

Multimodal imaging of the self-regulating developing brain

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Self-regulation refers to the ability to control behavior, cognition, and emotions, and self-regulation failure is related to a range of neuropsychiatric problems. It is poorly understood how structural maturation of the brain brings about the gradual improvement in self-regulation during childhood. In a large-scale multicenter effort, 735 children (4–21 y) underwent structural MRI for quantification of cortical thickness and surface area and diffusion tensor imaging for quantification of the quality of major fiber connections. Brain development was related to a standardized measure of cognitive control (the flanker task from the National Institutes of Health Toolbox), a critical component of self-regulation. Ability to inhibit responses and impose cognitive control increased rapidly during preteen years. Surface area of the anterior cingulate cortex accounted for a significant proportion of the variance in cognitive performance. This finding is intriguing, because characteristics of the anterior cingulum are shown to be related to impulse, attention, and executive problems in neurodevelopmental disorders, indicating a neural foundation for self-regulation abilities along a continuum from normality to pathology. The relationship was strongest in the younger children. Properties of large-fiber connections added to the picture by explaining additional variance in cognitive control. Although cognitive control was related to surface area of the anterior cingulate independently of basic processes of mental speed, the relationship between white matter quality and cognitive control could be fully accounted for by speed. The results underscore the need for integration of different aspects of brain maturation to understand the foundations of cognitive development.

executive function | cognitive conflict | inhibition | morphometry

Self-regulation enables people to make plans, choose from alternatives, control impulses, inhibit thoughts, and regulate social behavior (updated reviews in refs. 1 and 2). Several neuropsychiatric conditions and problems have been related to deficiencies in self-regulation [e.g., Attention Deficit Hyperactivity Disorder (3), addiction (4), risk behavior (5), conduct problems (6), and poor school and academic performance (7, 8)]. Although development of self-regulation in children is the result of a dynamic interaction between maturation and learning, we have scarce knowledge about the role played by structural brain characteristics in this process. Recent reports indicate that adjustment problems in childhood psychopathology are related to structural brain characteristics (9–13), but the brain basis for development of self-regulation in normal children is less well-understood. Thus, the purpose of the

present paper was to use multimodal neuroimaging to map the structural brain characteristics related to self-regulation and cognitive control in a large sample of 735 children between 4 and 21 y of age.

Self-regulation is closely tied to the concepts of cognitive control, attention, and executive functions (14). The ability to handle response conflict in pure cognitive tasks has been shown to correlate with parents' reports of their children's behavioral control (e.g., to delay actions and avoid lying, cheating, or other antisocial behavior) (6, 15). Executive attention and effortful control have been related to academic outcome, aspects of social adjustment (16), and inhibitory control to early arithmetic competency (17). More specifically, lower performance on the flanker task (see below) has been related to poorer social behavior, increased rates of peer rejection and more disturbing behavior in the classroom (18), dimensions of school competence (19), and parent-reported temperamental effortful control (20). This finding makes it possible to study the neural foundation of self-regulation by using validated cognitive tasks with a high degree of experimental control. Evidence has converged on an executive attention network, with the anterior cingulate being the central structure, as the major network responsible for resolving cognitive conflicts (21, 22). Of special interest for the current investigation is that this network seems less differentiated from other attention networks in infancy and young childhood. The work by Posner (22) suggests that the

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anterior cingulate cannot exercise full control of other networks until longer connections form during childhood. Thus, differentiation of cognitive control networks is obtained through maturation of major white matter (WM) tracts, which is measurable by diffusion tensor imaging (DTI) (23–27), and therefore, gradually, an adult organization of cognitive control and self-regulation emerges. Thus, to be able to understand the structural foundation for self-regulation and cognitive control during development, it is necessary to map structural maturation of the anterior cingulate especially but also, long-distance projection fibers constituting the major WM tracts of the brain.

Strikingly, in addition to their presumed critical role in the development of cognitive control in normal children (28), structural differences in prefrontal and cingulate cortices have repeatedly been identified in children with a range of different psychopathological conditions related to self-regulation and attention, including Attention Deficit Hyperactivity Disorder, conduct disorder, and prenatal substance exposure (10–13, 29–34). Thus, at the neuroanatomical level, there seems to be a link between brain areas involved in cognitive control and inhibition tasks and brain areas associated with regulatory problems in different neurodevelopmental conditions. At the cognitive level, there seems to be a relation between performance on cognitive control tasks and reported daily life behavior. On this background, the purpose of the present study was to conduct a detailed mapping of the relationship between cognitive control, as indexed by performance on a well-validated version of the classical Eriksen flanker task (35), implemented as part of the National Institute of Health toolbox for Assessment of Neurological and Behavioral Function (36, 37) and MRI measures of brain structure (*Materials and Methods*). This mapping allowed us to test the combined influence of cortical and WM maturation on performance of the anterior cingulate control network. We hypothesized that cortical thickness and surface area of prefrontal regions, especially the anterior cingulate, would be related to cognitive control. Cortical thickness is the distance from the gray matter/WM boundary (i.e., the WM surface) to the outer surface of the brain (i.e., the pial surface), likely partly reflecting the number of cells within cortical columns (38). Cortical area for a participant describes the 2D extent of the cortex compared with a standard brain, and it seems more closely related to the number of cortical columns (38). Area and thickness are genetically unrelated (39) but often confounded in measures of cortical volume, which is the product of the two. In addition to cortical thickness and area, we hypothesized relationships between microstructure of major WM tracts and cognitive control. More specifically, we expected high fractional anisotropy (FA) and low apparent diffusion coefficient (ADC), both indications of WM tract maturation and integrity, to be related to cognitive performance.

Results

Flanker Task Performance. Age relationships were analyzed with a nonparametric correlation (Spearman ρ) in cases where substantial nonlinearity was observed; otherwise, a parametric correlation was used (Pearson r). The task used was a version of the flanker task, and the participants were to indicate which direction an arrow presented on a computer screen pointed (*Materials and Methods*). In the congruent condition, the target arrow was surrounded by arrows pointing in the same direction, whereas in the incongruent condition, the surrounding arrows pointed in the opposite direction. Mean reaction time (RT) in the congruent condition was 789 ms (SD = 217) vs. 906 ms (SD = 293) in the incongruent condition ($t = 20.83, P < 10^{-75}$), and both were negatively related to age (Spearman ρ , congruent RT = $-0.53, P < 10^{-53}$; incongruent RT = $-0.61, P < 10^{-76}$). Mean incongruence effect (cognitive conflict) on RT was 14.8% and negatively related to age (Pearson $r = -0.33, P < 10^{-19}$). RT in each condition as well as the incongruence effects were plotted as a function of age, and smoothing spline (40) was used to estimate age trends (Fig. 1). RT decreased rapidly in the first part of the age range, plateauing at about 12–13 y in the congruent condition and about 14–15 y in the incongruent condition. The cognitive conflict effect followed the same basic age trajectory. Perfect accuracy was used as inclusion criterion, and therefore, it could not be analyzed (*Materials and Methods*).

Cortical Surface Area. First, RT in the incongruent condition was regressed on cortical area point by point on the surface without anatomical constraints by general linear models, with genetic ancestry factor (GAF) (*Materials and Methods*), scanner, sex, age, and RT in the congruent condition included as covariates of no interest. This analysis was run in the full sample and the young (age ≤ 12 y) and older (age > 12 y) age ranges separately. A cluster of negative effects covering the entire right anterior cingulate was found for the young group (cluster size = 2,077 mm², clusterwise $P = 0.019$, corrected) (Fig. 2) but not for the older group or the total sample. For comparison purposes, the same analyses were run for RT from the congruent and incongruent conditions without congruent RT as a covariate. No relationships survived corrections for multiple comparisons.

To illustrate the strength of the relationship, surface area of the right caudal anterior cingulate was extracted as a region of interest following the borders of the effect in Fig. 2 (i.e., in a completely data-driven way) and regressed on incongruent RT, with GAF, scanner, sex, and age included as covariates separately for the younger and older parts of the sample by multiple linear regression analysis. Partial β was -0.23 ($P < 0.05$) for the younger sample compared with -0.02 [not significant (n.s.)] for the older sample. With RT from the congruent condition included as an additional covariate, the corresponding partial β values for incongruent RT were -0.32 ($P < 0.05$) for the younger group and -0.01 (n.s.) for

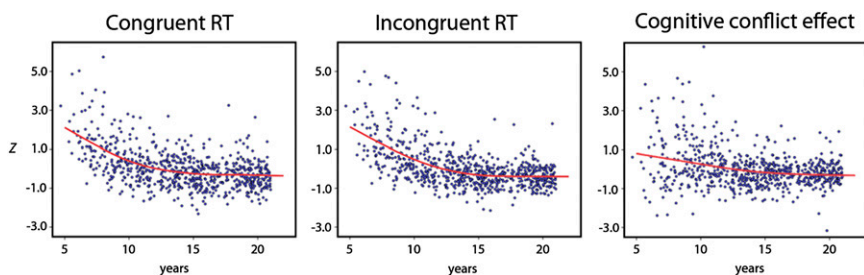


Fig. 1. Cognitive performance and age. RT in z scores, corrected for sex, site, and GAF, plotted as a function of age for congruent (Left) and incongruent (Center) stimuli as well as the cognitive conflict effects operationalized as the percentage of slowing of RT for incongruent relative to congruent stimuli (Right). The red lines represent the smoothing spline function, with the harshness of the smoothing parameter chosen to minimize Bayesian information Criteria (BIC) (40).

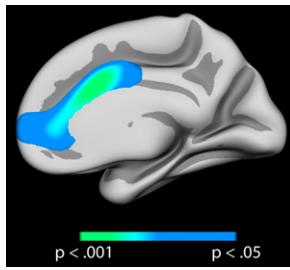


Fig. 2. Cortical surface area and cognitive conflict. Relationship between incongruent RT and local cortical surface area in the participants 12 y or younger corrected for age, sex, scanner, GAF, and congruent RT. The analyses were unbiased, with no anatomical constraints imposed. The effect was corrected for multiple comparisons by *z* Monte Carlo simulations and thresholded at $P < 0.05$.

the older participants. RT from the congruent condition did not contribute significantly. Additional analyses showed relationships of marginally less strength in the left hemisphere (partial $\beta = -0.24$ vs. -0.02 in the young and older groups, respectively, with congruent RT as a covariate). The same type of analysis was done for thickness of the right caudal anterior cingulate to test whether the observed effects were specific to area. Although thickness did not survive permutation testing, a significant relationship was found (partial $\beta = 0.11$, $P < 0.05$). When congruent RT was added as a covariate, this relationship ceased to be significant (partial $\beta = 0.09$, n.s.). Adding household income as a proxy for socioeconomic status as an additional covariate did not affect any of the reported relationships. There were no effects of sex on RT, but a positive significant effect on anterior cingulate surface area for boys (partial $\beta = 0.18$, $P < 0.10^{-6}$) was found.

The relationship between right anterior cingulate surface area and incongruent RT was plotted as a continuous function of age. The relationship was strongest for the youngest part of the sample, and it decreased linearly in strength with age (Fig. 3).

DTI. The relationships between RT in the incongruent condition and the ADC and FA in the 14 major tracts were tested by multiple regressions, with GAF, scanner, sex, and age included as covariates (Fig. 4). Significant positive RT relationships with forceps major were seen for both ADC ($\beta = 0.18$, $P < 0.014$, corrected for the number of comparisons) and FA ($\beta = -0.20$, $P < 0.0014$, corrected). ADC and FA are related to WM integrity, and lower ADC and higher FA indicate more mature WM tracts. Adding socioeconomic status as an additional covariate did not affect the relationships. Sex had no effect on the DTI measures. Forceps major represents the posterior, occipital portion of the corpus callosum. The exact delineation of the tract will vary somewhat between individuals, which is illustrated in Fig. 4.

Analyses run separately for the youngest and oldest parts of the sample did not yield significant results for either ADC or FA. In contrast to the cortical results, where a linear reduction in strength of the relationship with age was seen, the relationship between ADC/FA and cognition was strongest around 6–10 and above 16 y, with correlations not significant in the middle part of the age range (Fig. 3). The coefficient strength at different ages was generally not very different and should be interpreted with caution.

The analyses were rerun with congruent RT as an additional covariate. Neither of the RT measures was uniquely related to the DTI variables for any of the tracts. To test to what degree the different DTI parameters were complementary in explaining RT incongruent, analyses were run where RT incongruent was the dependent variable, and DTI parameters were included pairwise as simultaneous predictors [ADC and FA, ADC and transverse diffusion coefficient (TDC), ADC and longitudinal diffusion coefficient (LDC), FA and TDC, and FA and LDC]. In no cases did

a DTI parameter explain unique variance when it was entered simultaneously with FA, whereas the opposite was true in most instances. When FA and ADC in forceps major were entered, FA was still significantly related to incongruent RT ($\beta = -0.11$, $P < 0.01$), whereas ADC ceased to be significant. The same was true when FA was entered with TDC ($\beta = -0.12$, $P < 0.005$) and LDC (forceps major FA $\beta = -0.14$, $P < 0.00005$). LDC and TDC did not explain any additional variance to FA. In forceps major, both ADC and TDC explained unique variance in incongruent RT (ADC $\beta = 0.53$, $P < 0.005$; TDC $\beta = -0.43$, $P < 0.02$), and the same was seen when ADC was entered with LDC (ADC $\beta = 0.22$, $P < 0.00002$; LDC $\beta = -0.15$, $P < 0.005$).

Multimodal Analysis. A final multiple regression analysis was run, with RT from the incongruent condition as the dependent variable and FA in forceps major and the area of the right caudal anterior cingulate as joint predictors, with GAF, scanner and site, sex, and age included as covariates of no interest. In this analysis, both cortical area ($\beta = -0.10$, $P < 0.002$) and FA ($\beta = -0.13$, $P < 0.00005$) contributed significantly to explain RT.

Discussion

The present study represents a major multicenter initiative to understand the relationship between cognitive control and brain structure in development. Cognitive control performance showed a protracted developmental trajectory, and it was related to individual variability in brain structure. Interestingly, the relationships between the brain measures and cognitive function were very different for cortex and WM in terms of specificity and how the relationships varied with age. The results underscore the need for integration of different aspects of brain maturation to understand the structural foundations of cognitive development. Furthermore, the data indicate that brain–cognition relationships are not constant across development. Finally, the present results show that large multicenter collaborative studies are feasible in neurodevelopmental research, yielding extended possibilities to increase sample size and statistical power. Albeit cross-sectional and hence, not well-suited to investigate change per se, the present study is based on a very large sample, and it should be well-suited to

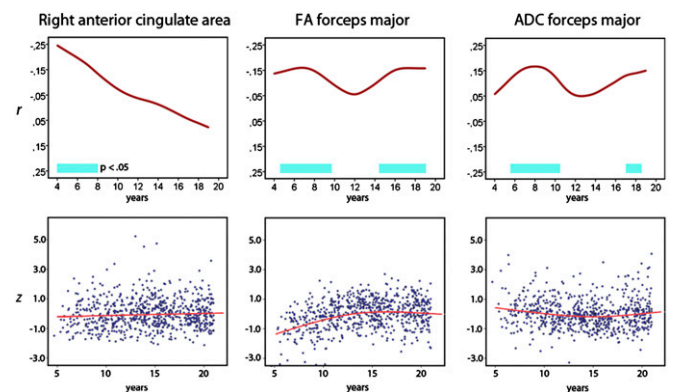


Fig. 3. Age relationships. (Upper) Correlations between incongruent RT and area of the right caudal anterior cingulate (Left), FA (Center), and ADC (Right) in forceps major. Correlations were calculated in 5-y age bins, with a moving time window of 1 y and the results smoothed (smoothing spline). *P* values are from the nonsmoothed correlations. Age, sex, scanner, and GAF were regressed out from all variables in addition to RT from the congruent condition for the area correlations. (Lower) Relationships between age and the imaging variables residualized for GAF, scanner, and sex. The age trajectory is estimated with smoothing spline (see above). Age did not correlate with right caudal anterior cingulate surface area (Pearson $r = 0.06$, $P = 0.10$), whereas the correlations for FA and ADC were significant (Spearman $\rho = 0.25$, $P < 0.10^{-10}$ and Spearman $\rho = -0.08$, $P < 0.05$, respectively).

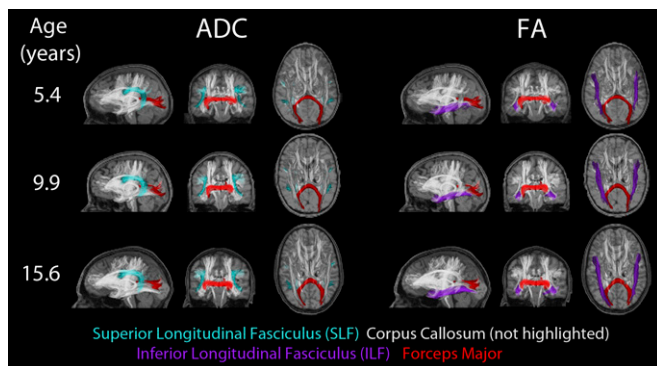


Fig. 4. Probabilistic tractography. Selected tracts in individual participants of different ages. These tracts were all significantly related to incongruent RT at $P < 0.05$ (ADC: corpus callosum and superior longitudinal fasciculus; FA: corpus callosum and inferior longitudinal fasciculus), but only forceps major survived Bonferroni corrections (ADC and FA).

capture general trends in brain–behavior relationships with age in development. The implications of the results are discussed below.

Structural Brain Maturation and Self-Regulation. Most children enter a stage of self-regulation about preschool age, at which time they are able to use rules, strategies, and plans to guide their behavior (41). From around 4 y of age, an executive attentional network is assumed to gradually differentiate from orienting and alerting systems and become the dominant factor in cognitive control (6, 22). The present results show age differences that are in coherence with a steep developmental trajectory of cognitive control from 4 y, which gradually decreases in slope and plateaus at around 14–15 y. Increases in processing speed could not account for all age-related improvements in conflict processing, indicating that self-regulating and executive abilities continue to develop throughout childhood and well into adolescence (42–47).

Although strong group-level age-related performance enhancement was seen, not all children develop the same degree of cognitive control at the same pace. The hypothesis of the present study was that different structural brain features can explain parts of the individual differences in self-regulation seen during development. The relationship between cortical surface area and cognitive control was found in the right caudal anterior cingulate, and post hoc analyses showed a similar but weaker relationship in the opposite hemisphere. Thus, although only the right hemisphere survived proper multiple comparison corrections, we do not believe that the data yield support to hemispheric asymmetry of effects. An early study found a correlation between total right anterior cingulate area and controlled processing in a group of children (28), which fits very well with the present results. The anterior cingulate cortex is implied as a critical region for executive attention, cognitive control, and self-regulation (15, 22, 48, 49), and its structural characteristics have been found to be related to self-regulation in a number of neurodevelopmental conditions (9–13, 32, 50, 51). An intriguing possibility is that individual variation in cortical morphology is related to problems with self-regulation and executive attention on a continuous scale from normality to pathology. Even in normally developing children, variations in the same brain structural features that are seen in groups with different risk factors, conditions, or pathology emerge as predictors of cognitive function. Two recent studies of normal children found that parent-reported hyperactivity, impulsivity (11), and conduct problems (32) were related to cortical thickness in several areas, including the anterior cingulate. The present results suggest that a similar phenomenon is observed even in a controlled experimental situation. This finding also yields support from a previous study of adults and the elderly, where executive control was related

to anterior cingulate thickness, and it was suggested that cortical maturation could be the driving causal factor (52). Other studies have not found cognitive control to correlate with cortical morphometry in the anterior cingulate (46). However, cortical surface area has, to our knowledge, not been directly investigated in previous studies.

Improvement in cognitive control and self-regulation may be tightly coupled to differentiation of the executive attentional subsystem from other attentional networks in the brain, likely depending on maturation of major long-distance projection tracts and enabling anterior cingulate and likely, other prefrontal structures to take more dominating roles (22). Although the present data cannot be used to test this idea of network differentiation, it is interesting to note that, although anterior cingulate area shared unique variance with cognitive control, the relationship between characteristics of the WM tracts and cognitive control was dependent on mental speed as measured by congruent RT. Thus, cortical surface area was a more specific predictor of cognitive control than WM maturation, which in the present data, was more related to general improvement in mental speed. WM characteristics may be a general factor of importance for a range of cognitive tasks, including general intellectual abilities or g (53–56). Furthermore, forceps major is not assumed to be especially important for cognitive control. This assumption does not exclude the possibility that maturation of specific WM tracts can be related to more specific cognitive functions (57–60), but it will likely also have general beneficial effects on major cognitive functions through facilitation of processing speed (61–71).

The independence of cortical area and WM properties in explaining cognition was also evident when testing how the brain–cognition relationship varied continuously as a function of age. Although the relationship between cortical area and control was strongest for the young participants and linearly dropped off with increasing age, the DTI–cognition relationships showed a more complex age function. Different developmental slopes for cortical structure and WM properties (27), only weakly related and complementary in explaining intellectual development (54), have been shown previously. Varying brain–cognition relationships across age have also been shown (55, 72) but seldom with multimodal imaging data (73). The time-varying relationship may reflect the processes that are of most importance at different stages in development.

One limitation is the cross-sectional design, which prevents depiction of individual trajectories and differences in change and direct estimation of relationships between change across different variables. The conclusions from the present study should be replicated in longitudinal studies, but very few such studies exist. Another limitation is the use of a single standardized measure of cognitive control. Self-regulation is a wide concept, which could be measured both inside and outside the laboratory with different tasks and procedures, and the generalizability of the findings needs to be investigated in a wider context in future studies.

Conclusion. Cognitive control develops rapidly during childhood years, with protracted development in adolescence, and it was related to an area of the anterior cingulate. This finding is intriguing, because anterior cingulate is related to impulse, attention, and executive problems in a range of neurodevelopmental disorders, indicating an overlapping neural foundation for self-regulation abilities from normality to a spectrum of neurodevelopmental disorders. WM properties added to the picture by explaining additional variance in cognitive control.

Materials and Methods

Sample. Data used in the preparation of this study were obtained from the Pediatric Imaging, Neurocognition, and Genetics (PING) Study database (<http://ping.chd.ucsd.edu>), which was funded in 2009 by the National Institute on Drug Abuse and the Eunice Kennedy Shriver National Institute of Child Health & Human Development as a 2-y project of the American Recovery and

Reinvestment Act (*SI Text*). The human research protections programs and institutional review boards at the universities participating in the PING project approved all experimental and consenting procedures, and all participants or their legal guardian gave informed consent. Participants were screened for history of major developmental, psychiatric, or neurological disorders, brain injury, or other medical conditions that affect development. The sample used for the present analyses included participants registered and processed at the University of California at San Diego by February 12, 2012. Only participants with cortical and subcortical segmentations that passed quality check who were not twins or triplets and met the flanker task performance criteria (see below) were included. The final sample consisted of 735 children ages 4.7–21 y (mean = 14.3 y, SD = 4.2, 354 girls). Of these children, 684 children had usable DTI scans. A GAF was calculated as a proportion of European, African, Native American, East Asian, Central Asian, and Oceanic decent based on genotype analysis, or when missing ($n = 38$), values from self-report were used to predict GAF. Each of nine US sites (Weil Cornell Medical College, University of California at Davis, University of Hawaii, Kennedy Krieger Institute, Massachusetts General Hospital, University of California at Los Angeles, University of California at San Diego, University of Massachusetts Medical School, and Yale University) contributed to the sample.

Cognitive Task. A modified version of the Eriksen flanker task (35) included in the National Institutes of Health Toolbox Cognitive Function Battery was used (37) (*SI Text*). This well-validated task is suitable to induce response conflict, reflecting more complex cognitive processing, including inhibitory processes and generally, more top-down and controlled attention (74). The participants are required to press a button to indicate to which direction a target arrow points. The target is surrounded by arrows (flankers) that point in the same (congruent) or opposite (incongruent) direction of the target. After a practice block, 20 trials (13 congruent and 7 incongruent) were presented; 75 of 836 participants were excluded, because they did not meet performance criteria of accuracy and RT (26 participants were excluded because of the additional exclusion criteria described above).

Imaging Data Acquisition and Processing. Across nine sites and 12 3T scanners, a standardized multiple-modality high-resolution structural MRI protocol was implemented involving 3D T1-weighted volumes and a set of diffusion-

weighted scans (*SI Text*). Acquisition protocols were identical or nearly identical across all sites. Image postprocessing and analysis were performed using a fully automated set of tools available in the FreeSurfer software suite (<http://surfer.nmr.mgh.harvard.edu/>) (75–81) as well as an atlas-based method for delineating and labeling WM fiber tracts (82). Continuous maps of cortical surface area were obtained by computing the area of each triangle of a standardized tessellation mapped to each subject's native space using a spherical atlas registration procedure (76) (*SI Text*).

Statistical Analyses. Scanner, age, sex, and GAF were included as covariates in all analyses of brain–cognition relationships. All analyses were run for the whole age range and the youngest (age ≤ 12 y) and oldest (age > 12 y) parts of the sample separately because of substantial nonlinearity in RT across age. Developmental trajectories were estimated by use of a nonparametric approach, the smoothing spline (*SI Text*) (40), without any restrictions on the shape of the curve. To show effect sizes in regions and tracts, Pearson correlation were used for approximate linear relationships, and Spearman ρ was used for nonlinear relationships. Relationships between RT and cortical thickness and areal were tested vertexwise by general linear models. z Monte Carlo simulations, as implemented in FreeSurfer (83, 84), were used for multiple comparison corrections across space and synthesized with a cluster-forming threshold of $P < 0.05$ (two-sided). The results were thresholded at $P < 0.05$, corrected. FA and ADC in 14 tracts of interest were tested by multiple regression analyses, and P values were Bonferroni-corrected by a factor of 28 (14 tracts \times 2 metrics). Additional analyses were run with LDC and TDC.

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