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Abstract

Prior research points to a positive concurrent relationship between reasoning ability and both fronto-parietal structural connectivity, as measured by diffusion tensor imaging (e.g. Tamnes et al., 2010), and fronto-parietal functional connectivity, as measured by fMRI (e.g. Cocchi et al., 2014). Further, recent research demonstrates a link between reasoning ability and functional connectivity of two brain regions in particular: rostrolateral prefrontal cortex (RLPFC) and the inferior parietal lobe (IPL) (Wendelken et al., 2016). Here, we sought to investigate the concurrent and dynamic, lead-lag relationships between fronto-parietal structural connectivity, functional connectivity, and reasoning ability in humans. To this end, we combined three longitudinal developmental datasets with behavioral and neuroimaging data from 523 male and female participants between 6 and 22 years old. Cross-sectionally, reasoning ability was most strongly related to functional connectivity between RLPFC and IPL in adolescents and adults, but to fronto-parietal structural connectivity in children. Longitudinal analysis revealed that RLPFC-IPL structural connectivity, but not functional connectivity, was a positive predictor of future changes in reasoning ability. Moreover, we found that RLPFC-IPL structural connectivity at one time point positively predicted future changes in RLPFC-IPL functional connectivity, while in contrast, functional connectivity did not predict future changes in structural connectivity. Our results demonstrate the importance of strong white matter connectivity between RLPFC and IPL during middle childhood for the subsequent development of both robust functional connectivity and good reasoning ability.

Significance Statement

The human capacity for reasoning develops substantially during childhood and has a profound impact on achievement in school and in cognitively challenging careers. Reasoning ability depends on communication between lateral prefrontal and parietal cortices. Thus, to understand how this capacity develops, we examined the dynamic relationships over time between white matter tracts connecting fronto-parietal cortices (i.e., structural connectivity), coordinated fronto-parietal activation (functional connectivity) and reasoning ability in a large longitudinal sample of 6-22-year-olds. We found that greater fronto-parietal structural connectivity in childhood predicts future increases in both functional connectivity and reasoning ability, demonstrating the importance of white matter development during childhood for subsequent brain and cognitive functioning.

Introduction

Reasoning, or the capacity to solve problems in novel situations, is a form of high-level cognition that improves dramatically over childhood, and to a lesser extend during adolescence (McArdle et al., 2002; Ferrer et al., 2009). Much of the research on the neural underpinning of reasoning has focused on its localization to specific brain regions (Prado et al., 2011; Wendelken et al., 2011; Krawczyk et al., 2012). However, reasoning, like other higher cognitive operations, depends on the coordinated action of multiple regions. Thus, characterizing patterns of inter-regional communication, and how such communication changes over time, is critical for understanding developmental changes and individual differences in reasoning. Doing so requires insight into both structural connectivity, or the white matter tracts that connect disparate brain regions, and functional connectivity, or the coordinated activity of different regions.

Considerable effort has been devoted to understanding the development of functional connectivity and how it relates to higher cognition. In particular, prior research has emphasized the importance of functional connectivity among components of the lateral fronto-parietal network (LFPN), which supports reasoning and other higher cognitive functions (Jung & Haier, 2007; Shokri-Kojiri et al., 2012; Cocchi et al., 2014). Prior studies have also examined links between structural connectivity and reasoning, reporting associations between reasoning and multiple white matter tracts (Tamnes et al., 2010; Peters et al., 2013), or between reasoning and global white matter during childhood (Ferrer et al., 2013).

Our prior fMRI research in adults has emphasized the importance for reasoning of two brain regions in particular: rostrolateral prefrontal cortex (RLPFC) and the inferior parietal lobule (IPL) (e.g. Wendelken et al., 2010, 2011, 2012; for reviews, see Vendetti & Bunge 2016; Krawczyk et al., 2012). In a cross-sectional fMRI study that focused on functional connectivity among key nodes of the LFPN, we demonstrated that RLPFC-IPL FC and a composite measure of reasoning ability were associated in adolescents, but not in children under 12 (Wendelken et al., 2016). The present study examines concurrent and longitudinal predictors of reasoning ability in a large, pooled dataset that includes the earlier sample.

To understand how LFPN functional connectivity emerges as a contributor to reasoning ability, it is critical to also understand the relevant changes in structural connectivity and how these relate to changes in functional connectivity and reasoning ability. Prior work relating structural and functional connectivity has focused on the default mode network (Greicius et al., 2009; Horn et al., 2014; Khalsa et al., 2014) or on global patterns of connectivity (Honey et al., 2009), with little attention given to the LFPN connections that are critical for higher cognition. Moreover, while concurrent relationships between structural and functional connectivity have been explored for some networks, the dynamic, lead-lag relationships between these measures remain largely uncharted.

Here we considered two, non-mutually exclusive, hypotheses about the lead-lag relations between structural and functional connectivity in the LFPN. First, structural connectivity could enable the development of functional connectivity such that increased structural connectivity would be associated with greater potential for future increases in functional connectivity. Second, functional interaction between regions could drive physiological changes in the white matter connections. In this case, higher functional connectivity would be associated with future increases in structural connectivity. We then sought to determine whether structural connectivity and/or functional connectivity relate to reasoning development. It is possible that any relationship between structural connectivity and behavior, whether concurrent or lagged, is mediated by functional connectivity. Alternatively, even where there is a

concurrent relationship between functional connectivity and behavior, structural connectivity may still prove to be a better predictor of behavioral change. In this case, earlier maturation of white matter tracts may be associated with earlier improvements in reasoning performance. However, delayed maturation might be advantageous (c.f. Shaw et al., 2006). The present study tests these hypotheses regarding the lead-lag relationships between structural connectivity, functional connectivity, and reasoning ability over development.

Materials and Methods

Experimental Design

To begin to answer these questions about the lead-lag relationships between structural connectivity, functional connectivity, and reasoning ability, we conducted an analysis of longitudinal DTI, fMRI, and behavioral data from over 520 participants enrolled in longitudinal brain imaging research. We focused our analyses on the LFPN connections that have been implicated previously in studies of reasoning, and in particular on the RLPFC-IPL connection that our own prior research has highlighted as a key contributor to reasoning ability. The present study extends this prior work by examining how functional connectivity among frontal and parietal ROIs relates to structural connectivity, and by examining longitudinal relationships among these brain variables and behavior.

Participants & Measures

This study incorporated data from three different sources: 1) the "Neurodevelopment of Reasoning Ability" study (NORA; UC Berkeley, PIs: S. Bunge & E. Ferrer), 2) the "Hippocampal Investigation of Pediatric Populations over Time" study (HippoTime; UC Davis; PIs: S. Ghetti & S. Bunge), and 3) the "Predicting Late-Emerging Reading Disability" study (LERD; Vanderbilt University; PI: L. Cutting). Altogether, the current study included data from 523 participants (254 females), including 193 from the NORA dataset, 211 from the HippoTime (HIPPO) dataset, and 119 from the LERD dataset. Longitudinal data from two (NORA), three (HIPPO), or four (LERD) timepoints were available for 345 of these participants. Participants ranged in age from 6 up to 21.7 years old, with a mean age of 10.74 years (SD = 3.29 years). A more detailed breakdown of participant demographics is given in **Table 1**.

The NORA and HIPPO studies both involved a cohort-sequential longitudinal design, wherein T1 samples were collected from a broad initial age range, and follow-up scans were collected at different intervals. For NORA, T2 data collection was conducted on average 1.5 years after T1 data collection (ranging from 0.9 to 2.2 years). For HIPPO, longitudinal visits were separated by an average of 1.3 years (ranging from 0.73 to 2.9 years). LERD employed a traditional longitudinal design in which all T1 data were collected from participants at age 7, and subsequently at 1-year intervals.

We considered three principal measures for each participant: reasoning ability, indexed via raw scores from the WASI Matrix Reasoning test (Wechsler 1974); structural connectivity, indicated by fractional anisotropy (FA) of selected white-matter tracts; and functional connectivity, calculated as task-independent inter-regional correlations in fMRI timeseries data. Structural connectivity data were available for all timepoints, in all three studies. However, HIPPO participants had Matrix reasoning scores from only T1 and T3, and LERD participants had Matrix Reasoning scores only at T1, and

functional connectivity only at T1 and T4. While the LERD dataset included resting-state fMRI data, both NORA and HIPPO contributed task data. NORA fMRI data were collected while subjects performed a visual analogy task (Whitaker et al., in preparation; task described in Wright et al., 2008). HIPPO fMRI data were collected while subjects performed a source memory task (Sastre et al., 2016).

In our prior investigations of reasoning ability with the NORA dataset, we had computed a reasoning ability factor score on the basis of multiple reasoning measures, including Concept Formation and Analysis-Synthesis from Woodcock-Johnson III (Woodcock et al., 2001) as well as Block Design and Matrix Reasoning from WASI (Ferrer et al., 2013; Wendelken et al., 2016). Matrix Reasoning, the only measure that was available across the three studies that we consider here, loaded strongly onto the reasoning factor score in NORA in previous analyses (Ferrer et al., 2013).

MRI Data Collection and Preprocessing

NORA data were collected at the University of California at Berkeley Brain Imaging Center and the University of California at San Francisco Neuroimaging Center, on 3T Siemens TIM MR scanners with 12-channel head coils. HIPPO data were collected at the UC Davis Imaging Research Center on a 3T Siemens Trio Tim scanner with a 32-channel head coil. LERD data were collected at Vanderbilt University Institute of Imaging Science on a 3T Philips Achieva MRS scanner. Details of each scan type are included in **Table 2**.

DTI data were analyzed using the FMRIB Diffusion Toolbox (FDT) software tool (Behrens et al., 2003). First, eddy correction was run on the DTI images to correct for eddy current distortions, and brain extraction was performed to exclude non-brain voxels from further analysis. Following these preliminary steps, a diffusion tensor model was fit to each voxel to calculate directions and magnitude of diffusion. This procedure produces an FA image for each participant.

All fMRI data were preprocessed in SPM8 (Wellcome Trust Center for Neuroimaging, London). Functional images were corrected for differences in slice acquisition timing and were realigned to the first volume by means of a 6-parameter rigid-body transformation. Each participant's T1 structural image was coregistered to his/her mean realigned functional image and then spatially normalized to SPM's T1 template. Normalization parameters obtained from this process were then applied to the functional images to produce a set of functional images in SPM standard space (MNI152), with 3x3x3mm voxels. Functional images were then smoothed with an 8-mm FWHM isotropic Gaussian kernel. Finally, volumes associated with a high degree of motion (> 1mm scan-to-scan translation) or signal spiking (> 2% signal change) were corrected (interpolated) using the ArtRepair volume correction tool (ArtRepair, Stanford Psychiatric Neuroimaging Laboratory). Scans with more 25% corrected volumes were excluded from further analysis, resulting in exclusion of 346 separate scans, or 11% of the total number available.

Functional Connectivity Analysis

We sought to understand the relationships between reasoning ability, structural connectivity, and intrinsic patterns of functional connectivity – correlations in regional activation that are relatively stable across task demands and that are thought to reflect the long-term history of coordination between regions (Seely et al., 2007; Cole et al., 2014). Thus, we adopted the methods of intrinsic functional

connectivity analysis. This approach contrasts with analyses of task-related functional connectivity that focus on higher frequency correlations that differ as a function of task demands. Although our pooled dataset included data from several fMRI scans (NORA and HIPPO) in addition to resting-state scans (LERD), our analysis was designed to minimize the effect of task on the connectivity measure.

ROIs were 5-mm spheres that we have utilized previously in the examination of functional connectivity and reasoning (Wendelken et al., 2016; see **Figure 1**). Each ROI was centered on coordinates selected from a large set of ROIs that have been used previously to examine global connectivity properties (Power et al., 2011). Specifically, we selected coordinates that corresponded to the left and right RLPFC, DLPFC, IPL, and SPL regions that are typically engaged during reasoning tasks (Krawczyk et al., 2012; Vendetti et al., 2014).

Intrinsic functional connectivity between these regions was assessed by measuring low-frequency correlations between BOLD activation time series extracted for each ROI and for each participant. Several steps were undertaken to minimize the effects of physiological noise and motion on the extracted time series. These steps included: 1) regressing out average signal from CSF and from white matter; 2) regressing out volume-to-volume motion for six dimensions (three translation directions and three rotation axes); 3) regressing out task-related signal where applicable (Fair et al., 2007); 4) band-pass filtering (with a minimum frequency of .008 Hz and a maximum frequency of .09 Hz); and 5) scrubbing (Power et al., 2012) to remove time points associated with high motion and/or signal spikes (as determined by ArtRepair). Correlation values were transformed to Z-scores using Fisher's R-to-Z transformation, prior to the main statistical analyses.

Structural Connectivity Analysis

White matter tracts were obtained via probabilistic tractography, using the FDT ProbtrackX tool. Tractography was conducted using T1 data from the NORA dataset, and these tracts were subsequently used for the analysis across all longitudinal timepoints and datasets. The same lateral prefrontal and parietal coordinates that were used in analyses of functional connectivity (as centers for the spherical ROIs) were also used as endpoints for tractography. Computed tracts included left and right fronto-parietal, intra-frontal, and intra-parietal connections (**Figure 2**). For each participant and each target tract, 1000 attempts were made to find a streamline from one endpoint to the other. Specifically, each streamline was started randomly from a white matter voxel within a 12 mm radius of the start point, and terminated successfully if it reached a voxel within 12 mm of the end point. (The 12-mm radius was selected to ensure sufficient white matter voxels within the sphere). A voxel was considered to be part of a subject's tract if at least two streamlines passed through that voxel. Group average tracts were obtained by registering binarized subject tracts to MNI space, summing these together, and then thresholding to include in the final group tract voxels that were present in at least 25% of the contributing subject tracts. For each participant, the group tracts were mapped to subject space and masked with segmented subject white matter, to produce subject-specific versions of each tract. For the resulting masks, average FA values were extracted from the participant's FA map, and these FA values were submitted to statistical analyses.

Statistical Analysis

All statistical analyses were conducted in R (R Core Team, 2013).

To account for possible differences between the three datasets (e.g., due to scanner, testing conditions), all values were normalized to the NORA sample. Specifically, for each measure from the LERD or HIPPO dataset (e.g. left RLPFC-IPL fractional anisotropy), a mean value was calculated both for the LERD/HIPPO sample and for the equivalent age range from the NORA sample. The difference was then subtracted from the LERD/HIPPO sample values to produce a set of normalized values for that measure. For HIPPO Matrix Reasoning, due to the fact that different test versions were used at the two different time points, data from each time point were normalized separately to the relevant NORA sample mean. In addition to normalization, we also included study (NORA, HIPPO, or LERD) as a covariate of no interest in relevant analyses (as noted).

We consider the combination of datasets, as described above, to be the best approach given the available data. First, although our full participant sample is large, no individual dataset contributed sufficient numbers of data points to fully support our planned longitudinal analyses. Second, individual datasets included narrower age ranges and/or gaps in coverage relative to the combined dataset. Nevertheless, our approach may not fully succeed at controlling for differences between datasets, and there is added value in also examining results from the separate datasets. Thus, for each of the main results that we present in the manuscript, we also report corresponding results from each individual dataset.

Prior to normalization, we conducted outlier correction separately for each dataset and relevant measure. We removed data points that were more than three standard deviations from the mean for that dataset. In addition, after normalization, we removed data points that were more than three standard deviations from the mean of the entire sample. In total, 8 subject time points were excluded due to outlier Matrix Reasoning scores, another 5 due to outlier functional connectivity values, and another 10 due to outlier structural connectivity values.

Concurrent relationships and age effects were examined using mixed model regression, which accounts for subject repetition, on the full longitudinal dataset (nlme package in R, Pinheiro et al., 2013). Longitudinal analyses involved modeling and regression of change scores, and were limited in all cases to data from two longitudinal time points.

In order to test for age differences in the relationships between variables, we split the full age range into two separate age groups. Having previously shown a developmental shift in functional connectivity that occurs at around age 12 (Wendelken et al., 2016), we created a subdivision between children under 12 (ages 6-11, here termed “younger participants”) and adolescents and young adults (ages 12-22, termed “older participants”). This procedure resulted in 423 individuals (209 females) in the former group, and 99 individuals (48 females) in the latter.

In addition to splitting the data by age group for a subset of analyses, we also examined nonlinear age-related changes in our key variables using age as a continuous variable. For our key measures, including Matrix Reasoning, RLPFC-IPL functional connectivity, and RLPFC-IPL structural connectivity, trajectories of age-related change, computed across the entire age range, were fit using the cumulative normal distribution (“pnorm” function in R). This function includes two parameters: μ, the age of maximal change, and σ, the spread of change around that age. This model can fit a variety of different

trajectories, including linear, asymptotic, and s-shaped curves, and has the advantage of doing so with a single functional form that yields readily interpretable parameters (c.f. Wendelken et al., 2016).

Results

Developmental improvement in reasoning ability

Reasoning ability, as indexed by scores on the Matrix Reasoning task, demonstrated robust developmental improvement. In cross-sectional analysis of the full age range, we observed a nonlinear pattern of age-related increase, with the greatest increases occurring amongst the youngest participants ($b = 33.4$, $t(311) = 27.6$, $p < .001$; **Figure 3**). We found that age-related increases were maximal at age 6 – i.e., at the beginning of the examined age range. There was no effect of gender on behavioral performance. Although younger participants demonstrated the larger increase in reasoning ability, in both linear cross-sectional and longitudinal analyses (cross: $b = 2.4$, $t(149) = 19.1$, $p < .001$; long. change in R: $\Delta = 3.97$, $t(201) = 11.2$, $p < .001$), older participants also showed significant improvement (cross: $b = 0.53$, $t(60) = 5.9$, $p < .001$; long: $\Delta = 1.8$, $t(45) = 3.0$, $p = .004$).

Test of potential confound for brain imaging analyses

Recent research has suggested that many behavioral measures, including reasoning ability, might be related to in-scanner head motion (Siegel et al., 2016). Thus, we sought to test for this possibility in our own data by regressing Matrix Reasoning score against average volume-to-volume translational displacement. While increasing age was associated with decreasing head motion in our sample, as expected, the relationship between motion and reasoning ability was not significant after accounting for age ($p = .34$). Further, there was no interaction between motion and age group (younger vs older participants) in their effect on reasoning ($p = .41$). Despite the lack of a relation between head motion and reasoning ability in our sample of participants, we did, as described previously, employ methods designed to reduce the impact of head motion on computed functional connectivity measures (regression of motion parameters and scrubbing).

Connectivity and reasoning ability: concurrent effects

Before addressing the key question of the lead-lag relationships between structural connectivity, functional connectivity, and reasoning, we sought to extend, in this larger sample, prior results obtained with the NORA dataset that were focused on the separate cross-sectional relationships between reasoning ability and functional connectivity (Wendelken et al., 2016) and between reasoning ability and structural connectivity (Ferrer et al., 2013). The former study included 132 participants (76 males, age 6-19), with T2 longitudinal data for 56. The latter study included cross-sectional data from 103 participants (55 males, age 6-18). All of these participants were included in the present analysis.

As reported previously for a subset of the present dataset (Wendelken et al., 2016), there was an interaction between age group (6-11 vs 12-22) and RLPFC-IPL functional connectivity ($b = 8.2$, $t(100) = 2.6$, $p = .009$), with the functional connectivity-reasoning relation present in older participants

(controlling for Age and Study: b = 5.44, t(18) = 3.1, p = .006), but not in younger participants (p = .24). The result in older participants was driven by a significant effect for left RLPFC-IPL (b = 4.2, t(19) = 2.8, p = .01) and a non-significant trend for right RLPFC-IPL (b = 2.1, t(19) = 1.5, p = .16). Separate analysis of older participants in the NORA and HIPPO datasets revealed similar positive effects: significant in the former and marginally significant in the latter (NORA: b = 8.2, p = .002; HIPPO: b = 4.2, p = .1). In contrast, there was no effect for younger participants in any of the three datasets examined separately (all ps > .2). There were no main effects or interactions involving gender (ps > .2). In summary, we found a relationship between RLPFC-IPL functional connectivity and reasoning only for adolescents and young adults.

Next, we examined LFPN functional connectivity more generally. However, we found no significant relationship between reasoning ability and either average fronto-parietal connectivity (i.e. average across connectivity of all frontal to parietal connections) or average network connectivity (i.e. average across all fronto-parietal, intra-prefrontal, and intra-parietal connections), in either younger or older participants (ps > .21). Thus, reasoning ability among adolescents and young adults was related to functional connectivity of RLPFC-IPL, particularly in the left hemisphere, but not to connectivity among other nodes in the LFPN.

In the next set of analyses, we focused on structural connectivity. Having shown in cross-sectional analyses of a subset of the NORA dataset that structural connectivity averaged across all white matter in the brain was positively related to reasoning ability (Ferrer et al., 2013), we tested here whether structural connectivity within the LFPN and/or for fronto-parietal connections in particular would be related to reasoning ability. First, we computed average structural connectivity across all of our tracts: fronto-parietal tracts as well as intra-frontal and intra-parietal tracts. Mixed-model regression analyses conducted on the full sample revealed a marginally significant positive relation between average fronto-parietal network structural connectivity and reasoning ability (controlling for Age and Study; b = 23.3, t(128) = 1.8, p = .06).

To test whether this marginal relation was driven by a subset of connections within the network, we broke down LFPN structural connectivity into three separate components: fronto-parietal structural connectivity, intra-frontal structural connectivity, and intra-parietal structural connectivity. In a stepwise regression across the entire age range, only fronto-parietal structural connectivity survived as a predictor of reasoning ability. This overall relationship between fronto-parietal structural connectivity and reasoning was marginally significant when controlling for both Age and Study (b = 26.1, t(127) = 1.9, p = .06; **Figure 4**). There was no interaction between structural connectivity and gender (p > 0.2).

Next, we asked whether this relationship between fronto-parietal structural connectivity and reasoning varied as a function of age. We included an Age x structural connectivity interaction term into the regression model and found a negative interaction between the effects of age and fronto-parietal structural connectivity on reasoning (b = -16.5, t(127) = -5.2, p < .001), such that there was a bigger effect of structural connectivity on reasoning among younger participants. Further, the main effect of structural connectivity on reasoning was significant in this model (b = 194.0, t(127) = 5.5, p < .001). A similar analysis that incorporated age as a categorical group rather than as a continuous variable revealed a similar interaction (age group x structural connectivity: b = -13.5, t(127) = -3.8, p < .001), such that there was a strong positive relationship between fronto-parietal structural connectivity and reasoning in younger participants (b = 88.7, t(64) = 5.4, p < .001), but not in older participants (p = .54).

In summary, stronger structural connectivity within fronto-parietal tracts was associated with better reasoning ability in children but not in adolescents and adults.

To better understand this key finding of a positive effect of fronto-parietal structural connectivity on reasoning in younger participants, we repeated the previous age interaction analysis separately in each of the three datasets. The negative interaction between age and structural connectivity was observed in all three datasets (NORA: b = -21.8, t(44) = -4.9, p < .001; HIPPO: b = -9.7, t(81) = -2.3, p = .03; LERD: b = -256.9, t(84) = -1.7, p = .09). Further, in the presence of this interaction, the positive main effect of structural connectivity on reasoning was also apparent in all three datasets (NORA: b = 251.0, t(44) = 5.2, p < .001; HIPPO: b = 120.4, t(81) = 2.3, p = .03; LERD: b = 1919.1, t(84) = 1.7, p = .09).

Next, we sought to determine whether the association between fronto-parietal structural connectivity and reasoning ability was present in particular in the RLPFC-IPL connection, for which the functional connectivity-reasoning relationship has been established. Further, we sought to determine if there were differences between left and right-side connections. Across the entire age range, there was a marginal positive relationship between RLPFC-IPL structural connectivity and Reasoning (controlling for age and study: b = 19.1, t(128) = 1.6, p = 0.1). This result was driven by a significant effect in the left hemisphere (controlling for age and study: b = 23.1, t(129) = 2.0, p = .04) with no effect in the right hemisphere (p = 0.3). Consistent with what we had observed for average fronto-parietal structural connectivity, we found a significant negative interaction between RLPFC-IPL structural connectivity and age (b = -14.4, t = -4.9, p < .001), as well as a significant main effect of structural connectivity on reasoning (b = 172.4, t(127) = 5.1, p < .001). In this analysis, similar interaction effects were observed for left and right RLPFC-IPL connections (left: b = -13.3, t(128) = -4.7, p < .001; right: b = -13.2, t(128) = -5.8, p < .001). Moreover, inclusion of the interaction term revealed a significant main effect of structural connectivity on reasoning for both the left and right RLPFC-IPL connections (left: b = 166.6, t(128) = 5.7, p < .001; right: b = 151.5, t(128) = 6.8, p < .001). Thus, as for average fronto-parietal structural connectivity, RLPFC-IPL structural connectivity demonstrated a positive association with reasoning ability that was stronger in younger than in older participants.

Finally, we sought to determine whether the relationship between structural connectivity and reasoning ability was mediated at least in part by functional connectivity. For this analysis, we focused on the left RLPFC-IPL connection that demonstrated the strongest relationship between functional connectivity and reasoning. Because the functional connectivity effect was limited to older participants, and the structural connectivity effect was driven by younger participants, we did not expect to find a mediating relationship. Indeed, comparison of two models, one that included functional connectivity as a mediator of the structural connectivity-reasoning relationship, and the other that did not, revealed a clear preference for the model without mediation (AIC: 4734 vs 3966, p < .001).

Developmental changes in structural and functional connectivity

To better understand the relationship between frontoparietal connectivity and reasoning, it is important to identify the developmental trajectory associated with each connectivity measure. We have previously reported a nonlinear pattern of age-related change for RLPFC-IPL functional connectivity, with the largest increases occurring during late childhood and early adolescence (Wendelken et al., 2016). Results from the current expanded sample are consistent with this finding: the optimal fit curve indicated a

maximal rate of increase in functional connectivity at age 13 ($\mu = 13$, $\sigma = 2$, $b = 0.15$, $t(1,583) = 10.8$, $p < .001$; **Figure 5a**).

For RLPFC-IPL structural connectivity, larger increases were observed in younger participants, with the maximal rate of increase at age 7 ($\mu = 7$, $\sigma = 6$, $b = 0.07$, $t(1,778) = 14.7$, $p < .001$; **Figure 5b**). Average fronto-parietal structural connectivity demonstrated a similar pattern of age-related change. In summary, developmental increases in RLPFC-IPL structural connectivity are greatest in younger children, while developmental increases in RLPFC-IPL functional connectivity peak in early adolescence.

Relationships between structural and functional connectivity

Having observed age-related and longitudinal increases in both structural and functional fronto-parietal connectivity, we next sought to understand the relation between these two connectivity measures. Because both measures increased with age**,** it is unsurprising that they demonstrated a strong positive relationship, across our sample, before accounting for age ($b = 1.6$, $t(206) = 5.6$, $p < .001$). However, after accounting for age and study in a mixed-model regression, the relationship between average fronto-parietal structural connectivity and average fronto-parietal functional connectivity did not achieve statistical significance ($b = .45$, $t(205) = 1.5$, $p = .14$). Further, there was no interaction with Age ($p = .8$) or Age Group ($p = .6$). Similar results were observed when the analysis was limited to the RLPFC-IPL connection (controlling for Age and Study: $b = 0.81$, $t(205) = 1.7$, $p = .08$). In this case, there were trend-level positive interactions with Age ($p = .13$) and with age group ($p = .17$). Thus, we observed overall positive but weak concurrent relationships between fronto-parietal Structural and functional connectivity, over and above the common effect of increasing age.

Next, we conducted longitudinal analyses to test whether stronger structural connectivity at one time-point might drive future increases in functional connectivity. We focused our investigation of such lead-lag dynamic relationships on the RLPFC-IPL connection. To test whether RLPFC-IPL structural connectivity would predict future increases in corresponding functional connectivity, we conducted a linear stepwise regression with longitudinal change in functional connectivity as the dependent variable, and with T1 values for functional connectivity, structural connectivity, and Age, and longitudinal change in Age and structural connectivity as independent variables. The resulting model included T1 functional connectivity, T1 structural connectivity, T1 Age, and change in structural connectivity as significant predictors of change in functional connectivity (**Figure 7a**). As expected, T1 functional connectivity was a negative predictor of functional connectivity change ($b = -.62$, $t(134) = -8.9$, $p < .001$), as individuals who already exhibit higher functional connectivity at T1 change less over time. Change in structural connectivity was a positive predictor of functional connectivity change, but this relationship was not significant after controlling for Study ($p = .4$). Critically, T1 structural connectivity was a positive predictor of functional connectivity change (controlling for Study; $b = 1.7$, $t(134) = 2.6$, $p = .009$), such that participants with higher RLPFC-IPL structural connectivity at T1 showed greater longitudinal increases in RLPFC-IPL functional connectivity. There was no effect of age group on this result (T1 structural connectivity x Group: $p = .31$), nor was there an effect of gender (T1 structural connectivity x Gender: $p = .94$). Similar effects of T1 structural connectivity on functional connectivity change were observed in each of the three datasets considered separately, although they only reached significance in the combined analysis (NORA: $b = 1.5$, $p = .18$; HIPPO: $b = 1.6$, $p = .07$; LERD: $b = 3.3$, $p = .16$).

Having established that RLPFC-IPL structural connectivity predicts future changes in functional connectivity, we next sought to determine whether the converse relation was also present. To test whether RLPFC-IPL functional connectivity predicts future increases in corresponding structural connectivity, we conducted a linear stepwise regression analysis with longitudinal change in structural connectivity as the dependent variable and with T1 values for functional connectivity, structural connectivity, and Age, and longitudinal change in Age and functional connectivity as independent variables. The resulting model included T1 functional connectivity, T1 structural connectivity, T1 Age, and functional connectivity change as predictors of structural connectivity change (**Figure 7b**). After controlling for Study, T1 structural connectivity was a negative predictor of structural connectivity change ($b = -1.8$, $t(135) = -3.9$, $p < .001$), as expected. However, none of the other variables (i.e., T1 Age, T1 functional connectivity, and functional connectivity change) showed statistically significant values (p's $> .39$). Aside from a marginal negative relation between structural connectivity change and T1 Age in the younger participants ($b = -.001$, $p = .08$), a similar pattern of results was obtained for both age groups. Adding gender to the model yielded no additional effects. Further, examination of each of the three datasets separately revealed a similar lack of effect in each (p's $> .2$). Thus, we found no evidence of functional connectivity driving structural connectivity for the RLPFC-IPL connection.

Connectivity and Longitudinal Changes in Reasoning Ability

Finally, we sought to test whether structural and/or functional connectivity would predict longitudinal changes in reasoning ability. Because it was the left RLPFC-IPL functional connectivity that demonstrated the strongest cross-sectional association with reasoning ability, we narrowed our focus to this specific connection for all further analyses. We conducted a stepwise linear regression with change in Reasoning as the dependent variable, and T1 values for Age, Reasoning, structural connectivity for left RLPFC-IPL, and functional connectivity for left RLPFC-IPL, and longitudinal changes in Age, structural connectivity, and functional connectivity, as independent variables. The resulting linear model included T1 Reasoning, Age, and structural connectivity.

As expected, T1 Reasoning was a negative predictor of Reasoning change (controlling for Study: $b = -0.74$, $t(144) = -11.1$, $p < .001$). Both T1 structural connectivity and T1 Age were positive predictors of Reasoning change, though these effects were only marginally significant after controlling for Study (structural connectivity: $b = 28.6$, $t(144) = 1.8$, $p = .07$; Age: $b = 0.24$, $t(144) = 1.9$, $p = .06$). Notably, dropping either Age or structural connectivity from the regression yielded a significant effect for the other factor (structural connectivity: $b = 37.6$, $t(145) = 2.4$, $p = .02$; Age: $b = .31$, $t(145) = 2.6$, $p = .01$). Numerically similar but non-significant effects were observed separately in both datasets that contributed to this pooled analysis in NORA ($b = 37.5$, $p = .06$) and in HIPPO ($b = 38.0$, $p = .16$). Adding gender to this model yielded no additional effects or interactions.

Given the significant age effects that we had observed in our prior analyses relating Structural and functional connectivity to reasoning ability, we repeated this analysis separately for younger and older participant groups, even though we did not observe a significant interaction of T1 structural connectivity with either Age or Age Group in the stepwise linear regression (p's $> .2$). For younger participants, only T1 structural connectivity survived the stepwise regression as a positive predictor of Reasoning change, and remained significant after controlling for Age and Study ($b = 43.9$, $t(119) = 2.1$, $p = .04$; **Figure 8a**). For older participants, by contrast, T1 Age was the only positive predictor (Age: $b = .44$, $t(20) = 2.6$, p

= .01; **Figure 8b**). T1 Reasoning was a negative predictor in both groups, as for the entire sample. Thus, the marginal relationship between left RLPFC-IPL structural connectivity and reasoning observed in the entire sample was driven by a significant positive relationship in children under age 12.

Discussion

This study represents, to our knowledge, the first to examine lead-lag relations between structural and functional connectivity within the fronto-parietal network, and the first to examine the dynamic lead-lag relationship between these measures and reasoning ability. Below, we discuss the developmental changes observed for each of our measures separately, and then discuss their dynamic interrelations.

Age-related changes in structural connectivity, functional connectivity, and reasoning ability

In all three of the measures that we examined, we found both cross-sectional age-related increases as well as within-person longitudinal increases. However, distinct developmental trajectories were apparent. Reasoning ability exhibited large increases in younger children and relatively smaller but continuing increases into adulthood. This result is consistent with prior reports that have pointed to the early school years as a period of peak improvement in reasoning ability (McArdle et al., 2002; Ferrer et al., 2009).

Increases in fronto-parietal functional connectivity, by contrast, were relatively minimal in younger children, and were most pronounced at the point of transition between childhood and adolescence. This marked increase in fronto-parietal functional connectivity in late childhood is consistent with reports from prior investigations (e.g. Barber et al., 2013; Ernst et al., 2015; Smit et al., 2012).

Fronto-parietal structural connectivity demonstrated substantial increases in younger children and continuing change into adolescence. This demonstration of fronto-parietal white matter development extended across a relatively broad age range is consistent with prior reports (e.g. Asato et al., 2010; Lebel et al., 2012). Notably, development of structural connectivity appears to both precede and follow the period of greatest change in functional connectivity.

Fronto-parietal functional connectivity supports reasoning in adolescents and adults

As reported previously with the NORA dataset (Wendelken et al., 2016), we observed a positive concurrent relationship between RLPFC-IPL functional connectivity and reasoning ability in adolescents in the expanded sample. Among HIPPO study participants, who were not included in the previous report, this effect was marginally significant. Notably, the HIPPO sample did not include older adolescents, who made up a significant share of the NORA sample. Thus, it is possible that the somewhat weaker effect for the HIPPO dataset was due to the different age distribution.

Although we and others have demonstrated development of a concurrent relationship between fronto-parietal functional connectivity and reasoning (Bazargani et al., 2014; Wendelken et al., 2016), we did not observe here any lead-lag developmental relationship between these two measures. Specifically, while RLPFC-IPL functional connectivity was associated with reasoning ability in adolescents and adults,

the level of RLPFC-IPL functional connectivity did not predict future changes in reasoning ability. This outcome suggests that communication between RLPFC and IPL is characteristic of a *mature* reasoning system, but that robust communication between these regions may not be a prerequisite for the *development* of reasoning. By contrast, the maturation of fronto-parietal white matter tracts during childhood may well be a prerequisite for the emergence in early adolescence of both advanced reasoning ability and the robust RLPFC-IPL functional connectivity on which this depends.

It is entirely possible that functional connectivity of different connections, or involving other functional brain networks, might predict future change in reasoning or other higher cognitive abilities. In addition to the fronto-parietal network, the cingulo-opercular network – most frequently linked to cognitive control – has also been implicated in reasoning (Cocchi et al., 2014). Future investigations should assess whether cingulo-opercular and/or other connections also contribute to reasoning development.

Fronto-parietal structural connectivity supports the development of reasoning ability

Structural connectivity, as well as functional connectivity, had an impact on reasoning development. First, we observed a strong positive relationship between fronto-parietal structural connectivity and reasoning ability in children. Although this relationship was not specific to the RLPFC-IPL connection, it does appear to be specific to fronto-parietal connectivity and not to interhemispheric connections within the prefrontal or parietal cortices. This effect was not mediated by functional connectivity.

Second, we observed a lead-lag relationship between RLPFC-IPL structural connectivity and reasoning ability, whereby higher structural connectivity led to subsequent increases in reasoning ability. Thus, the state of white matter connection between RLPFC and IPL in childhood appears to be important for developmental improvements in reasoning ability.

Several prior studies have linked structural connectivity, and particularly fronto-parietal structural connectivity, to reasoning ability and to other higher cognitive operations. For example, Tamnes et al (2010) reported a concurrent positive relationship between reasoning ability and FA within the cingulum bundle and inferior longitudinal fasciculus in children and young adults. Further, Peters et al (2013) reported a concurrent association in children and young adults between FA in both cingulum bundle and inferior fronto-occipital fasciculus and average performance across a range of cognitively demanding tasks. Using the NORA dataset that contributed to our current larger sample, we observed a positive relationship between global (average whole-brain) FA and reasoning ability in children and adolescents, mediated by processing speed (Ferrer et al., 2013). While we did not have a common measure of processing speed in our pooled dataset, we were able to extend our prior results by demonstrating a specific link between reasoning ability and fronto-parietal connectivity – but not intra-frontal or intra-parietal connectivity – that we had not detected previously. These results build on our prior work by demonstrating that not all white matter pathways contribute equally to the development of reasoning.

Fronto-parietal structural connectivity supports emerging functional connectivity

Since both structural and functional connectivity are seen to affect reasoning development, but at different points along the developmental trajectory, we considered it essential to our understanding of reasoning development to also understand the relationship between these two measures. For both the

fronto-parietal network generally, and more specifically for the RLPFC-IPL connection, structural and functional connectivity were not significantly related at a single timepoint after accounting for age and study site (despite a positive relation before accounting for these variables). This result is broadly consistent with prior investigations that have found overall positive concurrent relations between these measures but have also demonstrated functional connectivity in the absence of structural connectivity, consistent with the notion that functional connectivity reflects indirect (polysynaptic) as well direct (monosynaptic) communication between brain regions (Skudlarski et al., 2008; Honey et al., 2009).

Prior studies have told us something about the concurrent relationship between structural and functional connectivity, but they have not revealed the dynamic, lead-lag nature of this relationship. Here, focusing on the RLPFC-IPL connection, we found that structural connectivity was a predictor of future changes in functional connectivity. This result demonstrates that, at least for this connection, white matter connectivity enables the coordination between regions that is indexed by functional connectivity – and, moreover, that strong white matter connectivity allows for the emergence over time of increased coordination between regions. On the grounds that increased coordination between regions would promote the development of white matter tracts via mechanisms of experience-dependent brain plasticity, we had hypothesized that robust functional connectivity should also lead to future increases in structural connectivity. However, at least for the RLPFC-IPL connection that was examined here, we found no evidence for this relationship.

Limitations

A virtue of the present study is the large number of subjects afforded by the combination of three separate and independent longitudinal datasets. However, this combination of datasets, which reused existing data collected for other purposes, is also the source or several important limitations. First, the fact that the data come from multiple sites, with different research protocols and different scanning hardware, means that nominally equivalent measurements may not be directly comparable. This problem was compounded by the fact that each dataset covered a different age distribution. We addressed this problem in two ways: first, we normalized data from the HIPPO and LERD datasets to age-matched samples from the NORA dataset; second, we included study as a covariate of no interest in relevant analyses. In additional to potential differences in nominally equivalent measures, there was even greater potential for differences across datasets in our measure of functional connectivity, due to the fact that fMRI data came from different fMRI tasks, or in the case of LERD, from resting-state fMRI. Our functional connectivity data analysis, which involved low-pass filtering that excluded likely task frequencies, as well as explicitly regressing out task vectors, was designed to minimize these differences. Moreover, where the functional connectivity results demonstrate similar patterns in the separate datasets, this diversity may be seen as an asset. Nevertheless, the possibility that this difference between the datasets may have impacted the functional connectivity results remains a key limitation of the current study. Finally, interpretation of relative effects in younger versus older participants is somewhat limited by the fact that the older group was considerably smaller that the younger group, and in some cases by the fact that reasoning change was much greater among younger participants. In particular, either of these factors might contribute to the lack of relationship between structural connectivity and reasoning ability in older participants. It is important to note that the split at age 12 was motivated in part by the fact of this difference in reasoning trajectories, and also by previously

observed differences in the functional connectivity-reasoning relationship (Wendelken et al., 2016). Thus, we consider this to be the best choice for an age group split despite the size imbalance between the resulting subsamples. Analyses that incorporated age as a continuous variable, rather than categorical age groups, did not suffer from this limitation.

Conclusion

The present study is, to our knowledge, the first to examine the dynamic, lead-lag relationships between structural and functional connectivity and reasoning ability. We found that, while fronto-parietal, and specifically RLPFC-IPL, functional connectivity is a key correlate of reasoning ability in adolescents and adults, it is the underlying fronto-parietal structural connectivity that was more closely associated with reasoning ability in children, both cross-sectionally and longitudinally. These results establish the importance of fronto-parietal white matter development during childhood as a foundation for good cognitive functioning in adolescence. It will be important in future work to test the effects of demographic variables on the neurocognitive development of reasoning ability, and also to determine whether childhood is a sensitive period for plasticity in the lateral fronto-parietal network.

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Tables

Table 1. Number of participants with data for each measure, from each contributing dataset. N_p = number of unique participants, N_l = number of participants with longitudinal data, N_t = total number of participant visits.

Study	Age Range	Matrix Reasoning			DTI			fMRI		
		N_p	N_l	N_t	N_p	N_l	N_t	N_p	N_l	N_t
NORA	6-20	191	118	311	137	48	187	141	54	198
HIPPO	7-15, 18-21	211	105	314	181	131	392	164	97	322
LERD	7-11	119	0	119	116	78	244	91	9	100

Table 2. Scan parameters for the DTI and fMRI scans for each contributing dataset.

Study	DTI	fMRI
NORA	One 9.45 min EPI scan 64 dir, TR=7900ms, TE=102ms 2.2 mm^3 isotropic voxels B_1=0, B_2=2000 s/mm^2	Four 4.06 min EPI scans TR=2000ms, TE=25ms 33 slices, 2.0 x 1.8 x 3.0 mm^3 voxels Visual analogy task
HIPPO	One 8.32 min EPI scan 64 dir, TR=7400ms, TE=81ms 2.5 x 2.2 x 2.2 mm^3 voxels B_1=0, B_2=1000 s/mm^2	Six EPI scans (3 @ 5min & 3 @ 6.3min) TR=2000ms, TE=23ms 37 slices, 3 mm^3 isotropic voxels Source memory task
LERD	One 9.32 min EPI scan (HARDI) 60 dir, TR=8600ms, TE=66ms 2.5 mm^3 isotropic voxels B_1=0, B_2=2000 s/mm^2	One 5.87 or 7.32 min EPI scan (T1/T4) TR=2200ms, TE=30ms 35 slices, 3 mm^3 isotropic voxels Resting-state

Figures

Figure 1. Regions of interest, including RLPFC, DLPFC, IPL, and SPL. Smaller circles indicate the extent of the 5-mm spheres uses for functional connectivity analysis, while larger circles indicate the extent of the 12-mm spheres used as targets for probabilistic tractography.

Figure 2. White-matter tracts, obtained via probabilistic tractography, including A) fronto-parietal tracts from RLPFC or DLPFC to IPL (red) or SPL (blue); B) bilateral prefrontal tracts between left and right DLPFC (blue) and between left and right RLPFC (yellow); C) bilateral parietal tracts between left and right IPL (blue) and between left and right SPL (yellow). Endpoint masks (12-mm spheres) are indicated with white circles. Purple (part A) and green (parts B and C) indicate overlap between tracts.

Figure 3. Scatter-plot of the relationship between Age and Matrix Reasoning. Gray lines indicate longitudinal data. The fit line was calculated using the cumulative distribution function (pnorm in R). Optimal parameters $\mu = 6$ and $\sigma = 3.5$, extracted from the data, indicate maximal change at age 6 (i.e., at the beginning of the examined age range).

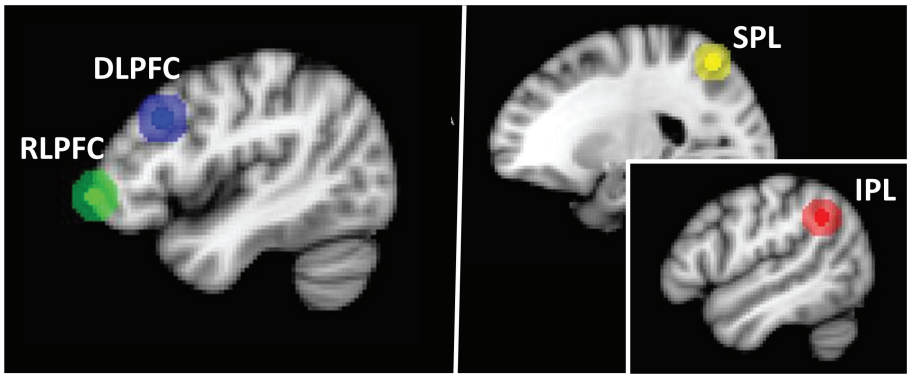
Figure 4. Scatter-plot of the relationship between average fronto-parietal structural connectivity (fractional anisotropy) and reasoning ability (Matrix Reasoning score). Lines between data points indicate longitudinal data. The fit line is linear.

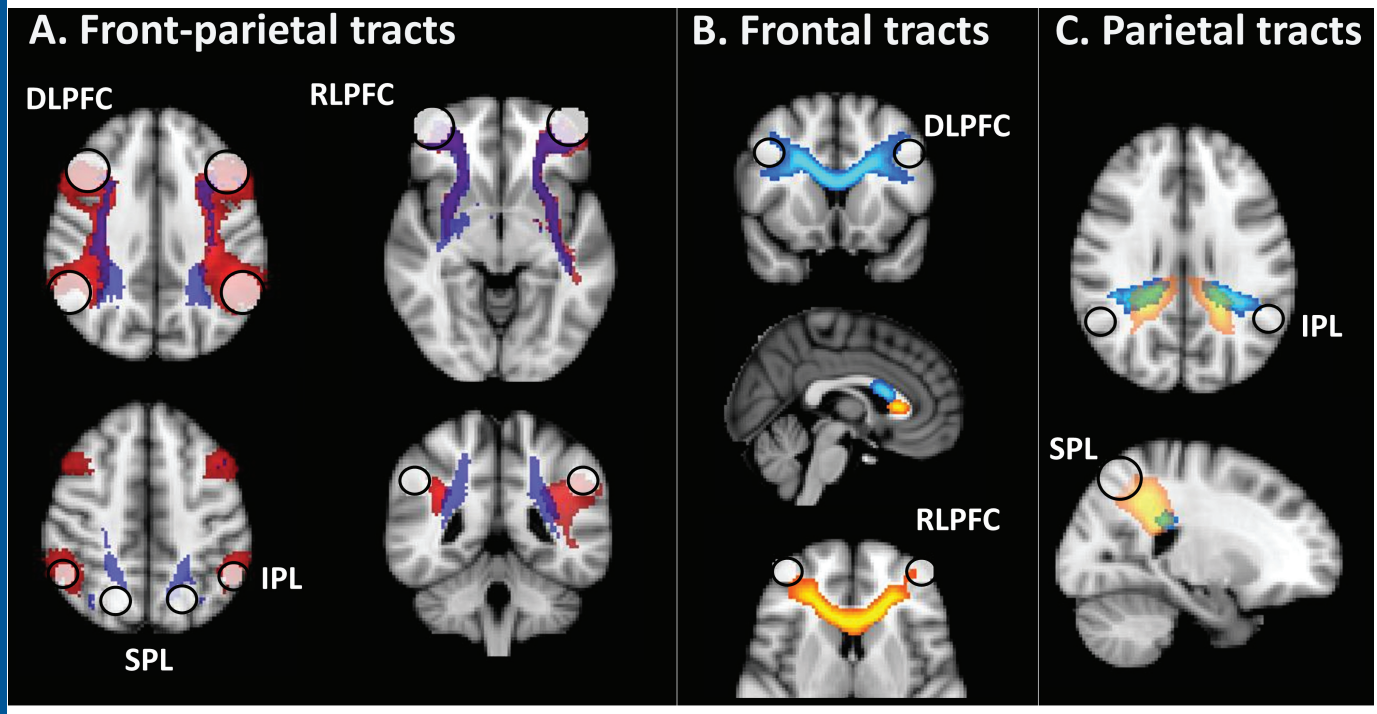
Figure 5. A) Scatter-plot of RLPFC-IPL structural connectivity (fractional anisotropy) versus age, with nonlinear (pnorm) fit line. B) Scatter-plot of RLPFC-IPL functional connectivity versus age, with nonlinear (pnorm) fit line.

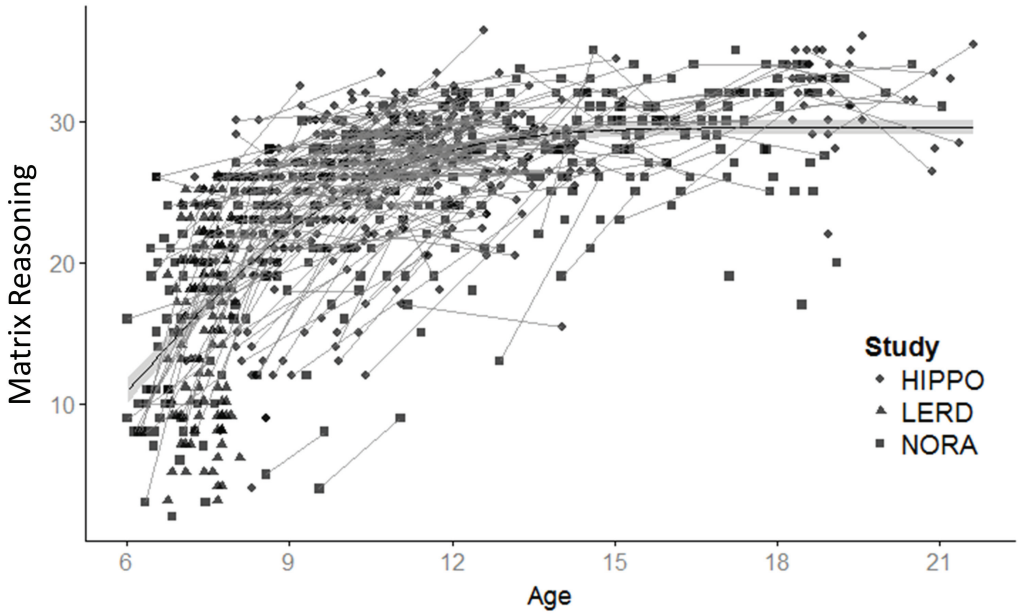
Figure 6. Scatter-plot of the relationship between Structural and functional connectivity for the RLPFC-IPL connection, with linear fit line. Lines between data points indicate longitudinal data.

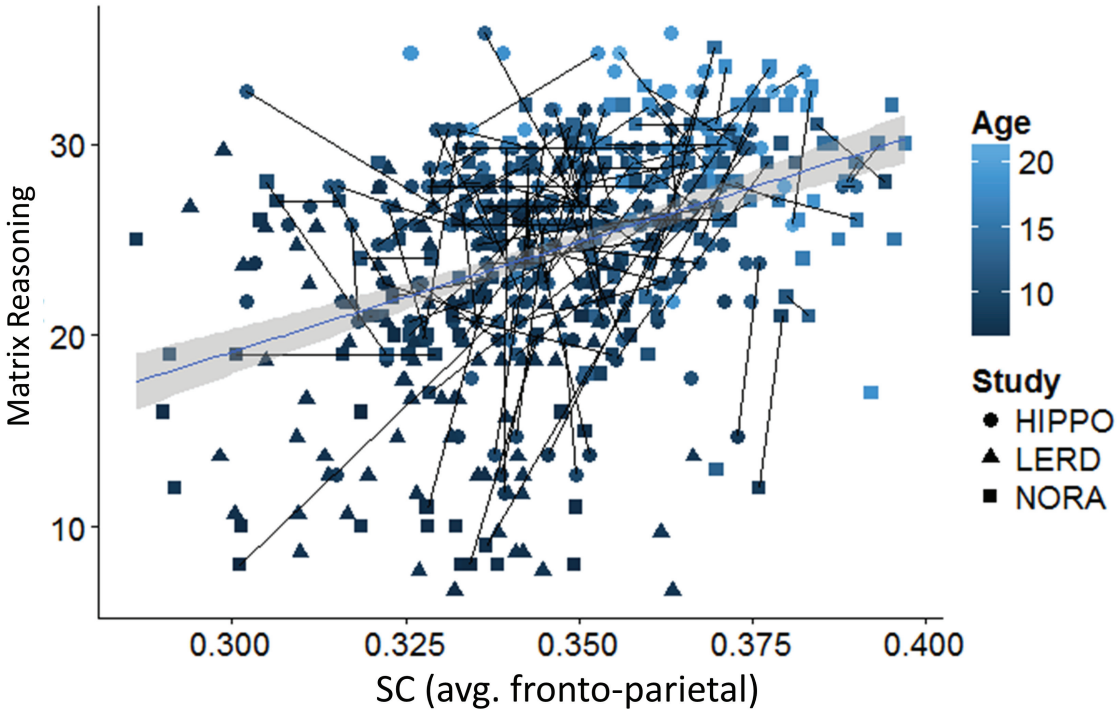
Figure 7. A) Predictors of RLPFC-IPL functional connectivity change. B) Predictors of RLPFC-IPL structural connectivity change. Shaded boxes indicate factors that survived stepwise regression. Solid lines indicate factors that survived both stepwise regression and correction for study site (with at least marginal significance).

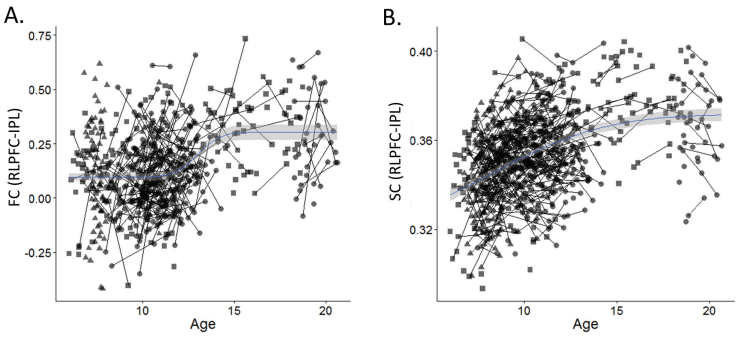
Figure 8. Predictors of change in reasoning ability (R), in A) younger participants (6-11 years old), and B) older participants (12-22 years old). Shaded boxes indicate factors that survived stepwise regression. Solid lines indicate factors that survived both stepwise regression and correction for study site (with at least marginal significance).

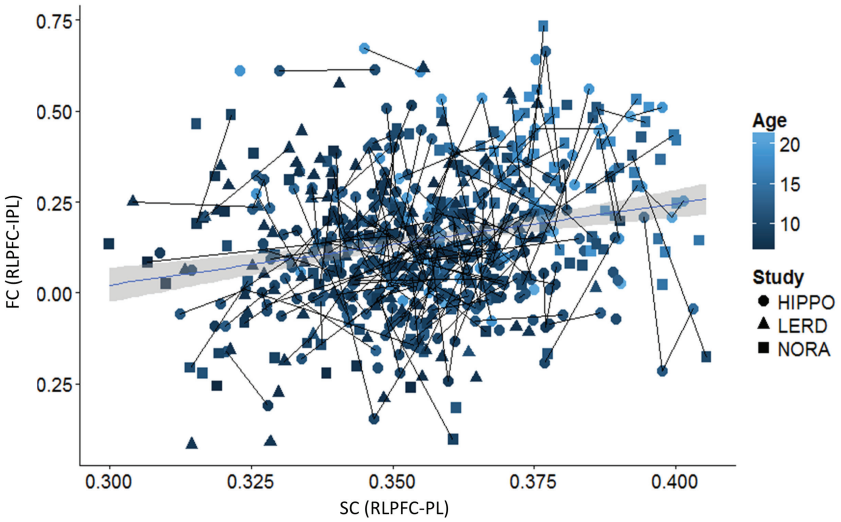




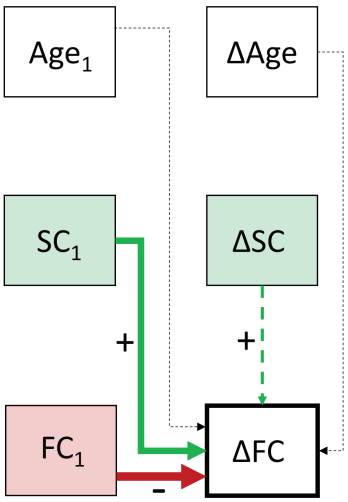




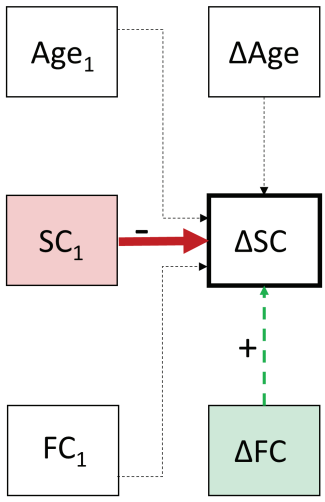




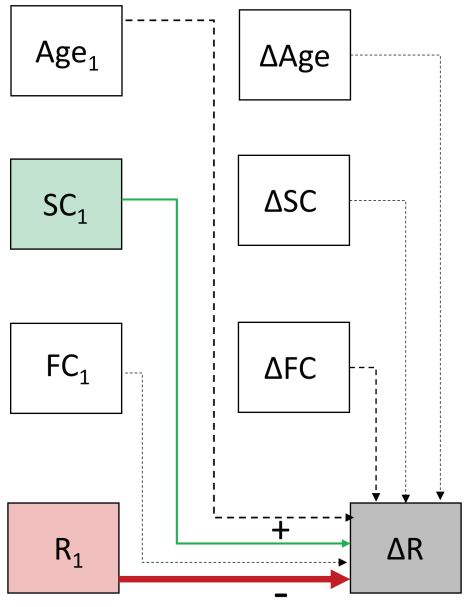
A.



B.



A. Younger participants (6-11 years)



B. Older participants (12-22 years)