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Neural Correlates of the Development of Cognitive Flexibility

Dina R. Dajani
University of Miami, d.dajani92@gmail.com

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NEURAL CORRELATES OF THE DEVELOPMENT OF COGNITIVE FLEXIBILITY

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Dina R. Dajani

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Dina R. Dajani

Approved:

_____ Lucina Q. Uddin, Ph.D. Assistant Professor of Psychology	_____ Jennifer C. Britton, Ph.D. Assistant Professor of Psychology
_____ Anthony S. Dick, Ph.D. Associate Professor of Psychology Florida International University	_____ Guillermo Prado, Ph.D. Dean of the Graduate School

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One aspect of executive function, cognitive flexibility, is necessary for implementing the appropriate and efficient adaptation of cognitions in the face of changing environments. In a recently proposed framework, cognitive flexibility is thought to involve multiple component functions: stimulus-driven attention and two related executive functions, working memory and inhibition. These executive functions commonly recruit the frontal, cingulate, and parietal brain regions, but it is unclear whether cognitive flexibility and its component functions arise from specific connectivity profiles within this superordinate fronto-cingulo-parietal network. The objectives of this study were to 1) index behavioral changes in attention, working memory, inhibition and cognitive flexibility across the lifespan (ages 8 to 83 years) in a cross-sectional sample, 2) delineate brain connectivity profiles unique to attention, working memory, inhibition and cognitive flexibility, and 3) characterize the neural correlates of attention, working memory, inhibition and cognitive flexibility in typically developing children and adolescents. Comparisons of brain networks across a continuum of ages between childhood and adulthood (8-50 years) was conducted to determine whether the development of cognitive flexibility arises from a linear increase in connectivity among nodes, or a qualitative shift in the specific nodes used to successfully implement cognitive flexibility. In general, we found that cognitive

performance declined with age. We identified brain circuits that relate to processes unique to attention and inhibition in adults, and demonstrate that these brain circuits change with age. However, brain circuits specifically related to working memory and cognitive flexibility were not identified. These results emphasize that the neural correlates of attention and inhibition in adults do not extend to children, and future work should aim to delineate the neural correlates of specific attentional and executive functions in children and adolescents.

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CHAPTER 1: INTRODUCTION

In the face of changing environments, cognitive flexibility allows one to efficiently and flexibly adapt cognitions in the service of goal-directed behaviors (Armbruster, Ueltzhoffer, Basten, & Fieback, 2012; Dajani & Uddin, 2015; Scott, 1962). Cognitive flexibility emerges from the combination of stimulus-driven attention and efficient executive functions, such as working memory and inhibition, enabling a range of flexible human behaviors. Across development, cognitive flexibility supports many important skills such as math and reading in children (Chen et al., 2014; Diamond, Barnett, Thomas, & Munro, 2007; Engel de Abreu et al., 2014) and keeping and maintaining a job in adulthood (Bailey, 2007; Hunter & Sparrow, 2012). Despite the importance of intact cognitive flexibility across development, the neural correlates of this skill are poorly understood.

Executive functions required for cognitive flexibility

As described in our previous work (Dajani & Uddin, 2015), several subdomains of higher-level cognition act coherently to successfully implement cognitive flexibility: salience detection and bottom-up attention, working memory, inhibition, and switching. Salience detection and bottom-up attention work towards a common goal to identify behaviorally relevant environmental stimuli. Once these changes are identified, one must ascertain whether a current strategy or a different one is necessary, by retrieving representations from working memory. Before one can switch to a more appropriate strategy, the previous, but now irrelevant, strategy must be inhibited. In addition to this cognitive inhibition, currently irrelevant behavioral responses may also need to be inhibited. At the core of cognitive flexibility is the reconfiguration of one's strategy to the

new goal, denoted *switching*. Flexible cognition in everyday instances cannot be sufficiently explained without adequate consideration of the attentional, working memory, and inhibitory processes involved. Below we review the putative neural correlates of these cognitive processes.

Salience detection and bottom-up attention

The salience network (SN), anchored in the anterior insula (AI) and dorsal anterior cingulate cortex (dACC) (Seeley et al., 2007; Uddin, 2015), supports salience detection. Specifically, the dorsal anterior insula (dAI) is thought to respond to detection of salient stimuli. Bottom-up attention, one component of the attention system, mediates stimulus-driven processing via the ventral attention network (VAN) (Corbetta & Shulman, 2002). The VAN includes the right temporo-parietal junction (TPJ) and what was originally described as the right ventral frontal cortex (VFC) (M. Corbetta & Shulman, 2002; Fox, Corbetta, Snyder, Vincent, & Raichle, 2006). Close inspection of the anatomical location of the VFC node suggests that it is more accurately labeled as dorsal anterior insula (see Farrant & Uddin, 2015 for an exploration of the "VFC" connectivity profile, emphasizing its location in the salience network). Therefore, the SN and VAN can be thought to share a node in the dAI, possibly aiding in their shared goal of capturing salient information.

Working memory

Working memory is the short-term storage of information and its 'online' maintenance and manipulation (Cohen et al., 1997). This information may take the form of task representations or strategies used to carry out goal-directed behaviors. In order to assert flexible cognition, working memory is necessary to hold and manipulate these

representations. Important brain regions involved in working memory include dorsolateral PFC (dlPFC), ventrolateral PFC (vlPFC), premotor, and parietal cortices (Thomason et al., 2009), regions comprising the executive control network (ECN) (Seeley et al., 2007).

Inhibition

Before a new strategy can be implemented to adapt to a new environment, previously engaged responses that are now irrelevant must be inhibited (Davidson, Amso, Anderson, & Diamond, 2006; Derrfuss, Brass, Neumann, & von Cramon, 2005). Task-based fMRI studies reveal the right vlPFC (Aron, Robbins, & Poldrack, 2004; Levy & Wagner, 2011), right AI, and the right inferior frontal junction (IFJ) (Aron & Poldrack, 2006) as important brain regions in inhibitory control. In particular, the IFJ, a functionally defined region found at the junction of the precentral sulcus and inferior frontal sulcus, is active across a range of inhibition and other executive function tasks, such as switching, *N*-back, Stroop, reorienting, and motor inhibition tasks (Derrfuss, Brass, & Von Cramon, 2004; Levy & Wagner, 2011). Due to its ubiquitous role in inhibition, it is thought to be involved in updating task rule representations (Armbruster et al., 2012; Derrfuss et al., 2005) or detection of behaviorally relevant stimuli (Levy & Wagner, 2011; Sebastian et al., 2015). Employing a network view may help clarify the role of IFJ in different tasks, by investigating its connectivity with other brain regions and how it relates to behavioral performance. Preliminary evidence from a meta-analysis of tasks measuring inhibition demonstrates that the IFJ co-activates more strongly than the vlPFC with the inferior and superior parietal lobules, suggesting that IFJ-parietal connectivity supports inhibition (Sebastian et al., 2015). This study tested whether IFJ-

SPL connectivity was related to performance specific to an inhibition task, and not other measures of executive function. Inhibition can be decomposed into cognitive inhibition, or the suppression of thoughts or cognitive representations, and response inhibition, or the suppression of behavioral responses (Friedman & Miyake, 2004). Although cognitive inhibition may be critical for cognitive flexibility, less is known about its neural correlates because fMRI paradigms of inhibition focus primarily on response inhibition tasks (Levy & Wagner, 2011).

Switching

Behavioral studies of executive function support the notion that component executive functions such as working memory and inhibition are associated with successful cognitive flexibility, but that they are insufficient to explain all the variance associated with cognitive flexibility. This points to the presence of another component process, over and above working memory and inhibition, that is required to successfully implement cognitive flexibility. This study tests the hypothesis that the process of *switching* may fill this role. Behavioral studies of EF in neurotypical adults (NT) reveal three independent components (working memory, shifting, and inhibition) that are related to one another (Miyake & Friedman, 2012) and explain variance in executive functioning. Further, when various EF tasks are analyzed, task interference management and set shifting scales cluster together but remain independent from response inhibition, working memory, and set maintenance (Testa, Bennett, & Ponsford, 2012). The concept of switching, as a process over and above the sum of attention, working memory, and inhibitory processes, has not been directly examined (Dajani & Uddin, 2015). Traditional neuroimaging studies of cognitive flexibility do not isolate its component processes, but

measure multiple processes at once due to the inherent necessity of attention, working memory, and inhibition to successfully implement cognitive flexibility. In the present study, we aim to identify the extent to which separable brain networks and functional connectivity profiles exist for attention, working memory, and inhibition, and switching.

Brain regions underlying cognitive flexibility

Meta-analyses of task-based neuroimaging studies including a range of executive functions (e.g., working memory, inhibition, cognitive flexibility) in NT adults have identified a distributed network of fronto-cingulo-parietal regions, including the dlPFC, anterior cingulate cortex (ACC), right AI, inferior and superior parietal cortices, and the precuneus (Niendam et al., 2012). In a meta-analysis restricted to cognitive flexibility tasks, a similarly broad group of regions emerged including the vlPFC, dlPFC, IFJ, AI, ACC, inferior and superior parietal cortices, caudate, and thalamus (Kim, Cilles, Johnson, & Gold, 2012). Specifically, the right IFJ and PPC are consistently activated across cognitive flexibility tasks that differ on the level at which switching occurs (cognitive set, response, or perceptual, Kim et al., 2012). In the present study, we aim to understand how these brain regions interact to produce successful cognitive flexibility.

In particular, the AI may be critical for the switching process in cognitive flexibility. While the posterior and mid-insula act to integrate and transmit interoceptive signals (Seeley et al., 2012), the AI plays a critical role in orchestrating dynamic interactions between large-scale brain networks for externally-oriented and internally-oriented attention in NT adults and children (Uddin, Supekar, Ryali, & Menon, 2011). This study tests the hypothesis that neural flexibility, coordinated by the AI, is essential for cognitive flexibility. One lesion study supports the importance of the right AI in task

switching (Hodgson et al., 2007). Hodgson et al. (2007) showed that patients with right AI damage, compared to patients with left AI lesions, made significantly more errors, even when provided feedback, on a rule switching task. The AI, via its integral role in initiating brain network shifting, may be critically involved in switching attention to the new response set.

Development of cognitive flexibility and its component functions

At about 5 years, cognitive flexibility skills begin to emerge (Zelazo, 2006) and become largely mature by 10 years of age (Dick, 2014). Still, cognitive flexibility skills continue to improve past 10 years of age (Anderson, 2002; Hunter & Sparrow, 2012), with skills peaking between the ages of 21 and 30 (Cepeda, Kramer, & Gonzalez de Sather, 2001). When considering the development of cognitive flexibility, one must also take into account the development of the component executive processes that contribute to successful cognitive flexibility: attention, working memory, and inhibition (Dajani & Uddin, 2015). These processes follow varying developmental trajectories (Anderson, 2002), and it may be true that the component executive processes for cognitive flexibility must be functional before cognitive flexibility skills can emerge.

Development of attention. Few studies have examined the development of human attention networks. In an fMRI study comparing attention in children (8-12 years) and adults, children activated different regions (occipital and temporal regions) than adults (frontoparietal regions) during an alerting task (Konrad et al., 2005). Additionally, a resting state fMRI study revealed that contrary to traditional VFC-TPJ connectivity in adults, the nodes of the VAN in children tend to be more strongly coupled to the salience network (higher VFC-ACC connectivity) than traditional VAN nodes (i.e., the TPJ)

(Farrant & Uddin, 2015). Taken together, these findings suggest a qualitative difference in attention networks between children and adults. To the best of our knowledge, no study to date has examined the development of attention networks using intrinsic connectivity approaches in adolescence.

Development of working memory. The development of the neural mechanisms subserving one aspect of working memory, maintenance, involves the maturation of frontoparietal regions such as the inferior parietal lobule (IPL) and dlPFC (Thomason et al., 2009). In a task-based fMRI study of spatial and verbal WM maintenance in children (7-12 years) and adults, Thomason et al. (2009) reported that children activated the same brain regions as adults, but adults exhibited greater activation of these fronto-temporo-parietal regions. As working memory load increased, adults compensated for this increase in difficulty by engaging frontoparietal regions more strongly. Alternatively, children did not display as large of a load-dependent increase in brain activation, leading to greater inaccuracy in children compared to adults. In support of the Thomason et al. (2009) results, Schweinsburg and colleagues (Schweinsburg, Nagel, & Tapert, 2005) showed that across adolescence (12-18 years), IPL activation increases to support maintenance during a spatial working memory task. In a study of working memory maintenance *and* manipulation in children (8-12), adolescents (13-17), and adults (18-25), Crone and colleagues (2006) found that children did not activate the right dlPFC and bilateral SPL to the extent that adolescents and adults did while performing manipulation. On the other hand, brain activity in the IFJ was similar in children and adults during working memory tasks (Crone, Wendelken, Donohue, van Leijenhorst, & Bunge, 2006). These data suggest that while children may use the same brain regions as adults to perform WM

maintenance, such as the IPL and dlPFC (Thomason et al., 2009), children do not recruit the necessary brain regions to perform manipulation tasks (Crone et al., 2006). Instead, children may rely on IFJ recruitment to perform manipulation while adolescents and adults recruit the dlPFC.

Development of inhibition. A major contribution to the maturation of inhibition from childhood to adulthood is the emergence of right vlPFC recruitment (Bunge, Dudukovic, Thomason, Vaidya, & Gabrieli, 2002; Konrad et al., 2005; Marsh et al., 2006). In a task-based fMRI study of inhibition in children (8-12 years) and adults, Bunge et al. (2002) showed that children do not recruit the right vlPFC to perform inhibition, even when children and adults are matched on accuracy. But, children who perform at similar accuracy levels to adults (compared to children with poorer accuracy) show activation of bilateral IPL. In children, greater activation in the right middle frontal gyrus, at the IFJ, supports better inhibitory control. During adolescence, the right vlPFC begins to be recruited to support successful inhibition (Marsh et al., 2006; Rubia et al., 2006). Overall, these data suggest that children engage different brain regions than adults to successfully implement inhibition, and adolescents tend to activate brain regions similar to that of adults.

Development of neural flexibility and cognitive flexibility. The salience network plays a critical role in directing neural resources in order to implement cognitive control (Menon & Uddin, 2010). The nodes of the salience network are more functionally connected to each other and to nodes of the ECN in adults compared with children ages 7-9 years. The dAI shows properties of causal outflow in childhood, but the strength of causal outflow from the right dAI to the dACC and from the right dAI to the right dlPFC is higher in

adults than children. Further, dAI-dACC and dAI-dlPFC structural connections are stronger in adults than children (Uddin et al., 2011). Thus, salience detection and the subsequent dynamic network configuration initiated by the dAI become more efficient throughout development. To the best of our knowledge, no study to date has examined the development of the salience network during adolescence.

fMRI task-based studies of cognitive flexibility comparing children and adults report inconsistent results, with some reporting higher activation in adults (Ezekiel, Bosma, & Morton, 2013; Rubia et al., 2006), others reporting higher activation in children (Ezekiel, Bosma, & Morton, 2013), and still others reporting little differences between groups (Wendelken, Munakata, Baym, Souza, & Bunge, 2012). Further work needs to be conducted to understand the neural correlates of the development of cognitive flexibility. One of the goals of this proposal is to shed light on these developmental processes from a functional connectivity framework to complement the findings of task-based studies.

Taken together, these studies offer insights into the neural mechanisms of cognitive flexibility and its development. However, several open questions remain such as the validity of decomposing cognitive flexibility into attentional, working memory, and inhibitory components. It is still unclear how the neural correlates of cognitive flexibility, including its component functions, develop across age and whether a quantitative or qualitative shift in network connectivities emerge to support cognitive flexibility from childhood to adulthood. This study addresses these questions.

Specific Aims and Hypotheses

Specific Aim 1: To determine whether there are dissociable and specific network connectivity profiles in NT adults for the component functions of cognitive flexibility: attention, working memory, inhibition, and switching.

Hypotheses: Cognitive flexibility emerges from the interplay of specific nodes in the frontal, cingulate, and parietal cortices, all of which are necessary, while each provides a relatively specific functional contribution. These nodes may not be specific to cognitive flexibility, but are activated across a range of other EFs such as attention, working memory, and inhibition (Niendam et al., 2012). The neural context in which these nodes operate, such as their connectivity with other nodes (McIntosh, 2004), may determine which cognitive operation is carried out. The attentional components will induce dAI-TPJ connectivity. The working memory component will be supported by dlPFC-IPL connectivity. IFJ-SPL connectivity will support inhibition in the context of cognitive flexibility. Finally, connectivity between the dlPFC and the dorsal AI will be specifically related to the switching component of cognitive flexibility.

Specific Aim 2: To characterize the brain connectivity profile necessary for successful cognition across ages 8 to 50 years and test whether these networks change from childhood to adulthood.

Hypotheses: The connectivity profile of regions supporting successful attention in children will be qualitatively different than the adult network (Farrant & Uddin, 2015), with dAI-ACC connectivity supporting attention in children and dAI-TPJ connectivity supporting attention in adults. Since attentional control tends to reach adult levels by 8 years of age (Anderson, 2002), it is expected that adolescents will exhibit brain

connectivity similar to that of adults to support attention. Children will exhibit different brain regions supporting successful working memory (Crone et al., 2006), where greater IFJ-IPL connectivity in children and greater dlPFC-IPL connectivity in adolescents and adults is expected. There will be a qualitative difference in the inhibitory control component in children compared with adults (Bunge et al., 2002), where stronger IFJ-IPL connectivity will support inhibition in children. Children will exhibit a salience network similar to that of adults (Uddin et al., 2011), with greater dAI-dlPFC connectivity in children, adolescents, and adults supporting greater cognitive flexibility.

CHAPTER 2: METHODS

Participants are a subset of a publicly available dataset from the Enhanced Nathan Kline Institute- Rockland sample (NKI-RS, Nooner et al., 2012), which is an ongoing effort to collect neuroimaging and neuropsychological data from a large community sample that ranges in age across the lifespan. In an effort to maintain a representative sample, minimal exclusion criteria were used, leading to a heterogeneous sample that includes some participants with psychiatric diagnoses (Table 1). This procedure ensures the greatest generalizability of results. Three analyses were conducted: 1) behavioral analysis on a lifespan sample ages 8 to 83 ($N = 429$, "lifespan" sample), 2) brain-behavior analysis on a subset suitable for fMRI data analysis in adults ages 21 to 50 ($n = 52$, "brain-behavior adult" sample) and 3) brain-behavior analysis on a developmental sample ages 8 to 50 ($n = 93$, "brain-behavior developmental" sample). Participants with missing data on any of the behavioral measures used in the analysis were excluded. Participants with intellectual deficits or memory impairment (for ages 60 and older) were excluded. The subsets for brain-behavior analyses also excluded anyone greater than 50 years old, left-handed individuals, and participants with poor quality fMRI data (see below for more details).

Psychiatric diagnoses

A psychiatric diagnostic summary was performed by study staff for each subject based on consultation with a psychiatrist and information from the Adult ADHD Clinical Diagnostic Scale (ACDS, Kessler et al., 2010), Structured Clinical Interview for DSM-IV-TR Axis I Disorders- Non-Patient Edition (SCID-I/NP, First, 2002), the Yale-Brown Obsessive-Compulsive Scale (Goodman et al., 1989) for adults and the Kiddie Schedule

for Affective Disorders and Schizophrenia (K-SADS, Kaufman et al., 1997) for children. See Table 1 for a complete list of diagnoses present in this sample.

Table 1. Characterization of psychiatric diagnoses.

	Lifespan sample (*n*=385)	Brain-behavior adults (*n*=50)	Brain-behavior dev. (*n*=86)
No diagnosis	**221 (57%)**	**26 (52%)**	**49 (57%)**
Diagnoses	**164 (43%)**	**24 (48%)**	**37 (43%)**
-Current, Past	68, 120	9, 19	18, 25
-Substance Dep./Abuse	80	10	14
-Mood	68	10	13
-Anxiety	42	7	14
-Behavioral	26	5	8
-Body/eating	6	1	1
-Tic	6	0	1
-Enuresis/Encopresis	4	0	1
-Delusional	1	0	0

Note: Samples exclude outliers on behavioral measures. Numbers of specific disorders and current, past do not sum to 100% because there are participants with multiple diagnoses and both current and past diagnoses. Mood disorders include major depressive disorder, dysthymic disorder, and bereavment. Anxiety disorders include agoraphobia, posttraumatic stress disorder, panic disorder, generalized anxiety disorder, social phobia, and specific phobia. Behavioral disorders include conduct disorder, oppositional defiant disoder, disruptive behavior disorder, and attention deficit/hyperactivity disorder. Substance dependance/abuse disorders include alcohol, cannabis, hallucinogens, sedative/hypnotic/anxiolytics and opioids. Eating disorders include bulimia nervosa, anorexia nervosa, and body dysmorphic disorder. Tic disorders include transient tic disorder and chronic motor or vocal tic disorder.

Intelligence

To ensure intact intellectual function, participants with Full Scale IQ measured by the Wechsler Abbreviated Scale of Intelligence (WASI-II, Wechsler, 1999) below 80 were excluded.

Age

Although the NKI-RS dataset includes children as young as 6 years, some of the cognitive measures used required that participants were 8 years and older, thus the minimum age for this study was 8 years. There was no upper limit for age in the lifespan sample. On the other hand, age was restricted to 50 years and younger for the brain-behavior analyses to ensure brain volume was similar across participants.

Handedness

To ensure similarity of brain structure and laterality among participants, left-handed participants were excluded from the brain-behavior analyses.

Memory problems

The Older Adults Self Report (Achenbach, Newhouse, & Rescorla, 2004) assesses problems in adults ages 60 and older including memory/cognition problems. T-scores on the memory/cognition problems scale below 65 are considered normal, and scores above 65 are considered borderline clinical or in the clinical range. Older adults with T-scores 65 and higher on the memory/cognition scale were excluded from the lifespan sample.

Behavioral measures

Various tasks were administered to participants to assess higher cognitive functions. In the present study, we focused on tests of attention, working memory, inhibition, and cognitive flexibility.

Attention network test

The attention network test (ANT, Fan, McCandliss, Sommer, Raz, & Posner, 2002), developed based on the cued reaction time (Posner, 1980) and flanker tasks (Eriksen & Eriksen, 1974), tests three components of attention in children and adults: the alerting, orienting, and executive control systems. The goal of the task is to identify the direction of the target arrow, which can appear in either the top or bottom of the screen. There are two types of cues that offer no spatial information about the location of the upcoming target: the double-cue condition, which is spatially ambiguous by providing a cue in both the top and bottom of the screen, and the no cue condition, which simply has

a cross hair in the center of the screen. Of interest is the alerting task, which is measured by the difference in response time (RT) between the no-cue and double-cue trials. Because no spatial cue is provided for the alerting task, this can be conceptualized as a process requiring bottom-up attention (Corbetta & Shulman, 2002). The alerting system generally activates right vlPFC, left SPL, and the right posterior cerebellum in NT adults (Konrad et al., 2005). The orienting measure, given spatial information about where the target will appear, captures top-down attention. The executive control of attention is a measure of attention given conflict or competing information, provided by incongruent arrows flanking the target arrow.

Computerized neurocognitive battery: Letter N-Back task

The computerized neurocognitive battery (CNB, Gur et al., 2010) is a battery of neuropsychological tests validated on a sample 8-84 years old (Gur et al., 2012). The letter N-back task developed by Ragland and colleagues (LNB, Ragland et al., 2002) is a measure of two components of working memory- maintenance and manipulation. Letters are presented for 500 ms on a computer screen, and the participant has an additional 2000 ms to respond by pressing the spacebar. There is a 0-Back ("press the spacebar when the letter presented is an 'X'"), 1-Back ("press when the letter presented is the same as the previous letter"), and 2-Back condition ("press when the letter presented is the same as the one just before the previous letter"). The 1-Back condition generally assesses maintenance skills while the 2-Back condition requires both maintenance and manipulation (Ragland et al., 2002). Tasks requiring both maintenance and manipulation (2-Back minus 0-Back contrast) activate right dlPFC, left vlPFC (Broca's area), right insula, right MTG, and bilateral IPL in NT adults. Of note, this task is sensitive to

developmental increases in accuracy and decreases in RTs with age (Gur et al., 2012). Maintenance skills were measured using the RT (for correct trials) for the 1-Back condition. This variable was only used to calculate the development of WM maintenance across the lifespan. Because cognitive flexibility most likely involves both maintenance and manipulation, of interest to fMRI analyses in the present study are RTs for the 2-Back condition.

Delis Kaplan Executive Function System: Color-Word Interference Test

The Delis Kaplan Executive Function System (D-KEFS, Delis, Kaplan, & Kramer, 2001) is a comprehensive battery of higher cognitive function assessments designed for ages 8 to 89 years. The Color-Word Interference Test (CWIT) is a version of a classical test of inhibition- the Stroop test (Stroop, 1935). There are four conditions presented that increase in complexity. The first two identify whether the participants can name colors and read words successfully. Then, there is the inhibition condition, followed by the inhibition/switching condition. The condition of interest for the present study is the inhibition condition, which measures inhibition of verbal responses by requiring the naming of ink colors that are discordant with the word presented. Total time to complete the inhibition condition (in seconds) was used as the dependent variable in this study.

Computerized Neurocognitive Battery: Penn Conditional Exclusion Test

The Penn Conditional Exclusion Test (PCET, Kurtz, 2004b) was administered as a subtest of the CNB (Gur et al., 2010). For this task, participants must choose which one of four objects presented does not belong based on three sorting principles (e.g., shape, size, and line thickness). Feedback about accuracy is provided. After 10 consecutive

correct responses, the sorting principles change. This measure of cognitive flexibility requires hypothesis testing, abstraction, and shifting between rules when the sorting principles change. The PCET has good discriminant validity against other unrelated cognitive measures such as verbal memory and facial emotion recognition (Kurtz, 2004a) and good convergent validity with a classic test of cognitive flexibility, the Wisconsin Card Sorting Task (Kurtz, 2004a). Median RT for correct trials was used as a measure cognitive flexibility.

Data acquisition

Structural images were acquired for each participant using a 3.0-T Siemens MAGNETOM TrioTim (TR = 1900 ms, TE=2.52 ms, flip angle = 9°, FOV = 250mm, voxel size= 1mm isotropic, number of slices = 176, 1 mm slice thickness). Resting state fMRI data (rs-fMRI) was acquired using multiband echo planar imaging (TR = 1400ms, TE = 30ms, flip angle = 65°, 1 volume FOV = 224mm, voxel size = 2mm isotropic, 2mm slice thickness, number of slices = 64, multiband acceleration factor = 4, duration = 10 min). Multiband EPI sequences allow for the simultaneous excitation and acquisition of multiple brain slices, decreasing the time it takes to image the entire brain and allowing for a reduction in TR while maintaining high spatial resolution. Therefore, multiband EPI allows for higher spatial and temporal resolution than single-slice excitation EPI sequences (Moeller et al., 2010).

Data preprocessing

Data preprocessing was conducted on the brain images to increase the signal to noise ratio (SNR) by reducing artifacts introduced during data acquisition. First, raw structural and resting state images were quality checked and excluded if there were

concerns such as brain coverage, excessive motion slice artifacts, or extreme signal loss. Data was preprocessed using the Data Preprocessing Assistant for Resting-State fMRI-Advanced edition (DPARSF-A, Yan & Zang, 2010). Rigorous correction for motion artifacts was employed considering the detrimental effects of motion on rs-fMRI data (Power, Barnes, Snyder, Schlaggar, & Petersen, 2012) and the excessive motion children exhibit during data acquisition. Participants were excluded if their absolute rotational or translational motion exceeded 2mm or 2°. Then, functional data underwent removal of the first 5 time points, slice time correction, spatial realignment, nuisance covariate regression (linear trends, Friston 24 motion parameters [6 rigid motion parameters of the current volume, previous volume, and these 12 parameters squared (Friston, Williams, Howard, Frackowiak, & Turner, 1996)], white matter (WM), and cerebrospinal fluid (CSF) signals), band-pass filtering (0.01-0.08 Hz), normalization to the standard MNI152 template, spatial smoothing with a 4mm kernel, and motion scrubbing at a 0.5 mm threshold (Power et al., 2012). Structural data underwent brain extraction, coregistration to the functional image, and segmentation into grey matter, WM, and CSF. Participants who required more than 25% of their data removed due to scrubbing were excluded. Data quality was assessed following brain extraction and normalization steps and participants were excluded if these steps failed (i.e., poor normalization).

Analytic plan

Behavioral analyses

In order to determine how attentional and executive processes change with age (i.e., bottom-up attention, top-down attention, executive control of attention, working memory-maintenance, working-memory-manipulation, response inhibition, and cognitive

flexibility), a correlation between age and cognitive ability for each of the above processes was computed on the lifespan sample. If scatter plots indicated a curvilinear relationship might exist, quadratic relationships between the cognitive measures and age were also investigated using multiple linear regression analyses.

Brain-behavior analyses

For the brain-behavior analyses, a subset of the lifespan sample from the behavioral analysis was used.

Region of interest selection

Regions of interest (ROIs) were selected based on their known functional role in cognitive flexibility or its component functions from previously published studies. Two ROIs were chosen per cognitive process. ROIs originally reported in Talairach coordinates were converted to MNI space using the tal2mni.m script developed by Matthew Brett.

For bottom-up attention, the right dAI (39, 23, -4) and right TPJ (60, -48, 22) were chosen based on a meta-analysis of task-based studies of attention (Fox et al., 2006) and their known involvement in the VAN (M. Corbetta & Shulman, 2002). The dAI coordinates chosen were near to, but not exactly centered on, the "VFC" node reported in Fox et al. (2006) (42, 20, -6). We chose to instead use the coordinates reported in Uddin et al. (2011) to represent the dAI, which we also used to test connectivity related to cognitive flexibility in this study. The Uddin et al. (2011) coordinates were used to represent both bottom-up attention and cognitive flexibility to reduce the total number of ROIs investigated and avoid highly overlapping nodes. An additional ROI, the dACC (6,

24, 32) (Uddin et al., 2011), was used to test whether children have stronger dAI-ACC connectivity to support VAN activity.

For working memory, the right anterior dlPFC (antdlPFC, 38, 29, 32) and right IPL (40, -54, 41) were chosen based on a meta-analysis of task-based working memory fMRI studies (Niendam et al., 2012). Based on previous studies, the IFJ (46, 14, 30) was used to represent connectivity supporting working memory in children. The IFJ seed was chosen based on a Neurosynth (neurosynth.org) search of the keyword "cognitive control" displaying results for 319 studies; this seed was also used in a preliminary study of cognitive flexibility and prefrontal-cortical connectivity (Dajani & Uddin, presented at the annual meeting for the Organization for Human Brain Mapping 2015). Previous work suggests that verbal working memory tasks induce greater activation in the left hemisphere than the right (d'Esposito et al., 1998; Smith, Jonides, & Koeppe, 1996). Therefore, in addition to the right hemisphere seeds, we also used left hemisphere seeds for working memory based on the meta-analysis of working memory studies (antdlPFC, -40, 27, 32; IPL, -38, -54, 41, Niendam et al., 2012).

Inhibition was represented by the right IFJ and SPL (36, -58, 62). The IFJ seed was chosen using Neurosynth, as stated above. The SPL seed was chosen based on a meta-analysis of a specific inhibitory control task- the stop signal task (Sebastian et al., 2015). Connectivity related to inhibition in children was represented by the IFJ and the IPL, which was used to investigate working memory.

Finally, cognitive flexibility was represented by connectivity between the right dAI (39, 23, -4) and superior dlPFC (supdlPFC, 36, 20, 44), based on previous studies

(Uddin et al., 2011) and the preliminary cognitive flexibility study mentioned above (Dajani & Uddin, presented at the Organization for Human Brain Mapping 2015).

ROIs were a 4mm sphere predominantly located in the right-hemisphere, due to right lateralization of some nodes (e.g., dAI and IFJ) and to reduce the number of analyses. The exception to this are the left-hemisphere seeds representing verbal working memory, antdlPFC and IPL. The ROIs and estimated connectivity values are listed in Tables 2 and 3 and displayed in Figure 1. Functional connectivity was estimated using the REST toolbox (Song et al., 2011). Fisher's r to z transformed values were used in the regression analyses.

Table 2.

Hypothesized connectivity profiles supporting cognitive processes

	Adults	Children	Behavioral Measure
Bottom-up attention	dAI-TPJ	dAI-ACC	ANT
Working memory	antdlPFC-IPL	IFJ-IPL	LNB
Inhibition	IFJ-SPL	IFJ-IPL	CWIT
Cognitive flexibility	dAI-supdlPFC	dAI-supdlPFC	PCET

dAI: dorsal anterior insula; TPJ: temporo-parietal junction; ACC: anterior cingulate cortex; antdlPFC: anterior dorso-lateral prefrontal cortex; IFJ: inferior frontal junction; IPL: inferior parietal lobule; SPL: superior parietal lobule; supdlPFC: superior dorso-lateral prefrontal cortex; ANT: attention network test; LNB: letter N-back task; CWIT: color-word interference test; PCET: Penn conditional exclusion test

Table 3.

ROI selected for present study

	MNI Coordinates		
ROI	x	y	z
TPJ	60	-48	22
ACC	6	24	32
antdlPFC (R)	38	29	32
antdlPFC (L)	-40	27	32
IPL (R)	40	-54	41
IPL (L)	-38	-54	41
IFJ	46	14	30
SPL	36	-58	62
dAI	39	23	-4
supdlPFC	36	20	44

dAI: dorsal anterior insula; TPJ: temporo-parietal junction; ACC: anterior cingulate cortex; antdlPFC: anterior dorso-lateral prefrontal cortex; IFJ: inferior frontal junction; IPL: inferior parietal lobule; SPL: superior parietal lobule; supdlPFC: superior dorso-lateral prefrontal cortex

Brain-behavior analyses: Testing component processes of cognitive flexibility in adults

In order to determine the specificity of each ROI pair's connectivity with a behavioral measure, a hierarchical linear regression was computed for each ROI pair (4 regressions total). To complete Aim 1, only adults were included in this analysis (ages 21 to 50, $n = 52$). The ROI-pair connectivities for "adults" listed in Table 2 served as the outcome variables in each regression analysis. At step 1, the number of time points removed due to scrubbing was entered to ensure the brain-behavior relationships are not due to motion confounds. At step 2, the predictors were each of the four behavioral measures assessed by the ANT, LNB, CWIT, and PCET. The specificity of the ROI-pair's connectivity with a certain component of cognitive flexibility was determined by assessing whether the hypothesized behavioral measure is the only significant predictor in the regression. For example, if the only significant predictor out of the four behavioral

measures of dAI-dlPFC connectivity is the PCET, it is said that dAI-dlPFC connectivity is specific to cognitive flexibility because there is a brain-behavior relationship present after controlling for the effects of attention, working memory, and inhibition. Predictions were as follows: dAI-TPJ connectivity was expected to be specific to ANT scores, antdlPFC-IPL connectivity was expected to be specific to LNB scores, and IFJ-SPL connectivity was expected to be specific to CWIT scores (Table 2).

Testing developmental effects

In order to test both qualitative and quantitative differences in the neural correlates of cognitive flexibility across development, hierarchical linear regression analyses were conducted across the brain-behavior developmental sample (ages 8 to 50, n = 93). The six ROI-pair connectivities listed in Table 2 served as outcome variables for a total of 7 regressions. At step 1, the number of time points removed due to scrubbing was entered. At step 2, the four behavioral measures were entered. All four behavioral measures were entered into the model so that interactions between age and the behavior of interest were controlled for the influence of the other three behavioral measures, ensuring specificity of the interaction with the behavior of interest. At step 3, age and the square of age (age^2) were entered. The last step included the interaction term between age and the behavioral process of interest and the interaction term between age^2 and the behavior of interest (i.e., the behavioral measure hypothesized to be specific to the ROI pair used as the outcome variable). This resulted in 9 predictors per regression. All predictors were centered, which is a prerequisite for following up significant interactions with a simple slopes analysis. Qualitative differences in connectivity supporting the component processes of cognitive flexibility were determined by significant interactions

between age or age^2 and the cognitive measure of interest. Specifically, a significant age by cognition interaction was expected for ROI pairs (e.g., dAI- TPJ) that do not support a cognitive measure in children but do support it in adults (e.g., attention). Similarly, a significant age by cognition was expected for ROI pairs (e.g., dAI- ACC) that support a cognitive measure in children (e.g., attention) but not in adults. An age by cognition interaction is expected for connectivity between the dAI-TPJ, antdlPFC-IPL, IFJ-SPL, dAI-ACC and the IFJ-IPL. A linear relationship is expected for dAI-supdlPFC connectivity and age (i.e., no significant interaction between age and cognitive flexibility) (Figure 1B).

Betas of predictors with high multicollinearity (i.e., VIF > 5) were not interpreted. In these cases, variables were removed which contributed to the multicollinearity to ensure beta estimates were valid. In particular, two predictors (ANT and age^2 by ANT) had high multicollinearity in two out of the seven models tested (dAI-TPJ/ANT and dAI-ACC/ANT). For these models with high multicollinearity, the age^2 by ANT predictor was tested separately from the age by ANT predictor.

Significant interactions were followed up with tests of regions of significance (Preacher, Curran, & Bauer, 2006), which determine the upper and lower bounds of the moderator (i.e., age or age^2) at which the relationship between the focal predictor (i.e., 'x', the cognitive measure) and the outcome variable (i.e., 'y', connectivity) are significant (http://www.quantpsy.org/interact/mlr2.htm). To illustrate the interaction, the relationship between x and y were plotted for values of the moderator where simple slopes were significant and non-significant.

CHAPTER 3: RESULTS

Sample characteristics for the three samples analyzed (lifespan, brain-behavior adults, and brain-behavior developmental) can be seen in Table 4.

Table 4. Sample characteristics

	Lifespan (n = 385)		Brain-behavior adults (n=50)		Brain-behavior dev. (n=86)	
	Range	M (SD)	Range	M (SD)	Range	M (SD)
Sex	M=133 F=252		M=17 F=33		M=36 F=50	
Age (years)	8-83	39.11 (21.08)	21-50	32.40 (10.99)	8-50	25.36 (12.39)
FSIQ	81-142	105.16 (12.48)	84-135	101.08(12.18)	84-135	102.91 (11.98)
Alert (ms)	-70-184	35.12 (31.18)	-23-86	28.14 (23.44)	-36-122	33.94 (29.42)
Orient (ms)	-65-123	20.40 (24.82)	-20-69	17.6 (16.59)	-45-80	18.13 (20.84)
Conflict (ms)	-9-267	107.10 (43.78)	37-189	99.36 (32.34)	36-375	98.34 (45.67)
LNB 1-back (ms)	300-890	489.47 (102.55)	365-860	484.63 (107.76)	335-900	480.15 (110.27)
LNB 2-back (ms)	330-960	530.08 (124.94)	367-875	542.52 (126.07)	350-875	528.41 (126.38)
CWIT (s)	26-123	55.91 (15.38)	26-79	51.06 (11.63)	26-105	53.38 (13.87)
PCET (ms)	871-5720	2283.03 (912.03)	1165-2910	1933.76 (462.34)	871-2910	1864.63 (445.55)
Motion	-	-	0.07-0.31	.19 (.06)	0.07-0.32	.18 (.06)

Brain-behavior dev.: developmental sample used in brain-behavior analyses. FSIQ: Full-scale IQ; Alert, Orient, and Conflict are measures from the Attention Network Task; LNB: letter N-back; CWIT: Color-Word Interference Test; PCET: Penn Conditional Exclusion Test; motion: mean framewise displacement, Power et al., 2012 calculation

Behavioral analyses: Executive function across the lifespan

Based on the cognitive measures, 44 outliers (3 SD from the mean) were excluded from the lifespan sample (remaining $n = 385$). Following the removal of outliers, all variables, including age, were normally distributed (skew and kurtosis between -3 and 3). Age was correlated with the conflict measure on the ANT, which measures the executive control of attention, $r(383) = .35$, $p < .001$. In addition, both the LNB measures of

working memory maintenance and manipulation were correlated with age, 1-back: $r(383) = .13$, $p = .009$, 2-back: $r(383) = .16$, $p = .002$. The PCET, a measure of cognitive flexibility, was also correlated with age, $r(383) = .58$, $p < .001$. For these measures, as age increased, performance on the tasks decreased (Figure 2). There was a quadratic relationship between a measure of inhibition, the CWIT, and age, such that performance increased with age until 41 years, when performance began to decline with age (quadratic $R^2 = .16$; Figure 3).

Brain-behavior analyses

Adults: 21 to 50 years

Two participants were excluded as outliers on the cognitive measures (remaining $n = 50$). All variables were normally distributed. As expected, dAI-TPJ connectivity was specifically related to the alerting measure of the ANT, $\beta = -0.38$, $t(44) = -2.62$, $p = .01$. As dAI-TPJ connectivity increased (became more positive), performance on the ANT improved. Contrary to our hypotheses, antdlPFC-IPL, IFJ-SPL, and dAI-supdlPFC connectivity were not specifically related to any cognitive measures ($ps > .05$). Connectivity of left hemisphere seeds, antdlPFC-IPL, was not specifically related to verbal working memory.

Developmental sample: 8 to 50 years

Seven participants were excluded as outliers on the cognitive measures (remaining $n = 86$). All variables were normally distributed. In the dAI-TPJ/ANT model, both the ANT and age^2 by ANT terms had high multicollinearity (VIFs > 5), rendering their beta estimates invalid. Therefore, these predictors were tested in a separate model that excluded the age by ANT predictor, resulting in all VIFs < 5. This alternative model

was only used to assess the significance of the ANT and age^2 by ANT predictors; all other predictors were assessed in the original model. Age and age^2 were significantly related to dAI-TPJ connectivity, age: $\beta = 0.40$, $t(76) = 2.40$, $p = .02$, age^2: $\beta = -0.32$, $t(77) = -2.05$, $p = .04$. In addition, there was a significant age by ANT interaction, $\beta = -0.32$, $t(76) = -2.13$, $p = .04$. In the model that excluded the age by ANT term, neither the ANT nor age^2 by ANT variables were significantly related to dAI-TPJ connectivity. To follow up the significant age by ANT interaction, regions of significance testing were computed, revealing that the relationship between ANT and dAI-TPJ connectivity was only significant for adults ages 24 to 50 (at age 37, simple slope = -0.006, $t(76) = 2.33$, $p = .02$.) Consistent with results from the brain-behavior analysis in adults, higher dAI-TPJ connectivity was related to better bottom-up attention in adults, but not in children or adolescents (Figure 4).

For the dAI-ACC/ANT model, two predictors had high multicollinearity: ANT and age^2 by ANT. Therefore, the parameter estimates for these predictors were examined in a separate model excluding the age by ANT term, reducing all VIFs below 5. This alternative model was only used to assess the significance of the ANT and age^2 by ANT predictors; all other predictors were assessed in the original model. Age^2 was negatively related to dAI-ACC connectivity, $\beta = -0.33$, $t(76) = -2.03$, $p = .046$. Neither of the interactions terms was significantly related to dAI-ACC connectivity.

There were no significant predictors in the antdlPFC-IPL/LNB or IFJ-IPL/LNB models. When using left hemisphere seeds, there were still no significant predictors in the antdlPFC-IPL/LNB models.

Scores on the ANT and CWIT were related to IFJ-SPL connectivity (ANT: β = 0.30, $t(76) = 2.66$, $p = .01$; CWIT: β = -0.41, $t(76) = -2.29$, $p = .03$.) Although CWIT was negatively related to IFJ-SPL connectivity, indicating more positive connectivity was related to better performance, this result must be interpreted in light of a significant age^2 by CWIT interaction, $\beta = 0.46$, $t(76) = 2.81$, $p = .006$. Regions of significance testing was computed to determine at which points along the moderator, age^2, a significant relationship between CWIT and IFJ-SPL connectivity existed. This analysis revealed that for values of age^2 between 0-45 (i.e., 19 - 33 years), there was a negative relationship between CWIT and IFJ-SPL connectivity (at age 26, simple slope = -0.01, $t(76) = 2.25$, $p = .03$.) For values of age^2 between 401-600 (i.e., 46 – 50 years), there was a positive relationship between CWIT and IFJ-SPL connectivity (at age 48, simple slope = 0.01, $t(76) = 2.27$, $p = .03$.) For values of age^2 between 46-400 (i.e., 8-19 and 33-46 years), there was no significant relationship between CWIT and IFJ-SPL connectivity. This illustrates that for young adults, higher IFJ-SPL connectivity was correlated with better performance on an inhibition task (Figure 5). On the other hand, for older adults, higher connectivity was related to *poorer* inhibitory abilities. For children, adolescents, and middle-aged adults, there was no significant relationship between CWIT and IFJ-SPL connectivity.

There were no significant predictors in the IFJ-IPL/CWIT model, nor were there any significant predictors in the dAI-supdlPFC/PCET model, except for number of time points scrubbed ($\beta = -0.28$, $t(76) = -2.51$, $p = .01$.)

CHAPTER 4: DISCUSSION

Cognitive flexibility is an important aspect of executive function that allows for efficient adaptation to changing environmental demands in the pursuit of goals (Scott, 1962). This skill, and its proposed component functions of attention, working memory, and inhibition, begin to emerge in early childhood and follow varying developmental trajectories (V. Anderson, Jacobs, R., Anderson, P.J., 2008). Although some studies have addressed the development of cognitive flexibility in childhood, it is important to understand its development from childhood to older age in the context of the efficiency of its component functions.

Previous studies have examined development of executive functions across early childhood and adolescence into adulthood, or examined aging populations. Few single studies have investigated a battery of executive functions in a sample spanning childhood to older adulthood; such studies are critical for understanding how executive functions develop and change across the lifespan. Of those that have examined executive functions across the lifespan (Alloway & Alloway, 2013; De Luca et al., 2003; Uttl & Graf, 1997; Waszak, Li, & Hommel, 2010), none have encompassed the breadth of measures captured with the large sample size investigated in this study.

Here we addressed this gap in the literature by first conducting a comprehensive investigation of behavioral changes in a range of executive functions—attention, working memory, inhibition, and cognitive flexibility—across the lifespan. Next, to better understand the biological basis contributing to the development of these behaviors, we analyzed a subset of participants to test whether brain connectivity between specific

fronto-parietal regions related to differences in executive functioning from childhood to adulthood.

Behavioral analyses: Executive function across the lifespan

In general, performance on executive function tasks was linearly and negatively related to age across the lifespan. Inhibition exhibited a quadratic relationship with age: performance positively related to age until 41 years, after which performance was negatively related to age.

Attention has previously been characterized as comprising three largely independent networks enabling alerting, orienting, and executive control of attention (Posner & Petersen, 1990). In this study, these networks exhibited disparate relationships with age, such that performance only for the executive control of attention had a negative relationship with age, whereas alerting and orienting did not change with age. Prior studies converge with our finding of no relationship between age and orienting (Jennings, Dagenbach, Engle, & Funke, 2007; Rueda et al., 2004; Zhou, Fan, Lee, Wang, & Wang, 2011), suggesting that orienting reaches maturity before 8 years and remains intact in aging. On the other hand, the absence of an association with age and alerting does not converge with prior literature (Jennings et al., 2007; Rueda et al., 2004; Zhou et al., 2011), which shows that adults perform better than children *and* older adults. The literature has mixed results concerning the development of executive control of attention, but our results converge with one study that demonstrated a linear decline with age, even after taking into account individual differences in reaction time (Zhou et al., 2011). Overall, these results provide evidence that orienting is fully developed by 8 years and does not deteriorate with old age, and that executive control of attention declines with

age. It is less clear how alerting changes with age, as our results did not converge with three prior studies of alerting.

Contrary to our findings that working memory declines from 8 to 83 years, prior literature suggests that working memory follows a protracted development, reaching maturity in late adolescence (Alloway & Alloway, 2013; De Luca et al., 2003; Gur et al., 2012; Huizinga, Dolan, & van der Molen, 2006). Our finding of worse working memory in older adults is supported by prior studies (Borella, Carretti, & De Beni, 2008; De Luca et al., 2003). The discrepant results for the development of working memory in childhood may be explained by methodological differences. First, two of these prior studies used a spatial working memory task (De Luca et al., 2003; Huizinga et al., 2006), unlike the verbal task used here. Spatial and verbal working memory tasks may not be directly comparable given that these tasks can be dissociated using both confirmatory factor analytic and task-based fMRI studies (Alloway & Alloway, 2013; d'Esposito et al., 1998; Smith et al., 1996). Another study that used the same task to measure working memory as the current study reported improvement with age from 8-21 years, which held for both accuracy- and reaction time-based measures. But, the researchers combined the effects of maintenance and manipulation, rendering direct comparison to the results of this study difficult.

Our finding of a quadratic relationship of inhibition with age largely converges with a range of prior studies, including developmental (Davidson et al., 2006), aging (Van der Elst, Van Boxtel, Van Breukelen, & Jolles; Wecker, Kramer, Wisniewski, Delis, & Kaplan, 2000), and lifespan studies (Uttl & Graf, 1997). These results indicate

that inhibition follows a protracted development that reaches peak performance in young to middle adulthood, and begins to decline at 40-50 years of age.

Unlike our results revealing cognitive flexibility declines from 8 to 83 years, prior studies suggest that this skill continues to improve into late adolescence, although this improvement is only moderate (Gur et al., 2012). Our finding of poorer flexibility in older adults converges with prior studies (Kray, Li, & Lindenberger, 2002; Wecker, Kramer, Hallam, & Delis, 2005). Using the same task as employed in this study, Gur et al. (2012) showed that cognitive flexibility improved from 8 to 21 years, and that this effect was attenuated when using a reaction time measure rather than accuracy. The present study used a reaction time measure, and therefore the moderate improvement with age in childhood to adolescence may not have been detectable in this sample.

Overall, these results suggest that executive functions such as the executive control of attention, working memory, inhibition, and cognitive flexibility decline in older adults. Additionally, these results showed that children as young as 8 years had peak performance in executive functions (except for inhibition), contrary to evidence showing these skills continue to improve into adolescence. One possibility for this discrepancy may be that fitting a simple linear model to the data masked more nuanced relationships between age and executive functions, which may be remedied in the future by using more complex models.

An alternative explanation to the conclusion that executive function declines in normal aging is that age-related changes are due to declines in processing speed and not executive functions themselves (Salthouse, 2000), but this explanation does not seem likely based on prior studies. For example, one study of the executive control of attention

showed that, after taking into account individuals' overall reaction times for the battery of attention tasks, older adults still showed worse performance than young and middle-aged adults (Zhou et al., 2011). Similarly, a study of age-related changes on the Stroop task measuring inhibition showed quadratic relationships, even after controlling for an individual's time to complete the component tasks of color naming and word reading (Van der Elst et al., 2006). Finally, an accuracy-based measure was used in a study of working memory, and showed age-related decline, consistent with our results using a measure of reaction time (Borella et al., 2008). Taken together, these data suggest that although processing speed does decline with age (Kray et al., 2002; Waszak et al., 2010), speed does not fully account for age-related decline in executive functions. Nonetheless, to be sure the age-related changes in executive functions are not confounded with general cognitive slowing, future studies should explicitly control for individuals' reaction time when analyzing the relationship between age and executive functions.

Brain-behavior analyses

We examined brain connectivity specific to attention, working memory, inhibition, and cognitive flexibility in a sample of children and adults ages 8 to 50 years. We found stronger connectivity between the right dAI and TPJ was specifically related to better performance on tasks of bottom-up attention, but this was only true for adults 24-50 and not children nor adolescents. Performance on a task measuring inhibition, controlling for attention, working memory, and cognitive flexibility, was related to IFJ-SPL connectivity. From young adulthood to older age, the relationship between IFJ-SPL connectivity and inhibitory abilities switched, such that in young adulthood, IFJ-SPL connectivity was related to better inhibition, in middle age, this relationship was not

significant, and by older age, IFJ-SPL connectivity was related to poorer inhibition. We did not identify brain connectivity that specifically related to working memory or cognitive flexibility in children, adolescents, nor adults. These results are the first to provide evidence of how individual differences in brain connectivity may support a diverse array of executive functions, unique from related attentional and executive processes.

In young- and middle-aged adults, stronger connectivity between nodes of the ventral attention network, the right dAI and TPJ, was related to better bottom-up attention measured with an alerting task. Consistent with these results, task-based studies of target detection towards unattended stimuli activate right TPJ (Corbetta, Kincade, Ollinger, McAvoy, & Shulman, 2000; Fan, McCandliss, Fossella, Flombaum, & Posner, 2005). These results suggest that right dAI-TPJ connectivity supports bottom-up attention in adults. On the other hand, we were unable to identify brain connectivity specifically related to bottom-up attention in children or adolescents. This is most likely due to the dearth of developmental studies of attention, which caused us to form hypotheses based on only two studies (Farrant & Uddin, 2015; Konrad et al., 2005). Clearly, more research must be done to understand how the brain executes bottom-up attention from childhood to adolescence.

Contrary to our hypotheses, dlPFC-IPL connectivity was not related to performance on a measure of working memory, possibly due to incorrect choice of brain regions important for a verbal *N*-back task. Moreover, using connectivity restricted to the left hemisphere still did not specifically relate to working memory performance. Although meta-analyses offer a great vehicle for identifying reliably activated regions for

a given construct, they also involve the conglomeration of many different task paradigms that render reduced specificity. In this study, we used a meta-analysis of tasks designed to tap working memory (Niendam et al., 2012), which combined studies measuring verbal and spatial working memory, possibly rendering the nodes chosen impertinent to our specific study of a verbal *N*-back task. Although previous research indicates that children engage a qualitatively different network during tasks measuring working memory (Luna, Padmanabhan, & O'Hearn, 2010), the hypothesized nodes of this study (IFJ-IPL) did not specifically relate to working memory performance in children. Therefore, more research is needed to identify the brain networks that support working memory, above and beyond attentional and other executive processes, in children.

As predicted, more positive IFJ-SPL connectivity was related to better performance on a task measuring inhibition in young adults, specifically those between 19 and 33 years. The fact that this result held only for young adults is not unexpected given that the studies used to identify the IFJ and SPL seeds relied on samples of young adults (Derrfuss et al., 2004; Levy & Wagner, 2011; Sebastian et al., 2015). The IFJ is activated across a range of tasks, including various inhibition tasks (such as Stroop), working memory, and switching tasks (Derrfuss et al., 2005; Jan Derrfuss et al., 2004; Levy & Wagner, 2011). This general activation has led researchers to speculate of its role in updating task representations (Armbruster et al., 2012; Derrfuss et al., 2005) or detecting behaviorally relevant stimuli (Levy & Wagner, 2011; Sebastian et al., 2015). On the other hand, a network view would insist that the role of the IFJ depends on its connectivity with other brain regions, and in this study, we demonstrate that connectivity between the right IFJ and SPL is *specifically* related to inhibition on a Stroop task,

controlling for the effects of bottom-up attention, working memory, and cognitive flexibility. These results emphasize that the IFJ is not simply accomplishing a "domain general" function which is implemented for all executive function tasks, but that IFJ-SPL connectivity plays a specific role in inhibition of a pre-potent verbal response.

On the other hand, there was no relationship between connectivity and inhibition in middle adulthood (33-46 years). In older adulthood (46-50 years), stronger IFJ-SPL connectivity was related to poorer performance. This parallels our findings from the behavioral analysis, which showed that at 41 years and older, inhibition declined with age. This shows that as inhibition begins to decline overall with older age, the brain performs differently to maintain successful inhibition. During middle adulthood, it is possible that brain regions outside of IFJ and SPL come online to support inhibition. Consistent with this view, studies investigating the neural correlates of inhibition in aging have shown that from middle- to older-adulthood, a broader cortical area is activated, including stronger left-hemispheric activation while performing a Stroop task (Mathis, Schunck, Erb, Namer, & Luthringer, 2009; Zysset, Schroeter, Neumann, & von Cramon, 2007). Additionally, older adults tend to more strongly activate regions involved in inhibition, such as IFJ and vlPFC, than younger adults (Zysset et al., 2007). Interestingly, higher activity in predominantly left-lateralized regions such as the parietal cortex, dlPFC, and MFG relate to poorer performance on a Stroop task (Mathis et al., 2009; Nielson, Langenecker, & Garavan, 2002). The only study, to our knowledge, to examine age-related changes in inhibition using ages similar to our results (young: 18-31 and middle-aged: 33-55) did not find any regions that were activated more strongly in the middle-aged group compared to young adults, which does not lend support to the idea of

a network outside of IFJ-SPL supporting inhibition in older adults. But, this discrepancy may be the result of 1) their categorization of "middle-aged" adults (33-55 years) combines our middle- and older-adult groups (33-46 years, 46-50 years, respectively), possibly masking discrete effects, 2) we examined connectivity in the context of resting-state fMRI, and not brain activation during a task, and 3) we studied individual differences in inhibition across age instead of comparing categorical age groups. To determine whether adults 33-46 years engage different brain networks to enable successful inhibition, future studies should conduct exploratory analyses of connectivity across a wider set of brain regions and relate this to behavioral performance, which would complement the results of the hypothesis-driven study employed here.

Older adults who had minimal to moderate positive connectivity between IFJ and SPL performed best on the Color-Word interference test, highlighting the importance of assessing individual differences in cognition across age. Here, we provide preliminary evidence that in older adults *who exhibit intact inhibition*, a compensatory brain mechanism takes hold, which includes lower connectivity of the nodes that support inhibition in young adults and presumably engagement of another network to support inhibition in older adults. Specifically, the more strongly coupled the IFJ and SPL was in older adults, the worse they performed, suggesting that tight network coupling may be detrimental in older age. To test this hypothesis directly, future studies should investigate age-related changes in the dynamics of functional connections across the duration of a scan (Allen et al., 2012).

Contrary to our hypotheses, IFJ-IPL connectivity was not specifically related to inhibition in children. Developmental studies show that children activate a more

extensive area of cortex to inhibit prepotent responses compared to adults, who tend to activate more focal areas such as vlPFC (Tamm, Menon, & Reiss, 2002). This may help explain why connectivity between circumscribed regions like those used in this study do not capture neural correlates of executive function in children.

Contrary to our hypotheses, dAI-dlPFC connectivity was not related to a specific aspect of cognitive flexibility: switching. There is a dearth of neuroimaging research attempting to isolate switching from the component processes of cognitive flexibility (bottom-up attention, working memory, inhibition), causing our hypothesized ROIs to be based on few studies of network switching (Menon & Uddin, 2010; Supekar & Menon, 2012; Uddin et al., 2011). Past studies have revealed that the dAI has causal influence over the dlPFC, which is thought to underlie the role of dAI in initiating a switch in network engagement. In this study, we assumed that the dAI's role in network switching related to efficiency of cognitive switching necessary to perform cognitive flexibility tasks. Here, we could not confirm that network switching is related to cognitive switching, but this may be due to multiple reasons. The dAI not only directly influences the dlPFC, but also the ACC, vlPFC, PCC and PPC (Supekar & Menon, 2012; Uddin et al., 2011). Therefore, it is possible that connectivity between the dAI and a node other than the dlPFC may be related to switching necessary for cognitive flexibility. Although we explored whether dAI-ACC connectivity relates to switching, and found no relationship, future studies should explore the relationship between dAI-PPC connectivity and switching. In addition, the studies that revealed the dAI's role in network switching employed effective connectivity analyses, which take into account the temporal structure of brain activity to determine how activity of one region affects another. Here, we used

functional connectivity, which assesses the simultaneous activity of brain regions, and this may have limited our ability to relate nodes important for network switching and cognitive flexibility.

An alternative way to identify brain regions important for switching is to employ task-based studies of cognitive flexibility *and* its component functions to isolate switching-specific activity via subtraction paradigms. Unfortunately, most task-based studies of cognitive flexibility (and other executive functions) only attempt to isolate executive from non-executive processes, but not one specific executive process from another (Collette, Hogge, Salmon, & Van der Linden, 2006). The few studies that have attempted to isolate cognitive flexibility processes from other executive components (e.g., working memory) do find specific activity in parietal cortex, but not prefrontal regions (Collette et al., 2005; Sylvester et al., 2003). Although these studies bring us closer to identifying process-specific brain activity, using subtraction-based paradigms on BOLD activity will inherently disregard brain regions used in multiple executive functions, whose exact operations depend on the context of their network connectivity. In this way, exploring process-specific functional connectivity may provide more information regarding the role of nodes for specific executive functions. Future studies should continue to employ functional and effective connectivity analyses in resting-state and task-based paradigms to better isolate specific executive function processes (e.g., switching) from component executive processes.

In children and adolescents, we were unable to identify functional connections for specific executive functions, beyond the contribution of attentional and related executive processes. The current study asserted strong hypotheses about the structure of executive

functions in children (that they are separable) and that various connectivity profiles would differentially relate to specific attentional and executive functions. Although we did not find relationships between hypothesis-driven connectivity profiles and *specific* attentional and executive functions, this does not preclude the possibility that some of the connectivity profiles tested are related to general attentional and executive abilities shared across measures. Nonetheless, the lack of finding a specific relationship between connectivity and attention, working memory, inhibition, and cognitive flexibility are most likely due to the paucity of studies and difficulty in assessing the development of executive functions from childhood to adolescence. Unlike many of the ROIs chosen to represent connectivity in adults, the ROIs chosen for connectivity in children came from single-studies instead of meta-analyses, making it difficult to isolate reliable nodes. In addition, developmental neuroimaging studies suggest that brain activity is more diffuse in children and develops into more focal activity in adulthood (Durston & Casey, 2006; Durston et al., 2006; Tamm et al., 2002). For these reasons, it may be insufficient to capture executive function-related brain connectivity in children with two circumscribed ROIs. Future studies may instead employ data-driven approaches such as independent component analysis-derived networks, which capture a greater extent of brain regions, to explore brain connectivity underlying executive functions in children.

A limitation of this study includes the use of cross-sectional data to investigate age-related changes in executive functions. Due to the complexity of collecting longitudinal data across such a wide age range to represent the lifespan, there are few longitudinal studies of executive function across the lifespan (Casey et al., 2011), and most only span a few years. Ideally, longitudinal analyses should be employed to confirm

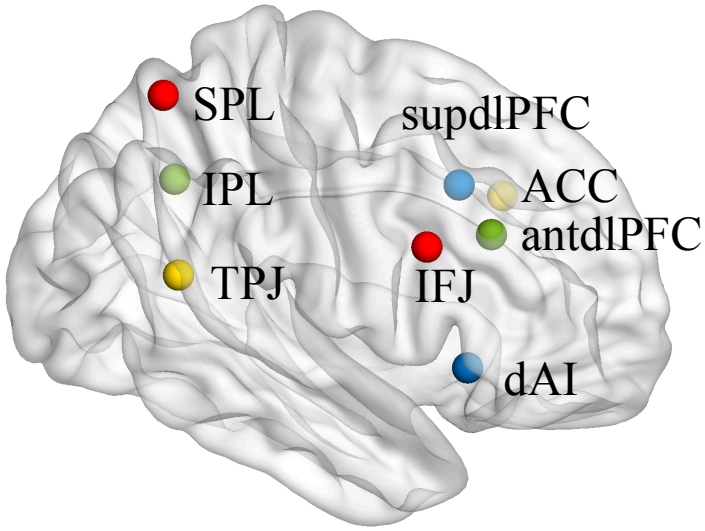
the results of this study. In addition, this study used a hypothesis-driven approach to investigate the neural correlates of specific executive functions across development. In this way, we were able to characterize how brain network connectivity supports unique components of executive function, but results only emerged for bottom-up attention and inhibition. Future studies using an exploratory approach, such as whole-brain analyses, may be able to characterize the neural correlates of processes specific to working memory and cognitive flexibility in children, adolescents, and adults.

Conclusions

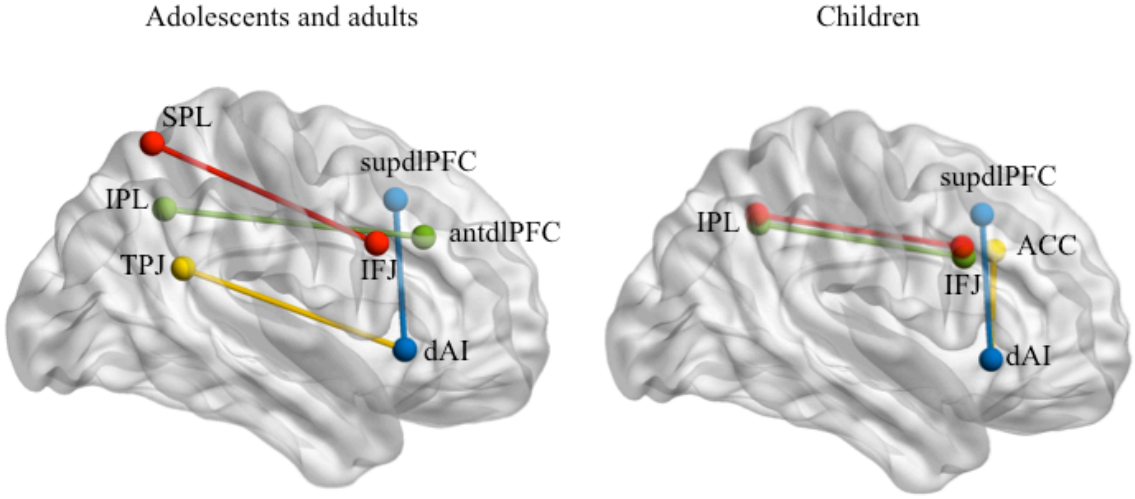
Cognitive flexibility and its component functions, bottom-up attention, working memory, and inhibition, exhibit different changes with age across the lifespan. Common to working memory, inhibition, and cognitive flexibility, these skills were poorer in older adulthood. Although bottom-up attention did not change with age, the neural correlates did, with only adults showing a relationship between dAI-TPJ connectivity and attention. Better inhibition was positively related to age from childhood to middle-adulthood, and we found that higher IFJ-SPL connectivity was related to better inhibition in young adults. Inhibition was poorer in older adults, which was reflected by a change in its neural correlates, with higher IFJ-SPL connectivity in older adults relating to *worse* inhibitory skills. We did not identify brain connectivity specifically related to working memory or the switching component of cognitive flexibility, nor connectivity related to unique components of executive functions in children. These analyses provide the first results to demonstrate how individual differences in brain connectivity support specific processes of higher-level cognition across the lifespan, and emphasize the importance of studying age when investigating the neural correlates of executive function.

FIGURES

Figure 1. Nodes and hypothesized connectivity profiles in the present study.
A. Nodes for functional connectivity analyses

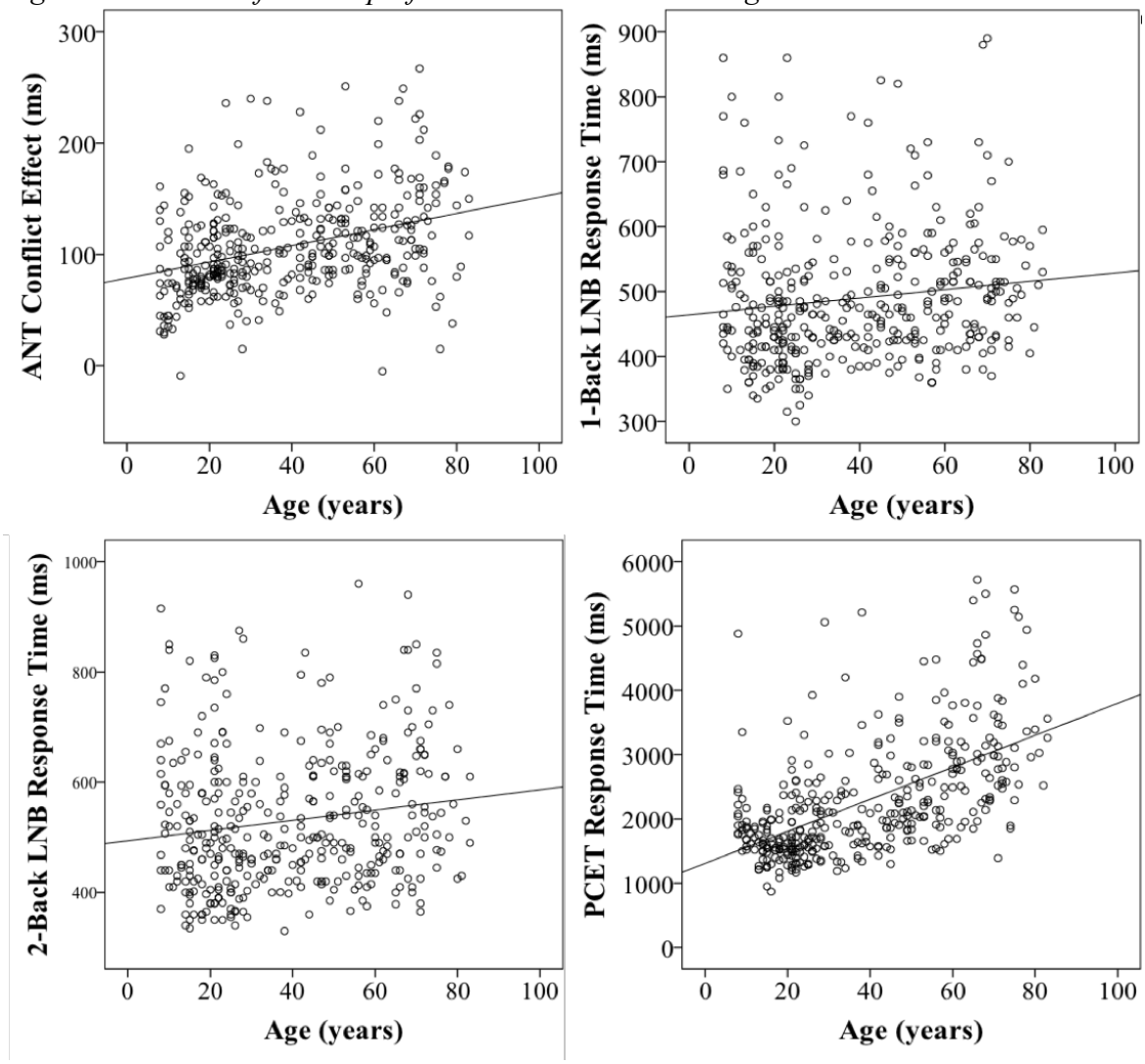


B. Hypothesized connectivity profiles for cognitive flexibility components across development.



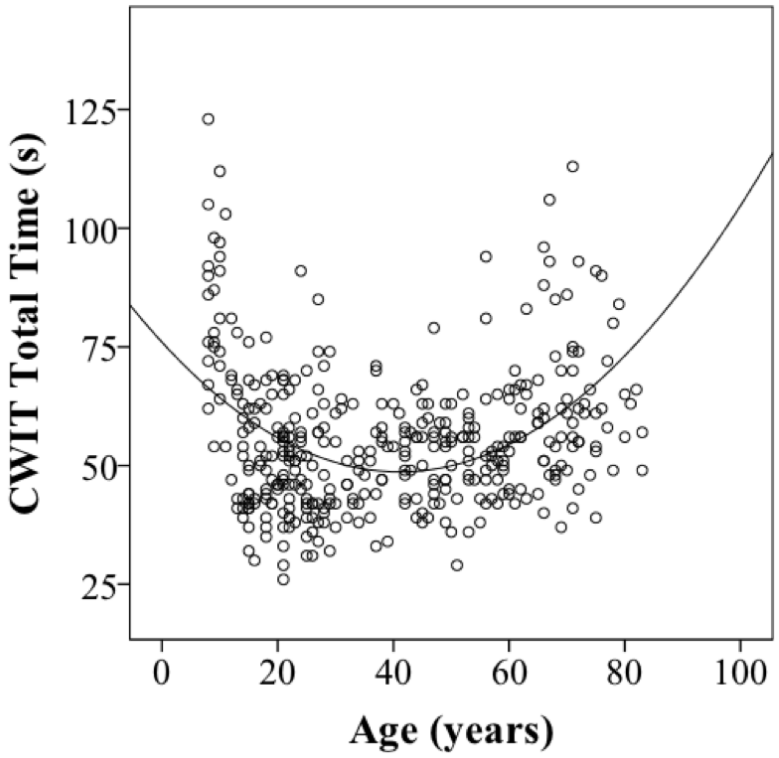
Yellow edges represent bottom-up attention, green edges represent working memory, red edges represent inhibition, and blue edges represent cognitive flexibility. Note: The hypothesized connectivity profiles in children for working memory and inhibition are both represented by IFJ-IPL connectivity.

Figure 2. Executive function performance decreases with age.



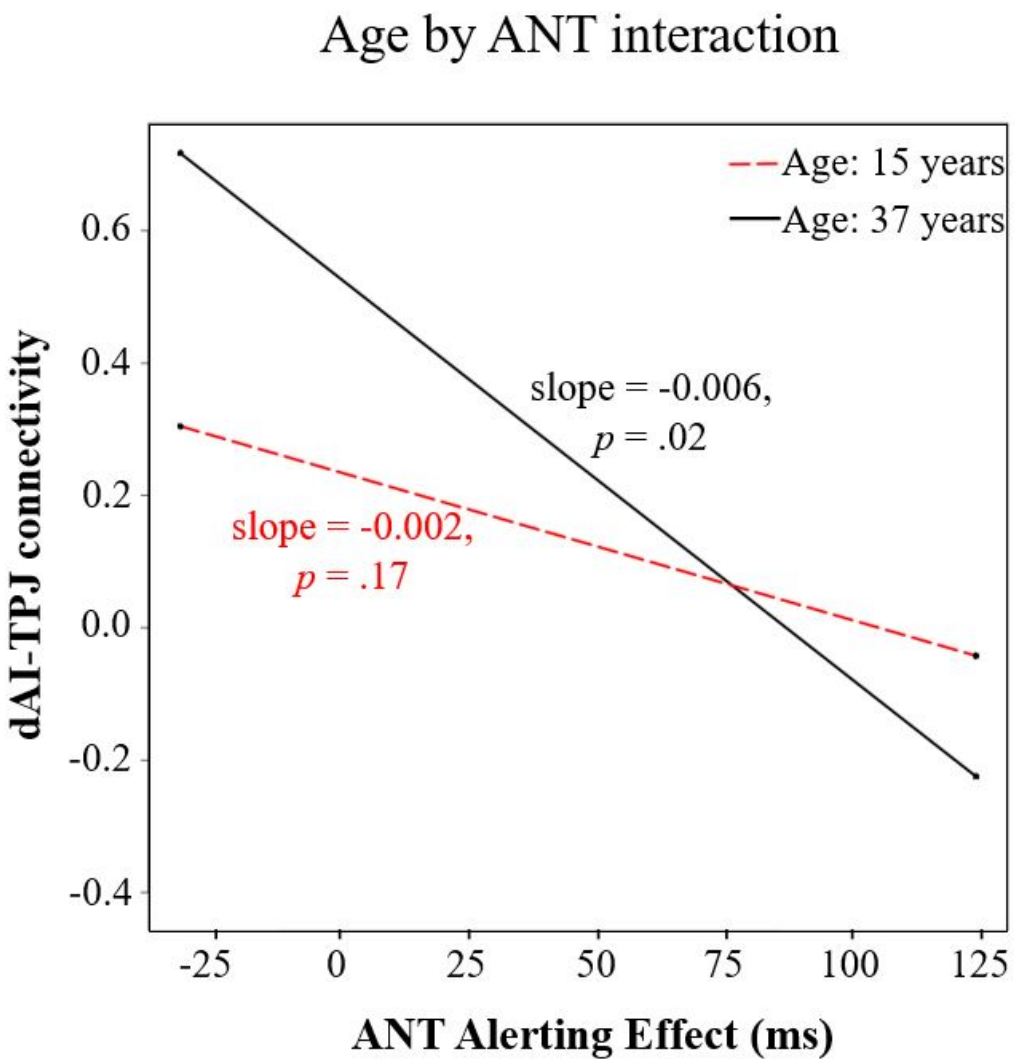
ANT: attention network test, LNB: letter n-back, PCET: Penn conditional exclusion test. All correlations are significant at $p < .01$.

Figure 3. Curvilinear relationship between age and inhibition.



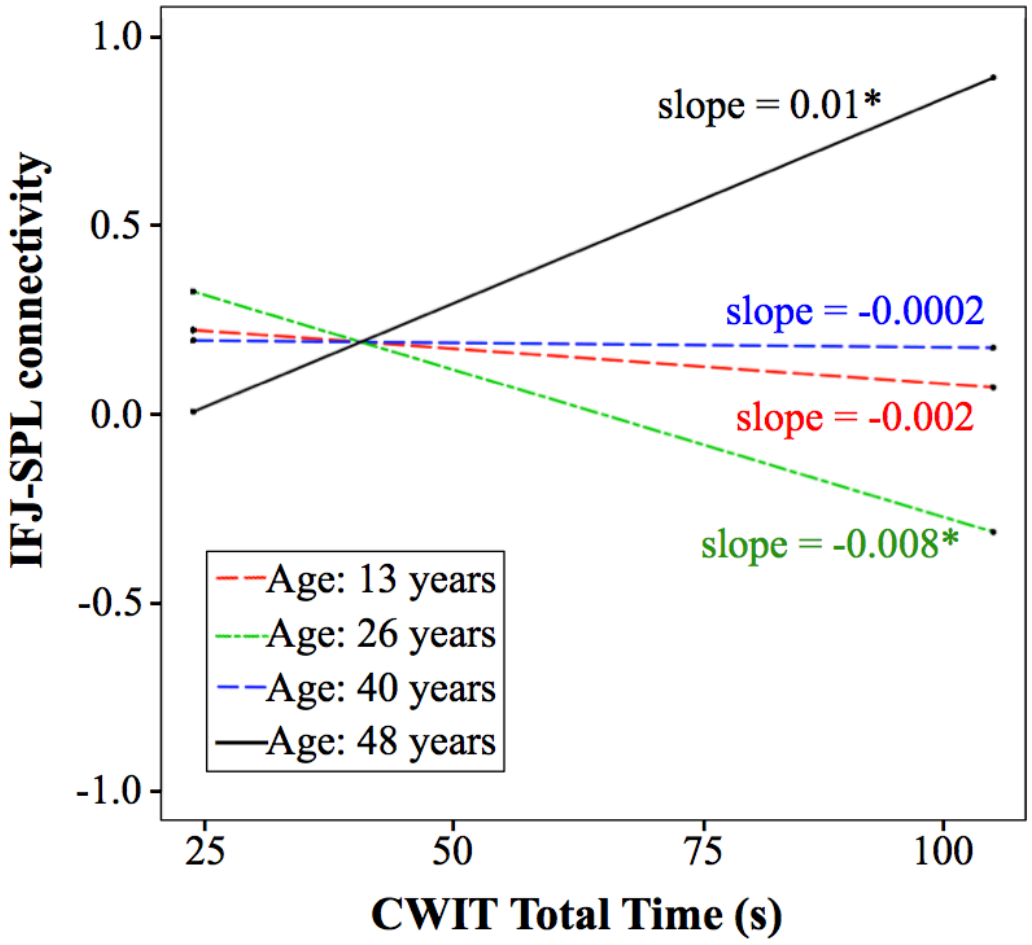
Inhibition improves with age up until 41 years, where performance begins to diminish.
CWIT: Color-Word interference test of the Delis-Kaplan Executive function battery.

Figure 4. Age by ANT alerting interaction in predicting dAI-TPJ connectivity.



In adults ages 24-50, higher dAI-TPJ connectivity is related to better alerting abilities, but this relationship is not present in children and adolescents 8-23 years. ANT: attention network test.

Figure 5. Age^2 by CWIT interaction in predicting IFJ-SPL connectivity.



There was a positive, negative, or no relationship between performance on an inhibition task and IFJ-SPL connectivity, depending on age. CWIT: Delis Kaplan Color-word interference test. *indicates significance at $p < .05$.

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