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Age-related cognitive gains are mediated by the effects of white matter development on brain network integration

Michael C. Stevens[1,2], **Pawel Skudlarski**[1,2], **Godfrey D. Pearlson**[1,2], and **Vince D. Calhoun**[1,2,3,4]

[1]Olin Neuropsychiatry Research Center, 200 Retreat Avenue, Hartford, CT 06106

[2]Department of Psychiatry, Yale University School of Medicine, New Haven, CT 06510

[3]The MIND Institute, 1101 Yale Blvd., Albuquerque, NM 87106

[4]Department of Electrical and Computer Engineering, University of New Mexico, Albuquerque, NM, 87131

Abstract

A fundamental, yet rarely tested premise of developmental cognitive neuroscience is that changes in brain activity and improvements in behavioral control across adolescent development are related to brain maturational factors that shape a more efficient, highly-interconnected brain in adulthood. We present the first multimodal neuroimaging study to empirically demonstrate that maturation of executive cognitive ability is directly associated with the relationship of white matter development and age-related changes in neural network functional integration. In this study, we identified specific white matter regions whose maturation across adolescence appears to reduce reliance on local processing in brain regions recruited for conscious, deliberate cognitive control in favor of a more widely distributed profile of functionally-integrated brain activity. Greater white matter coherence with age was associated with both increases and decreases in functional connectivity within task-engaged functional circuits. Importantly, these associations between white matter development and brain system functional integration were related to behavioral performance on tests of response inhibition, demonstrating their importance in the maturation of optimal cognitive control.

Keywords

CONNECTIVITY; DIFFUSION TENSOR IMAGING; NETWORK; RESPONSE INHIBITION; DEVELOPMENT; ADOLESCENT

Adolescence can be viewed as the final phase in a prolonged pattern of neural growth and maturation (Paus, 2005) during which there are changes in grey and white matter volume due to experience-dependent pruning of inter-cellular connections, dendritic elaboration and white matter myelination (Mukherjee and McKinstry, 2006). Because age-related speed and accuracy gains on Go/No-Go (Tamm et al., 2002) and similar speeded tasks of response inhibition or motor control (Band et al., 2000, Williams et al., 1999) occur predictably across these well-

Corresponding Author: Michael C. Stevens, Ph.D., Olin Neuropsychiatry Research Center, Whitehall Building, The Institute of Living / Hartford Hospital, Hartford, Connecticut 06106, (860) 545-7552 Ph, (860) 545-7997 Fax, email: msteven@harthosp.org.

described stages of healthy neural development, it is often suggested that cognitive development is the result of ongoing maturation of the neural systems engaged for successful behavioral control (Goldman-Rakic, 1987, Luna et al., 2001). Goldman-Rakic proposed over twenty years ago that white matter development might mediate task improvements by enhancing functional integration between prefrontal and parietal cortex (Goldman-Rakic, 1987). Indeed, diffusion tensor imaging (DTI) studies have linked increasing myelination of major white matter tracts across adolescence (Barnea-Goraly et al., 2005, Schmithorst et al., 2008) to both brain activation maturation and cognitive test performance (Nagy et al., 2004, Olesen et al., 2003), particularly the relationship of frontostriatal tract development with Go/No-Go task performance (Liston et al., 2006). Other studies have reported increases in the strength of functional integration among brain regions engaged for cognitive control across adolescence (Fair et al., 2008, Fair et al., 2007, Stevens et al., 2007b). However, the hypothesis that cognitive development or white matter maturation is related to greater functional integration of activity among grey matter regions has not been tested. Support for a developmental relationship between white matter and functional connectivity would come from analyses that find significant relationships between age-related development of specific white matter tracts and functional connectivity among brain regions engaged for behavioral control known to be connected by those pathways.

When distributed brain regions display strongly correlated patterns of neural activity change, it is taken as evidence that these regions are functionally connected (Friston, 2002) into widely distributed networks of synchronous neural activity via reciprocal excitatory neurotransmission through long distance white matter pathways (Bressler and Kelso, 2001, Fingelkurts and Kahkonen, 2005, Tononi et al., 1998). We recently reported the first study that examined differences between healthy adolescents and adults in the strength of regional connectivity and interaction of distributed neural circuits engaged by response inhibition task performance (Stevens et al., 2007b). That study described adolescent over-engagement of prefrontal regions into a network of prefrontal-parietal-subcortical brain regions relative to adults. These brain regions are well-known to be engaged during so-called ‘executive’ tasks (e.g., working memory, attentional control, etc.; (Collette et al., 2006) and there is evidence that they are functionally integrated for volitional, adaptive cognitive control (Cole and Schneider, 2007). Because this developmentally-immature pattern was associated with less influence over other neural network activity and poorer overt behavioral performance in adolescents, it appeared to play an important role in maturation of executive control. This is consistent with neural constructivist models that postulate that attainment of adult-level cognitive or behavioral control is more likely related to the formation of an efficient and flexible representational structure, rather than to improvements in the computational capacities of specific brain regions during adolescence (Blakemore and Choudhury, 2006, Luna et al., 2001, Quartz and Sejnowski, 1997, Westermann et al., 2006). This model would predict that there would be enhanced functional connectivity of distal brain regions through anatomical connective media (i.e., white matter) as those connections mature. The purpose of the current study was to use multimodal imaging to test whether there was a relationship between white matter maturation and the functional integration of brain regions into the executive network we previously described. This would provide the first direct evidence for the widely-held premise that age-related gains in cognitive ability are mediated by the effect of structural development on brain network integration (Blakemore and Choudhury, 2006, Luna et al., 2001, Quartz and Sejnowski, 1997, Westermann et al., 2006).

To address this aim, we used an extension of independent component analysis (ICA) for multimodal neuroimaging data termed ‘joint ICA’ (jICA) (Calhoun et al., 2006) to identify significant relationships between DTI-measured fractional anisotropy (FA) and functional connectivity measurements in 25 healthy adolescents and 25 adults. We then queried the original data within the regions identified by jICA using SPM2 regression to characterize age-

related changes in white matter structure and regional functional connectivity strength. We hypothesized that regional functional connectivity strength within this executive network would be associated with ongoing development in long-distance white matter connections among the network's cortical and subcortical regions – specifically in the superior or inferior longitudinal fasciculi association tracts that connect prefrontal to parietotemporal cortices, projection fibers connecting cortical areas with the striatum, thalamus, or brainstem, and portions of the rostrum, genu, and splenium of the corpus callosum. These are the major white matter tracts connecting the cortical and subcortical regions of the executive network under examination. We additionally hypothesized that these associations would differ by age, and that age-related differences in relationships between white matter and functional connectivity measures would be significantly associated with behavioral differences in task performance.

Materials and Methods

Participants

Participants were 50 healthy, right-handed volunteers (64% male) between the ages of 11 and 37; mean (SD) = 19.9 (6.76). Fig. 1 displays a histogram of participant ages. Participants were recruited via advertisements and word-of-mouth at the Olin Neuropsychiatry Research Center, Hartford, CT. Participants provided written informed consent in protocols approved by Hartford Hospital's Institutional Review Board. For legal minors, parents provided written permission and minors provided written assent. All research procedures were conducted in adherence to ethical standards required for human subjects protection.

Experimental Design

The fMRI Go/No-Go task consisted of frequent 'X' (P = 0.85) and infrequent 'K' stimuli presented at 3 × 5 visual degrees for 50 msec each. The minimum interstimulus interval was 1,000 msec. Intervals between K stimuli were in the range 10–15 seconds. Participants were instructed to make a speeded button press with their right index finger to rapidly-presented visual 'X' (Go) stimuli, but to withhold response to pseudo-randomly interspersed 'K' (No-Go) stimuli. Speed was emphasized over accuracy during a practice trial in order to ensure engagement of a prepotent response tendency. A custom visual and auditory presentation package (VAPP, http://www.nrc-iol.org/vapp/) was used to closely control stimuli presentation timing. The stimulus sequences were projected to the participant via a screen visible to participants in the MRI by rear-facing mirror attached to the head coil. Prior to beginning the task, each participant performed a brief practice trial to ensure understanding of the instructions. A commercially available MRI compatible fiber-optic response device (Lightwave Medical, Vancouver, BC) was used to acquire behavioral responses. Stimulus events and behavioral responses were recorded and monitored online using a separate computer. Hits and errors were defined as a response occurring within 1,000 msec of an 'X' or 'K' trial, respectively.

Imaging Parameters and Processing

Imaging was implemented on a Siemens Allegra 3T system located at the Olin Neuropsychiatry Research Center. Each participant's head was firmly secured using a custom head holder. Localizer images were acquired for use in prescribing the functional image volumes. The echo planar image (EPI) gradient-echo pulse sequence (TR/TE 1500/28 ms, flip angle 65°, FOV 24 × 24 cm, 64 × 64 matrix, 3.4 by 3.4 mm in plane resolution, 1 mm gap, 5 mm effective slice thickness, 30 slices collected in sequential order) effectively covered the entire brain (150 mm) in 1.5 seconds. EPI images were visually checked to ensure they were free from commonly observed inhomogeneity effects. Head motion was restricted using a custom built cushion inside the head coil. The two stimulus runs each consisted of 294 time points, including a 9 second rest session at the beginning that was collected to allow for T_1 effects to stabilize. These

initial six images were not included in any subsequent analyses. Functional images were reconstructed offline and each run was separately realigned using INRIAlign (Freire et al., 2002) as implemented in statistical parametric mapping (SPM2). Each participants' translation and rotation corrections were examined to ensure there was no excessive head motion (i.e., > 1 voxel length or 3 mm translation, and 3º rotation). A mean functional image volume was constructed for each session from the realigned image volumes. This mean image volume was then used to determine parameters for spatial normalization to the EPI.mnc template using the Montreal Neurological Institute standardized space employed in SPM2. The normalization parameters determined for the mean functional volume (45 mm cutoff, medium regularization, and 16 nonlinear iterations) were then applied to the corresponding functional image volumes for each participant with resulting images comprising 3 mm isotropic voxels. Normalized images were corrected with a custom algorithm that used linear interpolation to remove variation in BOLD signal intensity due to slice acquisition temporal onset differences. Although slice timing corrections are often applied prior to normalization, our algorithm applies this correction later in the preprocessing pipeline. This practical step facilitated our re-analysis of previously examined data without having to unnecessarily perform spatial normalization again. The normalized functional images were smoothed with a 12 mm full width at half-maximum Gaussian filter.

FMRI comparison of youth and adults has been well-validated on methodological and physiological levels. Direct examination of the BOLD response indicates that despite having greater variability with its possible negative effects on signal-to-noise (Huettel et al., 2001, Thomason et al., 2005) and an earlier rise to peak in younger persons, the BOLD signal used in most fMRI research shows generally the same amplitude and duration at different ages (Richter and Richter, 2003). Because differences are slight, typical fMRI techniques produce comparable results in teens or adults (Kang et al., 2003). It also has been shown that normalization of functional images having a relatively coarse spatial resolution to an adult template coupled with common use of spatial smoothing effectively permits age comparisons (Muzik et al., 2000). Finally, we note that this 'fusion' analysis examines BOLD-based measures of functional connectivity using ICA methods described below. This data-driven approach is fairly robust to small deviations of BOLD signal variation, lending greater confidence in the obtained results. Therefore, there are few methodological barriers to examining fMRI-measured data from teens and adults within a common data processing framework such as that used in jICA.

DTI images were acquired using a single-shot EPI with pulsed gradient spin-echo technique (Stejskal and Tanner, 1965). Eddy current distortions were minimized by adding a second refocusing pulse (Reese et al., 2003). TR/TE=5800/87 msec, FOV=20 cm, acquisition and reconstruction matrices = 128×96 and 128×128, 8 averages, diffusion sensitizing orientations=12 with one b_0, b=1000 s/mm^2, 45 contiguous 3 mm axial slices gated with peripheral arterial pulse. Calculations were performed using DTI Studio (Johns Hopkins University, Baltimore, MD; http://cmrm.med.jhmi.edu). FA maps were converted to standardized 2 mm isotropic MNI space by applying transformations determined from spatial normalization of the b_0 maps to the SPM2 EPI.mnc template, then spatially smoothed with a 10 mm full width at half-maximum Gaussian filter.

Previous work has determined that the primary reasons to smooth voxelwise data are to 1) decrease high frequency noise, and 2) mitigate coregistration issues due to normal anatomical and functional variability. With this in mind, we note that each data modality is smoothed using a commonly-used kernel size appropriate to its data type (Friston, 2007, Liu et al., 2008, Mikl et al., 2008). The goal of data preparation for jICA is not to enforce the same effective smoothness because this could reduce sensitivity to true signal differences of interest across voxels within the data. Instead, because the original data has different smoothness already, the

goal is to smooth using FHWM appropriate to each data type that accurately represents the desired signal. Clearly however, the choice of smoothing kernel should be 'tuned' at the preprocessing stage in order to best fit data considerations for any modality entering a jICA analysis. Finally, putting both DTI and fMRI data into the same stereotactic space using the MNI EPI template permitted the two datasets to be displayed on the same structural underlay.

Functional Connectivity Data

Each participant had functional connectivity maps calculated during previous analysis of this dataset. These procedures are described in detail in previous reports (Stevens et al., 2007a, Stevens et al., 2007b, 2009). Briefly, the maps came from analyses of spatiotemporal associations within the fMRI data conducted using independent component analysis procedures and algorithms available in a Group ICA of FMRI Toolbox (GIFT v1.3b) implemented in Matlab (http://icatb.sourceforge.net). In this approach, a single ICA analysis was performed on the participants, followed by a back reconstruction of single-subject time courses and spatial maps from the raw data. For computational feasibility, the data were concatenated as described in our previous reports, then underwent three principal component analysis (PCA) data reduction stages, with the last stage including the application of ICA for the final rotation. Following calculation of the group solution, component time courses and spatial maps were then reconstructed for each individual participant. The resulting single-subject time course amplitudes were then calibrated (scaled) using the raw data so that they reflected percent fMRI signal strength and could be compared across participants. For greater detail, please see our previous report (Calhoun et al., 2001). Component spatial maps and timecourses then were parameterized using multiple regression to identify which components were significantly related to successful response inhibition trials on the Go/No-Go task by comparing the component timecourses to the SPM2 cananonical hemodynamic response model correctly-rejected stimuli. The functional connectivity data used in this jICA analysis were the spatial maps for each participant that represented an executive component engaged for response inhibition described in (Stevens et al., 2007b). In this instance, functional connectivity is defined as the statistical correspondence of each voxel's raw data BOLD timecourse to the average timecourse across the network identified by ICA. Therefore, the voxels in each participant's map represented regional strength of functional connectivity. All participant functional connectivity maps were resampled using SPM2 to 2 mm isotropic voxels to match the voxel dimensions of the DTI data.

Joint Independent Components Analysis (jICA)

The selected DTI and functional connectivity features were examined using jICA techniques as implemented in the Fusion ICA Toolbox v1.1beta (http://icatb.sourceforge.net). Although an approach that uses seed voxels to anchor automated fiber-tracking methods has been successfully used by other investigators to examine white matter relationships with cognitive ability (Liston et al., 2006), jICA is a multivariate technique that is not limited to *a priori*-defined regions of interest. Therefore, its use should provide comparable, but more extensive results compared to fiber-tracking methods. jICA has the additional advantage that it more precisely localizes which specific aspects of long-distance tracts are implicated in the association of white matter and brain function. In contrast, quantitative fiber-tracking methods typically assess fiber coherence across the entire tract, limiting the precision of the results. The development and validation of these jICA algorithms are fully described in a previous peer-reviewed report (Calhoun et al., 2006). While that report detailed a data fusion analysis of grey matter volume and fMRI activation maps, the jICA technique is amenable to various types of voxel-based medical imaging data, including DTI and fMRI-based functional connectivity maps (see also Calhoun and Adali, in press, Franco et al., In Press).

The jICA model assumes that spatially independent sources have joint patterns of signal change that are linearly mixed together, but can be identified and unmixed. In practical terms, jICA is a multivariate data 'fusion' analysis that identifies patterns in one neuroimaging modality that systematically covary with patterns found in another modality across the whole brain. The primary benefits of jICA in this context are that it can identify relationships among spatially remote brain regions within different data types, such as DTI and fMRI where the relevant signal changes typically are not coincident in the same voxels. In other words, the areas of interest in white and grey matter typically do not overlap in the two sets of maps (i.e., signal variations in fMRI will typically occur in grey matter regions, while DTI-measured FA will vary characteristically by age along major white matter tracts). Also, jICA can identify associations that occur between data types in distal brain regions (e.g., increased functional connectivity in frontal and parietal lobe regions associated with white matter FA changes in a major tract that interconnects them). Indeed, jICA does not even require the data from each modality to be in the same stereotactic space in order to identify joint associations. However, the fact that both datasets independently were spatially transformed into MNI stereotactic space using the same EPI template facilitates visual display and interpretation of the results.

The jICA analysis also produces a set of coefficients for the sample representing how strongly each participant manifested the relationship depicted in each joint component. These mixing coefficients provide a straightforward means to identify whether the expression of the relationship differs between age groups through simple *t* test. This allowed us to *a priori* restrict our examination only to joint components showing significant age effects that were of interest to this analysis. Note, jICA identifies relationships between the two datasets regardless of whether they are associated with age or some other between-subjects factor. A significant age-related difference from a test on joint component coefficients identifies an age-related difference in the strength of the relationship between the two image modalities. It does not simply capture an age-related difference in either data type. Therefore, interpretation of the results is facilitated by both coefficient testing and by examination of simple age-related differences in the original datasets. Therefore, we also conducted regression analysis for each data type separately to examine differences due to increasing age.

Both neuroimaging features were normalized to have the same average sum-of-squares (computed across all subjects and all voxels for each modality) to equalize the data ranges. A feature matrix was constructed wherein the DTI and fMRI data were juxtaposed to permit subsequent ICA modeling to estimate spatially independent joint source images that shared common mixing matrix parameters. PCA was used to reduce the dimensionality of the data down to ten joint components. This number was based on dimensionality estimates of the feature matrix using the minimum description length criteria (Li et al., 2007). The Infomax algorithm (Bell and Sejnowski, 1995) was used to decompose the reduced feature matrix to maximally independent component images and subject specific mixing (loading) parameters. Because the age distribution was slightly bimodal and because we wanted to ensure we captured both linear and nonlinear age effects (Fair et al., 2006), loading parameters were examined for a significant difference between age groups (n=25 adolescents ages 11–18 versus adults, n=25 ages 19–37) using a two-sample *t* test. Only joint components that significantly differed between age groups were subsequently examined, because these were the ones that represented relationships between white matter and functional connectivity that changed throughout adolescent maturation. The component with the most significant difference between age groups likely contains the most marked developmental changes in the relationship of white matter and functional connectivity, followed by the next most significant, etc. In order to validate the age-related functional significance of the jICA results, supplemental regression analyses examined the relationship of the mixing coefficients to behavioral performance and to measures of effective connectivity strength generated in previous work (Stevens et al., 2007b). For every

participant, the values in each feature of the joint component solution were scaled to Z scores and written as an image for supplemental age analyses.

The spatial structure of the joint component features were visualized through overlay of these images onto a canonical map of brain structure using an arbitrary, but fairly stringent statistical threshold of $Z = 2.5$ (i.e., 99.4% cumulative probability; Fig. 3). Localization of grey matter was obtained by reference to MNI labels. Because there is as yet no standardized electronic atlas of white matter tracts, white matter regions were labeled by visual reference to a published atlas (Mori et al., 2005).

Supplemental Analyses of Age Differences in jICA, DTI and fMRI Data

Age differences in the fractional anisotropy DTI maps and functional connectivity maps were examined in SPM2 using regression. These regression models included a mean-centered term to examine the linear effect of age, and the square of orthogonalization of this term to evaluate any possible quadratic (i.e., curvilinear) effects of age. In this way, we were able to depict the actual age-related changes in the DTI and fMRI data used for jICA in order to better interpret the patterns of the joint components. These results are available in a supplemental Table online.

Results

The jICA analysis identified two joint components depicting relationships between white matter and functional connectivity that were significantly different between adolescents and adults (1st joint component adolescent mean mixing coefficient = 0.018 + 0.005 SE versus adult = 0.098 + 0.005 SE, $t_{48} = -11.38$, $P < .000001$; 2nd joint component, adolescent mean mixing coefficient 0.382 + 0.004 SE versus adult = 0.402 + 0.004 SE, $t_{48} = -3.66$, $P = .0006$). The fact that these mixing coefficients showed significant age-effects means that the relationships between data types depicted in the components changed with age and merited further examination. *Post hoc* tests on the mixing coefficients for the joint components showed that the relationship between these changes and age was linear in nature (1st joint component Pearson $r = 0.683$, $P = .00000005$; 2nd joint component $r = 0.371$, $P = .008$). The linear relationships between age and jICA coefficient are depicted in Fig. 2.

Fig. 3 displays the spatial extent of both components' features at Z = 2.5 (99.4% cumulative probability). Fig. 3A shows the 1st joint component. White matter regions (Fig. 3A left) include bilateral rostrum of the corpus callosum, bilateral temporal lobe white matter, bilateral foci at the approximate location of the internal capsule genu, and bilateral cerebellum. Fig. 3A (middle) shows brain regions whose functional connectivity is either greater (yellow-red) or lesser (blue-green) with greater fractional anisotropy. It can be seen that greater white matter coherence in this component is associated with decreased regional functional connectivity in bilateral frontal poles/right lateral orbitofrontal cortex, and right inferior parietal lobule, caudate, and the brainstem, but increased functional integration of bilateral anterior temporal lobe. The 2nd joint component (Fig. 3B) shows a relationship between FA in the genu and splenium of the corpus callosum bilaterally, as well as in regions at the approximate location of cortical-subcortical/brainstem projection tracts bilaterally (Fig. 3B left). Greater FA in these regions was associated with greater functional connectivity in bilateral frontal poles, right dorsolateral and ventrolateral prefrontal cortex, and bilateral inferior/superior parietal lobules (Fig. 3B middle). The entire list of regions in both joint components can be found in Supplementary Table 1 online.

Although the analysis of the association of age with the jICA loading coefficients reported above identified which components had relationships between data types that changed with age, it was important to also visualize which brain regions in each feature had the greatest age-related changes in order to full interpret the patterns of results. The results of these analyses

that examined the association of age with both white matter and functional connectivity features are listed in Table 1. Numerous regions within each feature of the two joint components showed maturational effects that likely influenced the relationship between white matter coherence and functional connectivity in the executive network. In the 1st joint component, there were particularly strong age-related changes in fractional anisotropy within the internal capsule, bilateral inferior longitudinal fasciuli, and anterior corpus callosum. In the 2nd joint component, white matter changes were most evident in tracts connecting midbrain to the striatum.

In our previous work, there were developmental improvements in reaction time in this sample (Stevens et al., 2007b). In this study, there was a significant correlation between the 1st joint component mixing coefficient and false alarm reaction time reported in previous work, Pearson $r = -0.346$, $P = .013$, and a trend level correlation with Go reaction time, $r = -0.272$, $P = 0.056$. The 1st component mixing coefficients also were significantly associated with effective connectivity measures from that study (Stevens et al., 2007b), Pearson $r = 0.303$, $P = .051$. Effective connectivity coefficients indexed how strongly the executive circuit influenced activity in other key brain networks. In other words, the ability of this network to influence other brain systems engaged by successful response inhibition was significantly associated with the conjoint changes to white matter and regional functional connectivity observed in the current study. The 2nd joint component mixing coefficients were not significantly correlated with either behavioral or effective connectivity measures.

Discussion

Although the methods used in this study are still relatively novel, the interpretation of results is straightforward. jICA produces joint components that represent empirical relationships found between two or more data types. Within any joint component, regional signal changes in one data type significantly correspond to the increases or decreases observed in the second. The expression of the relationship is quantified by the mixing coefficient, which can be examined further using traditional random effects statistical tests (e.g., to identify age-related differences, as in this study). The relationships depicted in each component can be best understood by comparing the pattern of relationships to actual age-related differences between the DTI and fMRI data between age groups (Supplemental Table 1).

In the current results, the joint component with the strongest age-related differences identified a subset of normal age-related increases in white matter fractional anisotropy proximal to the rostrum of the corpus callosum, inferior longitudinal fasculi, and internal capsule. These brain structure changes were linked to concurrent decreases in the functional integration of bilateral frontopolar, right parietal cortex and right caudate head into the executive network engaged during response inhibition. Although the fractional anisotropy signal in part reflects cellular characteristics such as hydration, cell-packing density, fiber diameter, and directional coherence (Barkovich, 2000, Shimony et al., 1999, Virta et al., 1999), it is most commonly taken to reflect degree of myelination. Therefore, the most likely interpretation of the current results are that normal white matter myelination increases seen across development are linked to *decreases* in the need to tightly couple bilateral frontopolar prefrontal, parietal and caudate activation during response inhibition. At the same time, there were *improvements* in behavioral performance with age (i.e., reaction time) suggesting that this reduction in functional connectivity is advantageous and developmentally normal. In previous reports, frontopolar cortex activity has been observed during executive planning, problem solving, and reasoning, particularly the monitoring and management of task subgoals in working memory (Braver and Bongiolatti, 2002), resolving response conflict (Badre and Wagner, 2004), and switching between stimulus-oriented or internally-driven cognition (Gilbert et al., 2005). A recent study also has linked decreased activity in these regions to increasing automaticity of task performance through practice (Jansma et al., 2001). Kringelbach and Rolls (Kringelbach and

Rolls, 2004) have argued that the role of lateral orbitofrontal cortex in response inhibition may be specific to rapidly altering behavior in response to changes of stimulus-reinforcement contingencies. Parietal cortex is implicated in control over attentional re-allocation or orientation, which is known to show maturational changes (Konrad et al., 2005). We also found that white matter changes in this component also were linked to *greater* integration of rostral anterior cingulate and bilateral temporal poles into this network. The latter brain regions have been linked to emotional aspects of error detection on Go/No-Go tasks (Hester et al., 2005) and increase their activity across adolescent development (Stevens et al., 2009, Velanova et al., 2008).

The results depicted by this jICA component suggest that the changes to functional connectivity seen with increasing white matter myelination likely reflects a decreased reliance on relatively immature executive neural network function involving conscious, rigidly controlled cognition in favor of increasingly efficient, adult-like integration of distributed processing. This adult-like pattern presumably permits a more automatic, but accurate means of supervising ongoing response inhibition operation, likely through local processing contributions to cognition by paralimbic cortex structures (i.e., rostral cingulate and bilateral anterior temporal lobe regions). It is significant that the majority of white matter regions implicated in this 1st joint component connect prefrontal and parietal regions instead of major motor system pathways. This suggests that age-related reaction time gains do not simply reflect gains in signal conduction time through the descending motor pathways, but rather stem from the increased integration of information processing among 'higher-order' distributed brain regions. This interpretation is further bolstered by the association of this joint component with causal network dynamics measurements (i.e., 'effective connectivity'; (Friston, 2002) we described in our previous study (Stevens et al., 2007b). This indicates that the joint pattern of white matter development and functional connectivity changes among these prefrontal and parietal cortex regions is associated with the ability of this executive network to influence another profile of brain activity engaged for successful response inhibition.

jICA analysis also found a second joint component whose expression differed with age. Regions identified by the 2nd joint component showed lower adolescent fractional anisotropy in anterior and posterior corpus callosum, and regions from bilateral midbrain/brainstem projecting dorsally through the internal capsule into mid-sagittal white matter. These were linked to lower adolescent functional connectivity in right dorsolateral prefrontal cortex and portions of bilateral inferior parietal cortex in adolescents. In contrast, adults had greater functional connectivity of bilateral frontal pole/ventrolateral prefrontal cortex, and right parietal cortex. Because this joint component was not correlated with any behavioral performance or effective connectivity indices, its specific significance to cognitive development remains unclear. Although the average jICA mixing coefficients for the 2nd joint component significantly differed between age subgroups, the overall difference was slight (i.e., adolescent 0.382 versus adult 0.402). In contrast, the first joint component showed a trivially small mean adolescent loading compared to adults (i.e., 0.018 versus 0.098) suggesting there was a poorly organized relationship between the white matter regions and functional connectivity measurements in adolescents in the 1st component. Based on its slight degree of relative change with age, the 2nd joint component could depict ongoing development of an already established relationship between white matter pathways and functional connectivity. In the 2nd joint component, fractional anisotropy increases in the anterior aspect and the splenium of the corpus callosum and projection fibers running through the internal capsule to the brainstem were linked to increased functional connectivity of right dorsolateral prefrontal cortex, bilateral ventrolateral/frontopolar prefrontal cortex, and bilateral parietal regions. These frontal and parietal regions greatly overlap with regions in the 1st joint component that show a normative decrease with age, particularly in lateral orbitofrontal and frontopolar cortices.

This apparent contradiction might be resolved if one posits different functional roles within task performance for these two sets of associations.

We note that both joint components included white matter within the internal capsule. Liston and colleagues reported that diffusion of water perpendicular to tracts connecting the striatum with lateral prefrontal cortex had greater diffusivity values with age and was related to Go-No/Go speed and accuracy (Liston et al., 2006). Because jICA cannot follow these tracts to their termination as can be done with tract tracing, it is not possible to know whether the current results represent a more precise depiction of localized white matter changes related to maturation of functional connectivity or behavior that they reported, or implicate a different aspect of white matter development altogether. Comparison to a white matter atlas (Mori et al., 2005) suggests only that they are likely to be either the corticopontine tracts, the superior thalamic radiations, or even the corticospinal tracts. In future studies, it could be profitable to conjointly use jICA to identify relevant local aspects of white matter development in large tracts and fiber-tracking methods to confirm the cortical enervation of these tracts.

Overall, these observations are consistent with general predictions of neural constructivist theories which posit that increased functional and anatomical integration underlie cognitive control gains throughout adolescent development (Luna and Sweeney, 2004). Our results support and extend this proposal by confirming that the development of hypothesized longdistance white matter substrates play an important role in changes to regional functional connectivity strength and associated changes in executive behavior. Equally as significant, this study supports the proposal (Goldman-Rakic, 1987) that white matter development across adolescence is directly related to the establishment of mature neural network functional integration. Therefore, attainment of a mature, adult-level profile of functional connectivity and behavior is associated with increasingly ‘hard-wired’ white matter connections between frontal and parietal cortex and greater development of internal capsule projections connecting cortical and subcortical brain regions. These findings are consistent with developmental neuroimaging studies using other methods that report a staged shift of reliance from activity in some brain regions to others (Koenig et al., 2002, Segalowitz and Davies, 2004, Thatcher et al., 1987). These results extend those findings by demonstrating that adult-levels of functional integration among widely distributed brain regions results from complex shifts of the overall pattern of regional brain integration that either increase or decrease the net connectivity brain regions that are specialized for various ‘executive’ cognitive demands. The finding that increased white matter coherence can be associated with developmentally-normative decreases in functional integration might be considered by some to be counterintuitive. Both increases and decreases in regional functional connectivity were found to be associated with white matter development in the 1st joint component, and the 2nd age-related component depicted only increased functional integration with greater white matter coherence. Therefore, the current results do not contradict reasonable expectations for the relationship between increasing functional and increasing anatomical connectivity. However, the study supports the conclusion that some neural circuits are relied upon less throughout development as developmentally mature circuits are more greatly recruited to mediate cognitive processing. The current data show that performance relies less on frontoparietal-striatal regions acting in concert and more demands are made on anterior cingulate and bilateral temporal-polar regions.

The current study has direct relevance for numerous fields of neuroscience. It can been seen that changes in the structural substrates that mediate long-distance connections among distributed neural networks (Sporns et al., 2004) influence how strongly those networks are functionally integrated, which in turn is associated with behavioral control. Therefore, factors that influence normal growth and development of white matter (e.g., genotypes coding for mechanisms that influence myelination or other white matter structural characteristics) can

likely be shown to impact broadly distributed brain activity through their indirect effects on local neural processing. The greater speed or reliability of long-distance signaling likely also influences localized neural processing through its effects on mechanisms of intra- and intercellular signaling, which can be quantified in animal models. Investigation of these factors was beyond the scope of this study, but will prove essential to future studies for documenting the exact causes of the developmental changes depicted here. Further study of these mechanisms as a function of typical development likely will shed light on specific neurobiological factors that disrupt optimal neural network integration, which could directly contribute to the development of neurological or neuropsychiatric disorders.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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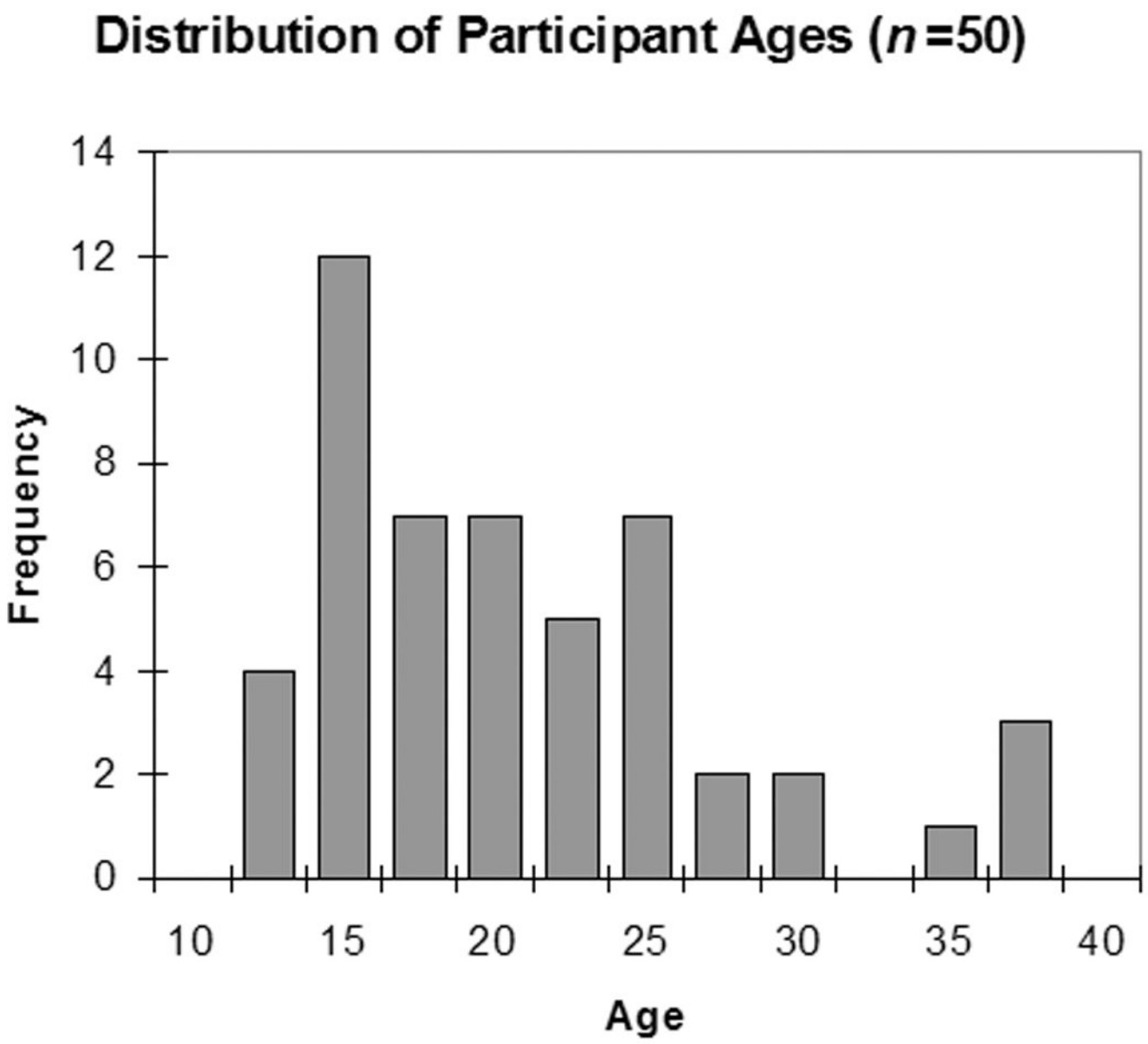

Figure 1.
is a histogram showing a bimodal distribution of participant ages in the sample.

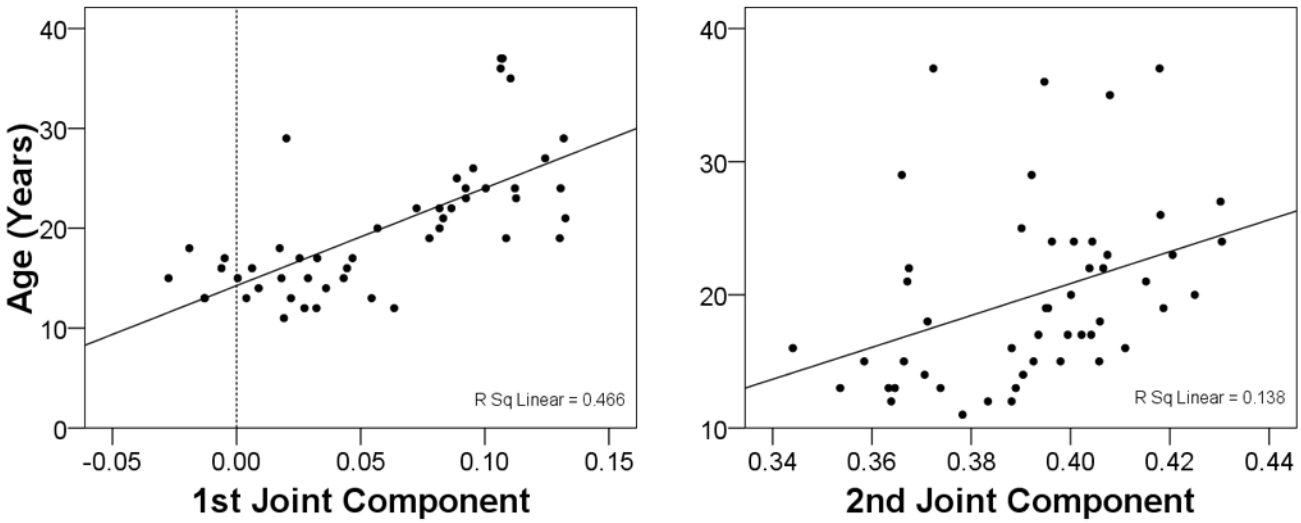

Figure 2.
depicts the association of age and jICA coefficient to demonstrate the linear relationship between white matter coherence and functional connectivity found in the two joint components.

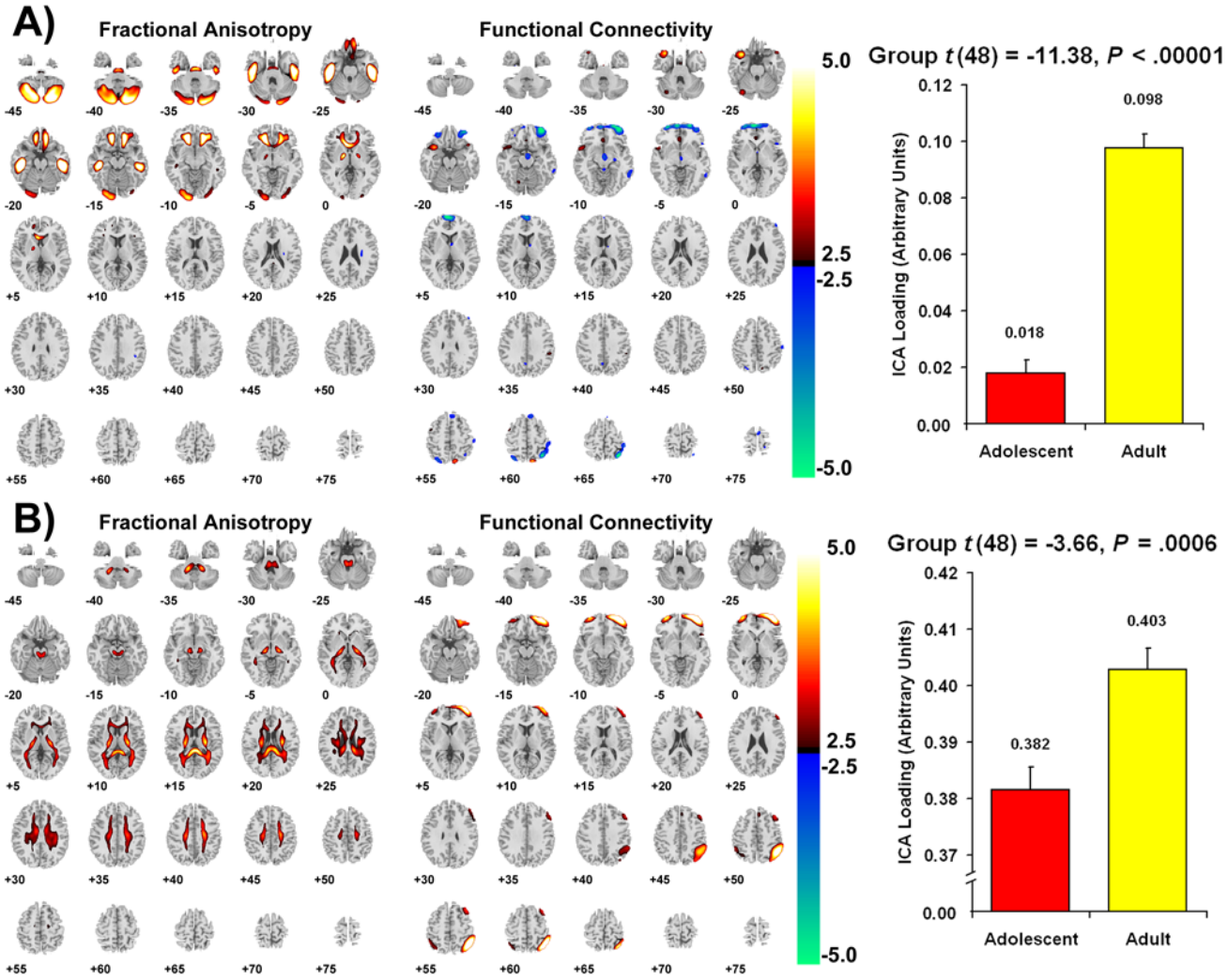

Figure 3.

Figure 3A and 3B depict joint component spatial structure conserved across participants (Z=2.5) and results of t test for age group on jICA mixing coefficents. (Left) Regions of white matter associated with strength of regional connectivity; (Middle) Regions of functionally-integrated gray matter associated with degree of myelination in specific white matter regions. (Right) Graph comparing significantly different average jICA mixing coefficients between adolescents and adults.

Table 1

List of brain regions in adolescents and adults within joint components depicted in Figures 1A–B showing significant linear relationships with age. Columns depict anatomical label and MNI coordinate for the voxel with the peak *t* score in each brain region.

Fractional Anisotropy	**x**	**y**	**z**	t_{48}	**Functional Connectivity**	**x**	**y**	**z**	t_{48}
1st Joint Component									
Adolescent < Adult					*Adolescent < Adult*				
R anterior corpus callosum	−12	32	−18	6.57	Anterior cingulate/medial frontal gyrus (BA 24)	−6	32	−6	2.95
R anterior corpus callosum	10	36	−16	7.28	R middle/precentral gyrus (BA 6)	−46	0	50	2.65
L temporal lobe (inf long fasciculus)	−38	−22	−24	10.82	R inferior parietal lobule/ supramarginal gyrus	52	−40	36	3.70
R temporal lobe (inf long fasciculus)	48	−24	−18	10.04	L superior temporal gyrus (pole)	−50	10	−4	4.92
L internal capsule	−22	−6	−2	10.61	R superior temporal gyrus (pole)	50	16	−24	3.35
R internal capsule	22	−6	−2	10.78	L cerebellum	−36	−68	−24	1.86
L lingual white	−22	−106	−2	5.04					
R lingural white	26	−100	−6	4.83	*Adolescent > Adult*				
L cerebellar white	−24	−96	−26	6.82	L superior/middle frontal gyrus (frontopolar)	−30	34	−18	2.54
R cerebellar white	16	−96	−30	7.49	R superior/midddle frontal gyrus (frontopolar)	26	38	−18	3.73
Brainstem/pons	2	−12	−28	6.68	R postcentral/inferior parietal lobule	48	−38	66	3.74
					L superior parietal lobule	−28	−74	56	2.59
Adolescent > Adult					R superior parietal lobule	36	−56	66	2.80
R parasaggital white	−26	−20	28	3.10	L precuneus	−6	−60	40	2.95
					L mid temporal gyrus (posterior)	54	−54	−8	4.40
					R caudate	8	−4	14	3.67
2nd Joint Component									
Adolescent < Adult					*Adolescent < Adult*				
Anterior corpus callosum	−2	22	2	4.68	R middle frontal gyrus (BA 9/46)	54	28	30	2.51
L middle/posterior internal capsule	4	−4	26	4.57	L inferior parietal lobule	−46	−48	50	4.23
R middle/posterior internal capsule	−8	−36	22	4.22	R inferior parietal lobule/ supramarginal gyrus	52	−44	38	3.46
L midbrain/striatum	−14	−8	2	7.08					
R midbrain/striatum	14	−6	0	8.78	*Adolescent > Adult*				

Fractional Anisotropy	x	y	z	t_{48}	Functional Connectivity	x	y	z	t_{48}
					L middle frontal gyrus	−46	48	−12	3.94
					R superior/middle frontal gyrus	32	58	−12	2.61
					R superior/inferior parietal lobule/ postcentral gyrus	36	−56	66	2.80