Development of white matter microstructure and executive functions during childhood and adolescence: a review of diffusion MRI studies

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ABSTRACT

Diffusion magnetic resonance imaging (dMRI) provides indirect measures of white matter microstructure that can be used to make inferences about structural connectivity within the brain. Over the last decade, a growing literature of cross-sectional and longitudinal studies have documented relationships between dMRI indices and cognitive development. In this review, we provide a brief overview of dMRI methods and how they can be used to study white matter and connectivity and review the extant literature examining the links between dMRI indices and executive functions during development. We explore the links between white matter microstructure and specific executive functions: inhibition, working memory and cognitive shifting, as well as performance on complex executive function tasks. Concordance in findings across studies are highlighted, and potential explanations for discrepancies between results, together with challenges with using dMRI in child and adolescent populations, are discussed. Finally, we explore future directions that are necessary to better understand the links between child and adolescent development of structural connectivity of the brain and executive functions.

1. Introduction

The field of developmental neuroscience has undergone a rapid evolution over the last three decades, and our understanding of how ongoing structural and functional brain maturation relate to changes in cognition during childhood and adolescence continues to expand. A broad literature of behavioural studies illustrates ongoing cognitive development across multiple domains (Akshoomoff et al., 2014; Gur et al., 2012; Waber et al., 2007). One domain of particular interest is executive functioning, the high-level cognitive processes that control lower level processes in the service of goal-directed behavior (Friedman & Miyake, 2017). Specific executive functions include abilities such as inhibition, working memory, and shifting. Additionally, less pure behavioral tasks, for example tasks focusing on decision-making or planning, can be considered complex executive function tasks that rely on broader sets of specific cognitive functions. Stereotypical adolescent behaviours, such as risky decision-making, have been linked to ongoing development of executive functions (e.g. Casey et al., 2008; Shulman et al., 2016). Furthermore, executive functions are predictive of educational attainment beyond general cognitive abilities (Donati et al., 2019), and are inversely associated with problem behaviors, albeit with modest effect sizes (Bloemen et al., 2018; Thompson et al., 2019).

In adulthood, executive functions show a general pattern of shared but distinct functions, a pattern described as "unity and diversity" (Miyake et al., 2000). However, during childhood, executive functions may occupy a more unified structure with a ‘common executive’, where distinct executive processes become increasingly differentiated from other cognitive functions and from each other with development (Akshoomoff et al., 2018; Lee et al., 2013; McKenna et al., 2017), indicative of qualitative developmental changes. Compared to many other cognitive domains, executive functions have particularly protracted developmental courses, with gradual quantitative improvements continuing throughout childhood and adolescence (Baum et al., 2017; Huizenga et al., 2006; Tamnes et al., 2010a). Performance on shifting
tasks seems to improve into adolescence, and working memory con-
tinues to improve into young adulthood. While it has been more chal-
lenging to estimate the development of inhibition, it seems to improve
rapidly at least until early adolescence (Huizinga et al., 2006).

The protracted development of executive functions through child-
hood and adolescence parallels the protracted structural development of
prefrontal cortical regions (Gogtay et al., 2004; Tamnes et al., 2013) and
white matter tracts that connect prefrontal regions with other parts of
the brain (Lebel & Beaulieu, 2011; Tamnes et al., 2010c). All cognitive
functions, and particularly so called “higher-order” or complex func-
tions, are supported by a large number of anatomically separated brain
regions (Gläscher et al., 2010; McKenna et al., 2017). This spatial dis-
tribution demands both short- and long-range efficient and precise ex-
change of information, and these cognitive functions are thus likely
strongly dependent on the structural and/or functional connectivity
between regions within brain networks (Colom et al., 2010; Deary et al.,
2010; Shaw, 2007).

The aim of this review is to discuss studies that have explored the
developmental links between executive functions and white matter
microstructure and structural connectivity, as inferred from diffusion
magnetic resonance imaging (dMRI), during childhood and adolescence.
Previous reviews have detailed the links between white matter micro-
structure measures and other aspects of cognitive development,
including social cognition development during adolescence (Wang et al.,
2018), and the development of numerical cognition (Moeller et al.,
2015), and have also addressed how the neural substrates related to
executive functions develop during early childhood (Fiske & Holmboe,
2019). To our knowledge, this is the first review to explore the literature
linking executive function development and white matter microstruc-
ture across childhood and adolescence. Longitudinal designs are argu-
ably the lifeblood of developmental science, and available longitudinal
data are emphasized. In order to understand the current literature, we
first summarise the methodology of dMRI, the key technique currently
used to study white matter microstructure and structural connectivity
in the living human brain, outlining the strengths and limitations of this
method in pediatric populations.

2. Probing white matter microstructure and connectivity
development with dMRI

The method of dMRI measures movement of water within tissue. In
the brain, water movement can be restricted or hindered by cell mem-
branes, myelin, and other macromolecules. Thus, measuring diffusion
offers a non-invasive way to assess tissue microstructure in vivo. DMRI is
especially useful for quantifying white matter microstructure because it
is highly sensitive to the ordered restriction imposed by axon mem-
branes and the myelin sheath. Because of this unique sensitivity, dMRI
techniques have been widely used to study relationships between brain
white matter structure and behavioural and cognitive outcomes,
including executive function. Diffusion imaging techniques and pro-
tocols have been extensively reviewed elsewhere (Alexander et al.,
2019; Novikov et al., 2019), so will only be covered briefly below.

The vast majority of previous literature using dMRI to study the
neural substrates of executive function has used diffusion tensor imaging
(DTI). DTI provides a three-dimensional model of diffusion distribution
within each voxel quantifying the diffusivity along three orthogonal
axes. The most common metric extracted from DTI studies is fractional
anisotropy (FA), a measure of the directionality of diffusion that ranges
from 0-1. High values (close to 1) reflect highly ordered diffusion that
occurs primarily in one direction. Lower values reflect isotropic diffu-
sion that is more equal in each direction. The principal diffusion axis in
the tensor is assumed to correspond to the primary axon orientation
within the voxel, and the diffusivity in this direction is referred to as
axial or parallel diffusivity (AD). The secondary and tertiary axes are
assumed to reflect diffusion perpendicular to the axon bundle, and are
typically averaged to produce a measure of radial, or perpendicular
diffusivity (RD). Diffusivity along all three axes is averaged to create a
metric called mean diffusivity (MD).

DTI is sensitive to multiple aspects of white matter microstructure,
and is not specific to any of them. FA and MD are both sensitive to
myelination, axonal packing, axon coherence, axon diameter, mem-
brane permeability, water content, and white matter volume, among
other things (Beaulieu, 2002). AD and RD may provide slightly more
specificity to microstructure than FA and MD. A series of animal studies
showed that RD provides particular sensitivity to myelination, while AD
is more sensitive to axonal injury (Song et al., 2002, 2003, 2005). How-
ever, anisotropy is observed even in the absence of myelin (Beau-
lieu & Allen, 1994; Kasprian et al., 2008), and therefore is not the only
driver of diffusion parameter changes. While it is impossible to know
from DTI the specific neurobiological processes driving changes in the
imaging measures, studies of healthy children’s brains tend to speculate
that changes in FA and RD reflect changes in myelination and/or axonal
packing and diameter (Krosgrud et al., 2018; Lebel, 2008), while
changes in AD are attributed to axon straightening (Giorgio et al., 2010).
More advanced dMRI techniques, including neurite orientation disper-
sion and density imaging (NODDI) (Zhang et al., 2012), diffusion kur-
tosis imaging (DKI) (Pieremans et al., 2011), fixture-based analysis (FBA)
(Raffelt et al., 2015), and others, provide additional metrics that can be
used to assess microstructural properties of tissue in more detail.

There are numerous ways to analyze dMRI data. After pre-processing
steps are complete and metric maps have been created (e.g., FA maps),
analysis can proceed directly on the metric maps by voxel-wise or
region-of-interest (ROI) approaches, or by using diffusion tractography
to virtually reconstruct white matter fibers. ROI approaches where re-

gions were drawn manually on parameter maps (e.g., FA maps) were
common in early DTI studies (Snook et al., 2005), but are rarely used in
current studies. Instead, tractography has become a substitute for ROI
approaches, creating a volume of interest from which one can extract
average parameters of interest. Different approaches to tractography
are covered in detail elsewhere (Jeurissen et al., 2019), but all use some
way to represent brain white matter pathways as three-dimensional struc-
tures that can be used for quantitative analysis. Once a pathway is
reconstructed via tractography, diffusion parameters are extracted,
either as an average across the entire tract, or examined in discrete
sections, using “along-tract” approaches (Chen et al., 2016; Colby et al.,
2012). These values can then be compared between groups or correlated
with a particular cognitive or behavioural measure.

Voxel-wise approaches examine small units individually, providing
local information on group differences or relationships with another
measure (e.g., behaviour or cognition). Tract-based spatial statistics
(TBSS) (Smith et al., 2006) is a commonly-used voxel based technique
which creates a white matter skeleton and then examines the central
portion of brain white matter tracts, helping to mitigate problems of
slight misregistration. The main advantage of voxel-based approaches is
their local specificity; voxel-based approaches are able to detect small
areas of white matter differences that may not be apparent when aver-
aging across a larger region or tract. However, a major tradeoff is the
large number of comparisons run in a voxelwise approach, which ne-
cessitates stringent multiple comparison correction to control Type I
errors.

The different indices produced using dMRI, together with the
different processing, quality control and analysis methods used across
the field, make comparisons of results between studies challenging, a
challenge further complicated when reviewing pediatric studies by

differing age ranges of participants across studies. dMRI studies of pe-
diatric populations also face specific methodological challenges and
potential pitfalls which have been discussed in detail elsewhere (Tamnes
et al., 2018; Turesky et al., 2021), and some of which are discussed in
Section 4 below. Despite these challenges, a number of studies have used
DTI and other dMRI methods and characterized the development of
white matter microstructure and connectivity (Lebel et al., 2019;
Tamnes et al., 2018). Here, we review the available research on how
these aspects of brain maturation are associated with cognitive development, specifically development of executive functions, during childhood and adolescence.

3. Linking white matter microstructure and connectivity and cognitive development

3.1. Higher-order cognitive functions

Cognitive functions, especially higher-order or complex functions, strongly rely on the structural connectivity in distributed neural networks in both adults (Chiang et al., 2009) and in children and adolescents (Koenis et al., 2018; Peters et al., 2014; Schmithorst et al., 2005; Simpson-Kent et al., 2020). For example, one cross-sectional study investigated the relationships between intellectual abilities and DTI measures in 168 participants 8-30 years old (Tammes et al., 2010b). Independently of age, both verbal and performance abilities were positively associated with FA and negatively associated with MD and RD, predominantly in the left hemisphere. Verbal abilities, but not performance abilities, were also found to be associated with age-related differences in DTI measures in widespread regions across both hemispheres. A follow-up cross-sectional multimodal imaging study showed that principal components of cortical thickness, white matter volume and MD, independently of age, accounted for unique portions of the variance in individual differences in intellectual abilities (Tammes et al., 2011). Different imaging modalities and measures, including DTI measures, thus seem to give complementary information about the neural substrates of general cognitive abilities in development.

In a large and innovative longitudinal study of 523 participants aged 6-22 years, Wendelken et al. investigated both the concurrent and the dynamic, lead–lag relationships among fronto-parietal structural connectivity as inferred from DTI, functional connectivity as measured by functional MRI, and reasoning ability (Wendelken et al., 2017). The longitudinal analysis showed that FA between the rostrolateral prefrontal cortex and the inferior parietal lobes was a positive predictor of change in both functional connectivity and reasoning ability. This suggests that structural connectivity in this pathway drives both functional connectivity and cognitive development.

While the relationships between differences in general cognitive abilities and DTI in youth are partly explained by individual differences in processing speed (Ferrer et al., 2013; Madsen et al., 2011; Peters et al., 2014) and intra-individual stability in reaction time may explain further variance (Tammes et al., 2012), it is clear that variation in DTI indices during development are behaviorally and cognitively relevant (see also Johansen-Berg, 2010). How is the regional and protracted development of different white matter pathways and connections related to the long-lasting development of executive functions? And are different regional and temporal association patterns seen for different specific executive functions?

3.2. Inhibition

Understanding the neurobiological development of inhibitory behaviour is pertinent as inhibitory performance has been associated with a range of neurodevelopmental disorders and mental health problems (Herba et al., 2006; Kerr et al., 1997; Mahmood et al., 2013; Roussy & Toupin, 2005; Tremblay et al., 1994; van Deurzen et al., 2012; Wilde et al., 2006). The ability to withhold an automatic response, to resist tempting behaviour, or to adjust behaviour to meet situational demands rapidly evolves during development (Davidson et al., 2006; Gur et al., 2012; Williams et al., 1999).

Inhibitory behaviour, also referred to as cognitive control, is typically measured using one of several standardized classic neuropsychological paradigms. These tasks include the Stroop task (Stroop, 1935), Go/No-go tasks (Donders, 1969), Flanker tasks (Eriksen & Eriksen, 1974), Stop Signal tasks (Lappin & Eriksen, 1966), and Anti-Saccade tasks (Hallett, 1978). Each of these tasks requires individuals to inhibit a prepotent response. Functional MRI paradigms employing modified versions of these tasks have shown recruitment of frontal and parietal cortical regions, including, but not limited to, the dorsolateral prefrontal cortex, inferior and middle frontal gyrus, medial prefrontal cortex, and posterior parietal cortices (see Seghete et al., 2013 for review).

In adolescents, better inhibitory performance has been associated with higher FA in the frontal lobes (Liston et al., 2006), including regions under the inferior frontal gyrus and the pre-supplementary motor area (Madsen et al., 2010), in the anterior corona radiata (Seghete et al., 2013), and in the corpus callosum (Fjell et al., 2012). Of these studies, Madsen and colleagues used TBSS region of interest methods, while the other studies used tractography to look at tracts of interest (Liston et al., 2006) or white matter tracts across the whole brain (Fjell et al., 2012; Seghete et al., 2013). Interestingly, many of these studies find that associations between inhibition and FA remain significant after statistically controlling for differences in age (see Fig. 1). Other studies, however, have found diffusion metrics within these regions to be either unrelated or inversely associated with inhibitory performance (Treit et al., 2014). Two large studies using data from the Pediatric Imaging, Neurocognition, and Genetics (PING) study, a public repository with data from 1493 children/youth aged 3-20 years (Jernigan et al., 2016), have found limited associations between DTI metrics and inhibitory behaviour. Ursache et al. (n = 1082) found no association between inhibitory performance (Flanker task) and DTI metrics within specific tracts of interest including the cingulate bundle, inferior longitudinal fasciculus, superior longitudinal fasciculus, or the anterior thalamic radiation (Ursache et al., 2016). Fjell et al. (n = 684) found that cognitive control was associated with individual differences in brain structure in participants below 12 years, specifically with surface area in the anterior cingulate cortex, and that FA in the forceps major explained additional variance (Fjell et al., 2012). Further, in a rare longitudinal TBSS study from Simmonds et al. (n participants = 128; n scans = 322), the authors suggest that earlier white matter microstructural development in adolescence is associated with better inhibitory control (Simmonds et al., 2014). Lower rates of inhibitory errors during the anti-saccade task were associated with higher mean FA levels in late adolescence/early adulthood in the left core limbic white matter, particularly the hippocampal portion of the left cingulum, and with higher rates of FA growth during mid-late adolescence. The opposite pattern was seen in the cingulum in early adolescence where higher mean FA levels were associated with higher inhibitory errors. Interactions between inhibitory error rates, age and both RD and AD were also seen in this study, with higher RD in the left and right fornix associated with lower error rates in childhood/early adolescence, but higher RD in the left fornix with increased error rates in early adulthood. Higher AD was associated with lower inhibitory error rates in childhood/early adolescence in the left body of the fornix.

Together, these results suggest that individual and perhaps also developmental differences in white matter microstructure are associated with differences in inhibitory performance. A number of white matter regions, particularly fronto-temporal regions, have been identified in the literature as being involved in inhibitory performance including the inferior frontal gyrus, the pre-supplementary motor area, the anterior corona radiata, the corpus callosum and forceps major, as well as limbic regions including the fornix and cingulum. This is in our opinion likely the reflection of network level changes in global white matter that reflect maturation and integration across important cortical hubs, although there is little reproducibility of these findings. This developmental increase in network complexity likely drives individuals toward more consistent behaviour and improves one’s ability to inhibit prepotent responses. Ultimately, these data, in particular the one longitudinal study available that highlights changing associations across adolescence, indicate the need for more longitudinal, within-subjects designs to detail the relationship between two highly age-dependent
phenomena.

3.3. Working memory

Traditionally, working memory is in the multicomponent model of memory contrasted with long-term memory, and refers to the ability to temporary store and manipulate information (Baddeley, 2012). The latter aspect is also often considered an executive function, often specified as the manipulation process of working memory updating (Miyake et al., 2000). Several current models, however, conceptualize working memory in terms of allocation of attention to internal representations (D’Esposito & Postle, 2015). The differentiation between temporary storage and manipulation is here replaced with modality specific systems for temporary representation of information and more general-purpose control functions. Based mainly on functional MRI (Rottschy et al., 2012), but also lesion and electrophysiological studies in both humans and other animals (Müller & Knight, 2006), we know that working memory involves a bilateral fronto-parietal network that includes lateral prefrontal and posterior parietal cortical regions. It is however possible that this network, and particularly its prefrontal portion, underlies a more general system for top-down control rather than specifically a system for updating and manipulation of information in working memory (D’Esposito & Postle, 2015).

In terms of development, the main structure of working memory appears to be in place already around age 6 years, but all the different modular components continue to improve their capacity throughout childhood and into adolescence (Gathercole et al., 2004). It has also been proposed that due to age-differential trajectories of posterior and frontal brain regions, low-level feature binding processes become relatively mature in childhood, while top-down control processes are not fully mature until young adulthood (Sander et al., 2012).

In children and adolescents, it has been found that developmental improvement in working memory performance is associated with structural development of fronto-parietal cortical regions (Tamnes et al., 2013), and with functional maturation of dorsolateral prefrontal regions (Andre et al., 2016; Crone et al., 2006). Based on the known distributed nature of the working memory network, several studies have used DTI to investigate microstructural properties of white matter tracts presumably connecting different nodes within this network, or tracts connecting the working memory network with modality specific regions for temporary representation of information.

At least two cross-sectional developmental studies have focused on the link between working memory in children and adolescents and DTI measures in the superior longitudinal fasciculus (SLF), a main route connecting parietal and lateral prefrontal cortices. These studies investigated verbal and spatial working memory, respectively, and found that better performance was associated with higher FA and lower RD in the SLF, independently of age (Östby et al., 2011; Vestegaard et al., 2011). However, in a more recent longitudinal study by Krogsrud et al. of 148 children scanned between the ages 4 and 11 years, 10 major white matter tracts hypothesized to be of importance for working memory were investigated, and there was in this younger sample no significant associations between development of either verbal or visuospatial working memory capacity and DTI changes in the SLF (Krogsrud et al., 2018). Instead, the results showed that improvement in visuospatial working memory capacity was associated with increasing FA and decreasing MD in the right inferior fronto-occipital fasciculus (IFOF) and the forceps major, as well as with decreasing MD in the inferior longitudinal fasciculus (ILF) and uncinate fasciculus (UF) in the right hemisphere (Krogsrud et al., 2018; see Fig. 2).

Another cross-sectional study measuring both cortical thickness and FA across the whole brain in children 5-15 years intriguingly found greater associations between the executive part of the working memory system and the corpus callosum and posterior temporal white matter in younger children, while for older children, this was more closely linked with the thickness of the occipito-temporal cortex (Bathelt et al., 2018). The authors interpreted the findings as suggesting that the underlying brain systems supporting working memory shift from long-range connections to more specialized local circuitry during development. Future studies are needed to replicate this finding, especially since cortical
DTI and fMRI to study brain structural and functional predictors of later development.

The central role of white matter microstructure for working memory capacity in a sample of 89 individuals

Klingberg performed a longitudinal study combining structural MRI, visuo-spatial working memory capacity in a sample of 89 individuals and striatal regions and studies have examined whether white matter microstructure of tracts connecting these regions support cognitive flexibility (Badre & Wagner, 2006; Gold et al., 2010). Additionally, higher FA and lower RD in anterior portions of the corpus callosum has been found to be associated with better task-switching, indicating an important role of inter-hemispheric communication (Vallesi et al., 2016).

In developing samples, only a few cross-sectional DTI studies have focused on shifting. Seghete et al. measured flexibility using the inhibition/task-switching condition from the Color-Word Interference task and performed whole brain voxel-based DTI analysis in 49 individuals 5-16 years (Seghete et al., 2013). The results showed age-independent positive correlations between task switching and FA in superior corona radiata and precentral gyrus white matter (see Fig. 3). Additionally, there was also an interaction effect between task switching and age on FA in the anterior corona radiata, with the positive association only seen in younger adolescents. In a similar type of study, Treit et al. measured cognitive flexibility using the switching condition in the NEPSY-II Inhibition task and performed whole brain voxel-based DTI analysis in 49 individuals 5-16 years (Treit et al., 2014). The results of this study showed several clusters in posterior brain regions where higher FA was associated with better cognitive flexibility. In sum, although positive associations between cognitive flexibility and FA were found in both these studies, the anatomical locations varied substantially, and both studies included relatively small samples.

3.4. Shifting

Fewer studies have examined the links between DTI metrics and shifting, or cognitive flexibility, in children and/or adolescents. Shifting is conceptualized as the ability to flexibly switch back and forth between multiple tasks, operations or mental sets (Miyake et al., 2000). Somewhat overlapping with findings for working memory, the capacity to flexibly switch between different operations or rules has in adults been associated with fronto-parietal and striatal regions and studies have examined whether the need to incorporate a greater number of different cognitive processes might make them more sensitive to age or other variables of interest. Might they also, from a neuroimaging perspective, be more sensitive to individual and development differences in white matter microstructure and connectivity?

An example of a complex executive function task is delay gratification (also referred to as temporal discounting or delay discounting). Delayed gratification tasks focus on the ability to sustain goal-directed communication (Vallesi et al., 2016).

Coherence of the corpus callosum has been found to be associated with higher FA and lower RD in anterior portions of the corpus callosum (Seghete et al., 2013). The results showed age-independent positive correlations between task switching and FA in superior corona radiata and precentral gyrus white matter (see Fig. 3). Additionally, there was also an interaction effect between task switching and age on FA in the anterior corona radiata, with the positive association only seen in younger adolescents. In a similar type of study, Treit et al. measured cognitive flexibility using the switching condition in the NEPSY-II Inhibition test and performed whole brain voxel-based DTI analysis in 49 individuals 5-16 years (Treit et al., 2014). The results of this study showed several clusters in posterior brain regions where higher FA was associated with better cognitive flexibility. In sum, although positive associations between cognitive flexibility and FA were found in both these studies, the anatomical locations varied substantially, and both studies included relatively small samples.

3.5. Complex executive functions

In addition to the specific executive functions of working memory, inhibition and shifting (Friedman & Miyake, 2017), other complex tasks requiring higher level cognitive functions and incorporating these key executive functions also show significant development during adolescence. From a cognitive perspective, these types of tasks are less specific, but the need to incorporate a greater number of different cognitive processes might render them more sensitive to age or other variables of interest. Might they also, from a neuroimaging perspective, be more sensitive to individual and development differences in white matter microstructure and connectivity?

Overall, there is broad consensus of an association between developing working memory and changes in white matter microstructure during childhood and adolescence, particularly of fronto-parietal (although note Krogsrud et al., 2018) and occipito-temporal tracts, although differences in focus of studies together with different methods and participant demographics still result in a mixed picture across the available literature.

Fig. 2. Scatterplots showing linear relationships between change in FA or MD and change in visuospatial working memory (assessed using a spatial span backward test). The plots show FA and MD in tracts of interest, plotted as z-transformed change values. For working memory scores age, sex and interval are regressed out, and for each tract age, sex, interval and motion at both time points are regressed out. The partial correlation (r) between change in FA and MD in specific white matter tracts and change in working memory scores, controlling for age, sex, interval and motion at both time points are presented in each plot. The color-coded scatterplots represent the color of each specific white matter tract. Colour codes refer to: Yellow: Inferior fronto-occipital fasciculus (IFOF), Red: Forceps major (FMaj), Light blue: Inferior longitudinal fasciculus (ILF) and Green: Uncinate fasciculus (UF). R = right. From Krogsrud et al. (2018).

thickness surprisingly was unrelated to age in this study. Also using a multimodal approach including probabilistic tractography, Darki and Klingberg performed a longitudinal study combining structural MRI, DTI and fMRI to study brain structural and functional predictors of later visuo-spatial working memory capacity in a sample of 89 individuals scanned 1-3 times in the age-range 6-25 years (Darki & Klingberg, 2015). Cross-sectional analyses showed associations between working memory capacity and all the different types of neuroimaging measures; thickness in parietal cortex, white matter volume and FA of fronto-parietal and fronto-striatal tracts, and activity in frontal and parietal cortical regions. Interestingly, however, the longitudinal analysis more specifically showed that FA in these white matter tracts and activity in caudate predicted future working memory capacity, stressing the central role of white matter microstructure for working memory development.

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In addition to the specific executive functions of working memory, inhibition and shifting (Friedman & Miyake, 2017), other complex tasks requiring higher level cognitive functions and incorporating these key executive functions also show significant development during adolescence. From a cognitive perspective, these types of tasks are less specific, but the need to incorporate a greater number of different cognitive processes might render them more sensitive to age or other variables of interest. Might they also, from a neuroimaging perspective, be more sensitive to individual and development differences in white matter microstructure and connectivity?

An example of a complex executive function task is delayed gratification (also referred to as temporal discounting or delay discounting). Delayed gratification tasks focus on the ability to sustain goal-directed cognition in the face of immediate rewards (de Water et al., 2014). It is hypothesised that delay gratification, being able to weigh up a preference for a larger, delayed reward compared to a smaller, more immediate reward, is dependent both on an individual’s impulse regulation but also on their reward processing, and that differences in task performance can be driven by either process separately, or by the interplay of both cognitive processes (Figner et al., 2009, 2010). fMRI studies investigating the neural correlates of delay gratification have implicated both frontoparietal and limbic brain areas, including the lateral prefrontal cortex, parietal cortex, ventral striatum, medial prefrontal cortex and posterior cingulate cortex (Scheres et al., 2013).
Three DTI studies have explored the link between white matter microstructure and delay gratification. Of these, one was a longitudinal study where 299 participants aged 8–26 years were scanned at two time-points (Achterberg et al., 2016). The authors identified striatal regions (including caudate, putamen and pallidum) and prefrontal (including the dorsolateral, ventrolateral and ventromedial prefrontal cortices) volumes of interest, and used deterministic streamline tractography to identify frontostriatal white matter tracts running between these regions. They found that age-related reductions in impulsivity (i.e. a greater ability to wait longer for a larger reward) were mediated by increases in FA and decreases in MD in this frontostriatal tract. Furthermore, greater FA at the first timepoint in the study was a significant predictor for greater delayed gratification skills at the second timepoint.

The two other published DTI studies of delay gratification were cross-sectional. The first explored the association between delay discounting and white matter microstructure using voxel-based TBSS in participants aged 9–23 years (n = 79) (Olson et al., 2009), and reported associations across a broad set of tracts. Higher FA was associated with both increasing age and improved delay gratification in bilateral anterior thalamic radiation, right superior and longitudinal fasciculi, right corticospinal tract, right inferior fronto-occipital fasciculus, left uncinate fasciculus, and the splenium of the corpus callosum. Lower MD was associated with both increasing age and greater delay gratification in the bilateral inferior and superior longitudinal fasciculi, anterior thalamic radiation and inferior fronto-orbital fasciculi, as well as the left corticospinal tract and cingulum. Some FA and MD associations with delay gratification performance were shown to be independent of age, suggesting that structural connectivity differences in white matter may contribute to both individual and developmental differences in executive functioning (Olson et al., 2009).

The other cross-sectional study assessed the relationship between frontostriatal tract ‘strength’, as determined by the proportion of seeded tracts extending from the striatum to a set of a priori fronto-cortical regions using probabilistic tractography, and delay gratification in adolescents (van den Bos et al., 2015). The authors reported an association between higher frontostriatal tract strength and a greater preference for delayed rewards. Changes in temporal discounting were driven by changes in cognitive control (as opposed to reward sensitivity), and using a conditional processes analyses, the authors concluded that age-related behavioural changes were mediated by differences in lateral prefrontal cortico-striatal structural connectivity. Together with Achterberg et al., this study highlights both age-related and age-independent associations between white matter microstructure and delay gratification, and suggests a role for structural connectivity in determining both developmental and individual differences in this behaviour.

Another complex cognitive task that incorporates executive functioning that has been prominent in the adolescent neuroscience literature is the stoplight task, a risky decision-making paradigm in which participants drive a simulated car through a series of intersections and decide whether to brake at each one (Steinberg & Monahan, 2007). If participants choose to brake at an intersection, they safely stop but take additional time to complete the course. Alternatively, if they proceed across the intersection, they can complete the course more quickly, but take on a risk that they will crash into an oncoming vehicle and suffer a significant time penalty. In a voxel-based analysis, Kwon et al. found that, in a sample of 34 males aged 18–19 years, participants who took more risks in this task had higher FA in the splenium of the corpus callosum compared to those who took fewer risks (Kwon et al., 2014). This cross-sectional study included only a small number of participants, and, of note, the extent of risky decision-making on the task did not correlate with self-reported levels of real-life risk-taking. A second study of risky decision-making reported that higher levels of self-reported risk-taking behaviour (measured using the Adolescent Risk Questionnaire (Gullone et al., 2000) in a cross-sectional sample of 14–18 year olds (n = 60) was associated with higher FA in the anterior portion of the corpus callosum and the right superior corona radiata (Berns et al., 2009). Both of these studies suggest that risky decision-making during adolescence may be associated with increased levels of FA, particularly in the corpus callosum. Since increased FA has been associated with more advanced white matter development during adolescence, both sets of authors postulated that greater levels of risk taking may be indicative of a greater maturity of the white matter network involved in this...
complex cognitive function.

4. Future directions and ongoing challenges in pediatric dMRI

Despite methodological challenges, recent developments offer promise for diffusion imaging to yield new and solid knowledge about the role of white matter microstructure and connectivity for the development of executive functions across childhood and adolescence. Firstly, the development of datasets encompassing larger sample sizes, longitudinal measurement and population-representative data is key to improving our understanding of white matter developmental patterns, and the relationship with cognition (Klapwijk et al., 2021; Marek et al., 2020). Many of the studies reviewed here have relatively small numbers of participants and very few have used longitudinal data, limitations which contribute to the disparate results reported. As recognition of the importance of adequate sample size and sample selection in neuro-imaging grows, the anticipated availability of large datasets from longitudinal cohorts like the ABCD project which incorporate neuroimaging (Casey et al., 2018) and cognitive measures (Luciana et al., 2018) alongside many others may be important to reliably explore the associations between white matter microstructural development and cognition including executive functioning (Glick et al., 2021).

Secondly, improving methodological rigor and replication studies, as well as the incorporation of advanced statistical methodologies (e.g. pattern analysis, machine learning, longitudinal structural equation modelling) will improve the validity and utility of findings from dMRI studies of the neural foundation for cognitive development across childhood and adolescence. The establishment of standards in both the measurement and analysis of brain microstructure would go a long way to improving our understanding of brain-behavior relationships in development. One example is in tackling the issue of head motion during scanning, which is known to be a key factor affecting the quality of all modalities of neuroimaging (Satterthwaite et al., 2019; Yendiki et al., 2014). Motion often manifests as signal drop-out and can in dMRI lead to erroneous measurements of anisotropy and diffusivity. Motion tends to be more prominent in younger children compared to older children (Roalf et al., 2016), though it is not always robustly associated with age (Thieba et al., 2018). A number of steps to minimize motion can be taken before scan acquisition, including the use of mock scanners (de Bie et al., 2010, 2012; Hallowell et al., 2008; Raschle et al., 2011) and environmental-mental training (Theys et al., 2014; Thieba et al., 2018), and scanning protocols can be optimized by minimizing sequence length and optimizing hardware (see Alexander et al., 2019; Tammes et al., 2018 for reviews). Post-processing methods can also incorporate strategies to mitigate motion. These may include manual visual inspection of data and removal of poor volumes and datasets (e.g., Reynolds et al., 2019) or automated quality checks (e.g., DTIprep (Oguz et al., 2014)). Most pre-processing software (e.g., FMRIB software library [FSL]’s eddy tool (Jenkinson et al., 2012); ExploreDTI (Leemans et al., 2009); QSI prep (Gieslak et al., 2021)) also includes motion correction strategies to help counter some head motion effects. Increasing awareness of reviewers and editors of the importance of accounting for head motion will all result in more reliable and valid data from which to build greater understanding of brain development and white matter microstructural development in particular.

Novel approaches for analysing DTI data are also yielding new insights into the behavioural relevance of white matter microstructural development. Techniques such as graph theory (Bullmore & Sporns, 2009) have been used to analyze diffusion data, but have so far rarely been used to study the links between white matter microstructure and executive functions during development. Baum and colleagues (2017) used diffusion tractography in a large cross-sectional cohort (n = 882, ages 8-22 years) to investigate how structural brain networks develop during adolescence (Baum et al., 2017). They demonstrated that structural network modules become more segregated with age, with strengthening of connections within modules, and weakening of connections between modules, and that this segregation was shown to be related to increased global network efficiency in the brain during adolescence. Critically, both the modular segregation and global network efficiency were associated with enhanced executive functioning (measured using a battery of tests incorporating mental flexibility, attention and working memory; Gur et al., 2010), mediating the age-related improvement in executive functioning seen with age in the study (Baum et al., 2017).

It is theorised that the development of increasing cognitive network efficiency during adolescence is driven by a need to reduce energy demand. A recent large cross-sectional study of 946 participants aged 8-23 years calculated the energetic cost required to activate the frontoparietal system based on a structural network using linear dynamical control theory, and demonstrated that the energy required decreased over development (Cui et al., 2020). This improving efficiency in the brain was correlated with executive function performance in the brain, with energetic requirements negatively correlated with performance, an association that was partially mediated by an association between executive function and age of participants (see Fig. 4). This study therefore suggests a mechanism by which activating the executive function network can become more energy efficient during adolescence (Cui et al., 2020). These novel analytical techniques allow existing DTI data to be utilised in original ways, meaning that we can continue to improve our understanding about the organisation and development of white matter microstructure by reexaming previously collected data.

DTI has been the main workhorse for probing white matter development for nearly two decades. But, a new generation of models have been developed that leverage different properties of diffusion. A previous review has detailed several advances (Tammes et al., 2018), but here we focus on two recent types of diffusion models: “tissue”-based and “signal”-based (Ferizi et al., 2017). Tissue-based models attempt to classify signal attributable to different classes or compartments of biological tissue. NODDI has become the most widely used (Zhang et al., 2012) multi-compartment modeling of diffusion images (Alexander et al., 2010; Assaf & Basser, 2005). NODDI estimates the directional distribution of neurites (axons and dendrites) in a voxel, and then matches diffusion patterns to that distribution. The result is an estimation of three volume fractions in each voxel: the segment of tissue that is intracellular, extracellular, and isotropic (e.g. CSF). NODDI-derived measures have appear to be more closely associated with age in youth than standard DTI metrics (Chang et al., 2015; Deligianii et al., 2016; Eaton-Rosen et al., 2015; Genc et al., 2018; Kodiwera & Wu, 2016; Mah et al., 2017; Nazeri et al., 2015; Ota et al., 2017). “Signal” based methods use quantitative, efficient and robust mathematical models to describe molecular displacements in brain white matter. Essentially, these models derive more nuanced characterizations of white matter with diffusion scans that measure both diffusion direction and gradient strength. An example, Mean Apparent Propagator MRI (MAP MRI) has shown promising accuracy (Ozarslan et al., 2013) and limited evidence in one study of development suggests improvement over typical DTI in measuring age-related associations (Pines et al., 2020). Future studies should employ these methods to further explore how white matter microstructural development is related to the development of different executive functions.

Adapting some of these new techniques and models to pediatric samples may continue to raise new challenges. Many of the more advanced dMRI techniques require sequences with higher b-values or multiple non-zero b-values compared to DTI, increasing the scan acquisition time needed, thereby potentially exacerbating the problems associated with head motion in pediatric samples discussed above (Tammes et al., 2018). Furthermore, some of the adult templates typically used in image analyses may not be appropriate for pediatric studies, especially for young children (Wilke et al., 2002; Yoon et al., 2009). More broadly, there is a potential trade-off between using identical methods across different ages or using different, but more age-appropriate methods for different developmental stages (Turesky
Scientific discoveries and technological advancements often occur together. MRI systems of 12 T and possibly even 20 T (Budinger et al., 2016) are on the horizon, and will offer the ability to visualize new white matter features in resolution of about 0.1 millimeters (Budinger & Bird, 2018). Currently, 7 T dMRI is implementable and well tolerated, however, significant challenges remain to achieve the promise of increased diffusion signal at 7 T (Gallichan, 2018). Yet, as the challenges are overcome, 7 T MRI is already offering additional insight into neurotransmitter systems that are not easily resolved at lower field strengths (Cai et al., 2012; Roalf et al., 2017) and that are directly relevant for the development of brain white matter. MRI has proven to be such a versatile technique that it is challenging, and almost foolish, to predict the full scope of research and clinical applications that may become available with ultra-high field systems. Unquestionably, these applications will see significant benefits from increases in field strength and these technological improvements will lead to studies of tissue energetics and neurotransmitter levels in brain function (Duyn, 2012) than can be coupled with dMRI techniques that will allow for better understanding of neurobiological development.

Finally, future studies on the relationships between brain and cognition development should seek to contextualize these changes and their interplay in the context of genetic factors and aspects of the individual child’s physical and social environment (Ferschmann et al., 2021). Genome-wide association studies (GWAS) have shown that DTI parameters are substantially heritable for multiple major white matter tracts (Zhao et al., 2019). Other studies document associations between differences in indices of socioeconomic position (SEP) and white matter microstructure and cognition (e.g. Johnson et al., 2021). Using the large PING dataset, Ursache et al. (2016) found that family income had a moderating effect on the association between cognitive flexibility and white matter microstructure, but not on the associations between inhibition or working memory and white matter (Ursache et al., 2016). More specifically, both globally and in the SLF, there was a positive association between flexibility and FA only in children from lower income families. This begs the question whether the developmental links between executive functions and white matter microstructure and connectivity might vary in different populations, but large longitudinal studies are needed to address this question.

5. Summary

Throughout childhood and adolescence, continued reorganisation and improvement of executive functions influences the development of behaviours and abilities, particularly in relation to the emergence of educational capacity, social abilities and problem behaviours. Several DTI studies have examined the link between inhibition and white matter microstructure and have found that better inhibitory performance is associated with higher FA in frontal white matter regions in children and adolescents, although other studies have found limited or no association. The only published longitudinal data suggest that faster white matter microstructural development earlier during adolescence is associated with better inhibitory control (Simmonds et al., 2014). Studies in children and adolescents have reported associations between better working memory and higher FA and lower RD in fronto-parietal and occipito-temporal tracts; a longitudinal study found that FA in
frontal tracts predicted later working memory capacity (Darki & Klingberg, 2015). Relatively fewer studies have examined associations between shifting ability and DTI indices in developmental samples. Although positive associations with FA have been reported, the localization of these effects is inconsistent across studies, and the association might vary in different populations (Ursache et al., 2016). Other studies have used more complex tasks and have reported associations between adolescents’ abilities to delay gratification or make risky decisions and regionally higher FA.

Across all executive functions and tasks, longitudinal data and analyses are scarce. This severely limits our understanding of how executive functions and brain white matter microstructure “grow together” during childhood and adolescence. Longitudinal studies, especially those following children for several years, are essential to further our understanding of how white matter development underlies development of executive functions. Future studies should also to a larger extent leverage the potential of statistical methodologies such as network analysis and more advanced dMRI models to further probe the role of extrinsic white matter connectivity development for improvements in complex cognitive functions and yield new knowledge about the specific neurobiological changes underlying this development. We are optimistic that these advances will improve our understanding of brain-behavior relationships in early and late neurodevelopment.

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Data Statement

All data included in this review are available from published peer-reviewed papers and are accessible via the relevant journals. There are no new data included within the manuscript.

Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.

Declaration of Competing Interest

The authors report no declarations of interest.

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