

Neuroanatomical correlates of executive functions in children and adolescents: A magnetic resonance imaging (MRI) study of cortical thickness

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ABSTRACT

A range of cognitive abilities improves in childhood and adolescence. It has been proposed that the protracted development of executive functions is related to the relatively late maturation of the prefrontal cortex. However, this has rarely been directly investigated. In this cross-sectional study, 98 healthy children and adolescents (8–19 years old) were tested with six tasks considered to index three frequently postulated executive functions; updating (Keep track and Letter memory), inhibition (Antisaccade and Stroop) and shifting (Plus minus and Trail making). Task performance was then related to magnetic resonance imaging (MRI) measures of cortical thickness. The behavioral results did not indicate any clear organization of the executive function measures in the domains updating, inhibition and shifting. Limitations associated with the use of speed-based scores from the tasks considered to index shifting ability were also indicated. Independently of the effects of age, performance on the Keep track task was associated with thinner cortex bilaterally in clusters encompassing parietal and frontal regions, including the left inferior frontal gyrus, while performance on the Antisaccade task was associated with thinner cortex bilaterally in occipital and parietal regions. Further, levels of performance on the Antisaccade and Stroop tasks were related to estimated rates of cortical maturation in posterior brain regions, but not in the prefrontal cortex. The results from the present study add to previous knowledge about the cortical correlates of executive functions by indicating an important role of posterior cerebral areas in executive development.

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1. Introduction

A range of cognitive abilities improves steeply in late childhood and further, at a slower rate, in adolescence (Luna, Garver, Urban, Lazar, & Sweeney, 2004; Segalowitz & Davies, 2004; Waber et al., 2007). Developmental studies have shown that executive functions have a protracted developmental course relative to many other cognitive functions (Anderson, Anderson, Northam, Jacobs, & Catroppa, 2001; Brocki & Bohlin, 2004; Garon, Bryson, & Smith, 2008; Huizinga, Dolan, & van der Molen, 2006; Romine & Reynolds, 2005; Welsh, 2002). Executive functions are control mechanisms that modulate the operation of other cognitive processes and thus regulate the dynamics of cognition and action (Miyake et al., 2000). Concurrently with the development of executive functions, the brain shows rapid structural maturation. Neuroimaging studies show sustained regional development of the cerebral cor-

tex, subcortical structures and white matter (WM) volume and microstructure from early childhood, throughout adolescence and even into adulthood (Giedd, 2004; Giorgio et al., 2010; Gogtay et al., 2004; Lebel, Walker, Leemans, Phillips, & Beaulieu, 2008; Østby et al., 2009; Shaw et al., 2008; Sowell et al., 2003; Tamnes et al., 2010; Westlye et al., in press). A reasonable hypothesis is that cognitive development is caused partly by the ongoing maturation of the brain. More specifically, the protracted development of executive functions has been tentatively attributed to the relatively late maturation of the prefrontal cortex (Anderson, 2001; Blakemore & Choudhury, 2006; Diamond, 2002; Luna et al., 2004). However, to our knowledge, no studies have directly investigated the relationships between development of executive functions and structural cortical maturation.

An important theoretical issue concerns whether executive functions should be conceptualized as unitary in the sense that they reflect the same core mechanism or ability, or non-unitary, i.e. including distinct sub-functions or sub-components. Three often-postulated sub-functions are updating, inhibition and shifting. Updating concerns the ability to monitor task-relevant incoming information and revise representations held in working mem-

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ory to accommodate new input (Miyake et al., 2000; Morris & Jones, 1990). Inhibition refers to the ability to deliberately suppress or stop dominant, automatic or prepotent responses when necessary (Logan & Cowan, 1984; Miyake et al., 2000). Shifting is conceptualized as the ability to flexibly switch back and forth between multiple tasks, operations or mental sets (Miyake et al., 2000; Rogers & Monsell, 1995). Using confirmatory factor analysis, Miyake et al. (2000) found that these executive functions were moderately correlated, but also clearly separable. A contemporary view is hence that executive functions show both unity and diversity at a cognitive level. A recent twin study indicates a combination of common and specific genetic influences on updating, inhibition and shifting and places executive functions among the most heritable psychological traits (Friedman et al., 2008). Further, a range of studies illustrate the predictive validity of these executive function constructs for other cognitive abilities and real-world performance and problems (Friedman et al., 2006, 2007; Geurts, Verte, Oosterlaan, Roeyers, & Sergeant, 2004; St Clair-Thompson & Gathercole, 2006; van der Sluis, de Jong, & van der Leij, 2007; Willcutt et al., 2001; Young et al., 2009).

Working memory updating and inhibitory control have both been shown to improve throughout childhood and adolescence, while the cost of shifting between tasks likely decreases as children grow older (Huizinga et al., 2006). Differential developmental trajectories have been observed for different executive functions, and adult levels of performance are attained at different ages on different tasks (Anderson, 2002; Anderson et al., 2001; Diamond, 2002; Huizinga et al., 2006; Welsh, 2002). Examining the developmental trends in task performance, Huizinga et al. (2006) found that working memory updating, inhibition and shifting reached adult levels of performance between 11 and 15 years. When analyzing latent variables extracted from confirmatory factor analysis, working memory updating was found to develop into young adulthood whereas shifting attained mature levels during adolescence.

The neural substrates of executive functions were originally assumed to be located in the frontal lobes, since patients with lesions in the anterior part of the brain frequently demonstrated impaired performance on a range of tasks assessing executive functions (Alvarez & Emory, 2006; Collette, Hogge, Salmon, & Van der Linden, 2006). Progress has been made regarding the fractionation of functions within frontal regions, but clear consensus has not yet been reached (Collette et al., 2005; Stuss et al., 2002). Although the importance of the frontal lobes to executive functions is established, neuroimaging and lesion studies suggest that executive functions depend on distributed networks encompassing both frontal and posterior (mainly parietal) associative cortices, as well as subcortical structures and thalamic pathways (Collette et al., 2006; Collette & Van der Linden, 2002; Heyder, Suchan, & Daum, 2004; Jurado & Rosselli, 2007; Sylvester et al., 2003). Knight, Staines, Swick, and Chao (1999) have proposed that prefrontal cortex provides a modulatory influence on basic processes subserved by posterior brain regions, so that performance on executive function tasks depend on both frontal and posterior regions, as well as their coordination. Consistent with this view, a recent diffusion tensor imaging (DTI) study suggests that age-related degradation of cortical association fiber tracts that connect regions of the frontal lobe and posterior association areas are important contributors to the decrease in set-shifting ability observed in aging (Perry et al., 2009).

Little is known about the relationships between executive functions and structural properties of the brain in development. Maturation of both the cerebral cortex (Shaw et al., 2006) and DTI derived measures of WM microstructure (Tamnes et al., *in press*) have been related to intellectual abilities. A recent multimodal imaging study showed that associations between WM microstructure maturation and functional connectivity measures were related

Table 1
Sample characteristics.

Age group (years)	Total	Females	IQ	
	N	N (%)	Mean	SD (range)
08–10	20	7 (35.0)	108.2	10.8 (87–127)
11–13	24	13 (54.2)	106.9	10.9 (92–141)
14–16	26	13 (50.0)	109.6	9.5 (91–124)
17–19	28	15 (53.6)	113.7	10.6 (91–132)
Total	98	48 (49.0)	109.8	10.6 (87–141)

to performance on an inhibition task (Stevens, Skudlarski, Pearlson, & Calhoun, 2009). These studies demonstrate associations between structural brain maturation and higher-order cognitive functions. However, the relationships between executive functions and structural cortical properties in development have not been thoroughly investigated. The aim of the present cross-sectional study was to explore the relationships between different executive functions and cortical thickness in development. 98 healthy participants aged 8–19 years completed a battery of neuropsychological tests considered to predominantly tap the executive functions updating, inhibition and shifting, and performance was related to MRI-derived cortical thickness measures. The main objective was to investigate whether cortical maturation, and more specifically maturation of the prefrontal cortex, was associated with levels of executive functioning. Since cortical maturation in adolescence is associated with thinning and more rapid thinning has been found to be associated with higher levels of general cognitive ability (Shaw et al., 2006), we expected negative relationships between executive functions and cortical thickness, and participants with higher levels of performance to show stronger negative associations between age and cortical thickness.

2. Methods

2.1. Participants

The sample was drawn from the first wave of an ongoing longitudinal research project at the Center for the Study of Human Cognition, University of Oslo (*Neurocognitive Development*). The study was approved by the Regional Ethical Committee of South Norway (REK-Sør). Volunteers were recruited by newspaper advertisements and through local schools and work places. Screening interviews were conducted with parent/guardian and with participants aged 16–19 years. Participants were required to be right handed native Norwegian speakers in the age range 8–19 years, have normal or corrected to normal vision and hearing, not be under psychiatric treatment, not use medicines known to affect central nervous system (CNS) functioning, including psychoactive drugs, and not have injury or disease known to affect CNS function, including neurological or psychiatric illness, or serious head injury. 116 participants satisfied these criteria. Written informed consent was obtained from all participants older than 12 years of age and from parent/guardian of volunteers under 18 years of age. Oral informed consent was given by participants under 12 years of age. For the present study, 4 participants were excluded due to lacking MRI data and 13 participants due to incomplete behavioral data. All subjects' MR scans were examined by a specialist in neuroradiology (P.D.-T.) and required to be deemed free of significant anomalies. One participant was excluded on this basis. For the remaining 98 participants (50 males/48 females), mean age was 14.3 years (SD = 3.4, range = 8.2–19.7). Mean age for males and females were 13.9 (SD = 3.4) and 14.7 (SD = 3.3) years respectively, not significantly different ($t(96) = -1.19, p = .237$). Mean full-scale IQ for the entire sample, as assessed by the Wechsler Abbreviated Scale of Intelligence (WASI) (Wechsler, 1999), was 109.8 (SD = 10.6) and no participants scored below 87. As there are no Norwegian norms available for WASI, the original U.S. norms were used. Demographic and intellectual characteristics of the total sample and classified in subgroups according to age are reported in Table 1. For the analyses of the relationships between general intellectual ability and the executive function measures, a full scale intellectual ability score not adjusted for age was created by averaging the z-transformed raw scores from the four WASI subtests.

2.2. Assessment of executive functions

Cognitive testing and MRI acquisition took place in two sessions. During cognitive testing, participants completed six tasks hypothesized to index one of the three target executive functions updating, inhibition, or shifting. Four of the tasks were adapted from Miyake et al. (2000), namely Keep track (updating), Letter memory

(updating), Antisaccade (inhibition) and Plus minus (shifting). Some modifications to these tasks were done to make them more appropriate for the age-range of the participants in the present study (see descriptions below). Two tasks were from the D-KEFS battery (Delis, Kaplan, & Kramer, 2001), namely Stroop (inhibition) and Trail making (shifting). Task administration was computerized or paper-and-pencil. Computerized procedures were administered using E-prime software (Schneider, Eschman, & Zuccolotto, 2002). Task characteristics were as follows:

2.2.1. Updating

The Keep track task was originally adapted by Miyake et al. (2000) from Yntema (1963). Participants were first shown several target categories on the lower-half of the computer screen. Sixteen words, including 2 or 3 exemplars from each of six possible categories (animals, clothing, colors, countries, fruit, and relatives), were then presented serially in a pseudorandomized order for a duration of 2000 ms per word. The target categories remained on the screen during the trial. The task was to recall the last word presented in each of the target categories. Thus, participants had to continuously update their working memory representations for the target categories. After each trial, participants were asked to recall these words and the task administrator wrote down their responses and encouraged the participant to guess if an insufficient number of words were recalled. Before the task, participants practiced on two trials with two and three target categories respectively. The task itself consisted of four trials with three target categories, four trials with four target categories and one trial with five target categories, for a total of 33 words to be recalled. The percentage of words recalled correctly was the measure of interest. For further analyses, percentage of words recalled correctly was transformed to z-scores.

The Letter memory task was adapted by Miyake et al. (2000) from Morris and Jones (1990). Letters were presented serially for 2000 ms per letter on the computer screen and the task was to recall either the last 3 or 4 letters presented in the list. Only consonants were used and the number of letters presented in each list varied between 5, 7, 9 and 11 across trials in a pseudorandomized manner to ensure that participants would have to continuously update their working memory representations until the end of each trial. To further ensure that the task required working memory updating, the participants were instructed to continuously rehearse the last 3 or 4 letters. The task consisted of 4 trials in which the participants were instructed to recall the last 3 letters presented and 8 trials in which they were instructed to recall the last 4 letters presented, for a total of 44 letters to be recalled. After each trial, participants wrote down their responses on a sheet of paper and were encouraged to guess if an insufficient number of letters were recalled. Before each set of trials, participants practiced on a single trial. The percentage of letters recalled correctly was the measure of interest. For further analyses, percentage of letters recalled correctly was transformed to z-scores.

2.2.2. Inhibition

The Antisaccade task was adapted by Miyake et al. (2000) from Roberts, Hager, and Heron (1994). Here, a fixation point was first presented in the middle of the computer screen for a variable duration (randomly selected from a list of nine values in 250 ms intervals between 100 and 2100 ms). A visual cue, a small black square, was then presented on one side of the screen (left or right) for 225 ms, followed by the presentation of a small black target arrow on the opposite side of the screen for 140 ms. The target arrow was then masked by gray cross-hatching for 200 ms. The task was to indicate the direction of the arrow (left, up, or right) with a button press. A PST Serial Response Box with millisecond accuracy was used. Since the target arrow was presented only briefly before being masked, participants were required to inhibit the reflexive response of looking at the initial cue because doing so would make it more difficult to correctly identify the direction of the target arrow. The task consisted of 18 practice trials and two blocks of 60 target trials each, for a total of 120 target trials. The percentage of target trials answered correctly was the measure of interest. For further analyses, percentage of correct target trials was transformed to z-scores.

The Stroop task (Stroop, 1935) employed was the D-KEFS Color-Word Interference Test (Delis et al., 2001). For the present study, only data from conditions one (Color naming) and three (Inhibition) were used. In the Color naming condition, participants were presented with a sheet of paper with five rows of ten squares, printed in one of three colors (red, blue or green), and were instructed to name the colors one-by-one and row-by-row as fast as possible until finished. In the Inhibition condition, participants were presented with five rows of ten color words ("red", "blue" and "green"), printed in incongruent colors (red, blue or green), and were asked to name the print colors as fast as possible until finished. Participants were thus required to inhibit an overlearned verbal response, i.e. reading the printed words, in order to generate a conflicting response of naming the incongruent ink colors in which the words were printed. Completion time for each condition was measured with a stopwatch. Before each condition, participants practiced on a small number of items. The interference effect was calculated as the ratio between the times to complete the Inhibition condition and Color naming condition. For further analyses, this ratio was transformed to z-scores and inverted to yield a measure of inhibition. In addition, the combined number of both corrected and uncorrected errors on each condition was counted.

2.2.3. Shifting

The Plus-minus task was adapted by Miyake et al. (2000) from Jersild (1927) and Spector and Biederman (1976). Our abbreviated version consisted of three lists of 20 two-digit numbers on a single sheet of paper. The numbers ranged from 10 to 69 and were prerandomized without replacement. On the first list, participants were instructed to add 3 to each number and write down their answers next to the numbers. On the second list, participants were instructed to subtract 3 from each number. Finally, on the third list, participants were instructed to alternate between adding 3 and subtracting 3 from the numbers. Both accuracy and speed were emphasized in the instructions. List completion times were measured by use of a stopwatch. In addition, number of errors on each list was counted. The shift cost was calculated as the ratio between the time to complete the alternating list and the average of the times to complete the addition and the subtraction lists. For further analyses, this ratio was transformed to z-scores and inverted to yield a measure of shifting ability.

The Trail making task employed was the D-KEFS Trail-Making Test (Delis et al., 2001). Three conditions were administered: Number sequencing, Letter sequencing and Number-Letter switching. All three conditions consist of consecutively numbered circles from 1 to 16 and circled letters from A to P arranged randomly on a sheet of paper. In the Number sequencing condition, the task is to as fast as possible draw a line between the numbered circles in ascending order. In the Letter sequencing conditions, the task is to draw a line between the circles containing letters in alphabetic order as fast as possible. Finally, in the Number-Letter switching condition, the task consists of connecting each number with a letter and each letter with a number (1-A-2-B-3-C, etc.). In all conditions, errors made were immediately corrected. Before each condition, participants practiced on shorter versions. Completion times were measured by use of a stopwatch. The shift cost was calculated as the ratio between the time to complete the Number-Letter switching condition and the average of the times to complete the Number sequencing and Letter sequencing conditions. For further analyses, this ratio was transformed to z-scores and inverted to yield a measure of shifting ability.

2.3. MRI data acquisition

Imaging data were acquired using a 12 channel head coil on a 1.5-Tesla Siemens Avanto scanner (Siemens Medical Solutions, Erlangen, Germany) at Rikshospitalet University Hospital, Oslo. The pulse sequences used for morphometric analysis were two repeated 3D T1-weighted Magnetization Prepared Rapid Gradient Echo (MP-RAGE), with the following parameters: TR/TE/TI/FA = 2400 ms/3.61 ms/1000 ms/8°, matrix 192 × 192, field of view = 192. Each volume consisted of 160 sagittal slices with voxel sizes 1.25 × 1.25 × 1.2 mm. Scanning time for each of these sequences was 7 min, 42 s. The number of scans that should be used depends on a number of factors, such as coil, field strength, acceleration and motion. In the present study, 1.5 T was used, and since the signal-to-noise-ratio (SNR) is considerably less than at 3 T, we chose to average the two MP-RAGEs during post-processing in order to optimize SNR. Primarily due to motion distortion, only one MP-RAGE was available for 18 of the participants (18.4%). Most of these were younger participants and males (6 girls of mean age 10.4 years and 12 boys of mean age 11.2, in total mean age was 10.8 years, SD = 2.1, range 8.4–16.4). This might represent a possible confound in the present study. Note however that the number of acquisitions (single vs. multiple averaged) has previously been found to have negligible effects on reliability of cortical thickness measurements (Han et al., 2006). To directly test the effects of including one or two acquisitions, we reprocessed 18 participants with two usable scans (individually matched on sex and age to the participants with only one available scan) using one and two scans, respectively. Overall, there were few and relatively restricted regions showing absolute differences exceeding 0.10 mm (see Supplementary Figure 1). The protocol also included a 25 slices coronal T2-weighted fluid-attenuated inversion recovery (FLAIR) sequence (TR/TE = 7000–9000/109 ms) to aid the neuroradiological examination.

2.4. Image analysis

All datasets were processed and analyzed at the Neuroimaging Analysis Lab, Center for the Study of Human Cognition, University of Oslo, with the additional use of computing resources from the Titan Grid cluster (<http://hpc.uio.no/index.php/Titan>) run by the Research Computing Services Group at USIT, University of Oslo. Cortical thickness was estimated using FreeSurfer 4.05 and cluster-wise correction for multiple comparisons was performed with FreeSurfer 4.50 (<http://surfer.nmr.mgh.harvard.edu>). Cortical thickness was estimated at each vertex across the brain surface using a semi-automated approach described elsewhere (Dale, Fischl, & Sereno, 1999; Dale & Sereno, 1993; Fischl & Dale, 2000; Fischl, Liu, & Dale, 2001; Fischl, Sereno, & Dale, 1999; Fischl, Sereno, Tootell, & Dale, 1999; Salat et al., 2004; Segonne et al., 2004; Segonne, Grimson, & Fischl, 2005). In short, thickness measurements were obtained by reconstructing representations of the gray matter/WM boundary and the cortical surface and then calculating the distance between those surfaces at each point across the cortical mantle (Dale et al., 1999; Dale & Sereno, 1993). This method uses both intensity and continuity information from the entire three-dimensional MR volume in segmentation and deformation procedures to produce representations of cortical thickness. The maps are created using spatial intensity gradients across tissue classes and

Table 2
Descriptive statistics for separate conditions in the completion time tasks.

Task: condition	Completion time (s)				Errors (number)			
	Mean	SD	Min.	Max.	Mean	SD	Min.	Max.
Stroop: Color naming	33.08	8.48	20.8	63.0	0.52	0.86	0	5
Stroop: Inhibition	60.26	22.25	32.1	135.0	2.55	2.52	0	11
Plus minus: Plus	58.45	30.94	18.0	164.1	0.35	0.66	0	3
Plus minus: Minus	72.86	44.07	22.0	240.0	0.40	0.77	0	4
Plus minus: Shifting	89.51	52.14	25.0	252.9	0.46	0.84	0	4
Trail making: Numbers	29.54	9.78	11.0	64.7	–	–	–	–
Trail making: Letters	31.27	14.61	11.1	101.6	–	–	–	–
Trail making: Shifting	71.35	27.60	28.6	185.8	–	–	–	–

Notes: Number of errors was not recorded for Trail making. $N = 98$.

are therefore not simply reliant on absolute signal intensity. The maps produced are not restricted to the voxel resolution of the original data and are thus capable of detecting submillimeter differences between groups (Fischl & Dale, 2000). The measurement technique has been validated via histological (Rosas et al., 2002) as well as manual measurements (Kuperberg et al., 2003). Maps were smoothed using a circularly symmetric Gaussian kernel across the surface with a full width at half maximum of approximately 30 mm and averaged across participants using a nonrigid high-dimensional spherical averaging method to align cortical folding patterns (Fischl, Sereno, et al., 1999). This procedure provides accurate matching of morphologically homologous cortical locations among participants on the basis of each individual's anatomy while minimizing metric distortions, resulting in a measure of cortical thickness for each person at each point on the reconstructed surface. The relatively large smoothing kernel was chosen in order to reduce noise in the thickness measurements and increase sensitivity and validity of statistical analysis. Morphometry–cognition relationships are not believed to be very focal, at least not in developmental samples with wide age ranges, and we chose the kernel size accordingly. Note however that this also reduced the spatial resolution of the thickness maps (Han et al., 2006). Statistical surface maps were generated by fitting a general linear model (GLM) of the effects of each variable on thickness at each vertex, which were mapped on the semi-inflated surface of the average brain of the sample (Dale et al., 1999; Fischl, Sereno, et al., 1999).

2.5. Statistical analysis

Initial analyses of the behavioral data from the three completion time based tasks were performed with descriptive statistics for separate conditions. Paired samples t -tests were used to test for significant differences in completion times. Descriptive statistics were then performed for the six raw executive function measures. Analyses of the relationships between the z -transformed executive function measures, intellectual ability, sex and age were done using Pearson's bivariate correlations. Executive function measures were plotted as a function of age and both linear and quadratic models were fitted. Partial correlations among the six executive function measures and intellectual ability, controlling for the effects of age and sex, were then performed. Next, unique linear and quadratic effects of age on cortical thickness, while controlling for the effects of sex, were calculated for both hemispheres by GLMs at each vertex.

In order to investigate the relationships between executive functions and cortical thickness in development, we first fitted GLMs of the effects of executive function measures on cortical thickness at each vertex, controlling only for the effects of sex. Second, we fitted GLMs of the effects of executive function measures on cortical thickness, while statistically controlling for the effects of both age and sex. Third, in order to test whether individual differences in executive functions were related to differences in the development of cortical thickness, we fitted GLMs of the effects of interaction terms of executive function measures \times age on cortical thickness, while including age, sex and the respective executive function measure as covariates. A similar approach has previously been described in a seminal paper by Shaw et al. (2006).

The p statistics maps from the vertex-wise GLMs testing the associations between age and cortical thickness and executive function measures and cortical thickness (without adjusting for age) respectively, were thresholded corresponding to a commonly used criterion of false discovery rate (FDR) at 5% level (Genovese, Lazar, & Nichols, 2002). Note that this criterion will yield different p -value thresholds for different analyses. For the age-independent analyses and the analyses involving interaction terms of executive function measures \times age, corrections for multiple comparisons were performed by means of cluster size inference as implemented in FreeSurfer (Hagler, Saygin, & Sereno, 2006; Hayasaka & Nichols, 2003). Here, only clustered vertices are retained, the underlying idea being that true effects tend to extend over contiguous vertices, whereas noise has much less of a tendency to form clusters. Cluster size limits were estimated with synthesized Z Monte Carlo simulations using a method similar to that used in AFNI's AlphaSim (Ward, 2000) with 5000 iterations per analysis with an initial cluster-forming threshold of $p < .05$. The simulations are a way to get a measure of the distribution of the maximum cluster size under the null hypothesis and thus determine the probability of a certain

cluster size under the empirical null. A cluster-wise corrected $p < .05$ was regarded significant. The uncorrected results are provided as [supplementary material](#). FDR at 5% level was used for analyses of the associations between age and cortical thickness and executive function measures and cortical thickness (without adjusting for age), since we here expected effects across most of the surface. In these cases, there are likely no well defined clusters of effects present in the data, and cluster size inference may be less appropriate. For the other analyses, cluster size inference was used since we expected more focal effects, i.e. clusters of effects.

Finally, in order to visualize the results from the surface-based analyses, mean cortical thickness was calculated for the clusters showing significant effects. For the analyses testing the effects of executive function measures independently of age, mean cortical thickness from the significant clusters were plotted against the respective executive function measures both before and after correcting for the effects of age and sex on thickness. For the analyses testing the effects of the interaction terms, mean cortical thickness from the significant clusters were plotted against age after splitting the sample in two equally large groups based on the respective z -transformed executive function measures. Group assignment was done separately for approximately every two years and by splitting by the median within these age brackets. Thus, for each of these age brackets, the sample was split into equally sized groups with no overlap in z -transformed executive function scores. This procedure was performed separately for each relevant executive function measure. Across all ages, each group consisted of 49 participants. For convenience, the groups are described as low and high score groups, respectively, although no norms were available for the current measures and it is likely that the sample investigated scored above population mean. Note that these plots were included only to visualize the significant effects observed in the surface based analyses where continuous variables were explored in the sample as a whole.

3. Results

3.1. Behavioral results

Descriptive statistics for separate conditions in the completion time based tasks are shown in Table 2. For the Stroop task, paired-samples t -tests showed significantly longer mean completion time in the Inhibition condition than in the Color naming condition ($t(97) = 17.48, p < .001$). For the Plus minus task, significantly longer completion time was observed in the Shifting condition, than in both the Plus condition ($t(97) = 12.38, p < .001$) and the Minus condition ($t(97) = 8.54, p < .001$). For the Trail making task, significantly longer completion time was found in the Shifting condition, than in both the Numbers condition ($t(97) = 18.15, p < .001$) and the Letters condition ($t(97) = 19.33, p < .001$). These results indicate that the different test conditions yielded the expected behavioral effects.

Descriptive statistics for the executive function measures are shown in Table 3. For Keep track, Letter memory and Antisaccade, percentage correct responses are shown, while for Stroop, Plus minus and Trail making, ratio scores based on completion time measures are shown. For all further analyses, z -transformed measures were used to facilitate comparisons across tasks.

Pearson's bivariate correlations among the six z -transformed executive function measures, intellectual ability not adjusted for age as measured by WASI, sex and age are shown in Table 4. Note that the z -transformed ratio scores for Stroop, Plus minus and Trail making were inverted, so that higher scores on all measures reflect better performance. Moderate to large significant positive correlations were observed between four of the executive func-

Table 3
Descriptive statistics for raw executive function measures.

Measure	Mean	SD	Min.	Max.
Keep track	69.29	12.31	30.30	93.94
Letter memory	80.93	10.68	36.36	97.73
Antisaccade	76.46	15.24	30.83	98.33
Stroop	1.80	0.31	1.32	2.66
Plus minus	1.36	0.23	1.02	2.05
Trail making	2.43	0.71	1.08	4.89

Notes: Raw executive function measures are shown. For Keep track, Letter memory and Antisaccade, percentages correct are shown. For Stroop, Plus minus and Trail making, ratio scores based on completion times in separate conditions are shown. *N* = 98.

Table 4
Correlations among executive function measures, intellectual ability, sex and age.

Measure	1.	2.	3.	4.	5.	6.	7.
1. Keep track	–						
2. Letter memory	<u>.58</u>	–					
3. Antisaccade	<u>.51</u>	<u>.56</u>	–				
4. Stroop	<u>.45</u>	<u>.37</u>	<u>.32</u>	–			
5. Plus minus	.16	.07	.01	.13	–		
6. Trail making	.07	.14	.04	.00	.08	–	
7. Intellectual ability	<u>.65</u>	<u>.68</u>	<u>.61</u>	<u>.47</u>	.05	.09	–
Sex	.00	.10	.01	<u>.22</u>	.18	.03	.04
Age	<u>.63</u>	<u>.63</u>	<u>.66</u>	<u>.38</u>	.04	.07	<u>.80</u>

Notes: z-transformed executive function measures were used. For Keep track, Letter memory and Antisaccade, percentages correct were used. For Stroop, Plus minus and Trail making, inverted ratio scores based on completion times in separate conditions were used. Note that the intellectual ability score shown was not adjusted for age. Higher scores on all measures reflected better performance. Males are coded as 0 and females as 1. Bold characters indicate $p < .05$ and underlined characters indicate $p < .01$. *N* = 98.

tion measures, namely Keep track, Letter memory, Antisaccade and Stroop, while Plus minus and Trail making were not associated with any of the other executive function measures, including each other. Intellectual ability showed strong correlations with Keep track, Letter memory and Antisaccade, a moderate correlation with Stroop, and no correlations with Plus minus or Trail making. Only Stroop correlated with sex, with girls performing better than boys ($r = .22, p = .027$). Further, Keep track, Letter memory, Antisaccade and intellectual ability showed strong positive correlations with age, while Stroop showed a moderate positive correlation. Plus minus and Trail making were not correlated with age. Scatter plots of the executive function measures by age are shown in Fig. 1. For Keep track and Antisaccade, age² added significantly to the amount of explained variance. The quadratic models indicated most pronounced age-related improvement on Keep track and Antisaccade in late childhood and early adolescence; although, overall the quadratic models did not diverge dramatically from the linear models.

Partial correlations among the six executive function measures and intellectual ability, controlling for the effects of age and sex, are shown in Table 5. Moderate significant positive correlations were observed between Keep track and Letter memory, Keep track and Stroop, and Letter memory and Antisaccade, respectively. Plus minus and Trail making were not associated with any of the other measures when controlling for the effects of age and sex. Further, Keep track, Letter memory and Stroop showed moderate positive correlations with intellectual ability.

Since the correlation analyses did not indicate any clear organization of the measures according to the proposed executive sub-functions updating, inhibition and shifting, individual task measures from Keep track, Letter memory, Antisaccade, Stroop, Plus minus and Trail making were used for further analyses.

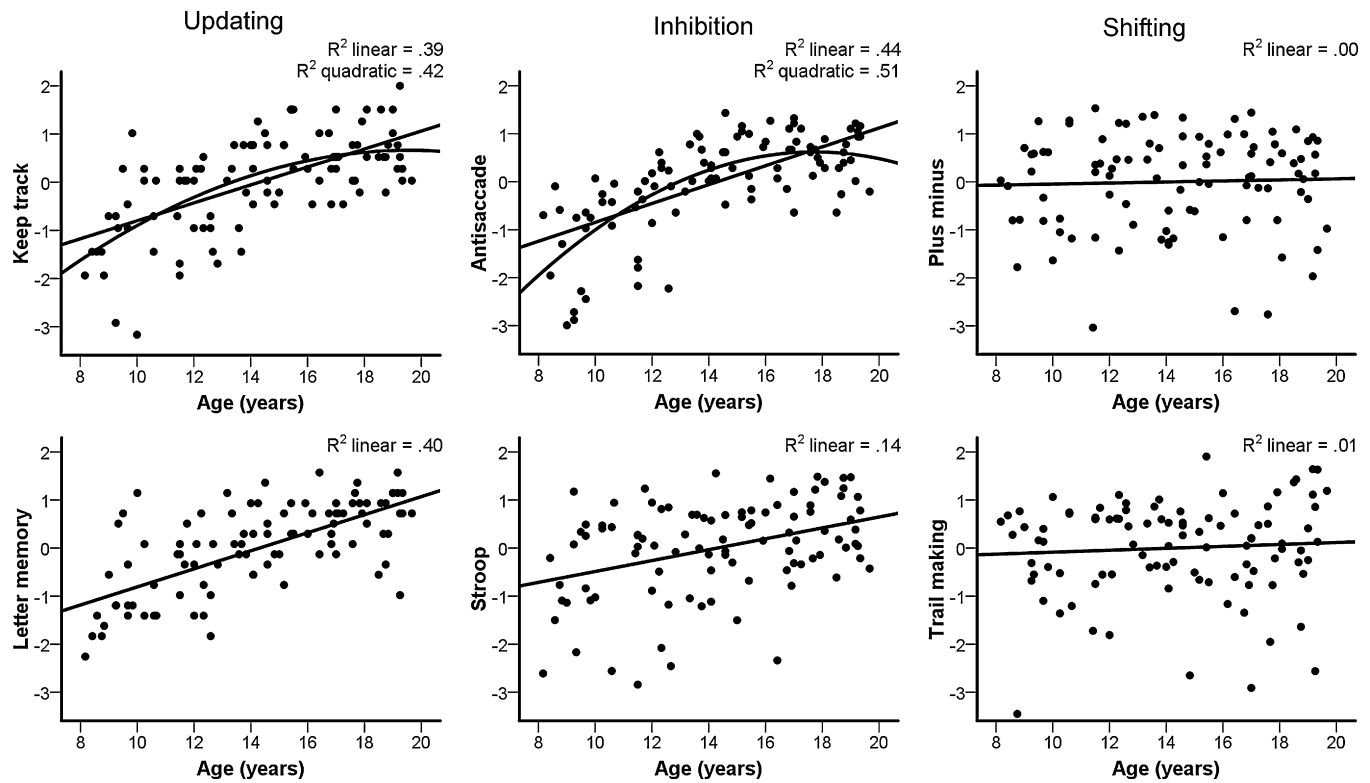


Fig. 1. Relationships between executive functions and age. Scatter plots for, column wise from left to right: the two updating measures (Keep track, Letter memory), the two inhibition measures (Antisaccade, Stroop) and the two shifting measures (Plus minus, Trail making), by age. For Keep track, Letter memory and Antisaccade, z-transformed percentage correct are shown. For Stroop, Plus minus and Trail making, inverted z-transformed ratio scores based on completion times in separate conditions are shown. Higher scores on all measures reflect better performance. Linear and significant quadratic models are fitted and explained variance is reported. The quadratic age term added significantly to the amount of explained variance for Keep track and Antisaccade.

Table 5

Partial correlations among executive function measures and intellectual ability, controlling for age and sex.

Measure	1.	2.	3.	4.	5.	6.
1. Keep track	–					
2. Letter memory	.31	–				
3. Antisaccade	.17	.24	–			
4. Stroop	.32	.18	.12	–		
5. Plus minus	.19	.05	–.01	.10	–	
6. Trail making	.04	.13	–.01	–.03	.07	–
7. Intellectual ability	.32	.37	.17	.32	.06	.06

Notes: z-transformed executive function measures were used. Higher scores on all measures reflected better performance. Bold characters indicate $p < .05$ and underlined characters indicate $p < .01$. $N = 98$.

3.2. Cortical thickness

The effects of age on cortical thickness across the surface were estimated by GLMs controlling statistically for the effects of sex. The results are shown in Fig. 2. When a commonly used approach to correct for multiple comparisons was employed (FDR 5%, corresponding to $p < .046$), negative linear associations between cortical thickness and age were observed across almost the entire cortical surface (Fig. 2A). When a more conservative threshold was used ($p < 10^{-6}$), strong negative associations with age were observed bilaterally in large areas in the parietal and occipital lobes (Fig. 2B). Strong associations were also evident in the superior medial frontal lobes and in the ventrolateral prefrontal, insular and right cingulate cortices. There were no significant unique effects of age² on cortical thickness.

3.3. Relationships between executive functions and cortical thickness

As an initial examination of the relationships between executive functions and cortical thickness in development, we fitted GLMs of the effects of executive function measures on thickness on a vertex-by-vertex basis, controlling only for the effects of sex. The results are shown in Supplementary Figure 2. A statistical threshold taking multiple comparisons into account was used (FDR 5%). Widespread

negative associations with cortical thickness were observed for Keep track, Letter memory and Antisaccade. No associations were observed between cortical thickness and Stroop, Plus minus or Trail making, respectively.

3.4. Age-independent relationships between executive functions and cortical thickness

The above analyses were repeated with both age and sex included as covariates. Simulation based cluster-size inference was employed to correct for multiple comparisons. The results are shown in Fig. 3. For Keep track, one cluster in each hemisphere was found, both showing negative associations with cortical thickness. In the left hemisphere, the cluster was centered on the pre- and postcentral gyri, but also encompassed substantial parts of the inferior frontal gyrus and the superior parietal cortex. In the right hemisphere, the cluster encompassed the pre- and postcentral gyri and superior medial areas in the parietal lobe (paracentral areas). For Antisaccade, negative associations were found in bilateral clusters located around the parieto-occipital cortices, cuneus, pericalcarine and the lingual cortices. Plus minus was negatively associated with cortical thickness in a lateral cluster around the central sulcus in the left hemisphere, while Trail making was positively associated with thickness in a cluster in the right occipital lobe. No significant clusters were found showing age-independent relationships between cortical thickness and Letter memory or Stroop, respectively. Details on the clusters showing significant associations are given in Table 6. Uncorrected results are shown in Supplementary Figure 3.

Fig. 4 shows mean cortical thickness from the significant clusters plotted against Keep track, Antisaccade, Plus minus and Trail making performance. Strong negative associations between thickness and both Keep track and Antisaccade were seen (top panel). After controlling for the effects of age and sex on cortical thickness (lower panel), as was done in the cluster-wise analyses above, negative associations between thickness and both Keep track and Antisaccade were found, with correlations ranging from $-.23$ to $-.30$. Plus minus showed a moderate negative correlation with thickness ($-.33$), while Trail making showed a moderate positive correlation ($.30$).

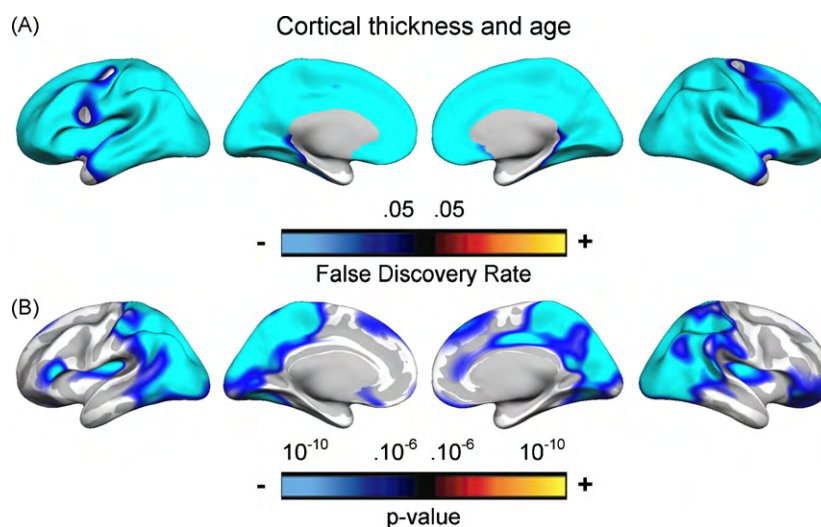


Fig. 2. Relationships between cortical thickness and age. The significance (p -values) of the effect of age on cortical thickness when controlling for effect of sex is color coded and projected onto a semi-inflated average template brain. The medial wall and corpus callosum are masked. $N = 98$. Panel A shows linear relationships corrected for multiple comparisons by using a p -value threshold corresponding to a commonly used criterion (FDR 5%, upper threshold $p = 10^{-5}$). Panel B shows linear relationships with a more conservative significance level (lower threshold $p < 10^{-6}$).

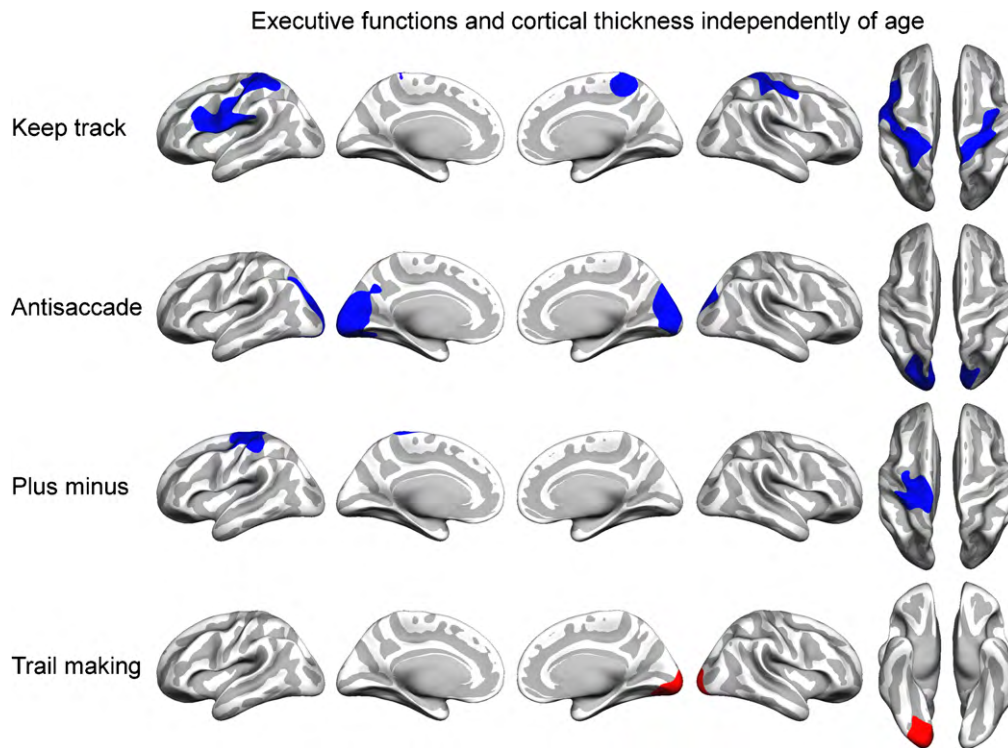


Fig. 3. Age-independent relationships between executive functions and cortical thickness. Clusters of vertices with significant associations between executive function measures and cortical thickness when controlling for the effects of age and sex, are projected onto a semi-inflated average template brain. All clusters, except the one for Trail making in the right hemisphere, showed negative associations between task performance and cortical thickness. The medial wall and corpus callosum are masked. Cluster-wise $p < .05$ (corrected for multiple comparisons across the surface) was used. No clusters with significant associations between cortical thickness and Letter memory or Stroop, respectively, were found. $N = 98$.

3.5. Relationships between executive functions and cortical maturation

In order to explore the associations between executive functions and estimated cortical maturation, interaction terms of executive function measures \times age were added to the GLMs. Fig. 5 shows the

results from GLMs testing for linear effects of the interaction terms on cortical thickness, while regressing out the effects of age, sex and the respective executive function measures. Cluster-size inference was used to correct for multiple comparisons. The interaction term Antisaccade \times age was negatively associated with cortical thickness in both hemispheres in clusters encompassing mainly the parieto-

Table 6

Details on clusters showing significant associations between executive functions and cortical thickness independently of age.

Analysis	Hemisphere	Cluster size (mm ²)	Talairach max vertex (X, Y, Z)	Cluster-wise p	Confidence limits for cluster-wise p	Annotation
Keep track	Left	8379.6	-39.6, -22.9, 59.1	0.0002	0.0000, 0.0004	Postcentral
Keep track	Right	4574.9	12.2, -35.2, 52.6	0.0144	0.0122, 0.0166	Paracentral
Antisaccade	Left	10258.6	-6.6, -87.1, 6.4	0.0002	0.0000, 0.0004	Pericalcarine
Antisaccade	Right	4974.7	5.8, -75.3, 17.7	0.0074	0.0058, 0.0090	Cuneus
Plus minus	Left	3940.7	-11.4, -26.7, 59.1	0.0340	0.0308, 0.0374	Precentral
Trail making	Right	3834.8	12.0, -92.0, -4.9	0.0392	0.0358, 0.0428	Lingual

Notes: Details of clusters with significant associations between executive function measures and cortical thickness, while controlling for the effects of age and sex. Corrections for multiple comparisons were performed by means of cluster size inference and a cluster-wise $p < .05$ was used. Only significant clusters are shown. All clusters, except the Trail making cluster, showed negative associations with cortical thickness. $N = 98$.

Table 7

Details on clusters showing significant associations between executive functions and cortical maturation.

Analysis	Hemisphere	Cluster size (mm ²)	Talairach max vertex (X, Y, Z)	Cluster-wise p	Confidence limits for cluster-wise p	Annotation
Antisaccade \times age	Left	7136.4	-37.5, -79.4, 26.3	0.0002	0.0000, 0.0004	Inferior-parietal
Antisaccade \times age	Right	5827.2	23.7, -77.0, 30.3	0.0020	0.0012, 0.0028	Superior-parietal
Stroop \times age	Right	5147.4	42.9, -54.1, 9.5	0.0054	0.0040, 0.0068	Inferior-parietal

Notes: Details of clusters with significant associations between the interaction terms executive function measures \times age and cortical thickness, while controlling for the effects of age, sex and the respective executive function measure. Corrections for multiple comparisons were performed by means of cluster size inference and a cluster-wise $p < .05$ was used. Only significant clusters are shown. Antisaccade \times age showed negative associations with cortical thickness, while Stroop \times age showed a positive association with cortical thickness. $N = 98$.

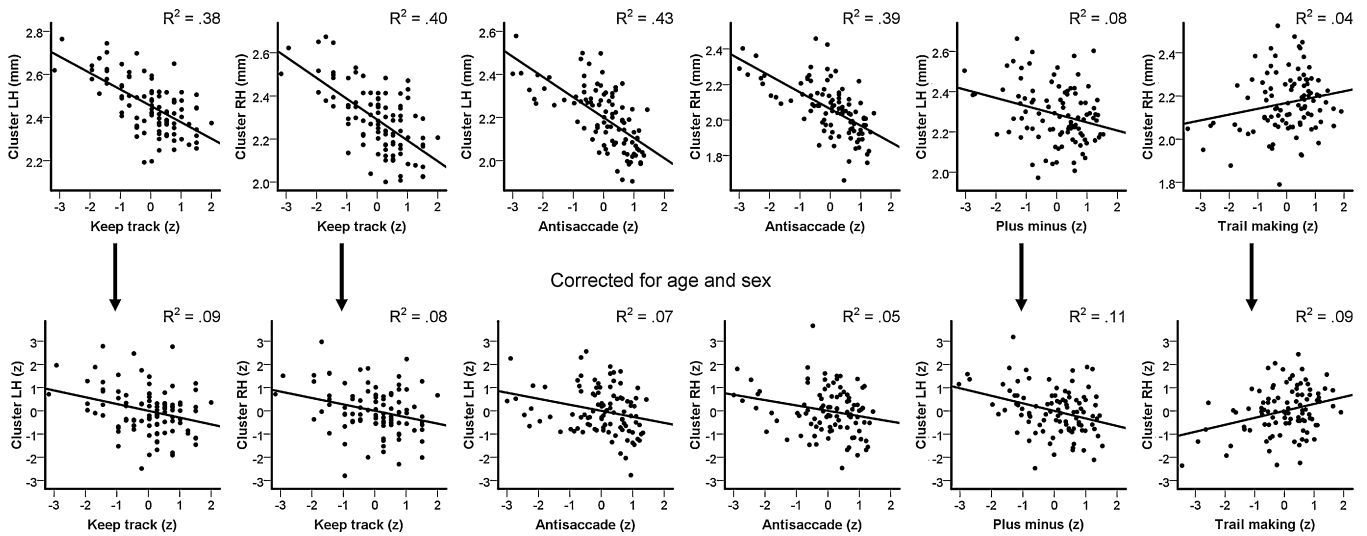


Fig. 4. Plots of the relationships between executive functions and cortical thickness. Average cortical thickness in clusters with significant associations (see Fig. 3) plotted against executive function measures. For Keep track, the clusters encompassed parietal and frontal areas around the central sulcus, and also the left inferior frontal gyrus and paracentral areas in the right hemisphere. For Antisaccade, the clusters encompassed occipital and parietal areas, including parieto-occipital cortices, cuneus, pericalcarine and the lingual cortices. For Plus minus, the cluster included areas around the central sulcus in the left hemisphere and for Trail making the cluster was located in the occipital lobe in the right hemisphere. The top panel shows cortical thickness in mm by executive function measures. The lower panel shows cortical thickness corrected for the effects of age and sex (in z-scores). $N=98$. LH: left hemisphere, RH: right hemisphere.

occipital cortices, with effects extending into the inferior, superior and medial parietal cortices. One cluster in the right hemisphere was found showing a positive association between Stroop \times age and cortical thickness. This cluster was located mainly around the posterior lingual and fusiform cortices, but also extended up to the inferior parietal cortex. No clusters with significant associations between cortical thickness and any of the other executive function measures \times age were found. Details on the clusters showing significant associations are given in Table 7. Uncorrected results are shown in Supplementary Figure 4.

In order to visualize the interactions, mean thickness from the significant clusters was plotted against age after splitting the sample in two equally large groups based on Antisaccade and Stroop performance, respectively (Fig. 6). The negative associations between the interaction term Antisaccade \times age and cortical thickness in the bilateral posterior clusters indicate that a higher level of performance on this task was associated with more pronounced cortical thinning in these regions in adolescence. The positive association between the interaction term Stroop \times age and

cortical thickness in the posterior right hemisphere suggests an opposite pattern, with higher level of performance on this task being associated with less cortical thinning in adolescence.

4. Discussion

The main findings from the present study were that (1) independently of age, performance on the Keep track and Antisaccade tasks were negatively associated with cortical thickness bilaterally in parietal and frontal (Keep track) and occipital and parietal (Antisaccade) regions, and that (2) the strength of the relationships between age and cortical thickness in posterior brain regions was associated with performance levels on the Antisaccade and Stroop tasks. The other behavioral measures did not show any associations with rates of cortical maturation as indexed by estimated cortical thickness. The results add to previous knowledge about the cortical correlates of executive functions by indicating an important role of posterior regions for the development of certain executive functions. The results are discussed in more detail below.

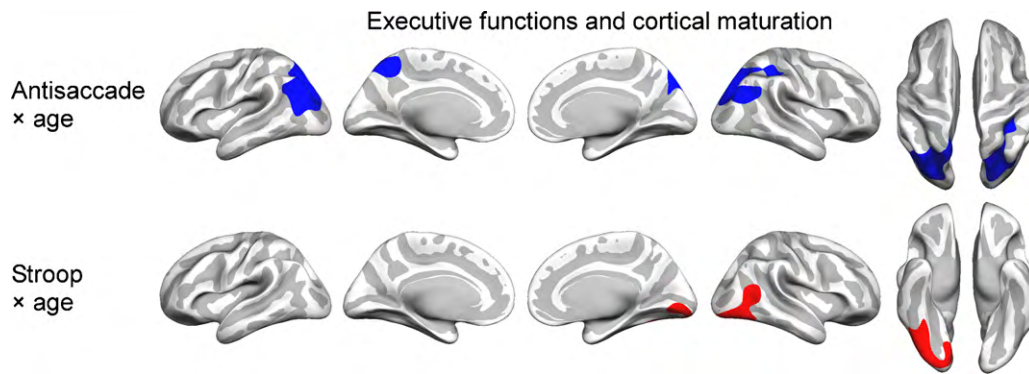


Fig. 5. Relationships between executive functions and cortical maturation. Clusters of vertices with significant associations between the interaction terms executive function measures \times age and cortical thickness, while controlling for the effects of age, sex and the respective task measure, are projected onto a semi-inflated average template brain. Antisaccade \times age showed negative associations with cortical thickness, while Stroop \times age showed a positive association. The medial wall and corpus callosum are masked. Cluster-wise $p < .05$ (corrected for multiple comparisons across the surface) was used. No clusters with significant associations between cortical thickness and any of the other executive function measures \times age were found. $N=98$.

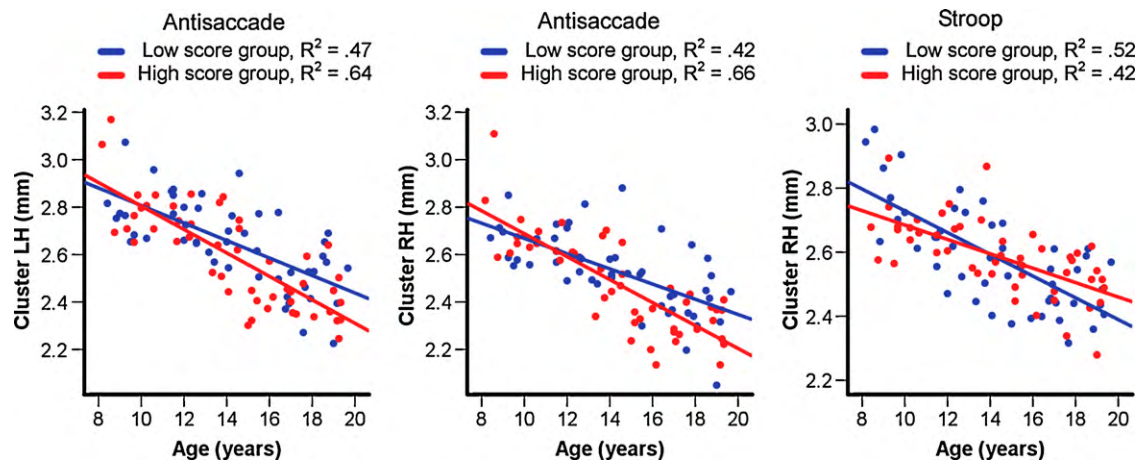


Fig. 6. Plots of the relationships between executive functions and cortical maturation. Average cortical thickness in clusters with significant associations (see Fig. 5) plotted against age separately for two groups with lower and higher levels of performance, respectively. For Antisaccade, the clusters encompassed mainly the parieto-occipital cortices, with effect extending into the parietal cortices. For Stroop, the cluster was located around the right posterior lingual and fusiform cortices, but also extended into the inferior parietal cortex. Details on group assignment are given in Section 2. The group labels refer to over and below median performance for that age in the current sample. LH: left hemisphere, RH: right hemisphere. Linear models were fitted for each group and explained variance in both groups is shown. $N = 98$.

4.1. Development of executive functions

The behavioral tasks used in the present study were primarily adopted from Miyake et al. (2000), who demonstrated that updating, inhibition and shifting were moderately correlated with one another, but also clearly separable. Similar, although not identical, organization of executive functions have since been found in young adults (Friedman et al., 2006), older adults (Fisk & Sharp, 2004; Hedden & Yoon, 2006; Hull, Martin, Beier, Lane, & Hamilton, 2008) and children (Huizinga et al., 2006; Lehto, Juujärvi, Kooistra, & Pulkkinen, 2003; St Clair-Thompson & Gathercole, 2006; van der Sluis et al., 2007; Willcutt et al., 2001). In a study of children aged 8–13 years, Lehto et al. (2003) observed a factor structure including all three factors updating, inhibition and shifting. Others have identified two factors in children, either updating and shifting (Huizinga et al., 2006; van der Sluis et al., 2007) or updating and inhibition (St Clair-Thompson & Gathercole, 2006). We found moderate correlations between the updating and inhibition measures, but no empirical support in favor of structuring the tests according to the updating, inhibition and shifting categories. Further, the size of the intercorrelations among the measures did not indicate a dominating underlying general executive function. Disparity across studies may reflect fundamental differences in the organization of executive functions between children, adolescents and adults and variations in or limitations associated with the specific behavioral tasks used. The lack of a clear organization likely reflects multiple factors, including the wide age-range of the sample, the limited number of tasks used and possibly age-related differences in subjective task demands. Our results indicate that more research focused on developing a set of reliable executive function tasks suited for both children and adolescents and on the organization of executive functions at different ages is needed.

Marked age-related improvements on Keep track, Letter memory, Antisaccade and Stroop were found, with slightly accelerated improvements in childhood compared to late adolescence on two of the measures (Keep track and Antisaccade). Age-related differences were not found for the Plus minus and Trail making measures and they were neither associated with each other nor with any other behavioral measures. The scoring procedure used for the shifting tasks might partly explain why we did not observe any age-related improvements on these measures. In order to control for the known motor and processing speed improvements in late childhood and adolescence (Gasser, Rousson, Caflisch, & Jenni, 2010; Kail & Ferrer,

2007), as well as development of basic arithmetic abilities, we used ratio scores based on completion times in different conditions. The same type of measure was computed from the Stroop task, which also showed less pronounced age-related improvement compared to the accuracy-based measures from the Keep track, Letter memory and Antisaccade tasks. Speed-accuracy tradeoffs may have influenced the results for the completion time based tasks. However, we deemed the number of errors made on these tasks to be too low to warrant separate analyses of number of errors or analyses within a speed-accuracy framework. Given a reasonable assumption that shifting ability does improve beyond childhood, our results indicate limitations associated with the use of conventional analysis of speed-based scores derived from the Plus minus and Trail making tasks as measures of shifting ability in developmental samples with wide age-ranges. These limitations are also indicated by a study showing that a global speed mechanism may account for large proportions of age-related variance in the speed of responding on executive function tasks in development (Span, Ridderinkhof, & van der Molen, 2004).

Interestingly, four of the six executive function measures, namely Keep track, Letter memory, Antisaccade and Stroop, were correlated with general intellectual ability. Independently of age, moderate correlations were found between intellectual ability and Keep track, Letter memory and Stroop, respectively. Using a similar battery of tasks on young adults, Friedman et al. (2006) have previously found that updating was highly correlated with measured intelligence, while inhibition and shifting were not. Our results largely support the conclusions that executive functions are differentially related to general intellectual ability and that working memory updating seems to be an executive function that is particularly closely related to intellectual ability.

4.2. Age-related cortical thinning

As expected, we observed age-related decreases in cortical thickness. Cortical maturation has been fairly well delineated in a number of MRI studies, showing that both cortical thickness and volume follow an inverted U-shaped developmental course with a period of initial childhood increase and a subsequent adolescent decline (Giedd, 2004; Gogtay et al., 2004; Shaw et al., 2008; Tamnes et al., 2010). The adolescent decline in thickness is followed by a period with slower decline in early adulthood (Shaw et al., 2008; Sowell et al., 2003; Tamnes et al., 2010). In the present study with

participants ranging from 8 to 19 years old, linear cortical thinning was observed across almost the entire cortical mantle. We did not observe any childhood cortical thickening in contrast to what has been reported in other samples (Giedd, 2004; Shaw et al., 2008); likely because the starting age of our sample was too high to detect this, at least with a cross-sectional design. Further, no significant quadratic effects of age on cortical thickness were observed. This is also likely a reflection of the age-range of the sample, as we have previously found decelerating cortical thinning in adolescence and early adulthood (Tamnes et al., 2010).

Relatively little is known about the neurobiological processes underlying structural brain maturation as delineated by the use of MRI. Cortical thinning in adolescence may reflect pruning and reorganization in the form of use-dependent selective synapse elimination (Bourgeois & Rakic, 1993; Huttenlocher & Dabholkar, 1997) which could play a key role in shaping neural circuits and thus provide a biological basis for development of cognitive functions (Hensch, 2004; Knudsen, 2004). In addition, neurobiological changes at the interface between the cortex and the subjacent WM might partly explain the apparent cortical thinning. Proliferation of myelin into the periphery of the cortical neuropil is one such possible biological event (Shaw et al., 2008; Sowell et al., 2004; Yakovlev & Lecours, 1967).

4.3. Relationships between executive functions and cortical thickness

When age was not included as a covariate, widespread negative associations were found between cortical thickness and both the updating measures (Keep track and Letter memory) and one of the inhibition measures (Antisaccade). The common influence of age likely explains most of these relationships, caused by concurrent age-related performance improvements on executive function tasks and age-related cortical thinning. This indicates that development of these cognitive functions are mirrored by the cortical maturation occurring in the same period, but cannot be used to infer a direct causal relationship between brain maturation and cognitive development.

Specific associations between different behavioral measures and cortical thickness were tested by including age as an additional covariate. Keep track performance, which is considered to index updating, was negatively associated with cortical thickness bilaterally in parietal and frontal regions. Performance on the Antisaccade task, which is considered to predominantly index inhibition, was negatively related to cortical thickness bilaterally in occipital and parietal regions. Further, Plus minus performance was negatively associated with thickness in a central lateral region in the left hemisphere, while Trail making showed a positive association with thickness in the right occipital lobe. Letter memory and Stroop performance did not show any age-independent associations with cortical thickness. To our knowledge, this is the first study to explore the relationships between different behavioral indices of executive functioning and cortical morphometry in children and adolescents.

Thinner cortices in bilateral parietal and frontal areas around the central sulcus, and also encompassing areas in the left inferior frontal gyrus and superior medial parietal areas in the right hemisphere, were associated with better working memory updating performance as measured by the Keep track task. This is largely consistent with functional imaging evidence from adults showing that working memory is associated with activations in the prefrontal cortex, anterior cingulate, parietal and occipital regions, but that the main components seem to include lateral prefrontal cortex and parietal regions (Cabeza & Nyberg, 2000a,b; D'Esposito, Postle, & Rypma, 2000; Glabus et al., 2003; Honey, Bullmore, & Sharma, 2000; Smith & Jonides, 1999). Working memory has also

been related to DTI indices of WM microstructure in children and adolescents in the left frontal lobe (Nagy, Westerberg, & Klingberg, 2004) and in older adults (Charlton et al., 2008). Further, a study combining fMRI and DTI suggests that working memory in children and adolescents rely on the integrity of a fronto-parietal network (Olesen, Nagy, Westerberg, & Klingberg, 2003). A distributed nature of the neural substrates of working memory is also supported by human lesion studies (Muller & Knight, 2006; Muller, Machado, & Knight, 2002). Our morphological results from the Keep track task are mainly in line with these fMRI and lesion studies. However, to a larger degree than expected, this association encompassed primary somatosensory and motor areas in addition to associative cortices. The other updating task employed, Letter memory, did not show any age-independent associations with cortical thickness in our sample.

Our results also showed age-independent neuroanatomical correlates of one of the two tasks predominantly considered to index inhibition, namely Antisaccade. However, thinner cortices bilaterally in occipital and parietal areas, not in prefrontal regions, were associated with better performance. Thus, although the Antisaccade task is considered mainly to index inhibition ability, these results suggest that areas engaged in visual detection and attention processes are also involved. Functional imaging studies from adults have shown that the Antisaccade task activates an extensive network including frontal and supplementary eye fields, occipital visual areas, parietal cortex, striatum and the lateral prefrontal cortex (Brown, Goltz, Vilis, Ford, & Everling, 2006; Ettinger et al., 2008; Matsuda et al., 2004; Raemaekers et al., 2007; Tu, Yang, Kuo, Hsieh, & Su, 2006). Similar areas are also activated in children and adolescents (Velanova, Wheeler, & Luna, 2008). The present results indicate that performance on the Antisaccade task in childhood and adolescence is more related to structural properties of the visual cortex than the prefrontal cortex. Thus, although inferences of localization of cognitive functions from relationships between structural properties and task performance should be drawn with caution, the present results suggest that Antisaccade may be more sensitive to development of the visual processing system than networks presumably related to cognitive control. The other inhibition measure employed, Stroop, did not show any age-independent associations with cortical thickness in our sample. Although the performed correction for speed in the Stroop measure is likely important in order to increase its specificity, the scoring procedure might partly also explain the lack of age-independent associations with cortical thickness.

Concerning the measures considered to index shifting, Plus minus and Trail making, the results were mixed. Plus minus showed an age-independent association with cortical thickness in the expected negative direction around the central sulcus in the left hemisphere, while Trail making surprisingly showed a positive association with thickness in the right occipital lobe. This means that the neuropsychological functions measured by these tests are related to brain morphometry, but since the performance does not increase in development, the relationships are not age-dependent. However, the interpretation of these results is unclear due to the above discussed possible limitations associated with the use of speed-based scores derived from the Plus minus and Trail making tasks in developmental samples. As the main purpose of this paper is to address the role of cortical maturation in development of executive functions, not brain-cognition relationships per se, these results are not discussed in more detail.

The present study also demonstrated that individual differences in task performance assumed to index inhibition (Antisaccade and Stroop) were related to differences in cortical maturation in posterior brain regions. A negative association between the interaction term Antisaccade \times age and cortical thickness in occipital and parietal regions was found, while a positive association between

Stroop \times age and cortical thickness in posterior regions in the right hemisphere was observed. Interestingly, these results suggest that performance on the Antisaccade task is associated not only with cortical thickness independently of age, but also with estimated rate of cortical maturation in overlapping and adjacent areas in parieto-occipital cortex. Although both Antisaccade and Stroop performance were related to maturational differences in posterior brain regions, it is unclear why these effects were in opposite directions. One might speculate that this relates to different associations with age for the two cognitive measures and regional differences in cortical maturation. As emphasized by Shaw et al. (2006), the direction of correlations between cognitive functions and cortical thickness is dependent of the age period studied.

No effects of the interaction terms executive function measures \times age were observed in the frontal lobes. Although an age-independent association between Keep track performance and cortical thickness in areas including lateral frontal regions was found, no direct evidence was thus found in this study that individual differences in levels of executive functioning were specifically associated with differences in the structural maturation of the prefrontal cortex as indexed by estimated cortical thickness. Using a similar approach, previous studies have found that general intellectual abilities are related to both cortical (Shaw et al., 2006) and WM microstructure maturation (Tamnes et al., *in press*). In these studies, high-functioning children showed a different pattern of structural brain maturation than average or lower functioning children. In a study of elderly participants, high-functioning participants showed thicker cortices in specific areas, but only when selected based on general cognitive functions, not when the selection was based on a number of tests related to executive function (Fjell et al., 2006). Thus, it is possible that developmental changes in macro-structural brain properties are more closely related to development of general intellectual functioning than performance on specific behavioral indices of executive functions.

Although general functions may be more closely related to brain structure than specific behavioral indices of executive functions, the question remains why such indices, with the exception of the age-independent associations between Keep track performance and thickness, mainly showed associations with cortical thickness and estimated cortical maturation in parietal and occipital areas and not in prefrontal regions. One reason could be that cognitive processes primarily supported by prefrontal circuits are more strategic and thus more variable across participants, while parietal and occipital areas are involved in more basic cognitive processes that vary less between subjects (Collette et al., 2005). Strategy usage is likely also age-related, and this could possibly explain the lack of associations between task performance and prefrontal cortical maturation observed in the present study. A related possibility is that between-subject variability in the exact prefrontal areas engaged in executive function tasks result in weaker relationships (Collette et al., 2005). In developmental samples, one might also expect correlations between anatomy and executive functions in different regions at different ages. Supporting this, a recent fMRI study suggests developmental changes to the functional networks underlying response inhibition and error-processing, with different areas of activation in young adolescents and adults (Braet et al., 2009). Finally, the use of single task measures instead of aggregated measures or latent variables might result in relationships with cortical regions involved in the idiosyncratic requirements that are specific to each task instead of relationship with regions involved in the postulated executive functions.

4.4. Limitations and conclusions

There are some limitations of the present study. First, the links between cognitive development and structural brain maturation

should ideally be investigated with longitudinal data including several time points, mapping individual developmental and maturational trajectories (but see Salthouse (2009) for a discussion of problems related to longitudinal designs). One possible confound in cross-sectional data include cohort effects other than age. These are probably negligible in this case since the age span was limited to 12 years. A more serious concern, however, is the possible loss of sensitivity due to large individual variation in brain anatomy and cognitive functioning. Thus, even though we did not observe a relationship between executive functions and age-related thinning of the prefrontal cortex, this should be tested with longitudinal data. Second, the present sample showed relatively high general cognitive function and may not be representative of the full range of individual differences in development. Third, the tasks employed are considered to predominantly index the executive functions updating, inhibition and shifting. This choice is not exhaustive, as there are various other proposed executive functions that should also be investigated, such as dual tasking, fluency, planning and decision-making. There is no current consensus on how best to measure executive functions and comparison across studies is difficult due to the diversity of conceptualizations, tasks and measures employed (Welsh, 2002). Further, the question of measurement invariance, i.e. whether we are actually measuring the same construct across age, is a considerable challenge for developmental studies (Huizinga et al., 2006). For instance, inhibition as measured in the Stroop task would likely be influenced by the degree to which reading is automated in children at various ages. Even though all children participating in the present study were capable readers, it appears safe to assume that the average level of reading skills was lower in 8 year olds than in 10 year olds. Further, the ability to sustain focused attention for longer time periods was likely better in the oldest compared to the youngest part of the sample. Thus, the degree to which other processes influence task performance may interact with age. By using ratio scores whenever possible, we hope that we have controlled for some of these confounding factors. Still, it is likely impossible to ensure that non-executive abilities do not have different influences at different ages. Finally, in the current study we investigated the relationships between single task measures and cortical thickness. Ideally, multiple measures for each postulated executive function should be subjected to latent variable analyses, due to idiosyncratic requirements that are specific to each task and the low reliability of many executive function tasks (Miyake et al., 2000). This was however not pursued in the current study, as no clear organization of the measures was evident from the correlation analyses. Further, we wanted to use established tests to ease comparisons with previous research, and possibly increase the clinical utility of the results.

In summary, the results in the current study showed concurrent age-related performance improvements on the Keep track, Letter memory and Antisaccade tasks, respectively, and age-related cortical thinning. Negative age-independent associations between a measure of working memory updating (Keep track) and a measure assumed related to inhibition (Antisaccade), and cortical thickness, were found in parietal and frontal and occipital and parietal regions, respectively. Further, individual differences in task performance presumed to index inhibition (Antisaccade and Stroop) were related to differences in estimated cortical maturation in posterior brain regions. No direct evidence was found in the current cross-sectional study supporting the hypothesis that individual differences in levels of executive functioning were specifically related to differences in the structural maturation of the prefrontal cortex as indexed by cortical thickness. This should however be tested with longitudinal data, mapping individual maturational trajectories. The results add to previous knowledge about the cortical correlates of executive functions by indicating an important role of posterior cerebral areas in executive development.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.neuropsychologia.2010.04.024.

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