Published in final edited form as:

Behav Brain Res. 2007 July 19; 181(1): 12–22.

Functional neural networks underlying response inhibition in adolescents and adults

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Abstract

This study provides the first description of neural network dynamics associated with response inhibition in healthy adolescents and adults. Functional and effective connectivity analyses of whole brain hemodynamic activity elicited during performance of a Go/No-Go task were used to identify functionally-integrated neural networks and characterize their causal interactions. Three response inhibition circuits formed a hierarchical, inter-dependent system wherein thalamic modulation of input to premotor cortex by frontostriatal regions led to response suppression. Adolescents differed from adults in the degree of network engagement, regional fronto-striatal-thalamic connectivity, and network dynamics. We identify and characterize several age-related differences in the function of neural circuits that are associated with behavioral performance changes across adolescent development.

Keywords

INDEPENDENT COMPONENT ANALYSIS; NETWORK; RESPONSE INHIBITION; BRAIN; MRI; DEVELOPMENT; ADOLESCENT

Response inhibition can be defined as the ability to withhold a prepotent response. It is often assessed using Go/No-Go tasks, which require people to make manual responses to rapidly presented visual or auditory cues (i.e., ‘Go’ stimuli), but to withhold responses in the presence of a different cue (‘No-Go’ stimuli). It has been proposed that deliberately withholding a response requires functional integration of prefrontal cortex regions, basal ganglia (Aron & Poldrack 2006, Band & van Boxtel 1999, de Jong, van Zomeren, Willemsen, & Paans 1996), and the thalamus to modulate subcortical input to cortical motor areas (C. H. M. Brunia 1997, Logan 1994, Logan & Cowan 1984). Event-related functional magnetic resonance imaging (fMRI) data consistently report that No-Go stimuli elicit activity in these brain regions (Braver, Barch, Gray, Molfese, & Snyder 2001, Fassbender et al. 2004, Kelly et al. 2004, Kiehl, Liddle, & Hopfinger 2000, Konishi, Nakajima, Uchida, Sekihara, & Miyashita 1998, C. S. Li,

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Huang, Constable, & Sinha 2006, Liddle, Kiehl, & Smith 2001, Watanabe et al. 2002). In particular, lesion (Aron, Fletcher, Bullmore, Sahakian, & Robbins 2003), transcranial magnetic stimulation (Chambers et al. 2006), and fMRI studies of children and adults (Bunge, Dudukovic, Thomason, Vaidya, & Gabrieli 2002, Durston et al. 2002, Konishi et al. 1998, Rubia et al. 2000, Rubia et al. 2006, Tamm, Menon, & Reiss 2002) suggest a critical role for the right inferior frontal cortex (i.e., superior and middle frontal gyral regions surrounding the inferior frontal sulcus) for successful response inhibition (Aron, Robbins, & Poldrack 2004). Comparative research has identified several anatomical pathways connecting these regions, including direct, indirect, and hyperdirect paths (Alexander, Crutcher, & DeLong 1990, Nambu, Tokuno, & Takada 2002). Of these connections, there is evidence that the indirect cortico-striatal-thalamic (Alexander et al. 1990) and hyperdirect cortico-subthalamic (Aron & Poldrack 2006, Nambu et al. 2002) pathways play a role in inhibiting responses. The indirect pathway consists of anatomical connections from cortex through the caudate, external globus pallidus, sub-thalamic nuclei and internal globus pallidus to the thalamus. To date, only one study has examined functional connectivity of indirect pathway brain regions during response inhibition. Rubia and colleagues (Rubia, Smith, Taylor, & Brammer in press) examined inter-correlations among brain regions active during successful response inhibition trials of a Stop Signal task. They report significant inter-correlation of among bilateral inferior prefrontal cortex, caudate, thalamus and cerebellum. However, this analysis was restricted only to regions identified in a contrast between successful and unsuccessful trials and did not directly compare functional connectivity measures between adolescents and adults. Therefore, differences related to normal maturation are as yet unknown.

Age-related improvements in the ability to countermand responses on Go/No-Go (Johnstone, Pleffer, Barry, Clarke, & Smith 2005, Tamm et al. 2002) or similar tasks (Band, van der Molen, Overtom, & Verbaten 2000, Schachar & Logan 1990, Williams, Ponesse, Schachar, Logan, & Tannock 1999) suggests there are normal maturational gains in response inhibition ability that can be observed with functional imaging. However, functional neuroimaging studies comparing adult and adolescent brain activity during response inhibition tasks have yielded inconsistent results, likely due to the variety of tasks used and differences in analytic procedures among studies (see reviews also by (Durston & Casey 2006, Rubia et al. 2006). Despite varying methods and results, fMRI studies of response inhibition show that youth typically activate bilateral inferior prefrontal cortex to No-Go stimuli, but adults have greater and more focal activity, particularly in the right hemisphere (Booth et al. 2003, Bunge et al. 2002, Casey et al. 1997, Durston et al. 2002, Rubia et al. 2000, Rubia et al. 2006, Tamm et al. 2002). Some of these studies (Bunge et al. 2002, Durston et al. 2002, Rubia et al. 2000) suggest that younger persons, particularly children who perform at adult levels (Bunge et al. 2002), more greatly engage some posterior brain regions when they successfully withhold inappropriate responses compared to adults. It is possible that this greater activity may reflect the need to overcome relatively weak anatomical connections among key brain regions through greater 'top-down' executive control. This is consistent with proposals that maturational performance gains may result from ongoing prefrontal cortex specialization and anatomical connectivity among prefrontal and posterior brain regions with increasing age (Diamond 1988, Goldman-Rakic 1987). The latter presumably would be reflected by age-related increases in functional connectivity among key brain regions during response inhibition. However to date, this possibility has not been examined.

This study had two objectives. First, we wished to identify functionally-integrated networks associated with response inhibition in healthy adolescents and adults. We also conducted analyses that examined how causal interactions among these distributed brain networks (i.e., 'effective connectivity'). We hypothesized there would be significant functional connectivity among key indirect pathway regions (i.e., lateral prefrontal cortex, basal ganglia, and thalamus), and that this neural circuit would influence activity within other neural circuits. The

second study objective was to determine whether age altered patterns of response inhibition-related functional or effective connectivity. Age-related differences in prefrontal cortex and parietal lobe activation observed in previous studies (Booth et al. 2003, Bunge et al. 2002, Casey et al. 1997, Durston et al. 2002, Rubia et al. 2000, Rubia et al. 2006, Tamm et al. 2002) could be related to differences in functional connectivity. Therefore, we hypothesized that adolescents, relative to adults, would show diminished connectivity of right inferior frontal cortex, striatal regions or thalamus in neural circuits engaged during successful response inhibition. We also predicted that there would be stronger causal influences among neural networks in the older age group, reflecting maturational improvements in higher-order behavioral control.

Material and Methods

Our aim was to quantify the coupling between brain regions involved with response inhibition. To do this, we decomposed brain responses elicited by performance on a rapid, event-related visual Go/No-Go cognitive task into a series of spatially independent components, or modes, using independent component analysis (ICA) (Calhoun, Adali, Pearlson, & Pekar 2001). ICA is a data-driven multivariate analysis method that identifies distinct groups of brain regions with the same temporal pattern of hemodynamic signal change. We then identified those components whose temporal expression significantly correlated with explanatory variables based upon the experimental design. This identified three such components, all correlating significantly with the occurrence of successful No-Go trials. Next, we applied dynamic causal modeling (Friston, Harrison, & Penny 2003) to the distributed brain responses to characterize interactive influences among the circuits. This is the first time such an analysis has been applied to data describing activation patterns across distributed brain networks, and we will describe it in some detail below. In brief, we modeled dynamic interactions among the three components to provide an estimate of how each component couples to the others. Dynamic interactions among these components also were modeled (under a bilinear approximation). Bayesian inversion of this model provided us with conditional estimates of the effective connectivity between the modes, which were analyzed using conventional *t* tests, with a specific focus on task-dependent changes in these connections. Note that this approach has a number of fundamental advantages over conventional voxel-based analyses. First, our inference about task-related responses involves a small number of *t* tests on the temporal expression of each component. This avoids the multiple comparisons problem entailed by searching over all voxels. Second, our application of dynamic causal modeling to study the coupling between distributed brain regions comprising each component avoids the *ad hoc* selection of regions of interest, commonly used in DCM.

Participants

Participants were 50 healthy, right-handed volunteers between the ages of 11 and 37. Participants were grouped by age into adolescents (11–17; mean 14.7 [2.04 SD]) and adults (18–37; mean 25.1 [5.68 SD]) recruited from several ongoing protocols at the Olin Neuropsychiatry Research Center. There were no significant differences in the gender proportion between adolescent and adult groups (i.e., 36% vs. 44%, $\chi^2 = 0.333$, *ns*). All participants had estimated intelligence in the average range, as measured by an assortment of tests that are highly correlated with IQ (e.g., Wide Range Achievement Test – 3rd Edition Reading subtest, Hopkins Adult Reading Test, etc.). Because different measures were used across projects, direct statistical comparison of estimated IQ between the two age groups was not possible and the age groups might differ somewhat in generalized intellectual ability. 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 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.psychiatry.ubc.ca/sz/nilab/software/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 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, 5 mm effective slice thickness, 30 slices) effectively covered the entire brain (150 mm) in 1.5 seconds. 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, Roche, & Mangin 2002). Each participants' translation and rotation corrections were examined to ensure there was no excessive head motion. 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 into Montreal Neurological Institute standardized space employed in statistical parametric mapping (SPM2). The normalization parameters determined for the mean functional volume were then applied to the corresponding functional image volumes for each participant. These 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. Finally, the normalized functional images were smoothed with a 12 mm full width at half-maximum Gaussian filter.

Independent Component Analyses

Analyses of spatiotemporal association were conducted using independent component analysis (ICA) procedures and algorithms described in previous reports (Calhoun et al. 2001). The ICA methods are available in a Group ICA of fMRI Toolbox (GIFT v1.3b) implemented in Matlab (<http://icatb.sourceforge.net>). This is a spatial ICA that is constrained by concatenation over subjects. In this approach, a single ICA analysis is performed on a group of participants, followed by a back reconstruction of single-subject time courses and spatial maps from the

raw data. Data were reduced through two principal component analysis (PCA) stages and concatenated at each stage for further reduction. This approach has shown to be a useful for group ICA analysis in previous reports (Calhoun et al. 2001, Schmithorst & Holland 2004). The dimensionality of the data (number of components) was estimated using the minimum description length criteria tool built into GIFT (Y. Li, Adali, & Calhoun in press). Independent component analysis estimated 25 components using a neural network algorithm that attempts to minimize the mutual information of the network outputs (Bell & Sejnowski 1995). Component time courses and spatial maps were then reconstructed for each 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. Calibration to percent signal change was calculated by first fitting the zero mean, unit standard deviation ICA timecourses to the original fMRI data via multiple regression, including an intercept term in the top 5% of voxels extracted from each component. The ICA time courses are then scaled to units of percent signal change using the resulting regression parameters.

Identification of Response Inhibition Components

The time course analysis involved parameterizing the time courses using multiple regression to provide estimates of the association between component time course and experimental design. The conditions in the Go/No-Go experiment were represented using the canonical hemodynamic response model in SPM2. This SPM2 model separately represented hemodynamic response to hits, correct rejects, and false alarm errors. These analyses yielded R^2 values that represented the overall association of each condition in the experimental design to each component time course. The mean β -weights showing the relation of each component to experimental condition (hits, correct rejects, and 'false alarm' errors) were examined using one-sample t tests against zero. Component loadings that differed significantly from zero indicated an association with that condition. Only three components were uniquely associated with successful response inhibition and examined further.

Visualization of Spatial Components

Although we have already established that the three components were significantly associated with successful response inhibition using the convolution model above, we also created statistical parametric maps that quantify how the spatial structure of these components is conserved over subjects. Note that this model was not performed in order to make inferences about regionally specific effects across the whole sample. Rather, we were simply quantifying the spatial loading of each of the three components in relation to their variability over subject. All response inhibition component spatial maps were transformed to z -scores, incorporating a bias term to center each image's distribution of z scores at zero. Z score maps for the two sessions obtained for each participant were averaged to produce one component map per participant. One sample t tests in SPM2 were used on these individual subject component maps to visualize which brain regions were statistically significant for each component. The components averaged over subjects are presented graphically in Figure 1 and, for localization purposes, the maxima of the associated t maps are described in the Tables. For ease of viewing, these images are displayed at the arbitrary threshold of $p < .001$ family-wise error rate (Worsley et al. 1996) correction for searching the whole brain. Component spatial structure was visualized by color-coded component maps overlaid on axial slices of representative brain anatomy.

Analysis of Network Dynamics

Dynamic Causal Modeling (DCM) (Friston et al. 2003) in SPM2 was used to evaluate whether there was a meaningful causal structure among component hemodynamic activity timecourses. Because the relationships among these components were unknown, the DCM included full

intrinsic connections. This allowed evaluation of all possible unidirectional and bidirectional causal influences. The onsets of correctly-rejected No-Go stimuli were used as a bilinear interaction term to evaluate whether effective connectivity changed as function of successful response inhibition. In these models, all 'X' and 'K' stimuli comprised information input to the system. Because it was not known which of these three components would best represent the source of information input, several methods were used to determine which component represented the best input source for the DCM. Bayesian Model Comparison (BMC) (Penny, Stephan, Mechelli, & Friston 2004) conducted on the results of Bayesian across-subject average contrasted the three possible input models (i.e., system input to the Yellow parietal-premotor component, versus input to Blue fronto-striatal-thalamic component, etc.). These results showed that the model specifying system input to the Yellow parietal-premotor component was superior to the others. This was confirmed using two random effects approaches to ensure generalizability. First, the product of Bayes factors (BFs) for individual BMCs also indicated that input to the Yellow parietal-premotor component was the best fit (Model Yellow > Blue BF = 3.89×10^{97} ; Model Yellow > Red BF = 1.82×10^{148}). Second, we examined a new DCM that specified input to all three components simultaneously. Random-effects one-sample *t* tests on the input pathway coefficients showed significant difference from zero only for input to the Yellow parietal-premotor component ($t_{49} = 2.619$, $p = .012$). Results for the fully-connected DCM with input to the Yellow parietal-premotor component were aggregated using Bayesian averaging and fixed effects statistical inference as implemented in SPM2.

Analysis of Age-Related Differences

Several approaches were used to examine these components for age effects. First, adolescent (ages 11–18) and adult (ages 19–37) β -weights (representing association of ICA timecourse and successful No-Go trials) were compared using two-sample *t* test for each component. Next, spatial maps for adolescents were compared with adults in three separate SPM2 random effects two-sample *t* tests. These spatial maps indicated the relative 'strength' of connectivity within each voxel for that participant. This determined if any specific brain regions in adolescents were more or less engaged compared to adults. Finally, to determine if patterns of effective connectivity differed by age, a series of two sample *t* tests contrasted the DCM intrinsic connection path coefficients and bilinear interaction path coefficients between age groups.

Analysis of Behavioral Performance

We also performed a series of correlation analyses to explore possible relationships between Go/No-Go task performance and both functional connectivity β -weights and DCM coupling coefficients.

Results

Network Structure and Interactions

The analysis identified three independent components associated principally with successful response inhibition performance. Each component depicts a distinct, functionally-integrated circuit of brain regions that have the same pattern of hemodynamic change over time. Table 1 lists these components and their association to all experimental conditions of the Go/No-Go task. Brain regions within each component are listed in Table 2, along with the x, y, and z coordinates of the peak *t* score for each brain region. An illustration of the components' spatial structures overlaid on a map of brain anatomy is shown in Figure 1A–C, separately color-coded for each component (i.e., Blue, Red, and Yellow). The first component (Figure 1A, Blue) showed fronto-striatal-thalamic integration during response inhibition, specifically among bilateral dorsolateral and right inferior frontal cortex in the frontal lobe, caudate, and thalamus. In this network, activity in the globus pallidus was observed only at liberal statistical thresholds

(i.e., $p < .001$ uncorrected), and only in the right hemisphere. The second component (Figure 1B, Yellow), showed integrated activity in right inferior frontal cortex, bilateral insula, and regions in parietal and temporal lobe along with reduced activity in bilateral precentral gyrus, inferior parietal lobule, and precuneus. The third component (Figure 1C, Red) included right inferior frontal cortex, numerous other frontal lobe regions, and several parietal lobe regions that were functionally integrated with left caudate, thalamus and cerebellum. Of note, analysis of the whole sample showed no activation of sub-thalamic nuclei in any circuit, even when inspected at liberal thresholds ($p < .05$ uncorrected).

For display purposes, the timecourses of these components were averaged over successful No-Go events across participants (Figure 2A). Inspection of these averaged timecourses showed earlier onset and peaks for the Blue fronto-striatal-thalamic and Yellow parietal-premotor components, which suggested a possible hierarchical structure. Dynamic causal modeling (DCM) was used to determine how activity in one component influenced another. DCM allows one to test hypotheses about the existence or strength of causal pathways among activity patterns. The DCM framework considers how the relatively sluggish hemodynamic response represents underlying neuronal activity (Friston et al. 2003). The magnitude of DCM coupling coefficients are per second. In other words, they can be considered as rate constants, of the sort seen in kinetic or compartmental models. This allows large, positive coefficients to be viewed as exerting 'stronger' causal influences, while negative coefficients represent an overall inhibitory influence of one brain region (or network, in the current application) over another.

DCM conducted on these timecourses found that the fronto-striatal-thalamic Blue network exerted direct inhibitory influence over activity in both the Red frontal-parietal (bilinear interaction coefficient = -0.382) and Yellow parietal-premotor (coefficient = -0.912) networks (Figure 2B). This inhibitory influence of the Blue fronto-striatal-thalamic network over the others was lessened during response inhibition trials, as indicated by the significant bilinear interaction with response inhibition for these paths. Successful inhibition of response also altered the reciprocal causal influences between brain regions in the Yellow parietal-premotor network with brain regions in Red frontal-parietal circuit. During successful No-Go trials the Yellow parietal-premotor circuit exerted a direct inhibitory influence over the Red frontal-parietal network (difference between intrinsic connectivity and bilinear interaction coefficients $0.725 - 1.386 = -0.661$). We note that DCM results are based on a sub-sample of $n=42$ participants as the individual DCM models for 5 adolescents and 3 adults failed to converge. This likely occurred because each model was based on a specific random pattern of response inhibition successes and failures that violated computational assumptions. Correlation analyses were performed on the available data.

Age Group Effects

Compared to adults, adolescents showed weaker association of the Red frontal-parietal timecourse to response inhibition ($t_{49} = -2.056$, $p = .045$). Figure 2C suggests these differences reflect lesser amplitude of hemodynamic change in younger participants. No significant timecourse differences were found for the other two networks.

Consistent with hypotheses, analysis of the ICA voxelwise connectivity coefficients found that right inferior frontal cortex ($x, y, z = 57, 30, -12$; $t_{48} = 3.06$, $p < .001$ uncorrected), right putamen ($x, y, z = -21, 9, 6$; $t_{48} = 3.69$, $p < .001$ uncorrected), and thalamus ($x, y, z = 9, -9, 6$; $t_{48} = 3.67$, $p < .001$ uncorrected) in the Blue fronto-striatal-thalamic network were relatively less engaged for adolescents compared to adults. Contrary to hypotheses that predicted only diminished adolescent connectivity, an area of right inferior frontal gyrus ($x, y, z = 48, 33, -18$; $t_{48} = 3.66$, $p < .001$ uncorrected) was relatively more engaged within the Red frontal-parietal component for adolescents compared to adults.

Age-contrasts of the DCM coefficients examined whether causal relationships among networks altered as a function of normal maturation. Two-sample *t* tests showed that the intrinsic connection from the Red frontal-parietal network to the Blue fronto-striatal-thalamic network differed as a function of age ($t_{48} = -2.234, p = .030$). Although statistical control for between-subjects variability provides confidence in this age group difference, this result did not survive stringent Bonferroni correction for multiple comparisons. Therefore, this result should be viewed tentatively until independent replication. Further interrogation of these data showed that the adolescent average coefficient (-0.004 ± 0.074 SEM; standard error of measurement) for this pathway was less than seen for adults (0.219 ± 0.067 SEM). When evaluated by a one-sample *t* test separately, adolescents did not show a significant effect ($t_{49} = -0.053, ns$), while the results for adults was highly significant ($t_{49} = 3.270, p = .003$). The absence of this pathway in adolescents likely accounts for its lack of overall significance in the dynamic causal model. The inhibitory modulation of the pathway from the Yellow parietal-premotor network to the Red frontal-parietal network also significantly differed ($t_{48} = -2.133, p = .038$) between adolescents (-0.020 ± 0.016 SEM) and adults (0.021 ± 0.010 SEM), indicating age-related differences in how these neural circuits interact during response inhibition.

Behavioral Performance

In the aggregated sample, there were no significant relationships among behavioral performance measures (hit percentage, false alarm percentage, hit reaction time, or false alarm reaction time) and either functional or effective connectivity measurements. These Pearson *r* correlation coefficients ranged from 0.001 to 0.277, all *ns*. However, when the two age groups were examined separately, adolescent participants had a significant relationship ($r = -0.449, p = .049$) between false alarm percentage and the strength of the DCM coupling between the Red frontal-parietal network and the Blue fronto-striatal-thalamic network. This relationship was absent in adults ($r = 0.275, ns$). For adolescents, the magnitude of response inhibition modulatory influence (i.e., bilinear interaction coefficient) of the pathway from the Red frontal-parietal network to the Yellow parietal-premotor network was significantly correlated with hit percentage ($r = -0.551, p = .012$), hit reaction time ($r = 0.543, p = .013$), and false alarm reaction time ($r = 0.545, p = 0.13$). Because of the exploratory nature of these tests, none of these tests were corrected for multiple comparisons.

Discussion

This study was undertaken to identify and characterize distinct, functionally-integrated neural networks engaged by successful response inhibition. To date, evidence for such networks has been inferred largely from comparative studies of anatomical connections among brain regions activated by fMRI tasks that require prepotent response inhibition. Therefore, this study represents a significant step towards understanding how brain systems mutually interact to effect cognitive and behavioral control. Independent component analysis identified three distinct neural circuits comprising brain regions associated with response inhibition (Braver et al. 2001, Fassbender et al. 2004, Kelly et al. 2004, Kiehl et al. 2000, Konishi et al. 1998, C. S. Li et al. 2006, Liddle et al. 2001, Watanabe et al. 2002). It is likely that each of these three networks make unique contributions to the complex cognitive process of arresting a prepotent response. This is supported by the fact that the components are temporally independent, they interact causally in a hierarchical function implying functional uniqueness, and their anatomical composition, although sometimes over-lapping, shows that brain regions with distinctly different functional roles are integrated into each circuit. For convenience, these components will be discussed in turn using the same color-codes from Figure 1 and a brief anatomical label.

Consistent with study hypotheses, the first component (Blue) showed functionally-integrated hemodynamic activity within a fronto-striatal-thalamic network consistent with the indirect pathway (Figure 1A). Within this fronto-striatal-thalamic network, activity in bilateral dorsolateral prefrontal cortex and caudate increased with corresponding reductions of hemodynamic activity in the thalamus and a premotor region known to be engaged by conditional motor response tasks (i.e., pre-PMd) (Chouinard & Paus 2006). The premotor deactivation in the fronto-striatal-thalamic Blue component is consistent with a study of non-human primate Go/No-Go neurophysiology by Weinrich et al. (Weinrich, Wise, & Mauritz 1984). These results extend Weinrich et al.'s report by localizing the premotor cortex deactivation in humans.

In a separate neural mechanism (Figure 1B, Yellow) activity in bilateral precentral gyri decreased in conjunction with activation of brain regions engaged during object recognition (i.e., inferotemporal cortex), polymodal integration (i.e., anterior insula), and successful response inhibition (i.e., right inferior frontal cortex). Some have proposed that regions in this network form the anatomical basis for the transformation of sensory information into actions (Chouinard & Paus 2006). Because premotor cortex is engaged for preparation and modulation of motor response, reduction of its activity is a plausible means of arresting response (Chouinard & Paus 2006), particularly when under executive fronto-striatal system control. Dynamic causal modeling confirmed the fronto-striatal-thalamic Blue network's control over activity in Yellow parietal-premotor circuit brain regions when a response was suppressed. Specifically, demands for response suppression lessen the inhibitory influence of the Blue fronto-striatal-thalamic circuit, which results in greater engagement of the Yellow parietal-premotor network.

A third response inhibition component showed that correctly rejected No-Go stimuli also engage a network comprising right inferior frontal gyrus, right dorsolateral and bilateral frontopolar prefrontal cortex, bilateral inferior parietal lobule, pre-SMA, thalamus, and the cerebellum (Figure 1C, Red). This Red frontal-parietal circuit also was associated with concurrent hemodynamic decreases within left caudate, ventral cingulate, caudal cingulate (i.e., rostral cingulate zone), right premotor cortex, and precuneus/posterior cingulate. Because most of these brain regions previously have been found to be active in tasks requiring attention, working memory, and executive control, the likely function of this network is to exert goal-directed influences through biasing of neural activity in other brain regions (Desimone & Duncan 1995, Miller & Cohen 2001). The dynamic causal modeling results indicate that this Red frontal-parietal network is engaged for response inhibition as the Blue fronto-striatal-thalamic network releases its inhibition. Notably, caudate hemodynamic increases are observed in the Blue fronto-striatal-thalamic network, whereas the Red frontal-parietal circuit is activated with concurrent caudate decreases, reflecting the key role of the caudate (a basal ganglia input structure) in mediating different system demands. During response inhibition, the mutually reciprocal influences of brain regions in the Red frontal-parietal and Yellow parietal-premotor networks are replaced by direct inhibition of the Yellow parietal-premotor network by the Red frontal-parietal circuit. This Red-to-Yellow inhibitory causal influence suggests the role of the frontal-parietal Red network is to help 'deactivate' neural processes that are suppressing response activation. This likely serves both to reset the response inhibition system for subsequent stimulus processing and to reinforce the neural representation of goal-directed response rules within working memory. The changing causal influences among the Yellow parietal-premotor and the Red frontal-parietal networks show a clear example of task-related disabling of a connection. Specifically, the relationship from the Red frontal-parietal to the Yellow parietal-premotor circuit is positive and large in the absence of the task-related bilinear effect, and then is rendered trivially small during response inhibition.

All three networks identified in this analysis function in concert to achieve successful prepotent response inhibition through a combination of direct and indirect inhibitory effects mediated by the Blue fronto-striatal-thalamic network. These findings support previous proposals that prepotent response inhibition is achieved through thalamic modulation of motor region input in a complex system of executive and subsidiary neural processes (Band & van Boxtel 1999, C. H. Brunia 1993, Logan & Cowan 1984). The results also are consistent with a previous report of functional connectivity among inferior prefrontal cortex, caudate, thalamus and cerebellum during successful Stop Signal task response inhibition (Rubia et al. in press). However, our results extend these analyses significantly by identifying several separate and independent networks, presumably with different functional roles, in which these brain regions interact.

Because performance on tasks demanding response inhibition improves throughout normal maturation, it is possible that these behavioral changes have a demonstrable neural basis. Therefore, the second study objective was to determine whether different age groups significantly altered patterns of brain functional connectivity during response inhibition. We found diminished amplitude of hemodynamic response in the Red frontal-parietal network in adolescents relative to adults (Figure 2C), which is consistent with event-related Go/No-Go and Stop Signal fMRI studies that report less adolescent activation in medial frontal gyrus and anterior cingulate (Rubia et al. 2006) and less child activation of bilateral inferior frontal gyrus, anterior and posterior cingulate, and several parietal and temporal lobe regions (Bunge et al. 2002, Durston et al. 2002). Consistent with study hypotheses, analyses of regional connectivity found that adolescents had less mutual engagement of right IFC, left putamen and thalamus into the fronto-striatal-thalamic (Blue) network compared to adults. This suggests these brain regions may be less specialized for inhibitory control during adolescence, or albeit indirectly, also suggests less anatomic connectivity among these regions. Because this fronto-striatal-thalamic network appears to mediate engagement of the other response inhibition-related circuits, diminished integration of these brain regions likely directly impacts response inhibition. The practical influence of age-related connectivity differences is illustrated by our *post hoc* analyses integrating ICA/DCM and behavioral performance data. Consistent with previous studies (Levin et al. 1991, Rubia et al. 2006), adults had quicker behavioral performance on the Go/No-Go task than did adolescents. Our analyses showed that the number of false alarm responses to 'K' stimuli decreased with increasing coupling between the Red frontal-parietal and Blue fronto-striatal-thalamic circuits in adolescents, but not adults. Therefore, the lack of integration between Red frontal-parietal and Blue fronto-striatal-thalamic networks in adolescence is associated with performance decrements. In addition, for adolescents (but not adults) stronger response inhibition modulation of the coupling between the Red frontal-parietal network and the Yellow parietal-premotor circuit was associated with slower reaction time and fewer 'X' stimuli hits. This suggests that although response inhibition demands generally temporarily 'switch off' the putative executive influence of the Red frontal-parietal network over the Yellow parietal-premotor network, this comes with a performance cost for adolescents, who presumably require greater online monitoring for task success. We also note that the effects of age on the relationships between network connectivity and behavioral performance are very specific. This argues against the possibility that the functional and effective connectivity differences reported in this study are merely the result of behavioral performance differences. Contrary to our hypotheses, adolescents also showed greater right ventrolateral prefrontal cortex engagement compared to adults in the Red frontal-parietal circuit. This indicates that specific regions around the inferior frontal gyrus likely have different functional roles (Aron et al. 2004). This finding is consistent with the idea that some regions within right ventrolateral prefrontal cortex are more strongly recruited in younger healthy persons to overcome immaturity of key circuits that continue to specialize with ongoing development.

In general, age comparison results support the proposal that ongoing brain development throughout adolescence (Diamond 1988) could underlie age-related differences in functional connectivity, possibly reflecting increased ‘top-down’ executive control to compensate for weaker anatomical connections or incomplete functional specialization. This interpretation is supported by the finding that activity in the Red frontal-parietal executive network significantly influences activity in the Blue fronto-striatal-thalamic network for adults, but not adolescents. Moreover, supplemental correlation analyses found performance costs in adolescents associated with weaker integration of the Blue fronto-striatal thalamic and Red frontal-parietal networks. Therefore, adult maturation appears to result in greater executive influence over a key frontostriatal modulatory agent of response inhibition. Because both Blue fronto-striatal-thalamic and Red frontal-parietal networks showed prefrontal-striatal functional connectivity, the structures in both networks likely contribute to increased executive control in adulthood. Although it is beyond the scope of the present work, greater understanding would result from studies that seek direct links between functional connectivity and anatomical changes that occur throughout normal development.

Previous evidence suggests that the right inferior frontal cortex is necessary for successful response inhibition (Aron et al. 2004). Consistent with this, all three response inhibition components included activation of portions of right inferior frontal cortex. Interestingly, distinct regions of right IFC were engaged by each component. Some have proposed that right IFC is specialized to mediate several similar types of response inhibition demands (Aron et al. 2004). The patterns of intra-regional variability in whole brain connectivity found here do not necessarily challenge that proposal. However, these findings do suggest there is much complexity in the exact role this broadly-defined brain region plays in successful response inhibition. This complexity highlights the value in closely examining micro-circuitry within IFC, connections between IFC and other brain regions, and how patterns of brain function within and across right IFC sub-regions may jointly participate in various forms of behavioral inhibition.

There are several other noteworthy comments about this study. First, the patterns of functional connectivity within each network are consistent with comparative studies of anatomical connectivity among these regions (Alexander et al. 1990, Barbas, Henion, & Dermon 1991, McFarland & Haber 2002, Petrides & Pandya 1999, 2002). Second, Alexander and colleagues describe two segregated “dorsolateral prefrontal” and “motor” circuits (Alexander et al. 1990) in their studies of frontostriatal pathways. It is not clear whether activity in the Red frontal-parietal network and Blue fronto-striatal-thalamic components directly represent either or both anatomical circuits. However, these networks’ anatomical composition and functional relevance make the former most likely. It also is possible that the Red frontal-parietal network and Blue fronto-striatal-thalamic circuits reflect two anatomically and functionally separate sub-circuits within the “dorsolateral prefrontal” corticostriatal loop. Second, in contrast to Aron et al. (2006), we found no evidence for subthalamic activation during response inhibition. Likewise, the cortex subsuming the substantia nigra did not appear to be functionally integrated. These two regions are primary basal ganglia output nodes that convey information to the thalamus. Inspection of the Red frontal-parietal network and Blue fronto-striatal-thalamic component structures at liberal statistical thresholds finds activation adjacent to, but not within voxels that most likely represented activity in the sub-thalamic nuclei. Because these are small anatomical structures, it is possible that this study’s relatively large voxel size and spatial smoothing kernel could have obscured the signal from these regions. Higher-resolution imaging, as performed by Aron et al. (2006), might help clarify the involvement of these regions in Go/No-Go response inhibition. It also is possible that there were several different activity timecourses in these regions that were not identified by ICA. Indeed, evidence indicates that each basal ganglia circuit comprises multiple sub-circuits running in parallel through these small nuclei, each likely having different functions (Alexander et al. 1990). Another possibility

is that hemodynamic activity timecourses within these nuclei simply are not functionally correlated with other indirect pathway structures, but are active in intersecting networks. Therefore, while the current results do not find functional connectivity evidence consistent with the direct anatomical link between neostriatum and thalamus reported in previous comparative research (Alexander et al. 1990), they do functionally link these latter regions through a yet-to-be-identified anatomical substrate.

The spatial structure of these neural circuits and their causal influences might not generalize to response inhibition tasks with different sensory or response demands (e.g., oculomotor response inhibition, Stroop effects, etc.). Research using different paradigms is needed to determine what elements of response inhibition might be generally mediated by a common neural network, or in what way network dynamics differ across tasks with different cognitive demands. Likewise, many factors have been shown to influence brain activation on response inhibition tasks. Brain activation on ‘executive’ type tasks also is known to be influenced by IQ, (Neubauer, Grabner, Fink, & Neuper 2005) personality style (Asahi, Okamoto, Okada, Yamawaki, & Yokota 2004) and genetic profile (Heinz & Smolka 2006, Ho, Wassink, O’Leary, Sheffield, & Andreasen 2005, Winterer et al. 2006). In particular, the lack of IQ data is a limitation to the current study. Although our participants were all in the average range of estimated intelligence, we are unable to describe the possible influence of individual differences in IQ on the relationship between age and functional connectivity. Because IQ is associated with variations in brain structure and function (Frangou, Chitins, & Williams 2004, Neubauer et al. 2005), it is possible that differences in generalized intelligence between the age groups could explain differences in BOLD response and thus strongly influence any explanation based on age-related functional maturation. Indeed, it has been speculated that high intelligence may be related to the relationship between frontal and parietal lobe activation (Lee et al. 2006). Therefore, these and other similar factors should be explored in future studies of response inhibition functional connectivity. We note that the spatial structure of these networks is complex. Our discussion centers on brain regions most relevant to the current hypotheses. Therefore, the functional roles of other brain regions in these three neural networks remain to be explored, and alternative interpretations are possible. Finally, because our implementation of ICA depends on a randomly generated seed ‘starting point’ for optimization, it is possible that the results are stochastic in that they may apply only for this particular analysis. However, these methods have proved robust in that multiple iterations provide surprisingly consistent results (Correa, Adali, & Calhoun in press).

In summary, this study used a multivariate approach to analyzing fMRI data to elucidate complex relationships among brain systems engaged for behavioral control. Results revealed that the majority of regions comprising the indirect pathway were functionally integrated during response inhibition, in at least two separate circuits. These data also demonstrate the role of the fronto-striatal-thalamic indirect pathway to exert inhibitory control over other neural networks also engaged by response inhibition demands. There were significant differences between healthy adolescents and adults in response inhibition network engagement, regional connectivity, and network dynamics. These results show that developmental differences in connectivity directly influence performance on this task, highlighting the importance of integrated fronto-striatal brain function to performance. The study provides a description of response inhibition neural dynamics in healthy humans and includes a novel use of dynamic causal modeling to characterize meaningful causal relationships among ensembles of different brain regions. These results can be used in future network simulation modeling in order to determine how alterations in specific connections, or how functional impairment of a particular brain region, might influence network activity in ways consistent with psychopathological conditions.

Acknowledgements

This work was supported in part by NIMH K23 MH070036 (PI Stevens) the Holton and Yanner Trusts, NIMH 1 R01 MH070539-01 (PI Kiehl) 1 R01 MH071896-01 (PI: Kiehl), NIDA RO1 020709 and NIAAA P50-AA12870 (PI Pearlson) and NIBIB R01 EB 000840 and NIBIB R01 EB005846 (PI Calhoun). The authors appreciate the input provided by Drs. Karl Friston, Thomas Ethofer, Darren Gitelman, and Christopher Summerfield on the analytic methods used in this study.

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Figure 1.

Brain regions in each component associated with successful response inhibition. 1A) fronto-striatal-thalamic indirect pathway engagement consistent with modulation of motor function (Blue); 1B) precentral gyri deactivation concurrent with prefrontal and inferotemporal activation (Yellow); 1C) frontoparietal circuit activity consistent with higher-order presentations of No-Go' response contingencies (Red). Statistical results are thresholded at a low of $p < .001$, corrected for searching the whole brain.

Figure 2.

Results of network modeling. 2A) Averages of each component ICA timecourse for successful No-Go trials; 2B) Dynamic causal model results showing significant connections among the regions and the effects of successful response inhibition on those pathways; 2C) Average of adolescent and adult ICA timecourses for the Red frontal-parietal neural network.

Table 1

The table lists the mean (SD) of percentage of 'Go' hits and 'No-Go' errors, along with reaction time (msec) to 'Go' hits and 'No-Go' errors for adolescents and adults. The table also lists *t* test results comparing adolescent and adult performance.

	Adolescents		Adults <i>t</i> ₄₈	Age <i>t</i> test <i>p</i>
Percentage of Correct Hits	96.0 (7.88)	98.2 (2.54)	-1.324	<i>ns</i>
Percentage of False Alarms	46.2 (16.07)	46.4 (15.75)	-0.034	<i>ns</i>
False Alarm Reaction Time	36.5 (4.10)	32.9 (2.73)	3.593	.001
Average 'Go' Reaction Time *	39.3 (4.92)	36.7 (3.29)	2.211	.032

* Computed for 'Go' trials that did not immediately precede or follow any 'No-Go' stimulus.

Table 2

The table lists each component (and its corresponding color code from Figure 1). The second three columns list the means and standard deviations of regression coefficients indicating the strength of association between each component's ICA time course and Go/No-Go task conditions. The table also lists the significance levels of the one-sample *t* tests used to determine whether these loadings are statistically different from zero. Unless noted, all reported *p* values surpass FDR-corrected α 0.05.

Component	Correct Rejects	Mean (SD) Errors	Hits	Correct Rejects	One-sample <i>t</i> -test <i>p</i> Errors	Hits
Yellow – Parietal-premotor	−0.44 (0.94)	0.03 (0.62)	−0.08 (0.91)	0.002	<i>ns</i>	<i>ns</i>
Blue – Fronto-striatal-thalamic	−0.37 (1.08)	0.16 (1.08)	−0.32 (1.12)	0.019	<i>ns</i>	.050 ^a
Red – Frontal-parietal	0.90 (1.21)	−0.17 (1.32)	0.31 (1.26)	<0.001	<i>ns</i>	<i>ns</i>

^a FDR correction indicates a trend level of significance

Table 3

List of which brain regions have significantly correlated hemodynamic activity within each component. Columns depict anatomical label, MNI coordinate for peak activation voxel in each brain region, and *t* score from random effects analysis across *n*=50 participants. Regions noted ↓ show relative hemodynamic activity decreases in that component.

Component	Regions	Brodmann Areas			x	y	z	<i>t</i> ₄₉
Blue	L middle frontal gyrus	46			-42	51	21	11.98
	R middle frontal gyrus	46			45	42	36	10.78
	L inferior frontal gyrus	10			-45	48	0	8.84
	R inferior frontal gyrus	10, 47			51	51	-6	8.28
	L cuneus	18, 19			-15	-96	33	12.11
	R cuneus	19			21	-96	30	10.77
	Bilateral caudate				6	9	15	10.85
	? L middle/superior frontal gyrus (pre-PMd)	8			-21	33	48	7.88
	? R superior/middle frontal gyrus (pre-PMd)	6, 8			24	36	48	9.87
	? Medial frontal gyrus	9, 10			0	54	18	14.70
	? Medial frontal gyrus	10			0	60	-3	12.53
	? Precuneus, posterior cingulate	7, 23, 30, 31			-9	-60	21	33.10
	? L inferior parietal lobule, supramarginal gyrus, angular gyrus, superior/middle temporal gyri	39, 40			-48	-66	24	19.62
	? R inferior parietal lobule, supramarginal gyrus, angular gyrus, superior/middle temporal gyri	39, 40			54	-54	18	17.62
	? L middle temporal gyrus (posterior)	21			-60	-33	-12	7.36
	? R middle temporal gyrus (posterior)	21			63	-39	-9	7.52
	? L middle/inferior temporal gyri, fusiform gyrus	20, 21			57	-6	-30	9.19
	? R middle/inferior temporal gyri, fusiform gyrus	20, 21			-57	-9	-27	7.03
	? L thalamus				-12	-15	9	10.28
	? R thalamus				9	-12	9	10.16
Yellow	L insula/inferior frontal gyrus	13, 47			-36	18	0	9.69
	R insula/inferior frontal gyrus	13, 47			33	21	0	8.89
	R inferior frontal gyrus	47			51	36	0	6.92
	L precuneus, superior/inferior parietal lobules	7			-18	-54	57	12.27
	R precuneus, superior/inferior parietal lobules	7			12	-60	60	14.61
	L posterior cingulate	29, 30, 31			-12	-57	9	15.64
	R posterior cingulate	23, 30, 31			9	-60	12	12.44
	L middle/inferior temporal, middle occipital	19, 20, 37, 39			-48	-69	-12	14.61
	R middle/inferior temporal, fusiform, middle occipital	19, 20, 21, 37			54	-51	-6	12.40
	? Medial/superior frontal gyri	9, 6, 8			-9	45	39	8.26
	? L precentral gyrus	6, 4			-57	-9	39	8.54
	? R precentral gyrus	6, 4			63	-6	30	11.37
	? Cingulate gyrus	24, 31			-3	-18	36	9.31
	? L inferior parietal lobule, angular gyrus	39, 40			-51	-60	48	13.70
	? R inferior parietal lobule, angular gyrus	39, 40			54	-60	48	12.85
	? L cuneus/precuneus	19, 7			-6	-90	33	14.17
	? R cuneus/precuneus	19, 7			6	-87	33	12.68
	? Brainstem				12	-21	-18	8.39
	R medial/superior frontal gyri (pre-SMA)	6, 8			6	33	45	13.95
	R superior/middle frontal gyri	6, 8, 9, 46			39	18	60	16.96
Red	L middle frontal gyrus	10, 11			-39	51	0	12.14
	R superior/middle frontal gyri	10, 11			24	60	0	23.29
	R inferior frontal gyrus	45, 47			36	21	-6	14.63
	R cingulate gyrus	31			6	-33	36	9.77
	L inferior/superior parietal lobule	7, 40			-42	-54	51	16.97
	R inferior/superior parietal lobules, supramarginal gyrus	7, 39, 40			51	-51	51	20.74
	R precuneus	7			9	-75	45	13.10
	R middle temporal gyrus	21			63	-30	-9	10.23

Component	Regions	Brodman Areas	x	y	z	t ₄₉
	R lingual gyrus	18, 19	9	-66	0	7.04
	Thalamus		12	-6	6	8.87
	L cerebellum		-36	-63	-42	11.82
	L cerebellum		-15	-81	-30	10.92
	Brainstem		6	-24	-30	7.52
	? L superior/medial frontal gyri	8, 9	-24	42	39	13.07
	? L anterior cingulate gyrus (RCZ)	24, 32	-9	21	30	12.37
	? R anterior cingulate gyrus (pregenual)	25	-6	18	-6	9.79
	? Pecuneus, posterior cingulate	31	-9	-60	21	11.78
	? L fusiform gyrus	20	-30	-33	-21	7.21
	? R fusiform gyrus	20	39	-36	-33	8.10
	? L caudate		-6	18	-6	9.79