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Neuropsychological development in adolescents: Longitudinal associations with white matter microstructure

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ABSTRACT

Important neuropsychological changes during adolescence coincide with the maturation of white matter microstructure. Few studies have investigated the association between neuropsychological development and white matter maturation longitudinally. We aimed to characterize developmental trajectories of inhibition, planning, emotion recognition and risk-taking and examine whether white matter microstructural characteristics were associated with neuropsychological development above and beyond age. In an accelerated longitudinal cohort design, n = 112 healthy adolescents between ages 9 and 16 underwent cognitive assessment and diffusion MRI over three years. Fractional anisotropy (FA) and mean diffusivity (MD) were extracted for major white matter pathways using an automatic probabilistic reconstruction technique and mixed models were used for statistical analyses. Inhibition, planning and emotion recognition performance improved linearly across adolescence. Risk-taking developed in a quadratic fashion, with stable performance between 9 and 12 and an increase between ages 12 and 16. Including cingulum and superior longitudinal fasciculus FA slightly improved model fit for emotion recognition across age. We found no evidence that FA or MD were related to inhibition, planning or risk-taking across age. Our results challenge the additional value of white matter microstructure to explain neuropsychological development in healthy adolescents, but more longitudinal research with large datasets is needed to identify the potential role of white matter microstructure in cognitive development.

1. Introduction

Adolescence is an important developmental period for higher-order and social-emotional cognition. It is characterized by a concomitant increase in executive functioning and risk-taking (Crone, 2009). The maturation of executive abilities and emotion processing has been related to well-being and vocational success (Meltzer, 2007; Wüstenberg et al., 2012). Increased risk-taking behavior, however, may have negative consequences: while heightened sensation and novelty seeking are part of normative adolescent development, difficulties in adequately exerting cognitive control may place adolescents at a greater risk for mental disorders (Luna et al., 2015; Crone et al., 2016). In order to understand atypical or aberrant neuropsychological development and how it might lead to behavioral difficulties or mental health problems, it is crucial to fully characterize normative neuropsychological development.

This study aimed to examine the developmental trajectories of inhibition, planning, emotion recognition and risk-taking during the

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dynamic phase of adolescence. Inhibition is considered to be a basic executive function (Best and Miller, 2010). It describes the ability to voluntarily withhold a pre-potent, goal-incompatible reaction in favor of a goal-directed response (Luna et al., 2015; Bari and Robbins, 2013). A more complex executive function is strategic planning (Anderson, 2003). It requires the capacity to generate and organize the necessary sequence of steps to reach a certain goal (Anderson, 2003). Emotion recognition is a key skill for successful interactions and is considered fundamental for developing social competences (Watling and Damaskinou, 2018). Risk-taking includes decision making in situations where outcomes carry a degree of uncertainty and involves choosing the option with the highest outcome variability (Crone et al., 2016). While it may entail negative consequences, it can be adaptive in other situations or phases in life (Crone and Dahl, 2012). In the following, when summarizing the four domains we studied, we refer to 'neuropsychological' (rather than 'cognitive') functions. This is to account for the fact that not all tasks are purely cognitive in nature.

The development of the above-mentioned skills has mainly been examined in cross-sectional studies. Steady improvements have been suggested from childhood up to adulthood, with varying time-scales depending on the complexity of the respective ability (Luna et al., 2015; Watling and Damaskinou, 2018; Christ et al., 2001; Bedard et al., 2002; Vaughn et al., 1984; Welsh et al., 1991; Unterrainer et al., 2015; Korkman et al., 2001; Anderson et al., 2001; Albert and Steinberg, 2011; Chronaki et al., 2015; Durand et al., 2007). Few longitudinal studies have shed light on developmental trajectories. Inhibition performance on a Go/No-Go task improved linearly from ages 5–10 (Troller-Renfree et al., 2019) and non-linearly on an anti-saccade paradigm (where the participant is instructed to make a saccade in the direction away from the stimulus; failure to inhibit a reflexive saccade is considered an inhibition error), with rapid changes between 9 and 15 and slower changes up to 25 years-of-age (Ordaz et al., 2013). One study further reported a moderate increase of complex planning abilities from age 13–15 (Frischkorn et al., 2014). Finally, a recent study showed that 5–12 year-olds improved in facial emotion recognition over a period of one year (Watling and Damaskinou, 2018). Inconsistent findings exist regarding the development of risk-taking, with some studies reporting decreases in risk-taking from childhood to adulthood (Paulsen et al., 2011; Van Duijvenvoorde et al., 2012). Other studies however, show that risk-taking peaks in adolescence (Burnett et al., 2010; Figner et al., 2009), which has recently been confirmed in two longitudinal studies (Braams et al., 2015; Peper et al., 2018). Although surprisingly few studies examined within-sample neuropsychological changes in the mentioned domains, the implementation of longitudinal designs is necessary to obtain an accurate picture of developmental trajectories in adolescent cognition (Grammer et al., 2013; King et al., 2018).

Coinciding with the dynamic neuropsychological changes in adolescence is the maturation of white matter microstructure (Lebel et al., 2012; Simmonds et al., 2014). By enabling efficient communication between brain regions, white matter facilitates coordinated information processing and is therefore vital for cognition (Geeraert et al., 2019). However, few studies have investigated white matter microstructural development in relation to neuropsychological development. Diffusion tensor imaging (DTI) allows the in vivo exploration of white matter microstructure. The most commonly used measure is fractional anisotropy (FA) which reflects the degree of diffusion anisotropy, with low values reflecting isotropic diffusion and high values reflecting anisotropic diffusion. Mean diffusivity (MD) reflects the amount of water diffusion within a region averaged over all directions. In typical development, FA increases (and MD decreases) rapidly during infancy and early childhood, after which changes occur gradually slower until they peak in early adulthood (Lebel et al., 2008; Tamnes et al., 2010; Peters et al., 2012). Changes in FA have been quantified around 10–25 % between 5 and 25 years of age (Lebel et al., 2008; Tamnes et al., 2010). There is considerable regional variation in white matter microstructural development (Lebel and Deoni, 2018).

A small number of longitudinal studies have examined associations between white matter microstructural maturation and the development of intelligence (for a review, see Kievit et al., 2019), reading (Yeatman et al., 2012; Wang et al., 2016), or visuo-spatial working-memory (Krogsrud et al., 2018). In a delay of gratification task, impulse control improved faster in 8–26 year-old individuals with higher fronto-striatal FA (Achterberg et al., 2016). Moreover, the higher fronto-striatal FA was at baseline, the better the ability to delay gratification two-years later (Achterberg et al., 2016). Another study found differential effects of FA growth on inhibition: while left cingulum FA growth in adolescence was associated with better inhibition, FA growth in adulthood was associated with worse inhibition (Simmonds et al., 2014). In this study, FA growth effects were not reported in association with developmental changes in inhibition, however the authors concluded that earlier white matter maturation in this limbic tract facilitated the development of inhibition (Simmonds et al., 2014). To sum up, while white matter characteristics have been linked to different neuropsychological domains, reports on the association between white matter maturation and neuropsychological *development* over time are scarce.

The first aim of this study was to add to the existing literature in characterizing the development of inhibition, planning, emotion recognition and risk-taking in typically developing adolescents between 9 and 16 years of age within a longitudinal study design over three years. We hypothesized steady performance increases with age in inhibition, planning and emotion recognition and an increase in risk-taking. The second aim of this study was to examine whether white matter microstructural development was related to associations between neuropsychological functioning and age. We hypothesized that higher FA and lower MD in white matter tracts - relevant to higher-order and social cognition - were associated with improvements in neuropsychological functioning over age.

2. Material and methods

This study reports results from the brain maturation study, an accelerated cohort longitudinal study conducted at the Department of Child and Adolescent Psychiatry, University Hospital Heidelberg in Germany. The study protocol was approved by the Ethical Committee of the Medical Faculty, Heidelberg University, Germany (S-604/2011) and carried out in accordance with the Declaration of Helsinki. All participants and their legal guardians provided written informed consent prior to inclusion in the study.

2.1. Procedure

The study involved cognitive assessments, magnet resonance imaging (MRI), a clinical interview and questionnaires in two cohorts at three time points, each one year apart. Assessments took place at the Department of Child and Adolescent Psychiatry, University Hospital Heidelberg, Germany. In the first appointment, the clinical interview and cognitive assessment were performed by trained psychologists. During this appointment, participants and their parents filled out questionnaires assessing demographics, handedness, behavior, temperament and pubertal development. At the second appointment, adolescents underwent the MRI exam. As a preparation, they were familiarized with the scanner environment and received detailed instructions. At each time point, participants received 25€ for taking part in the clinical assessment and 25€ for participating in the MRI session.

2.2. Participants

Two cohorts of participants aged 9 and 12 years were recruited for the present study. N = 2398 individuals from the community were contacted by mail, a study flyer or via an announcement on the Heidelberg University Hospital website. Of those, n = 228 individuals responded, expressing general interest to participate in the study.

During a telephone screening, the following inclusion criteria were checked: a) aged 9 years or aged 12 years, b) right handedness, c) German-speaking, d) psychiatric and neurological health, e) birth weight > 2000 g, f) gestational age ≥ 36 weeks' gestation, g) no intellectual disability (IQ ≥ 80) or developmental disorders (e.g. dyslexia), h) no dental braces, i) no twins, and j) no siblings of participants. Due to not fulfilling the inclusion criteria, n = 79 children and adolescents were not invited to participate in assessments (n = 43 (18.9 %) did not fulfill age criteria, n = 6 (2.6 %) left-handed, n = 5 (2.2 %) preterm, n = 8 (3.5 %) dyslexia, n = 9 (3.9 %) dental braces, n = 3 (1.3 %) twins or sibling already included in study, n = 5 (2.2 %) psychiatric diagnoses or in therapy). Further, another n = 24 (10.5 %) dropped out after the screening, before the first assessment took place (n = 2 (0.9 %) difficulties finding date for participation, n = 7 (3.1 %) did not want to participate anymore and n = 15 (6.6 %) were not reachable anymore). Consequently, n = 125 participants took part in the time point 1 (TP1) assessments. While at TP1 n = 125 took part in the interviews, n = 116 participated in the MRI session (n = 116 had T_1 imaging and n = 113 DTI). After TP1, n = 14 individuals dropped out, with n = 111 undergoing interviews and n = 97 taking part in MRI (n = 97 T_1 and n = 91 DTI) at TP2. After TP2, n = 5 adolescents dropped out, leaving n = 106 adolescents to participate in interviews and n = 84 in MRI at TP3 (n = 84 T_1 and n = 82 DTI). The sample used for the current study consisted of n = 112 individuals, each of whom had participated in at least two cognitive assessments. Of those, n = 109 took part in at least one MRI exam, while n = 3 participants did not want to participate in any MRI session. In total, n = 275 scans were usable for extraction of DTI data. In n = 54 cases across all time-points, no DTI scans were available, due to the following reasons: withdrawal due to loss of interest (n = 13, 4.0 %), no-show for appointments (n = 3, 0.9 %), not possible to find date (n = 1, 0.3 %), dental braces at follow-up (n = 18, 5.5 %), piercing (n = 2, 0.6 %), excessive in-scanner movement (n = 2, 0.6 %), termination due to feeling sick (n = 1, 0.3 %), claustrophobia during scan (n = 2, 0.2 %), failure in data storage (n = 1, 0.3 %), damaged data (n = 1, 0.3 %), diffusion scans were not of sufficient quality (n = 8, 2.4 %), incomplete acquisition of diffusion images (n = 1, 0.3 %), reason not documented (n = 1, 0.3 %).

2.3. Clinical and cognitive assessment

Psychiatric disorders were ruled out by conducting the Mini-International Neuropsychiatric Interview (M.I.N.I) for Children and Adolescents (Sheehan et al., 1998, 2010). IQ was estimated using the General Ability Index from the Wechsler Intelligence Scale for Children, German Version (Wechsler, 2003) consisting of the six core subtests of the Verbal Comprehension Index and the Perceptual Reasoning Index (Prifitera et al., 2005). All participants were right-handed, as determined by the Edinburgh handedness scale.

Four tasks were selected from the Cambridge Neuropsychological Test Automated Battery (CANTAB) (CANTAB®, 2018), which was administered by trained research assistants. The approximate duration to administer the four tasks was 45−60 min. These particular tasks were selected because they tap cognitive functions undergoing substantial development during adolescence and as such are likely sensitive to concomitant changes of the white matter microstructure.

2.3.1. Stop signal task

The stop signal task was used to assess the ability to inhibit a response. Participants are asked to respond as quickly as possible to an arrow stimulus by indicating per button press in which direction the arrow points. On some trials, an auditory "stop signal" (beep) occurs after presentation of the arrow, which notifies the participant to withhold their response and not press any buttons. A procedure is applied to track the participants' performance, by varying the stop signal delay (SSD) parameter after successful and unsuccessful stop attempts. Over time, this tracking procedure stabilizes the probability of successful inhibition around 0.5 for each subject. The variable of interest was a measure of the speed of the inhibitory process, namely the stop signal reaction time (SSRT), defined as the mean SSD subtracted from the mean go trial reaction time (ms), where shorter SSRT indicates better performance.

2.3.2. Stockings of Cambridge task

The stockings of Cambridge task was used to assess spatial planning. Participants are presented with a horizontally split screen and instructed to move the colored balls in the lower display, to match the pattern of colored balls in the upper display. Difficulty slowly increases from a minimum of two moves, to a minimum of five moves required to copy the pattern. The variable of interest is the number of problems solved in the minimum required moves, where better performance is reflected by a higher number of problems solved.

2.3.3. Emotion recognition task

The emotion recognition task assesses the ability to identify six basic emotions in facial expressions. The participant is presented with computer-morphed images derived from the facial features of real individuals, each displaying one specific emotion (sadness, happiness, fear, anger, disgust or surprise). After each trial, the participant makes a forced choice out of the six emotions. The variable of interest is the percentage of correct answers, where a higher number reflected better emotion recognition.

2.3.4. Cambridge gambling task

The Cambridge gambling task was used to assess risk-taking. On each trial of the task, the participant is presented with a row of ten boxes across the top of the screen, some of which are red and some of which are blue, with proportions varying in each trial. The participant is asked to guess whether a yellow token is hidden in a red or a blue box. Participants start with a number of points and must try to accumulate as many points as possible during the task. Depending on their confidence in the respective trial, the participant can select a proportion of their points, which are displayed in either rising or falling order. The variable of interest in this task was risk-taking, operationalized as the average proportion of points the subject bet on trials where the more likely outcome was chosen. Higher scores indicate higher willingness to taking risk.

For all tasks, observations containing outliers (performance below or above 3 standard deviations [SD] from the mean) were excluded from further analyses. For inhibition, n = 6 (1.9 %) observations with scores > + 3SD from the mean (slow performance, i.e. poor inhibition) and for risk-taking, n = 3 (0.9 %) observations with scores > +3SD (high willingness to take risks) were excluded. For emotion recognition, n = 1 (0.3 %) observation with a score <-3SD (bad performance) was excluded. No outliers were found in spatial planning. After removal of outliers, z-scores were calculated for each of the neuropsychological variables. Sensitivity analyses including outliers resulted in identical results on a level of two decimal places.

2.4. MRI acquisition

Whole brain images were acquired on a 3 T Siemens Magnetom Biograph system with a 16-channel head coil, at the Division of Radiography at the German Cancer Research Centre in Heidelberg, Germany. A T_1 -weighted MPRAGE sequence with repetition time (TR) =2300 ms, echo time (TE) =2.98 ms, field of view 256 mm, voxel size = 1 × 1 × 1 mm (Wüstenberg et al., 2012), acquisition matrix 256, flip angle 9° was acquired. An echo planar diffusion sequence was acquired with TR = 12, 100 ms, TE =112 ms, field of view = 240 mm, acquisition matrix 240, slice thickness 2.5 mm, with 64 gradient directions with b-values up to 3000 s/mm (Meltzer, 2007).

2.5. Image processing

DTI data were visually checked for quality assurance. Images were processed using TRActs Constrained by UnderLying Anatomy (TRACULA), as implemented in FreeSurfer 6.0 (Yendiki et al., 2011). TRACULA performs global probabilistic tractography with anatomical priors, using a participant's diffusion MRI data and cortical and subcortical segmentation labels from FreeSurfer (Fischl et al., 2002, 2004a; Fischl et al., 2004b). The software uses prior information of anatomical knowledge on white matter pathways from a set of healthy adult training participants. This prior information expresses the probability of each tract to pass through or lie adjacent to each of the anatomical segmentation labels from the cortical parcellation and subcortical segmentation of T_1-weighted MPRAGE images in FreeSurfer, calculated separately for every point along the pathway's trajectory. Further, TRACULA estimates the posterior probability of each tract, comprising a likelihood term which fits the tract to the diffusion orientations obtained from a ball-and-stick model of diffusion (Behrens et al., 2007). The output is a probabilistic distribution for each of the reconstructed tracts, derived in the individual diffusion space rather than transformed from an average brain space (Yendiki et al., 2014). TRACULA enables the reliable automated reconstruction of pathways, facilitating analysis of large data sets (Fischl et al., 2004b).

The above mentioned procedure allows the extraction of tensor-based measures (FA, axial diffusivity [AD], radial diffusivity [RD] and MD) for each of the reconstructed pathways (for a detailed description of the tracts, see (Wakana et al., 2007)). For the purpose of the present study, we examined FA and MD of the following tracts: L/R anterior thalamic radiation (ATR), L/R cingulum-cingulate gyrus bundle (CCG), L/R cingulum-angular bundle (CAB), L/R superior longitudinal fasciculus-parietal bundle (SLFp), L/R superior longitudinal fasciculus-temporal bundle (SLFt) and L/R uncinate fasciculus (UNC). As no specific hypotheses regarding laterality existed, values of the left and right tracts were averaged to reflect a mean FA/MD score for each tract. This approach was chosen because based on the previous literature and theoretical reasoning, we had no specific hypotheses regarding the laterality of effects. Further, this approach served to reduce the number of statistical comparisons and hence, to reduce type I error. Z-scores were calculated for each FA and MD variable.

2.6. Statistical analysis

The first aim was to test whether age was related to the development of inhibition, spatial planning, emotion recognition and risk-taking performance between 9 and 16 years. The second aim was to examine whether white matter microstructure (FA and MD) in defined tracts was related to the development of cognitive performance across age. All analyses were conducted in R version 3.5.1 (https://www.r-project.org/). Analyses were performed using mixed-effects models with the nlme package (version 3.1–137) implemented in R version 3.5.1 (Pinheiro et al., 2013) estimating the fixed effects of age on each measure, with nested random effects terms modeled for within person dependence of observations. All mixed-models followed a formal model-fitting procedure (Barr et al., 2013). That is, we started with a null model that only included a random intercept to allow for individual differences in starting points and account for the repeated nature of the data. The null model was then compared against two additional models that tested the grand mean trajectory of age. These models were created by adding two polynomial terms (linear and quadratic; mean-centered) for age to the null model. The best fitting model was determined by the Akaike Information Criterion (AIC (Akaike, 1974)), the Bayesian Information Criterion (BIC (Schwarz, 1978)) and log likelihood ratio (LR) statistics, in a step wise procedure, i.e. Model 1 (linear age) was compared to the null model; if Model 1 showed a better fit, it was compared to Model 2 (quadratic age). The model with the lowest AIC and BIC values that was also significantly different (as determined by LR tests $p < 0.05$) from the less complex models was chosen.

To test whether FA and MD improved the model fit beyond the effect of age, we used LR statistics to compare models including either FA or MD for each of the tracts (ATR, CCG, CAB, SLFp, SLFt and UNC) separately. FA or MD of the respective tract were added to Model 1 or Model 2 and compared to the less complex models including only age terms. To control for multiple comparisons, we divided the alpha level for these analyses by the number of tracts to 0.008. All analyses included the effects of cohort and sex as control variables. Additionally, interaction effects of sex and age were tested due to the known influence of sex on brain development. Interpretation of our findings was based on overall patterns and magnitudes of associations, rather than p-values alone (Wasserstein and Lazar, 2016). Our analysis script is publicly available on the Open Science Framework: https://osf.io/jfwya/.

3. Results

3.1. Participants

Participant characteristics for the three study time points are reported in Table 1 for both cohorts separately. We observed developmental increases in age and BMI. IQ was only assessed at TP1. Of the 112 participants, 47 % were female (n = 53), and 53 % were male (n = 59).

3.2. Relationships between neuropsychological functioning and age

Model comparisons between the null, linear and quadratic age models are presented in Table 2. Individual variability in intercepts was evident across all neuropsychological domains (Fig. 1). The relationship between inhibition and age was best explained by a linear model (Table 2; BIC diff. from Model 0 = 86.4, Likelihood Ratio [LR] = 74.1). The results of this model suggest that, on average, each yearly increase in age across the sample was associated with a decrease of 33.9 (0.36 SD) ms in SSRT (i.e. better inhibition) (Table 3).

The relationship between spatial planning and age was best explained by a linear model (BIC diff. from Model 0 = 18.8, LR = 24.5). The model suggests that on average, each yearly increase in age across the sample, was associated with an increase of 0.47 (0.24 SD) problems solved in the spatial planning task.

The relationship between emotion recognition and age was also best described by a linear model (BIC diff. from Model 0 = 110.6, LR = 116.3). On average, each yearly increase in age across the sample was associated with an increase of 4.1 % (0.41 SD) correct answers in emotion recognition.

The relationship between risk-taking and age was best described by a quadratic model (BIC diff. from Model 1 = 2.4, LR = 8.2). The model suggests that on average, each yearly increase in age was associated with an increase of 0.015 (0.10 SD) in the proportion of points the subject bet in the gambling task, with a positive rate of change (0.04). The graph illustrates that at group level, risk-taking was relatively stable during younger years (9–12), but increased between 12 and 16 years of age (Fig. 1). A main effect of sex indicated that girls were less risk-taking than boys (Table 3). There was no evidence for any interaction between sex and age on any measure of neuropsychological performance.

3.3. Relationships between neuropsychological functioning, white matter microstructure and age

According to the LR tests, including cingulum-angular bundle FA resulted in a better model for emotion recognition performance compared to the age model alone (BIC diff. from Model 1 = 2.8, LR = 8.3), see Table 4. The results of this model suggest that, on average, each SD increase in cingulum-angular bundle FA was associated with an 1.6 % (0.16 SD; b (95 % CI) = 0.16 (0.05, 0.27)) increase of correct answers in the emotion recognition task (see Table S1 for fixed effects estimates of this model). A visualization of the three-way interaction (Fig. 2) as

Table 1
Participant characteristics.

			Cohort 1			Cohort 2		
			TP1	TP2	TP3	TP1	TP2	TP3
		Age [1]	9.61 (0.35)	10.80 (0.39)	11.75 (0.42)	12.60 (0.32)	13.85 (0.40)	14.85 (0.41)
		BMI[2]	16.64 (1.80)	16.92 (1.86)	17.63 (1.93)	17.95 (2.25)	19.47 (3.88)	20.52 (3.79)
Neuropsychology		IQ [3]	119.40 (13.29)	–	–	118.35 (11.92)	–	–
		Inhibition [4]	280.85 (143.55)	212.90 (78.96)	190.53 (77.73)	214.58 (76.64)	172.05 (54.77)	161.78 (51.66)
		Spatial planning [5]	7.19 (1.82)	8.09 (2.03)	8.23 (1.80)	8.74 (1.94)	9.21 (1.62)	9.73 (1.60)
		Emotion recognition[6]	55.28 (9.10)	61.78 (8.38)	64.65 (9.08)	60.74 (9.10)	66.40 (10.05)	68.40 (8.01)
		Risk-taking [6]	0.54 (0.18)	0.54 (0.17)	0.55 (0.15)	0.51 (0.14)	0.54 (0.12)	0.59 (0.12)
White matter	FA [7]	Anterior thalamic radiation	0.45 (0.03)	0.46 (0.03)	0.46 (0.03)	0.48 (0.03)	0.48 (0.03)	0.49 (0.02)
		Cingulate gyrus	0.55 (0.06)	0.57 (0.04)	0.58 (0.04)	0.58 (0.05)	0.59 (0.04)	0.61 (0.04)
		Cingulum angular bundle	0.30 (0.04)	0.29 (0.03)	0.28 (0.04)	0.30 (0.03)	0.30 (0.04)	0.29 (0.04)
		Parietal sup. long. fasciculus	0.44 (0.03)	0.45 (0.03)	0.46 (0.03)	0.47 (0.03)	0.48 (0.03)	0.48 (0.02)
		Temporal sup. long. fasciculus	0.47 (0.03)	0.48 (0.03)	0.48 (0.02)	0.50 (0.03)	0.50 (0.02)	0.48 (0.02)
		Uncinate fasciculus	0.40 (0.03)	0.41 (0.03)	0.41 (0.03)	0.42 (0.03)	0.43 (0.02)	0.42 (0.02)
	MD[7]	Anterior thalamic radiation	0.44 (0.02)	0.44 (0.01)	0.44 (0.02)	0.43 (0.02)	0.43 (0.01)	0.43 (0.01)
		Cingulate gyrus	0.44 (0.02)	0.43 (0.01)	0.43 (0.02)	0.42 (0.02)	0.53 (0.02)	0.42 (0.02)
		Cingulum angular bundle	0.55 (0.02)	0.55 (0.02)	0.55 (0.02)	0.54 (0.02)	0.39 (0.01)	0.53 (0.02)
		Parietal sup. long. fasciculus	0.42 (0.02)	0.41 (0.02)	0.40 (0.01)	0.40 (0.02)	0.40 (0.01)	0.39 (0.01)
		Temporal sup. long. fasciculus	0.43 (0.02)	0.42 (0.02)	0.42 (0.02)	0.41 (0.01)	0.40 (0.01)	0.40 (0.01)
		Uncinate fasciculus	0.51 (0.02)	0.51 (0.02)	0.50 (0.02)	0.48 (0.02)	0.49 (0.01)	0.50 (0.02)

Note. Values are means and standard deviations in parentheses, for unstandardized variables. FA = Fractional anisotropy, MD = Mean diffusivity. MD in 10^{-3} mm^2/s, FA is a unitless ratio (range 0–1). Higher values in inhibition reflect worse performance. Higher values in risk-taking reflect higher proneness to taking risks. Higher values in spatial planning and emotion recognition reflect better performance.
[1] $n_{TP1} = 112$, $n_{T2} = 111$, $n_{T3} = 106$.
[2] $n_{TP1} = 101$, $n_{TP2} = 107$, $n_{TP3} = 102$.
[3] $n_{TP1} = 112$.
[4] $n_{TP1} = 112$, $n_{TP2} = 111$, $n_{TP3} = 101$.
[5] $n_{TP1} = 111$, $n_{TP2} = 110$, $n_{TP3} = 101$.
[6] $n_{TP1} = 112$, $n_{TP2} = 110$, $n_{TP3} = 101$.
[7] $n_{TP1} = 105$, $n_{TP2} = 88$, $n_{TP3} = 82$.

Table 2
Comparison of polynomial age models for each neuropsychological function.

		Model	df	AIC	BIC	BIC diff.*	logLik	Vs. Model 0		Vs. Model 1 (linear age)	
								L. Ratio	p-value	L. Ratio	p-value
Inhibition	Null model	0	5	843.3	862.1		−416.6				
	Linear age	1	6	771.1	793.7	86.4	−379.6	74.1	<.0001		
	Quadratic age	2	7	772.9	799.3	−5.6	−379.5	74.3	<.0001	0.2	0.655
Spatial planning	Null model	0	5	836.3	855.0		−413.2				
	Linear age	1	6	813.8	836.2	18.8	−400.9	24.5	<.0001		
	Quadratic age	2	7	815.6	841.8	−5.6	−400.8	24.7	<.0001	0.2	0.676
Emotion recognition	Null model	0	5	828.7	847.5		−409.4				
	Linear age	1	6	714.4	736.9	110.6	−351.2	116.3	<.0001		
	Quadratic age	2	7	714.4	740.8	−3.9	−350.2	118.3	<.0001	1.9	0.164
Risk-taking	Null model	0	5	818.6	837.5		−404.3				
	Linear age	1	6	812.2	834.8	2.7	−400.1	8.4	0.004		
	Quadratic age	2	7	806.0	832.4	2.4	−396.0	16.6	0.0002	8.2	0.004

Note. All models are computed including cohort and sex as control variables. df = Numerator degrees of freedom, AIC = Akaike Information Criterion, BIC = Bayesian Information Criterion, logLik = Log-Likelihood, L. Ratio = Likelihood ratio.
* Difference in BIC compared to the less complex model.

well as a comparison with the estimates of age (b (95 % CI) = 0.46 (0.39, 0.54)) and sex (b (95 % CI) = 0.38 (0.09, 0.68)) however, show that the effect of FA was rather weak.

Including parietal superior longitudinal fasciculus FA also improved the model beyond the effect of age alone (BIC diff. from Model 1 = 7.5, LR = 13.1). The model suggests that on average, each SD increase in parietal superior longitudinal fasciculus FA was associated with a 2.3 % (0.23 SD; b (95 % CI) = 0.23 (0.11, 0.36)) increase of correct answers in the emotion recognition task (see Table S2 for fixed effects estimates of this model). However, compared to the effect of age (b (95 % CI) = 0.40 (0.33, 0.47)) and sex (b (95 % CI) = 0.42 (0.12, 0.71)), the effect of FA was weak.

After Bonferroni correction, there was no evidence that FA or MD of any of the white matter tracts was related to inhibition, risk-taking or spatial planning across age (Table 4). Over all domains, there was no evidence for any interaction between sex and FA/MD on neuropsychological performance.

Latent growth curve models were additionally computed and yielded the same pattern of results.

4. Discussion

This study aimed at investigating normative longitudinal trajectories of inhibition, planning, emotion recognition and risk-taking and potential associations with white matter microstructure in a sample of 9–16 year-old adolescents. In an accelerated longitudinal cohort design, we used mixed-effects modelling to determine trajectories of neuropsychological development and FA as well as MD in six limbic and fronto-temporal white-matter tracts.

In our study, we found increases in inhibition, planning and emotion

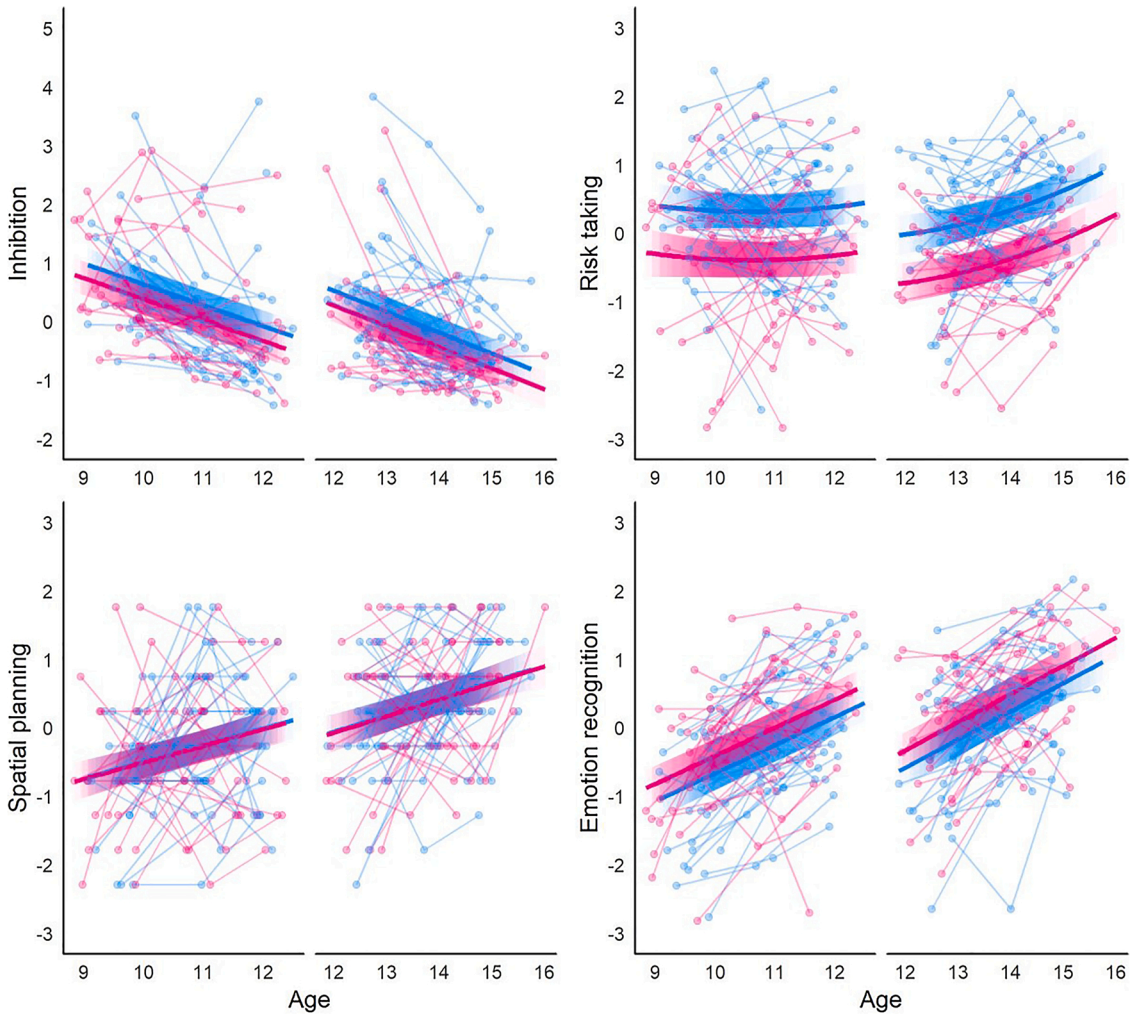

Fig. 1. Best fitting models for relationships between neuropsychological functioning and age. The line represents the predicted model fit and shading represents the 95 % confidence intervals. Raw data are plotted in the background, with each individual measurement represented by a circle and lines connecting data collected from the same individual across time. Female data is presented in pink and male data is presented in blue (z-standardized scores shown). Higher values in inhibition reflect worse performance. Higher values in risk-taking reflect higher proneness to taking risks. Higher values in spatial planning and emotion recognition reflect better performance.

Table 3
Fixed effects of best fitting models for neuropsychological functioning across age.

	Best fitting model	Intercept Estimate (95 % CI)	Linear age Estimate (95 % CI)	Quadratic age Estimate (95 % CI)	Sex Estimate (95 % CI)[a]	Cohort Estimate (95 % CI)[b]
Inhibition	1 - linear	0.53 (0.25, 0.81)	−0.36 (-0.43, -0.28)		−0.25 (-0.55, 0.05)	−0.61 (-0.98, -0.24)
Spatial planning	1 - linear	−0.06 (-0.33, 0.21)	0.24 (0.15, 0.34)		−0.01 (-0.27, 0.24)	0.05 (-0.33, 0.43)
Emotion recognition	1 - linear	−0.58 (-0.84, -0.31)	0.41 (0.34, 0.48)		0.25 (-0.03, 0.53)	0.74 (0.40, 1.08)
Risk-taking	2 - quadratic	−0.01 (-0.30, 0.27)	0.10 (0.02, 0.18)	0.04 (0.01, 0.06)	−0.71 (-0.99, -0.42)	0.40 (0.02, 0.78)

Note. Estimates ('betas') with 95 % confidence intervals (CI) of the best fitting models, z-standardized scores are presented.
[a] Positive estimate = higher values in girls, negative estimate = higher values in boys.
[b] Positive estimate = higher values in cohort 1, negative estimate = higher values in cohort 2. Higher values in inhibition reflect worse performance. Higher values in risk-taking reflect higher proneness to taking risks. Higher values in spatial planning and emotion recognition reflect better performance.

recognition performance as well as risk-taking from age 9–16. This is in agreement with the few previous longitudinal studies spanning cognitive development from early childhood up to adulthood (Watling and Damaskinou, 2018; Troller-Renfree et al., 2019; Ordaz et al., 2013; Frischkorn et al., 2014; Braams et al., 2015; Peper et al., 2018), and further reflects what has been suggested by numerous cross-sectional studies. One advantage of longitudinal studies is the potential to test for nonlinear developmental trajectories, which has rarely been done in the aforementioned studies. We found that in our sample of 9–16 year-old adolescents, linear relationships proved to describe the trajectories of inhibition, planning and emotion recognition best. For risk-taking, a quadratic relationship described the data best, with relatively stable performance in younger years (9–12) and a steady increase in later adolescence (12–16 years). However, the quadratic model did not outperform the simpler linear model considerably. It is possible that more complex nonlinear patterns of change might be visible in studies

Table 4
Model comparisons for models including FA or MD in association with neuropsychological performance across age.

			Model	df	AIC	BIC	BIC diff.[1]	logLik	Vs. Model 0		Vs. Model 1 [2]	
									L. Ratio	p	L. Ratio	p
Inhibition		Null model	0	5	712.1	730.0		−351.0				
		Linear age	1	6	651.0	672.5	57.5	−319.5	63.1	<.0001		
	FA	ATR		7	652.2	677.3	−4.8	−319.1	63.8	<.0001	0.8	0.384
		CCG		7	651.9	677.0	−4.5	−318.9	64.2	<.0001	1.1	0.297
		CAB		7	648.6	673.7	−1.2	−317.3	67.5	<.0001	4.4	0.036
		SLFp		7	648.7	673.8	−1.3	−317.3	67.4	<.0001	4.3	0.037
		SLFt		7	649.5	674.6	−2.1	−317.7	66.6	<.0001	3.5	0.061
		UNC		7	649.8	674.9	−2.4	−317.9	66.3	<.0001	3.2	0.073
	MD	ATR		7	652.7	677.8	−5.3	−319.4	63.4	<.0001	0.3	0.598
		CCG		7	652.5	677.5	−5	−319.2	63.6	<.0001	0.5	0.467
		CAB		7	652.7	677.8	−5.3	−319.3	63.4	<.0001	0.3	0.595
		SLFp		7	652.1	677.2	−4.7	−319.1	64.0	<.0001	0.9	0.348
		SLFt		7	651.7	676.7	−4.2	−318.8	64.4	<.0001	1.3	0.249
		UNC		7	652.5	677.6	−5.1	−319.3	63.5	<.0001	0.5	0.495
Spatial planning		Null model	0	5	713.9	731.7		−352.0				
		Linear age	1	6	692.3	713.6	18.1	−340.1	23.6	<.0001		
	FA	ATR		7	693.4	718.3	−4.7	−339.7	24.5	<.0001	0.9	0.353
		CCG		7	694.0	718.9	−5.3	−340.0	23.9	<.0001	0.2	0.621
		CAB		7	693.6	718.4	−4.8	−339.8	24.3	<.0001	0.7	0.409
		SLFp		7	691.3	716.2	−2.6	−338.7	26.6	<.0001	3.0	0.085
		SLFt		7	693.6	718.5	−4.9	−339.8	24.3	<.0001	0.7	0.399
		UNC		7	694.0	718.9	−5.3	−340.0	23.9	<.0001	0.2	0.618
	MD	ATR		7	694.2	719.1	−5.5	−340.1	23.7	<.0001	0.1	0.759
		CCG		7	693.9	718.8	−5.2	−340.0	24.0	<.0001	0.4	0.551
		CAB		7	694.1	719.0	−5.4	−340.1	23.8	<.0001	0.2	0.683
		SLFp		7	693.4	718.3	−4.7	−339.7	24.5	<.0001	0.9	0.345
		SLFt		7	694.0	718.9	−5.3	−340.0	23.9	<.0001	0.2	0.623
		UNC		7	694.3	719.2	−5.6	−340.1	23.6	<.0001	0.0	0.916
Emotion recognition		Null model	0	5	706.6	724.5		−348.3				
		Linear age	1	6	602.1	623.6	100.9	−295.0	106.5	<.0001		
	FA	ATR		7	603.3	628.4	−4.8	−294.6	107.3	<.0001	0.8	0.378
		CCG		7	603.4	628.5	−4.9	−294.7	107.2	<.0001	0.7	0.412
		CAB		7	595.7	620.8	2.8	−290.9	114.9	<.0001	8.3	0.004
		SLFp		7	591.0	616.1	7.5	−288.5	119.6	<.0001	13.1	0.0003
		SLFt		7	601.3	626.4	−2.8	−293.6	109.3	<.0001	2.8	0.095
		UNC		7	601.5	626.6	−3	−293.7	109.1	<.0001	2.6	0.108
	MD	ATR		7	602.4	627.5	−3.9	−294.2	108.2	<.0001	1.7	0.198
		CCG		7	601.7	626.8	−3.2	−293.8	108.9	<.0001	2.4	0.122
		CAB		7	601.3	626.4	−2.8	−293.6	109.3	<.0001	2.8	0.094
		SLFp		7	598.6	623.7	−0.1	−292.3	112.0	<.0001	5.5	0.019
		SLFt		7	602.2	627.3	−3.7	−294.1	108.4	<.0001	1.8	0.176
		UNC		7	600.7	625.8	−2.2	−293.3	109.9	<.0001	3.4	0.065
Risk-taking		Null model	0	5	690.2	708.2		−340.1				
		Quadratic age	2	7	680.1	705.3	2.9	−333.0	14.1	0.001		
	FA	ATR		8	680.7	709.5	−4.2	−332.4	15.4	0.002	1.4	0.243
		CCG		8	681.5	710.3	−5	−332.7	14.7	0.002	0.6	0.427
		CAB		8	681.9	710.7	−5.4	−332.9	14.3	0.003	0.2	0.651
		SLFp		8	680.5	709.3	−4	−332.2	15.7	0.001	1.6	0.206
		SLFt		8	680.5	709.3	−4	−332.2	15.7	0.001	1.0	0.328
		UNC		8	681.6	710.4	−5.1	−332.8	14.5	0.002	0.5	0.497
	MD	ATR		8	679.4	708.1	−2.8	−331.7	16.8	0.001	2.7	0.098
		CCG		8	681.1	709.9	−4.6	−332.6	15.0	0.002	1.0	0.325
		CAB		8	682.0	710.8	−5.5	−333.0	14.2	0.003	0.1	0.765
		SLFp		8	681.0	709.8	−4.5	−332.5	15.2	0.002	1.1	0.292
		SLFt		8	681.7	710.5	−5.2	−332.9	14.4	0.002	0.4	0.540
		UNC		8	681.7	710.5	−5.2	−332.9	14.4	0.002	0.3	0.547

Note. df = Numerator degrees of freedom, AIC = Akaike Information Criterion, BIC = Bayesian Information Criterion, logLik = Log-Likelihood, L. Ratio = Likelihood ratio.
[1] Difference in BIC compared to the less complex model.
[2] Comparison against model 2 in the case of risk-taking. Z-standardized scores shown.

covering a larger age range (Achterberg et al., 2016). We found that boys were more prone to risk-taking than girls, which is in line with consistent reports of sex differences in risk-taking across adolescence (Crone et al., 2016). Parallel slopes indicated similar rates of change in girls and boys over time.

We found some evidence that including FA improved model fit for describing the development of emotion recognition beyond the age effect. An increase in cingulum FA as well as superior longitudinal fasciculus FA was related with an increase of emotion recognition. The cingulum and superior longitudinal fasciculus are fronto-temporal tracts both of which have been implicated in higher-order cognitive processes and play a prominent role in emotion processing (Lebel et al., 2012; Catani et al., 2007; Parker et al., 2005). Those tracts have been shown to mature rapidly during early childhood (Reynolds et al., 2019), adolescence and adulthood (Lebel et al., 2012) and show the most prolonged development, with late peaks of FA (around age 40) compared to callosal fibers, the fornix or inferior longitudinal fasciculi (Lebel et al., 2012). While the effects of FA were weak, i.e. the models including FA were not considerably superior in explaining neuropsychological development than the age only model, our results suggest some

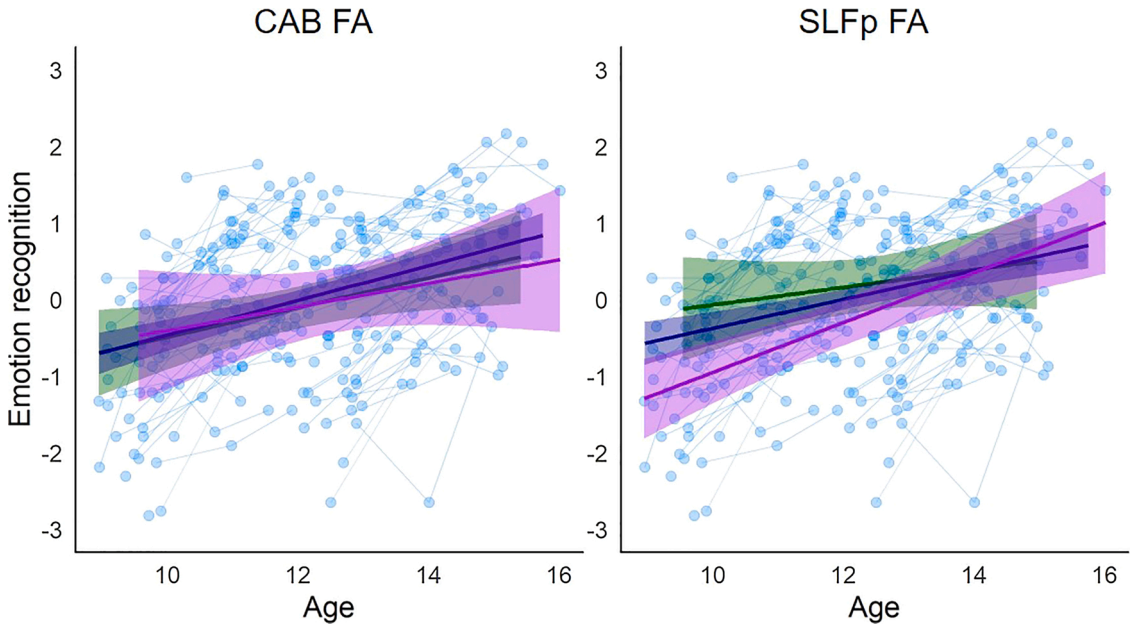

Fig. 2. Relationship between emotion recognition, age and cingulum angular bundle (CAB) and parietal superior longitudinal fasciculus (SLFp) FA. For the purpose of clarity, the variable of FA was grouped into three categories, although continuous analyses were performed: Green fit line represents predicted neuropsychological performance for an individual with +1 standard deviation (SD) FA from the mean; dark blue: mean FA; purple -1 SD FA from mean. Note that data from two separate cohorts is presented on a continuous age scale for illustration reasons. Raw data are plotted in the background, with each individual measurement represented by a circle and lines connecting data collected from the same individual across time. Higher values in emotion recognition reflect better performance. Note that the three fit lines with corresponding confidence intervals have similar starting points and overlap in large parts. This indicates that associations between emotion recognition and age are similar for varying degrees of FA.

predictive value of FA changes in these tracts. Interestingly, the superior longitudinal fasciculus has been suggested to play a role in psychiatric mood disorders typically emerging during adolescence, in schizophrenia and bipolar disorder, as well as in autism spectrum disorder (Kubicki et al., 2007; Libero et al., 2016). To the best of our knowledge this is the first study to report longitudinal associations between white matter microstructure and emotion recognition in adolescents.

Overall, in our study, FA was only weakly related to neuropsychological performance across age. Cross-sectional studies examining relationships between cognitive development and white matter microstructure in children, have mostly related better performance to increased FA and decreased MD (Walton et al., 2018; Van Beek et al., 2014; Vanderauwera et al., 2015; Nagy et al., 2004; Liston et al., 2006). It has often been suggested that higher FA and lower MD are reflective of more mature microstructural organization of white matter fiber tracts, and support better outcomes in children and adolescents. Up to now, however, few longitudinal studies have started to shed light on the question whether white matter microstructure maturation is related to higher-order cognitive development above and beyond the effect of ageing alone (Krogsrud et al., 2018; Achterberg et al., 2016). As an example, in a delay of gratification task, a faster development of reward-related impulse control was related with greater fronto-striatal FA Achterberg et al., 2016). In contrast, our study provides little evidence for white matter microstructure maturation to be associated with the development of inhibition: Increases in cingulum and superior longitudinal fasciculus FA were only weakly associated with the development of inhibition (with effect sizes of 0.13 and 0.15 SD). Overall, our results therefore question the contribution of white matter microstructure to neuropsychological development above age. However, the weak evidence in our study does not necessarily imply that white matter microstructure is weakly related to cognitive development in general. As is the case in any study, our findings are specific to the methodology we chose; e.g. the intervals between assessments might have been too large to detect peaks of white matter microstructural development potentially responsible for cognitive change (King et al., 2018). Even if we had found strong associations between our neuropsychological and brain structural measures, conclusions about the temporal dynamics of these changes would be difficult and concomitant cognitive and brain structural changes might be influenced by a third variable, e.g. a certain pattern of gene expression (Kievit et al., 2019). Needless to say, white matter microstructural changes may be associated more strongly with neuropsychological development in patients with psychiatric or neurological disorders. In this study, however, only typically developing adolescents in good psychiatric and neurological health, without intellectual disabilities, developmental disorders or preterm birth were included, which might have contributed to the weak effects. Hence, due to the limited amount of reports on longitudinal associations in healthy development, at this stage, conclusions are premature. Further, there is considerable methodological diversity in existing studies, complicating the integration of findings (Geeraert et al., 2019).

More findings on the association between higher-order cognitive development and brain maturation have been reported from studies examining grey matter maturation or the development of functional networks. The development of inhibitory control has been associated with age-related changes in prefrontal cortex and anterior cingulate cortex activity (Casey, 2015; Constantinidis and Luna, 2019). Activation increases in dorsal anterior cingulate cortex during error-processing in an anti-saccade task mediated developmental improvements in inhibition performance from childhood to early adulthood (Ordaz et al., 2013). Individual differences in functional brain connectivity (resting-state functional MRI) within and between regions of the cognitive control network (anterior cingulate cortex, prefrontal cortex, inferior frontal gyrus) and the valuation network (nucleus accumbens, pallidum, amygdala, medial orbitofrontal cortex, posterior cingulate cortex) were reported to account for variance in reward-related inhibition performance (delay discounting) (Anandakumar et al., 2018). A graph theory approach demonstrated that network integration (links to foreign networks, as opposed to within networks) of the salience network (cingulo-opercular regions) moderated the development of inhibition, with higher cross-network integration in the salience network and faster

development of inhibition (Marek et al., 2015). Risk-taking in adolescents measured with the Balloon Analogue Risk-taking Task (BART) was associated with grey matter volume growth in the medial orbitofrontal cortex such that a relatively fast development decreased risk-taking in girls, but increased risk-taking in boys, reflecting sex differences in the way the orbitofrontal cortex accounts for variance in risk-taking development (Peper et al., 2013). Less thinning of the orbitofrontal cortex also related to greater driving-related risk behaviors ('DRIVE' survey) at late adolescence (Vijayakumar et al., 2019). There has been increased interest in how trajectories of cortical thickness relate to cognitive development. Greater as well as less cortical thinning has been related to better cognitive functioning, which might be due to the age range studied, as faster rates of thinning might be advantageous in some age ranges but not others (Vijayakumar et al., 2018). Recognizing emotions from faces involves brain regions underlying perceptual processes, emotional reactions and conceptual knowledge of the emotion displayed. As such, the occipito-temporal cortex (fusiform gyrus), amygdala, orbitofrontal cortex, basal ganglia and parietal cortex are involved in adult emotion recognition (Adolphs, 2002). However, how the development of this ability during childhood and adolescence relates to brain maturation has received less attention (see Kilford et al., 2016 for a review on the 'social brain' in adolescence and neural correlates of basic face-processing, mentalizing, and perspective-taking).

As the findings from volumetric and resting-state functional MRI studies illustrate, multiple brain regions are simultaneously involved and interact to ensure efficient information processing underlying neuropsychological function. Therefore, to elucidate how white matter maturation contributes to neuropsychological development, network approaches might be more informative (Kim et al., 2016). Graph theory examines global and local brain network properties by metrics reflecting identification and quantification of network efficiency, organization and key regions (so-called hubs) within the network (Bullmore and Sporns, 2009; Sporns, 2014). While our approach was to examine individual tracts of interest, identifying an entire white matter fiber architecture might yield important insights in the contribution of white matter microstructure to neuropsychological development in adolescence.

4.1. Limitations

This study has several strengths including a three-wave longitudinal design, MRI scanning at one site, and assessment of four important neuropsychological aspects of adolescent development with a low attrition rate. We also acknowledge some limitations.

One important limitation is the inherent challenge of inferring underlying biological substrates from changes in the diffusion parameters studied in the current paper, as it is not possible to attribute any single diffusion parameter to a specific cellular property (Bach et al., 2014; Jones et al., 2013). Numerous factors restrict water diffusion in the white matter, such as axonal myelination, density, diameter and dispersion; and parameters of FA or MD do not differentiate between these factors (Jones et al., 2013). However, more advanced techniques have been developed that allow the examination of white matter microstructure with greater specificity, e.g. Neurite Orientation Dispersion and Density Imaging (NODDI), which assesses neurite orientation dispersion and neurite density (Zhang et al., 2012) or multi-compartment microscopic diffusion imaging based on the Spherical Mean Technique (SMT), which measures neurite density and intrinsic diffusivity, with the effects of neurite orientation dispersion factored out (Kaden et al., 2016). These newer methods might lead to a deeper understanding of the neurobiological relationship between white matter and functional outcomes. Nevertheless, DTI remains an unparalleled in vivo method for exploratory investigations of white matter, but replication of findings is strongly encouraged (Jones et al., 2013).

We used an accelerated cohort longitudinal design, a common approach in developmental neuroimaging studies (Vijayakumar et al., 2018). A drawback of this approach is, that, by design, each participants' measurement covers only part of the age range being studied, so that "missing data" occurs (Galbraith et al., 2017). Besides, cohort effects cannot be completely ruled out. To alleviate this problem, we included cohort as a covariate in all analyses. The obvious advantage of an accelerated longitudinal design is the shorter observational period and therefore reduced research costs. Most importantly, it has been recommended because it reduces attrition compared to longitudinal studies with more time-points (Galbraith et al., 2017).

The few studies examining neuropsychological development in relation to white matter microstructural development longitudinally, have collected data from youth between 8 and 26 (Achterberg et al., 2016) and 8–28 years of age (Simmonds et al., 2014). Compared with these studies, the age range we studied is considerably smaller. Our study covered development from 9–16 years of age, including the important phases of late childhood and early adolescence, in which rapid cognitive development occurs. However, larger age ranges are preferable in longitudinal study designs in order to cover the full spectrum of adolescent development.

5. Conclusion

In conclusion, this study showed longitudinal trajectories of neuropsychological development in four important neuropsychological functions undergoing substantial development during adolescence. Inhibition, planning and emotion recognition abilities improved linearly with age. Risk-taking was stable in early adolescence and increased in later adolescence. Overall, evidence for white matter microstructure to be associated with neuropsychological development across age was weak, with some evidence for tracts involved in higher-order cognitive and emotional processing to be related to the development of emotion recognition. Our results challenge the additional value of white matter microstructural measures to explain neuropsychological development above effects of ageing. Our study thereby adds to the sparse literature on the relationship between neuropsychological functioning and white matter microstructure.

Declaration of Competing Interest

None of the authors has any conflict of interest to declare.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.dcn.2020.100812.

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