participants' major and minor tracts, which generally conform to tract-labeling atlases despite some inherent lack of precision in the case of closely contiguous tracts, crossing fibers, or branches.

2.5. Analyses

Behavioral performance on each EF task was based on one dependent outcome variable from each. For Digit Span, Spatial Span, and Letter-Number Sequencing, the total raw score was used for analysis. Proxies for performance on the CPT-II, Stop Signal, and Antisaccade Tasks were commission errors, Stop Signal Reaction Time, and number of errors, respectively. The Local/Global Task outcome measure was response latency, and the other two shifting tasks (Meiran and CANTAB) used shift cost calculations. For more information on the behavioral tasks, please see the Supplementary Material. EF test data from the cognitive battery were fused with the DTI data using canonical correlation analysis + joint independent component analysis (CCA + jICA) (Sui et al., 2010). Essentially, the analysis links the two features (cognitive data and DTI data) by identifying where they jointly covary across datasets. This is a notable advantage of CCA + jICA, because separating multiple patterns exhibiting common covariation among individuals is not possible using other multivariate approaches such as multi-voxel pattern analysis (MVPA) (Kim et al., 2020). The jICA step assumes that the features share the same mixing coefficient matrix and maximize independence among the joint components. The CCA step maximizes inter-subject covariation across the features and generates two linked variables, one from each dataset (canonical variants; or CVs). Joint ICA is performed on the CVs, decomposing the remaining mixtures into joint independent components (ICs). In other words, the jICA explores the CVs and provides a loading coefficient representing each subject's expression of the relationships. One strength of CCA + jICA is DTI skeletons and EF scores can be used as input without elaborate pre-formatting (e.g., using principal component analysis to attempt to directly replicate the factor structure seen in Miyake et al., 2000). The CCA + jICA method incorporates PCA but uses a different algorithmic approach to separate each feature into components. This lends credibility to the component structure when results resembles known patterns in datasets such as Miyake's 3-factor EF structure, as well as offers a alternative method replication. For instance, if all 3 WM tasks strongly load onto one component, one can see that the component is driven by WM and reflects Miyake et al.'s factor structure. However, if tasks from two different domains both strongly shape a component, it should prompt fresh critical consideration of what underlying mechanisms may be driving that pattern, and what similarities exist between the outcome variables. Another strength of CCA + jICA is its stability for a wide range of sample sizes. This stability was demonstrated in its validation paper after several simulation studies (Sui et al., 2010).

The CCA + jICA produced four ICs depicting white matter FA values that covaried with test performance. Each IC can be thought of as a pattern of task performance that commonly occurred with a pattern of FA. The ICs consisted of loading coefficients for both the behavioral data and the DTI data. These loading coefficients are z-scores; loading coefficients with greater magnitudes reflect the feature had a stronger role in driving that particular EF-DTI relationship. Pearson correlation analyses were performed with the loading coefficients to analyze how each pattern changes with age for each feature (behavioral vs. DTI data) within each component. For the behavioral data we used a threshold of $z \geq +/- 1$ to identify tasks that were driving the relationships. For the DTI data, a threshold of $z \geq +/- 1.5$ was used to identify significant DTI data voxels that formed contiguous clusters. The tbss_fill FSL software function visually emphasized the voxels in each IC for depiction. Probabilistic localization of DTI clusters was facilitated using the XTRACT atlas (Warrington et al., 2020). This atlas provides an extended, ROI-based set of 42 tracts applicable to both human and macaque brains. The human atlas was created by applying the tractography protocols to 1065 subjects from the Human Connectome Project (Sotiropoulos et al., 2013; Van Essen et al., 2013) and 1000 subjects from the UK biobank (Miller et al., 2016).

CCA+jICA output interpretation is different from univariate analyses. Figs. 1–4 depict clusters that were meaningfully related to the EF components. The areas of low/high FA do not represent absolutes, but rather should be interpreted as relative associations within the linked features. For example, if an image shows that low FA in the corpus callosum and high FA in the IFOF are related to set shifting, we do not conclude that IFOF is responsible for set shifting individual differences. Rather, a more accurate interpretation would be that IFOF FA is positively related to set shifting *only* when the corpus callosum FA is also relatively low. It follows that with relatively greater IFOF and lower callosum FA comes more of an association with the cognitive feature depicted.

2.6. Secondary analyses

Although our study focus was on development, we also wanted to ensure that any age-dependent effects did not differ between boys and girls. Multiple regression analyses analyzed both the main effect of biological sex and an age × sex interaction term as predictors of the loading coefficients generated by CCA+jICA.

3. Results

3.1. Loading coefficients

CCA+jICA identified 4 linked component pairs (ICs) representing relationships between FA of white matter tracts and performance on EF tasks. Three of these ICs changed significantly with age (Table 1). Table 2 lists the nine cognitive tasks' loading coefficients (expressed as z-scores) with respect to each IC. Z-scores greater than one were considered to drive the relationships. The data were oriented so that loading coefficients accurately represent good versus poor test performance (i.e., positive loading values reflected relatively better task performance, negative indicated worse). Tabulations of significant clusters for each independent component can be found in supplemental materials (Tables S2 – S5).

3.2. IC 1

The neuropsychological profile of IC 1 was driven by poor set shifting test performance. The EF feature did not change with age ($p = 0.7246$), indicating the youngest adolescents who expressed this pattern were already mature in this profile of set shifting abilities and no further improvement of the particular test profile would be expected in older participants. However, the brain-behavior relationship described by this IC did change because the DTI pattern was significantly associated with age ($p = 0.0008$). FA-measured white matter microstructure in several ventral brain tracts was more greatly linked to set shifting performance in young adults, while several dorsal tracts were more important for task performance in adolescents. This joint-component profile suggests that as adolescents age, they begin to rely on different tracts to achieve the same level of set shifting performance (Fig. 1).

3.3. IC 2

Participants who strongly expressed IC 2 generally had strong working memory skills along with weak set shifting skills. This cognitive profile of relative strengths and weakness was more greatly expressed in older participants ($p = 0.0005$). In contrast, the DTI feature linked to this IC (Fig. 2) did not change with age ($p = 0.0843$). This can be taken to mean that the FA values in the implicated tracts did not systematically change into young adulthood. Overall, this pattern localizes a large number of white matter tracts whose greater or lesser FA collectively is linked to a cognitive profile that becomes more pronounced with age.

3.4. IC 3

For IC 3, both the behavioral feature ($p = 0.0096$) and the DTI feature ($p = 0.0091$) were significantly associated with age. Individuals who strongly expressed this profile displayed relatively lower response inhibition ability coupled with high working memory and set shifting abilities. This EF ability profile was expressed less with age – that is, adolescents matured out of the expression of this balance of relative

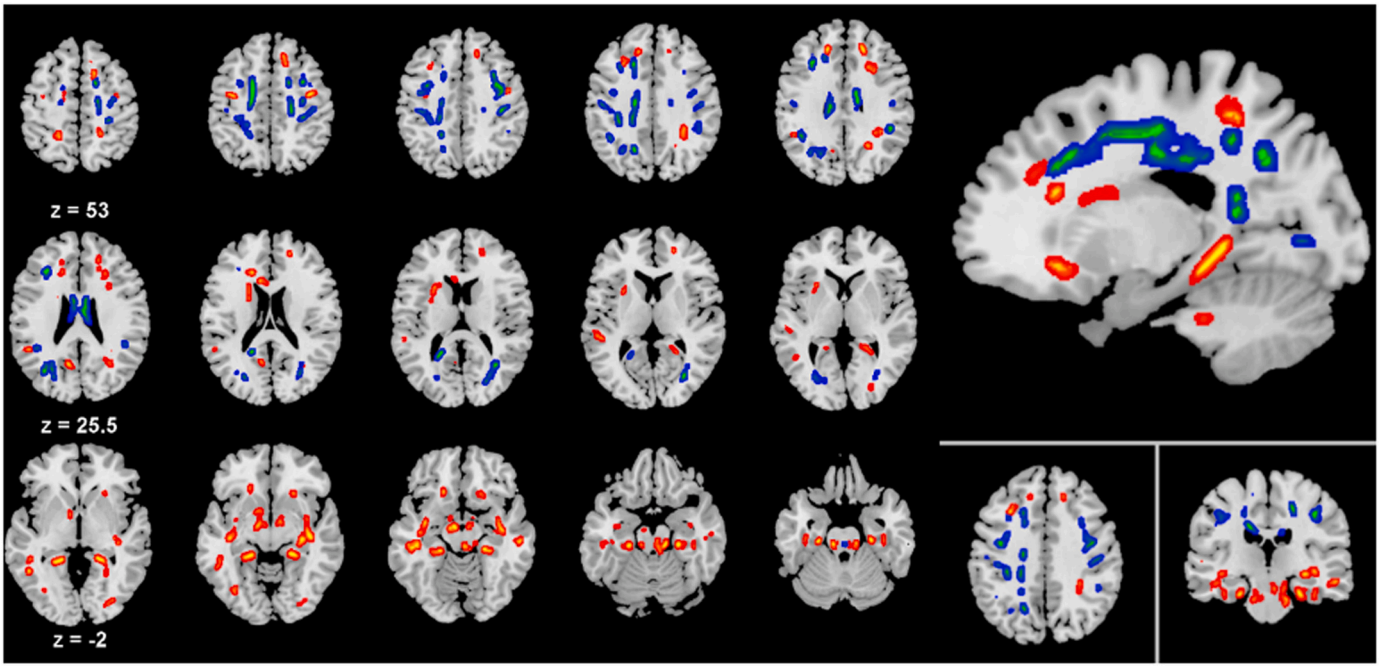

Fig. 1. Clusters from CCA + jICA analysis reflecting z-score-scaled magnitude of white matter voxels measured by FA. Positive associations between z- score and IC 1 behavioral expression are presented in warm colors, while negative associations are presented in cool colors. A threshold of $z = +/- 1.5$ was set to usefully visualize only white matter regions that had meaningful relationships with the EF component. The positive and negative relationships (warm and cool colors, respectively) depicted refer to how white matter FA is associated with the behavioral profile.

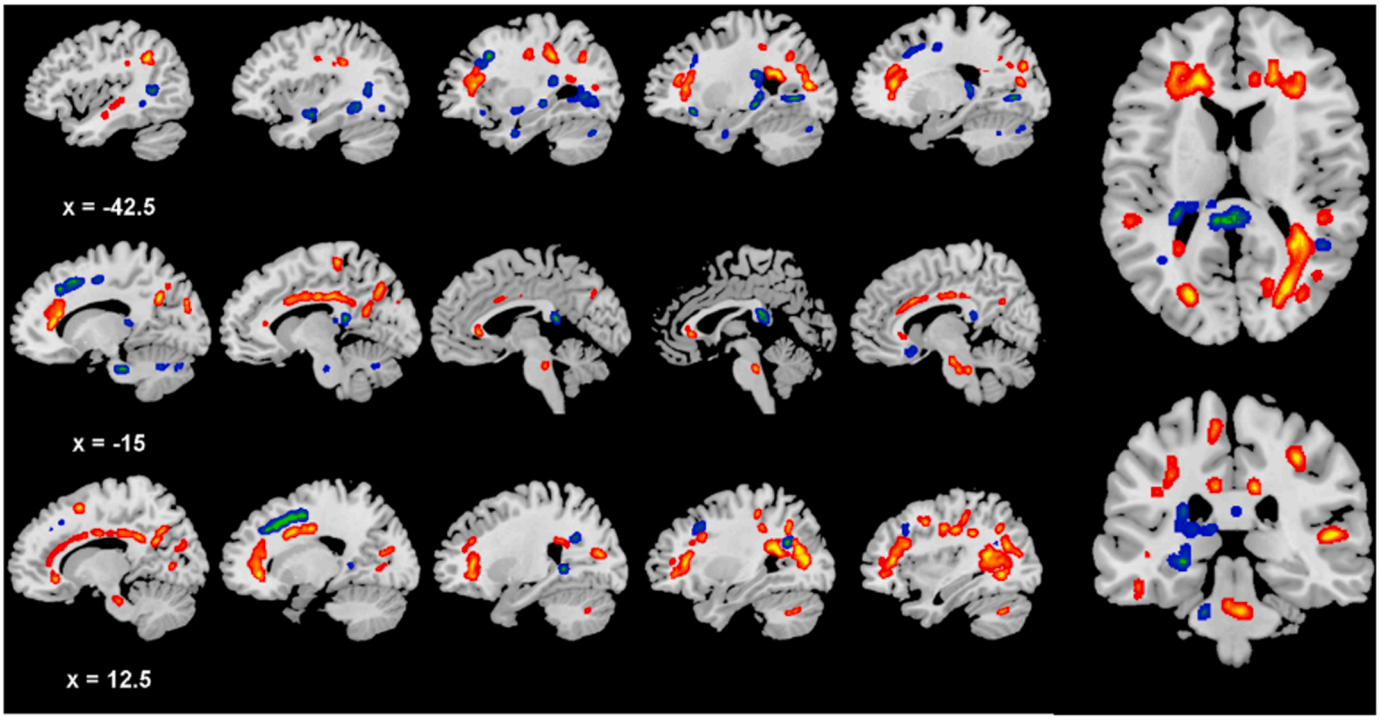

Fig. 2. Clusters from CCA + jICA analysis reflecting z-score-scaled magnitude of white matter voxels measured by FA. Positive associations between z- score and IC 2 behavioral expression are presented in warm colors, while negative associations are presented in cool colors. A threshold of $z = +/- 1.5$ was set to usefully visualize only white matter regions that had meaningful relationships with the EF component. The positive and negative relationships (warm and cool colors, respectively) depicted refer to how white matter FA is associated with the behavioral profile.

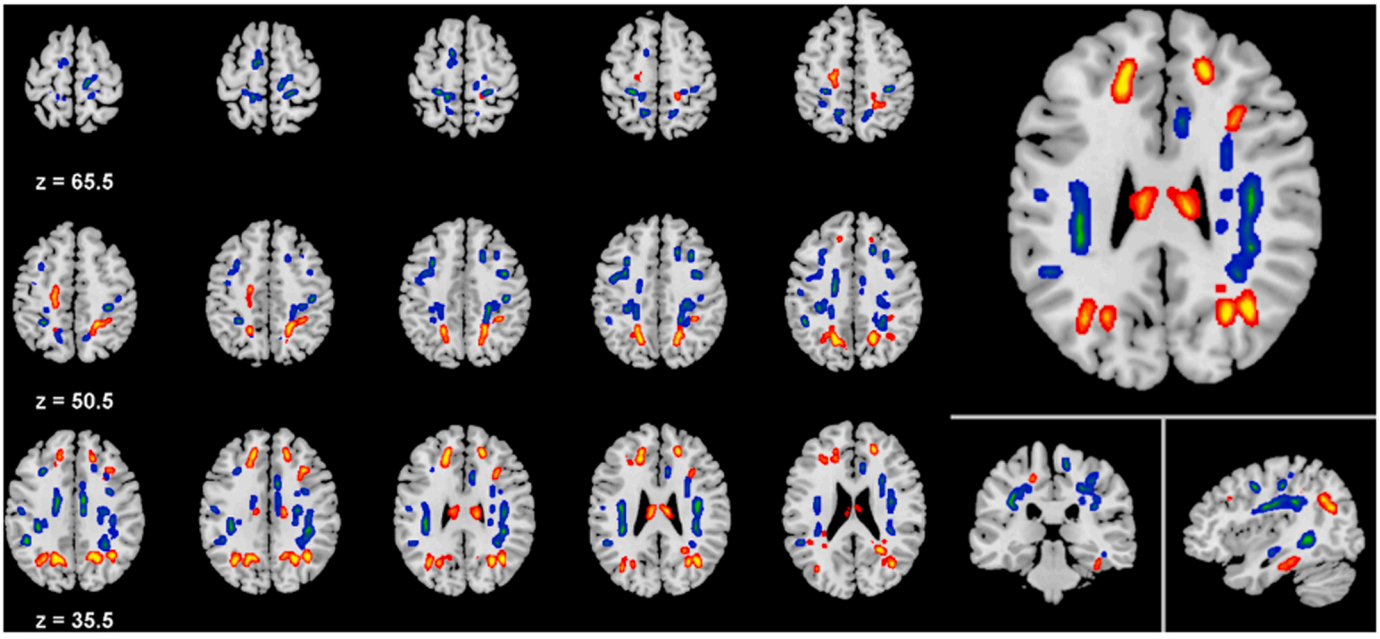

Fig. 3. Clusters from CCA + jICA analysis reflecting z-score-scaled magnitude of white matter voxels measured by FA. Positive associations between z- score and IC 3 behavioral expression are presented in warm colors, while negative associations are presented in cool colors. A threshold of $z = +/- 1.5$ was set to usefully visualize only white matter regions that had meaningful relationships with the EF component. The positive and negative relationships (warm and cool colors, respectively) depicted refer to how white matter FA is associated with the behavioral profile.

strengths and weaknesses. That cognitive change was directly linked to a white matter profile (Fig. 3) that also decreased with age. It implicated widespread areas of greater/lesser FA. Thus, IC 3 as a whole can be characterized as the depiction of developmentally immature brain-behavior association that normatively changes into young adulthood.

3.5. IC 4

IC 4 was heavily driven by relatively poor performance on two of the three set-shifting tasks. This was linked to microstructure of numerous tracts, including the corticospinal tract, superior longitudinal fasciculus

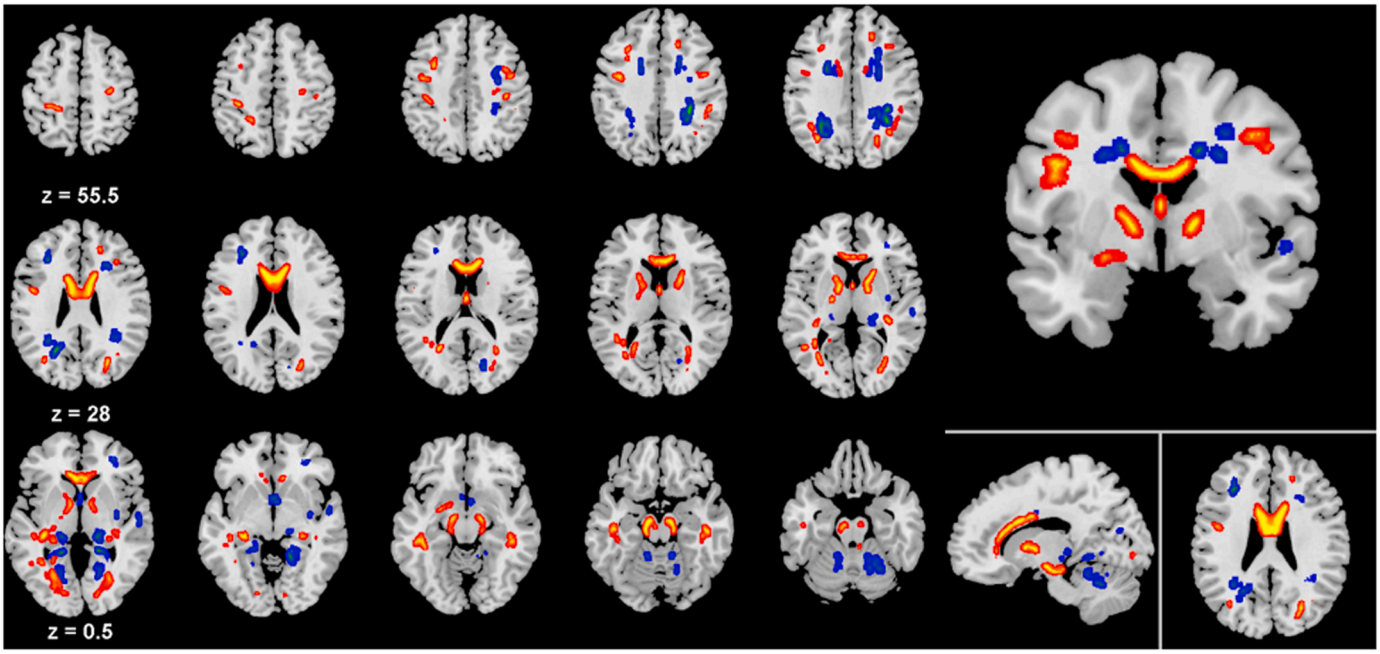

Fig. 4. Clusters from CCA + jICA analysis reflecting z-score-scaled magnitude of white matter voxels measured by FA. Positive associations between z- score and IC 4 behavioral expression are presented in warm colors, while negative associations are presented in cool colors. A threshold of $z = +/- 1.5$ was set to usefully visualize only white matter regions that had meaningful relationships with the EF component. The positive and negative relationships (warm and cool colors, respectively) depicted refer to how white matter FA is associated with the behavioral profile.

Table 1
Correlations between component loadings and age for both features.

IC	DTI feature		Behavioral feature	
	***t*-score**	***p* -value**	***t*-score**	***p*-value**
IC 1	3.45 *	0.0008 *	-0.35	0.7246
IC 2	1.74	0.0843	3.59 *	0.0005 *
IC 3	-2.65 *	0.0091 *	-2.63 *	0.0097 *
IC 4	1.43	0.1557	1.43	0.2976

* - significant at $\alpha = 0.001$

Table 2
Loading coefficients[a] for the nine test scores.

Cognitive Test	IC 1	IC 2	IC 3	IC 4
Letter-Number Sequencing	0.06	1.40	0.53	-0.30
Digit Span	0.30	1.55	0.91	0.22
Spatial Span	0.18	-0.11	1.05	-0.81
SSRT	0.31	-0.63	-1.52	-0.17
CPT Commissions	0.21	0.15	-1.02	0.83
Antisaccade	0.30	-0.30	-0.46	-0.55
IE/ED Shift	-1.35	-1.40	0.26	-0.27
Local/Global	-1.70	-0.34	0.91	-2.19
Meiran Shift	-1.71	-1.02	1.15	-1.14

[a] Loading coefficients are represented as z-scores which denote the relative importance of the variability of that specific test score to the IC. The sign of the coefficient matters in terms of interpretive direction.

2, and the inferior fronto-occipital fasciculus (Fig. 4). Neither the behavioral ($p = 0.2976$) nor the DTI feature ($p = 0.1557$) was associated with age. The absence of age-related associations makes this the simplest joint component to interpret. The IC likely represents a single profile of individual differences where set shifting ability is linked to specific tracts which appears already mature for even the youngest participants in the study.

3.6. Sex differences

The secondary multiple regression that explored possible biological sex effects found no significant age × sex interaction for any DTI or cognitive component loading coefficient. This indicates that the maturation-related differences from ages 12–24 described in this study generally did not differ between males and females. Several significant main sex effects were observed. These are summarized in the supplementary materials (Table S6).

4. Discussion

This study utilized a multivariate data-driven analysis approach to characterize examples of how the relationships between FA-measured white matter and EF cognitive test performance evolve from adolescence to young adulthood in complex, highly distributed ways. It offers two findings that represent interesting challenges to our theoretical expectations for how white matter development may reflect EF maturation. First, consistent with investigators' prior failure to reliably localize response inhibition, working memory, and set shifting to one or more specific white matter tracts (Goddings et al., 2021), none of our results emphasized one-to-one relationships between specific white matter tracts and specific executive skills. In contrast, we observed broad and diverse profiles of developmental change – numerous white matter tracts were linked to either specific EF domains or blends of different abilities. Because such strongly age-related observations are difficult to explain within a strict functional specialization framework, it should open the door to more thoughtful consideration of distributed network models of white matter development. But if specific tract characteristics might not be the most important driver of specific EF cognitive gains, an interesting question is raised as to what property of these widely-distributed white matter changes accounts for the cognitive refinements seen into early adulthood? One possibility is simply aggregate change in white matter across many tracts. Perhaps it might be useful to further develop and deploy an analytic framework that quantifies the aggregate changes to DTI-measured white matter microstructure themselves for developmental analysis. Alternatively, perhaps

EF individual differences can be predicted by aggregate DTI profile across separate canonical networks, implying greater inter-system communication among the important functionally-defined networks engaged for each ability. The latter idea is intriguing, because it again offers the possibility of ultimately finding at least some specificity in which canonical functional networks might drive maturation in discrete EF domains. However, that possibility seems less likely because the broadly distributed DTI profiles found to normatively change here do not appear – at least to visual inspection – to generally correspond with canonical functionally defined circuits (Figley et al., 2015). Certainly the snapshots found here were more diverse and broadly distributed than what fMRI functional connectivity analyses have suggested might represent canonical "cold" networks for cognition (Metcalfe and Mischel, 1999; Casey, 2015). This incidentally suggests neurodevelopmental models that have usefully described the staged maturation of "hot vs. cold" systems (i.e., one system prevailing over another) based largely on observations from functional neuroimaging (Casey, 2015) might be too simplistic when considered in the context of white matter/EF development. This is not a new idea, as some theorists already have begun to speculate in this direction (Casey et al., 2016). However, it might be interesting to attempt a similar multivariate data fusion analysis that asks what correspondence exists between white matter tract structure and different aspects of "hot" information processing, e.g., emotion, motivation or reward driven choices, or even thrill-seeking – all of which are well-known to normatively change between puberty and early adult years.

The second neurodevelopmentally-interesting finding that emerged from this study is a richer appreciation that adolescent white matter development should not be thought of as solely dependent on a simple linear process where gradual, normative, FA-measured increases in white matter conjointly produce more mature EF, presumably reliant on greater anatomical connectivity of distal brain regions (as seen for some general cognitive abilities, e.g., Wendelken et al., 2017). It is remarkable that few theories comment extensively or specifically on the role white matter changes play in the maturation of cognition. Most often, theoretical models of neurodevelopment simply presume some type of causality after noting how executive cognitive ability maturation roughly parallels the robustly-observed linear and nonlinear increases in FA-quantified cingulum, uncinate, and the superior longitudinal and superior fronto-occiptal fasciculi tract microstructure white matter across adolescence (Lebel et al., 2019). This study did not specifically set out to evaluate if a simple "white matter myelination = EF gain" model satisfactorily explains the period of adolescence to young adulthood. However, this straightforward possibility was not reflected in any of the multivariate profiles we observed. In contrast, we saw CCA + jICA capture immature DTI/EF relationships that diminished across adolescence into adulthood, ongoing changes in the white matter correlates for already-mature EF abilities, and age-related EF changes in the face of profiles of unchanged white matter. For instance, we observed patterns (IC 1 and IC 2) in which only one feature changed with age, but not the other. The lack of age-related EF differences in IC 1 suggests that all participants had already reached mature set shifting performance. But because FA in those IC 1-identified tracts continued to differ in various systematic ways in young adulthood participants, it can be interpreted that the same presumably mature level of cognition is actually maintained while its white matter correlates shift with age. IC 1 also showed a particularly striking profile where adolescents relied more on dorsal tracts for set shifting performance, while white matter microstructure of ventral tracts was more important for young adults. Conversely, in IC 2 only the behavioral performance changed with age, while FA in the implicated tracts remained constant from adolescence to adulthood. These illustrations are reminiscent of how some theoretical models characterize development as the fine-tuning of connections throughout adolescence to shift and optimize the flow of information throughout the brain (Casey, 2016). What this study adds to this idea is an emerging appreciation that this fine-tuning might be surprisingly complex – not simply nonlinear, but also a complicated mix of different progressive and regressive shifts in the relationship between whole brain white matter structure and cognitive performance.

Study strengths include the stringent efforts to ensure lack of psychiatric dysfunction in this sample of neurotypical adolescents and adults, the relative novelty of the CCA + jICA technique being applied to the question of DTI/EF normative developmental changes, and the boost to credibility from finding some correspondence between the multivariate result sets in this study with the piecemeal findings in prior studies that sought to learn if specific white matter tracts might covary with specific EF individual differences. For instance, Takahashi et al. (2010) conducted a study on 38 healthy volunteers and found that FA of the right cingulum was positively correlated with CPT performance. Similarly, in our IC 3, we found lower cingulum bundle FA associated with lower response inhibition ability. In Chiang et al. (2016) sample of 45 healthy youths, EF performance was associated with higher FA in the cingulum bundle, mirroring our findings of several cingulum subsection clusters driving IC 2′s profile of strong working memory performance. There are also some important study limitations. Foremost of these is a need for replication. Cross-sectional datasets cannot depict true developmental trajectories with the causal certainty of longitudinal studies. This study's results can, however, help build models and expectations that later can be tested in larger, prospectively-studied cohorts. In other words, we can only speculate on how the components evolve developmentally within individuals until comparable analyses using a longitudinal dataset can be done. We emphasize that firm conclusions about the nature of intra-individual development, maturation, behavioral gains necessarily awaits further investigation into white matter and EF maturation using a prospective study design. In addition, our sample size was not as large as some of the archival data resources that investigators recently have become accustomed to using for neurodevelopmental research. The sample size raises useful questions about the generalizability of the results and emphasizes the need for replication. Replication studies should attempt to obtain larger samples with more than 120 individuals spread across age 12–24. Moreover, replication also would partially address known limitations to TBSS, such as dataset-specific anatomical inaccuracies or bias in skeleton projection. Future use of Q-Ball or HARDI sequences that were not as commonplace when this study's DTI data were collected might also increase certainty of any replication. Another limitation is that it is inherently difficult to faithfully isolate each theoretical domain of executive functioning because they are all correlated in some way, and many tasks inadvertently tap into multiple domains at once (Miyake et al., 2000; Chung et al., 2013). Miyake and colleagues (2000) aptly describe these domains as having both 'unity' and 'diversity.' There was clear evidence of this in our CCA + jICA solution set, which at times depicted blends of different EF domains. Thus, this analysis could be repeated using an even wider battery of EF tasks for a more detailed understanding of the complexities. Finally, we did not formally examine processing speed in this study, which is a potential source of variation in participant performance. Peters and associates (2014) found that after controlling for processing speed, IFOF FA was no longer associated with cognitive functioning. Processing speed analysis was outside the scope of our main question, but replication studies could consider this and compare findings with those of Peters et al. (2014).

The results of the present study suggest many interesting new possibilities for future research. This study could be taken as proof-of-concept that justifies conducting similar multivariate analyses on archival datasets such as the Human Connectome Project (Sotiropoulos et al., 2013; Van Essen et al., 2013) and the ABCD dataset (Casey et al., 2018; Garavan et al., 2018) to identify even richer profiles of white matter development in ways that consider multiple cognitive abilities. In particular, the ABCD dataset's focus on development makes it a viable candidate for replication studies. Although they do not administer the exact same cognitive battery used here, partial replication would be possible because they do employ certain EF tasks, as well as DTI scans.

The patterns observed here could be studied longitudinally with this dataset as well, as the effort is intended to last ten years. It also should be possible to construct a detailed normative framework for these kinds of multivariate associations. By using emerging and popular brain decoder approaches to detect these "biosignatures" in individual datasets (Kelly et al., 2021; Molina et al., 2022; Stevens et al., 2021), it also should be possible to predict whether an individual's "brain age" with respect to these complex multivariate profiles meets developmental expectations; or alternatively, to ask questions about the nature of DTI/cognitive abnormalities in neuropsychiatric disorders that emerge in childhood or adolescence. A possible developmental disability or psychiatric risk factor might present itself as the immature IC 3 profile that persists into adulthood long after it would be expected. As one possible illustration, a recent meta-analysis of FA in adolescents and young adults with Major depressive disorder (MDD) (Zhou et al., 2022) identified significantly lower FA in the corpus callosum, left anterior thalamic projections, and left corticospinal projections, as well as reductions in the right frontal orbitopolar tract (FOPT) extending to the right IFOF. The results of that review, among other studies (Wu et al., 2020; Tymofiyeva et al., 2017), suggest that white matter microstructure may be a viable biomarker for risk of psychopathology in the developing brain. Aghajani et al. (2014) exhibited that white matter abnormalities were present *early on* in the course of MDD in their DTI study of 25 adolescents with MDD and 21 healthy controls, highlighting the importance of a developmental lens and the potential for early intervention. Utilizing a multivariate data-driven approach in these populations may uncover profiles of psychopathological risk that build upon those findings to link mood disorders, their brain structure correlates, and their presumed cognitive or clinical consequences in informative ways. Other multivariate methods, such as multi-voxel pattern analysis (MVPA) are likely to be informative as well. MVPA methods have already begun to uncover multivariate profiles for different cognitive and emotional processes (Kim et al., 2020; Taschereau-Dumouchel et al., 2020) and have been demonstrably useful for understanding psychopathology, successfully identifying potential biomarkers based on brain activity for MDD (Gärtner et al., 2018) and conduct disorder (Zhang et al., 2019). Techniques like MVPA have the capacity to discriminate healthy controls from individuals displaying psychopathology or neural dysfunction. For example, the cross-sectional components presented in this study can be applied to disorders involving executive dysfunction. It would be possible to quantify the degrees to which these profiles are expressed in individuals with ADHD, schizophrenia, and other neurologically-based disorders. These brain decoding and machine learning approaches already are sufficiently developed and accessible enough to permit substantial, informative scientific gains to be made if investigators shift their focus to more often consider multivariate approaches that go beyond one-to-one brain-behavior mappings to study structural and functional relationships.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data Availability

De-identified data from this study is available to qualified and experienced investigators upon written request.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.dcn.2023.101318.

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