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Relationships Between Cerebello-Cortical Functional Connectivity and Executive Functioning Across Childhood and Adolescence

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RELATIONSHIPS BETWEEN CEREBELLO-CORTICAL FUNCTIONAL CONNECTIVITY AND EXECUTIVE FUNCTIONING ACROSS CHILDHOOD AND ADOLESCENCE

by

SARAH V. CLARK

Under the Direction of Jessica Turner, PhD and Tricia King, PhD

ABSTRACT

The cerebellum is a modulator of both motor and cognitive functions, helping to make these behaviors both coordinated and efficient. It is structurally and functionally connected to the prefrontal cortex (PFC) through multisynaptic, closed-loop circuits. Neuroimaging studies have established that the posterior lobules of the cerebellum are active during executive function (EF) tasks and are functionally connected to cortical regions of EF-associated networks such as the fronto-parietal network (FPN) and cingulo-opercular network (CON). Despite much evidence that the developmental timecourses of EF and cerebello-cortical connectivity are similar, and early damage to the cerebellum can cause numerous cognitive deficits, relationships between executive functions and cerebello-cortical functional connectivity during childhood and adolescence have not yet been investigated. We therefore aimed to elucidate relationships between cerebello-cortical connectivity and EFs across childhood and adolescence, in a large, typically developing sample ages 8 – 21 (*N* = 554). Independent components analysis (ICA) was utilized to compute resting-state functional connectivity between posterior cerebellum and FPN/CON. Connectivity values were extracted and entered into multiple linear regression and conditional processes models predicting EF efficiency on tasks of attention, working memory, and flexibility. First, we observed positive linear relationships between age and cerebello-cortical connectivity. In addition, posterior cerebellum – PFC connectivity predicted attention and working memory efficiency. Further, left posterior cerebellum – anterior cingulate cortex (ACC) connectivity mediated the relationship between CON connectivity and both attention and working memory performance. However, age was a stronger predictor of EF efficiency than was connectivity, and mediation was not present when age was included in statistical models. Significant age × connectivity interactions were present, as well. Cerebellum – CON connectivity became stronger with age, as predicted, but the relationship between cerebellum – ACC connectivity and attention efficiency was only significant in younger children. We hypothesize that during childhood, the posterior cerebellum and ACC create and update internal models to facilitate sustained attention and conflict and error monitoring (i.e. executive attention) on attention and working memory tasks. Results shed light on relationships among age, cerebello-cortical connectivity, and executive functioning during typical development and can help to guide future clinical research questions.

INDEX WORDS: Cerebellum, Functional connectivity, fMRI, Executive function, Cognitive control, Neurodevelopment, Development

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by

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DEDICATION

This dissertation is dedicated to my incredibly supportive family, friends, and partner. Thank you for being there for me through all of the highs and lows of graduate school. I would not be where I am today without each of you. I can’t wait to hug you all again!

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1 INTRODUCTION ANDLITERATURE REVIEW

1.1 The cerebellum as a modulator of thought

The cerebellum, long known to be a motor modulator, is now also known to be a modulator of thought (E et al., 2014; Stoodley & Schmahmann, 2009). Cognitive and behavioral deficits were observed after cerebellar lesions as early as the 1800s (Schmahmann & Sherman, 1998), and more recently, functional magnetic resonance imaging (fMRI) studies have demonstrated significant cerebellar activity during complex cognitive tasks (Balsters et al., 2014; Clark et al., 2020; E et al., 2014; Niendam et al., 2012; Stoodley & Schmahmann, 2009). The cerebellum has unique structure and function that allow it to participate in many motor and cognitive processes.

Structurally, the cerebellum contains three uniform cortical layers with densely interconnected Purkinje cells and granule cells, intertwined with climbing fibers and Mossy fibers (D'Angelo, 2014). Tracing studies have illustrated multisynaptic closed-loop anatomical connections between the cerebellum and contralateral cortical areas that generate motor or cognitive commands (See Figure 1; Bostan et al., 2013; Hoshi et al., 2005). Loops begin in the cortical regions that create motor plans or thoughts (e.g. primary motor cortex, prefrontal cortex), synapse in the pons or red nucleus, and then synapse on the cerebellar cortex (Ramnani, 2006). Because of its uniform structure, the cerebellar cortex performs the same operation on whatever data it receives and sends updated information back to the cerebral cortex via the cerebellar deep nuclei and thalamus (Ito, 2008; Ramnani, 2006). Therefore, it has been hypothesized that the cerebellum is involved in domain-general processes that support other cognitive processes, making them more efficient and automatic (Koziol et al., 2009, 2011; Ramnani, 2014).

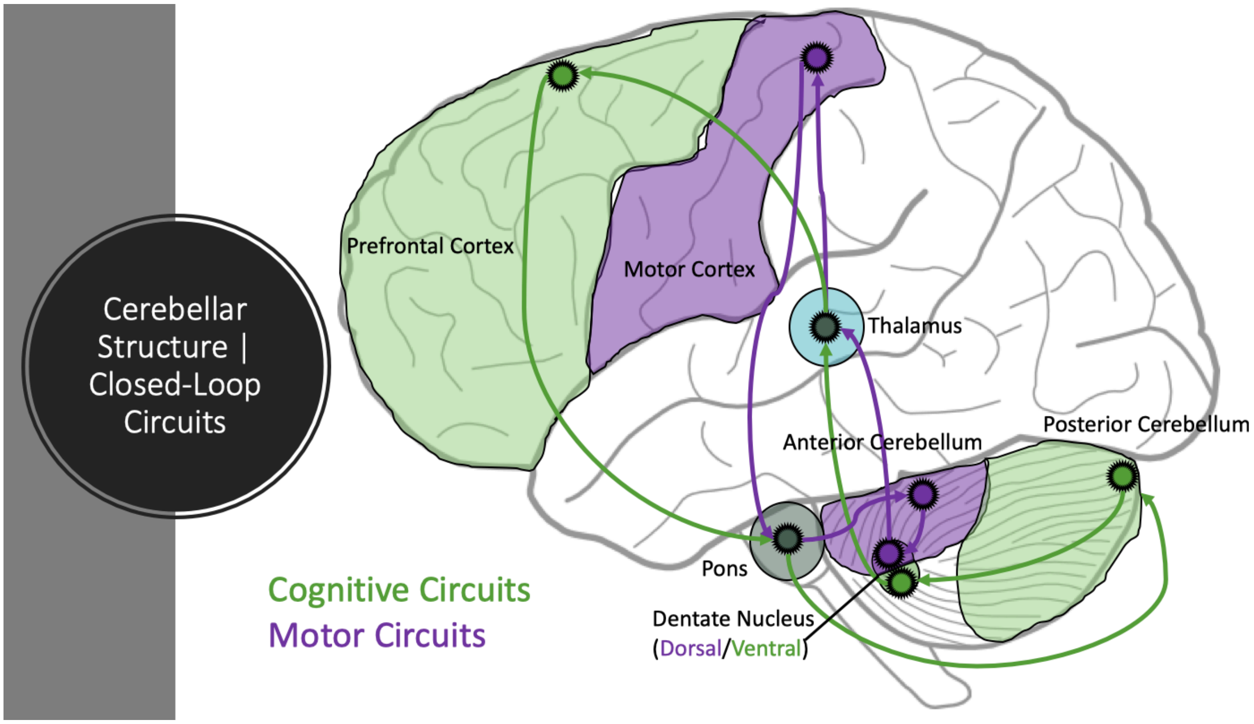

Figure 1 Illustration of cerebello-cortical loops for motor (purple) and cognitive (green) processing.

Whereas the cerebral cortex generates the movement or thought and is the "primary processor," the cerebellum uses internal models to modulate the information that originates in the cortex (Koziol et al., 2009). According to control theory, forward and inverse internal models predict and control behavior, respectively (Caligiore et al., 2017; Ito, 2008; Ramnani, 2006; Wolpert & Kawato, 1998). A forward model creates an efference copy of a controlled object, such as movement of a limb or a plan, compares the outcome to the prediction using error signals from the sensory system, and sends feedback to the input system (i.e. motor cortex, PFC) to adjust future commands. An inverse model is the opposite of a forward model: the cerebellum creates signals that act on the controlled object (i.e. limb, thought) after receiving feedback from the control system (Ito, 2008; Ramnani, 2014). Through repeated cycles, internal models fine-tune motor and cognitive behaviors, and over time, these behaviors become more coordinated and automatic and begin to be controlled by inverse models, resulting in automatic and unconscious processing (Koziol et al., 2009; Wolpert et al., 1998). Through cerebello-cortical circuits, primates (including humans) can execute smooth, coordinated, and efficient movements and thoughts (Caligiore et al., 2017).

The multisynaptic cerebello-cortical loops form structural and functional modules within the cerebellar cortex that are determined by cortical input (Ramnani, 2006, 2014). Generally, the anterior cerebellum (lobules I-V) is active during motor tasks, whereas the posterior cerebellum (lobule VI, Crus I/II, lobule VIIb) is active during cognitive tasks, and there is a secondary motor representation in lobules VIIIa/b that may also have some cognitive functions (Guell et al., 2018; Krienen & Buckner, 2009; Stoodley & Schmahmann, 2010). Lobules VIIIa/b have been associated with cognitive functions, as well, but a recent large study suggests that they are exclusively associated with motor control (Guell et al., 2018). Neuroimaging meta-analyses have demonstrated consistent posterior cerebellar activity during many cognitive tasks, including language, music, timing, working memory, and executive function (E et al., 2014; McKenna et al., 2017; Stoodley & Schmahmann, 2009). In addition, a meta-analytic connectivity modeling analysis demonstrated segregation of cerebello-cortical circuits depending on function: anterior lobules were active most often with sensorimotor regions during motor tasks, whereas Crus I and II were most often active with prefrontal cortex (PFC) and parietal cortex during cognitive tasks (Balsters et al., 2014).

Koziol et al. (2009) argued that executive functions (EFs) are specific cognitive functions that rely on the cerebellum for smooth and efficient processing. Executive functions are numerous effortful cognitive processes that generally enable humans to behave in a goal-directed manner (Diamond, 2013; Suchy, 2009). They include, broadly, suppressing inappropriate behaviors, flexibly adapting to one’s environment, and updating working memory (Diamond, 2013; Miyake et al., 2000; Miyake & Friedman, 2012). These domains of executive function are correlated, but also contain unique elements on which individuals differ (Akshoomoff et al., 2018; Huizinga et al., 2006; Miyake & Friedman, 2012). Consistent with these behavioral analyses, Niendam et al. (2012) demonstrated that a common network of fronto-parietal, subcortical, and posterior cerebellar regions are active during multiple EF tasks, and that there are dissociable regional activations for different EF domains, as well. Koziol and Lutz (2013) asserted that in the same manner as it influences the frontal cortex’s ability to anticipate movement, the cerebellum also “teaches the PFC to predict or anticipate thought outcomes,” consistent with the general role of EF in planning, coordinating, and controlling behavior.

The neural substrate of EFs is typically attributed to the prefrontal cortex and multiple executive networks such as the fronto-parietal network (FPN) and cingulo-opercular network (CON; Dosenbach, Fair, Cohen, Schlaggar, & Petersen, 2008; Suchy, 2009), but the PFC seems to be necessary and not sufficient to support EF (Alvarez & Emory, 2006). Neuroimaging meta-analyses have demonstrated that the cerebellum is a node of executive networks; cerebellar regions such as Crus I and II, and lobules VI, VIIb, and VIII, are active during EF tasks in adulthood over and above simple motor activity (Balsters et al., 2014; E et al., 2014; Niendam et al., 2012; Stoodley & Schmahmann, 2009). In addition, resting-state functional connectivity (rsFC) between left Crus I/II and the right FPN predicted better general EF ability (Reineberg et al., 2015). Further, frontal, parietal, and cerebellar regions have been consistently associated with EF deficits in neuropsychiatric disorders (Nowrangi et al., 2014). There is meta-analytic evidence for a cerebellar node of executive networks in children and adolescents (McKenna et al., 2017), but few studies have investigated how the cerebellum specifically is related to executive functioning across childhood and adolescence as EF ability and prefrontal and cerebellar structure are developing.

1.2 Developmental trajectory of executive functioning

Several developmental studies have demonstrated that in general, EF performance reaches a peak or plateau during adolescence and early adulthood, though there are task-specific differences. The basic abilities to use working memory, inhibit prepotent responses, and switch cognitive sets appear to come online relatively early in childhood, but precision, accuracy, and performance monitoring of these EFs continue to improve into later adolescence (Lee et al., 2013; Luna et al., 2010). Depending on the sample and the tasks investigated, specific EF abilities appear to reach adult-level performance between the ages of 15 and 21 (Crone & Steinbeis, 2017; Gur et al., 2012; Huizinga et al., 2006; Luna et al., 2004). Some have argued that “basic” stimulus- and rule-driven EF tasks, such as attention allocation and working memory, mature before “complex,” conscious and deliberative, EF tasks such as reasoning and problem-solving (Crone & Steinbeis, 2017; Nigg, 2017); however, tasks studied vary widely. Overall, it is generally agreed upon that executive functions come “on line” in childhood, and that accuracy and efficiency of EFs continue to improve throughout adolescence (Anderson, 2002; Lee et al., 2013; Luna et al., 2010).

Large studies including thousands of participants from the Philadelphia Neurodevelopmental Cohort (PNC), the dataset used for the current study, have shed light onto normative developmental trajectories of specific executive functions (Gur et al., 2012; Roalf et al., 2014). This dataset includes three EF tasks: the Penn Conditional Exclusion Task (PCET), a measure of cognitive flexibility, problem-solving, and concept formation, the Penn Continuous Performance Task (PCPT), a measure of attentional vigilance, and the Letter N-Back (LNB), a measure of working memory (Gur et al., 2010; Moore et al., 2015). Accuracy and speed on each of these measures significantly increased with age across a range of 8 – 21 years (Gur et al., 2012), with the largest effect present for attention (PCPT). In addition, within-individual variability across tasks decreased across this age span with regard to accuracy and showed a U-shaped curve for speed, suggesting refinement of these skills (Roalf et al., 2014). According to Gur et al.'s (2012) figures, there appears to be a large increase in both accuracy and speed (except for speed of PCET) after age 8 that tends to plateau after approximately age 16 – 17. Because Gur and colleagues did not utilize regression analyses, it is unclear whether these relationships between age and performance are linear, quadratic, or logarithmic. However, it is clear that EF performance significantly improves with increasing age, and improvements may be related to skill honing, echoing the cerebellum's role in coordinating cognition.

1.3 Neurodevelopmental trajectories of cerebello-cortical networks

Neurodevelopmental trajectories of the PFC and posterior cerebellum are similar to each other and to those of EFs. As a general pattern, phylogenetically older cortical areas reach structural maturity first, such as visual and sensorimotor cortex; phylogenetically younger areas such as the prefrontal and parietal association cortices mature latest (Gogtay et al., 2004; Lenroot & Giedd, 2006). Concomitantly, cerebellar maturation follows a similar pattern to the cerebral cortex, with the phylogenetically older anterior (motor) lobules maturing earlier than the phylogenetically younger posterior (cognitive) areas (Tiemeier et al., 2010). Thus, speculatively, the maturation of PFC and posterior cerebellum may underlie maturation of EF, consistent with the idea that development of motor skills, cognitive skills, and prefrontal – cerebellar circuits are closely intertwined (Diamond, 2000; Gottwald et al., 2016; Koziol & Lutz, 2013).

Generally, gray matter volume goes through massive growth during the first two years of life, and continues growing until adolescence, following an inverted U-shaped trajectory with probable gender differences (Giedd et al., 1999; Gogtay et al., 2004; Knickmeyer et al., 2008; Tiemeier et al., 2010; Wierenga et al., 2014). Prefrontal and parietal gray matter volume and density tend to increase until age 10 – 12 and then decrease, in contrast to somatosensory gray matter, which declines linearly starting in childhood (Giedd et al., 1999; Gogtay et al., 2004). Similarly, Tiemeier et al. (2010) and Wierenga et al. (2014) both observed a peak in total cerebellar gray matter volume at approximately age 15 for males, and Tiemeier demonstrated peak volume for females at 11.8 years whereas Wierenga observed a quadratic decrease over their entire age range (7 – 24 years). Tiemeier et al. (2010) also reported that the superior posterior (cognitive) lobules (Crus I/II) reached peak volume later than anterior and inferior (motor) lobules, at 15.8 years for females and 18.2 years for males. Altogether, prefrontal and parietal gray matter matures across a similar time frame to when EFs come on line, and posterior cerebellar gray matter matures across a similar time frame to when EFs become more efficient and accurate.

Myelination also continues linearly, well into adolescence, increasing the speed and efficiency of neural transmission with age (Silk & Wood, 2011). Generally, structural connectivity of white matter pathways predicts functional connectivity measured with fMRI; however, the extant literature has not been updated since improvement in motion and artifact correction methods, leaving this link as currently tenuous (Grayson & Fair, 2017). While a recent study of structural connectivity using diffusion-weighted imaging demonstrated that modular segregation of networks increases EF efficiency across adolescence, the authors did not include the cerebellum (Baum et al., 2017). However, the functional connectivity literature indicates that the cerebellum becomes more integrated into these cortical functional networks that functionally segregate throughout development (Dosenbach et al., 2010; Fair et al., 2007, 2009, 2013; Kundu et al., 2018); thus it may follow that this functional segregation and integration is also related to increasing EF efficiency.

Functional neuroimaging has also revealed neurodevelopmental changes in brain connectivity between the cerebellum and the cerebral cortex, though very few studies investigate the cerebellum directly during childhood and adolescence. Resting-state functional connectivity (rsFC) is one especially useful neuroimaging tool that investigators have used to infer functional (as opposed to anatomical) connections between brain regions, based on correlations of blood oxygen level dependent (BOLD) signals while a person is at rest (Biswal et al., 1995). It is thought to reveal the architecture of neural networks that are typically co-active for specific cognitive or motor functions (Allen et al., 2011; Fox & Greicius, 2010; Fox & Raichle, 2007). Resting-state functional connectivity is a useful tool for measuring functional brain architecture in children, specifically, as it does not require controlling for task compliance or performance (Uddin et al., 2010). It is also extremely useful in characterizing distributed multisynaptic networks (Van Dijk et al., 2009), such as cerebello-cortical networks, as well as fronto-parietal and cingulo-opercular functional networks that correlate with EF performance (Guell et al., 2018; Reineberg et al., 2015).

Resting-state functional connectivity has been instrumental in determining cerebellar and cerebello-cortical network functional architecture in relation to multiple cognitive domains, and a recent study demonstrated that task- and rsFC-derived cerebellar networks are remarkably similar (Guell et al., 2018). In addition, rsFC can reliably predict task activation, suggesting that resting-state networks are consistent with task-activated networks and can be accurately used in the prediction of cognitive function (Tavor et al., 2016). Further, cerebellum – prefrontal cortex connectivity distinguished children with ADHD, inattentive type from typically developing children and children with ADHD, combined type (Fair et al., 2013), demonstrating the clinical utility of rsFC (Fox & Greicius, 2010).

Broadly, functional connectivity changes throughout childhood and adolescence are characterized by strengthening of long-range connections and weakening of short-range connections, or weakening of local, within-network and strengthening of between-network organization (Dosenbach et al., 2010; Fair et al., 2007, 2009, 2013; Kelly et al., 2009; Kundu et al., 2018; Marek et al., 2015; Menon, 2013; Sato et al., 2014; Supekar et al., 2009; Uddin et al., 2010). Thus, neurodevelopment is thought to be marked by both (anatomical) integration and (functional) segregation of brain networks. Networks implicated in executive functioning including the FPN and CON feature prominently in these brain maturation models. For example, whereas in childhood, strong local connectivity within the PFC was observed, in adulthood, connectivity was stronger between frontal and parietal regions and within-PFC connectivity weakened (Dosenbach et al., 2010). Changes in functional architecture may even be driven by the functional roles of networks (Gu et al., 2015). Concomitantly, variance shared among EFs becomes increasingly segregated throughout adolescence, with the factor structure of EFs ranging from a single factor in young children to two or three factors in older children and adolescents (Akshoomoff et al., 2018; Lee et al., 2013), paralleling the increased specialization of functional brain networks.

Most studies of functional connectivity still consider the cerebellum to be a separate network to cortical networks, and thus do not always test for correlations between the cerebellum and cortical regions. However, numerous whole-brain rsFC studies have demonstrated that from childhood to early adulthood, long-range cerebellar connectivity with nodes of large-scale networks (i.e. fronto-parietal, cingulo-opercular, and default mode networks) strengthened, and cerebellar nodes became more integrated into these traditionally cortical networks (Dosenbach et al., 2010; Fair et al., 2007, 2009, 2013; Kolskår et al., 2018; Kundu et al., 2018; Solé-Padullés et al., 2016). In contrast, short-range connections within the cerebellum tended to be stronger in children than adults. Moreover, a whole-brain maturation model that included a large influence of strengthening cerebello-cortical connectivity across adolescence predicted functional maturity at approximately age 22, again paralleling the latter end of the period during which EFs mature (Dosenbach et al., 2010). Another whole-brain study showed greater cerebellar integration into functional networks through observing fewer independent components (i.e. more integrated networks) in adults than children, thus demonstrating greater spatial integration into adulthood (Kundu et al., 2018). The authors also found that two cerebellar nodes were the hubs most highly connected to other brain regions and that connectivity strength generally increased with age; thus, they hypothesized that increasing integration of spatially distributed large-scale networks may even be driven by posterior cerebellar regions (Kundu et al., 2018).

In one study that investigated the cerebellum specifically, functional connectivity evolved from exclusively between anterior cerebellar lobules and sensorimotor cortex in infancy (age 6 months) to between posterior lobules and executive and default mode networks in both childhood (ages 6 to 10) and adulthood (ages 23 to 38; Kipping, Tuan, Fortier, & Qiu, 2017). Cerebello-cortical functional connectivity was strongest in middle childhood (age 6 – 7), particularly in the lateral posterior lobules. However, this study did not include participants between ages 10 and 23, thus is unable to demonstrate functional network development during the crucial pre-adolescent through adolescent period. Partially filling this gap, a longitudinal study of whole-brain seed-to-voxel connectivity in pre-adolescence to adolescence demonstrated that left Crus II and lobule VIIb were significantly connected to the right dorsolateral prefrontal cortex (dlPFC) at age 13, but not age 10; therefore, the posterior cerebellum likely becomes integrated into the executive/fronto-parietal network in early adolescence (Sherman et al., 2014). In contrast, another longitudinal study in adolescents ages 12 – 21 using seed-to-voxel methods found a weakening of rsFC between Crus I and II and the PFC over one year (Bernard et al., 2016). The authors suggested that this pattern may be related to pruning and refinement of local connections in the PFC, rather than weakening of cerebello-cortical connections *per se*, in line with other studies demonstrating network segregation throughout development. Notably, the age range of Bernard et al.'s (2016) sample was older than most previous studies discussed, with their lower end (age 12) coinciding with peak PFC gray matter volume (Tiemeier et al., 2010). They also followed up with their participants after a shorter time period than Sherman et al. (2014), which may show different connectivity pattern changes. Taken together, these few cerebellum-specific studies suggest that cerebello-cortical connectivity strengthens at least until age 12 or 13, after which time it may decrease. These studies were all restricted by either specific anatomical seed regions of interest or limited age groups, so using data-driven methods to define cerebello-cortical connectivity in a larger sample with a wider age range may reveal different patterns. In addition, while Kipping et al. (2017) hypothesized that strengthening of cerebello-cortical connections during childhood may demonstrate a mediation effect on higher cognition development, this hypothesis has not been tested, leaving this link speculative thus far.

It should be noted that recently, awareness of motion artifacts affecting connectivity correlation strength has caused some to wonder whether general connectivity patterns of strengthening long-range connections are actually the result of motion contamination (Fair et al., 2013; Grayson & Fair, 2017; Satterthwaite et al., 2012). However, Fair and colleagues (2013) used several motion correction methods and replicated Dosenbach et al.'s (2010) results, also showing the same patterns including increases in connectivity strength between the cerebellum and cerebral cortex. Therefore, while motion undoubtedly influences functional connectivity and needs to be controlled for (Power et al., 2018; Satterthwaite et al., 2012, 2019), strengthening of long-range cerebello-cortical functional connections over development appears to survive motion correction.

Altogether, most studies of functional network developmental trajectories that included the cerebellum indicate that the cerebellum becomes integrated with and more strongly connected to nodes of large-scale cortical networks and these networks also segregate into specific functional modules throughout childhood and adolescence. Concomitantly, the age range over which this integration/segregation takes place corresponds roughly to the age range at which executive functions "mature" or performance plateaus (Dosenbach et al., 2010; Fair et al., 2009; Huizinga et al., 2006; Kundu et al., 2018; Lee et al., 2013; Luna et al., 2004; Uddin et al., 2010). Luna et al. (2010) characterized these neurodevelopmental changes as a "change in mode of operation" from local to distributed processing that allows individuals to process information more efficiently. These changes undoubtedly have functional consequences for development of cognitive processes.

1.4 Empirical relationships between cerebellar and executive function development

A few authors have proposed that EF development depends on coordinating executive abilities and increasing their efficiency, which suggests a potential role of the cerebellum in facilitating these processes throughout childhood and adolescence (Chevalier, 2015; Koziol & Lutz, 2013). This notion is supported by recent empirical investigations of both EF and fMRI, though there have been no studies thus far that have investigated cerebello-cortical functional connectivity in relation to cognitive abilities specifically in a typically developing population.

Whole-brain studies of working memory have demonstrated developmental differences in functional connectivity of the cerebellum. One study of the PNC found that the cerebellum, FPN, and CON acted as connectivity hubs during N-back performance, and that greater hub centrality of these networks predicted better performance, which they interpreted to indicate increasing network efficiency (Kolskår et al., 2018). The cerebellum's hub centrality also decreased over adolescence, which may indicate that it becomes less connected to itself and more influenced by other networks. In addition, load-dependent age-related differences in connectivity were observed in a fronto-parietal-cerebellar network during retrieval on a working memory task (van den Bosch et al., 2014). Connectivity was stronger in younger children at a lower working memory load, suggesting a possible compensatory mechanism, inefficient resource allocation, or greater effort expended (Hillary & Grafman, 2017); in older children connectivity strengthened with load, consistent with studies in adults (Küper et al., 2015). Differences between these studies are likely attributable to differing methods, as Kolskår and colleagues (2018) utilized graph theory whereas van den Bosch et al. (2014) employed independent components analysis, thus measuring different properties of functional connectivity. However, both show that the cerebellum is connected to the FPN and CON and is associated with working memory performance, with age-related changes across adolescence.

Similarly, another PNC study showed neural activation in frontal, parietal, and posterior cerebellar regions including Crus I and II during N-back working memory performance (Satterthwaite et al., 2013). This network was more strongly activated at greater N-back load (i.e. 2-back > 1-back), and activation was linearly correlated with both age and performance, as was also demonstrated in a study of verbal working memory (O'Hare et al., 2008). Interestingly, neural activation in Satterthwaite and colleagues' (2013) study was more strongly correlated with performance than age, and activation mediated the relationship between age and performance. Thus, the authors hypothesized that better working memory performance may be related to a more "mature" activation of the fronto-parietal-cerebellar network that is only partially related to age. Similar results were obtained when working memory performance outside of the scanner was used to predict brain function, as well, demonstrating that performance on tasks outside the scanner can reliably predict engagement of task-positive networks. Further, another PNC study revealed that behavioral dysregulation (i.e. symptoms associated with ADHD, oppositional defiant disorder, and conduct disorder) was related to poor working memory performance and reduced activation of a similar network, revealing behavioral correlates of dysfunctional executive network activation (Shanmugan et al., 2016). Altogether, while these investigations did not target the cerebellum specifically, they suggest that a network including fronto-parietal cortex and posterior cerebellum underlies working memory performance and behavioral regulation, and that these relationships become stronger with age.

One study that did specifically study the cerebellum in relation to EF connected cerebellar gray matter volume to domains of cognition in children and adolescents (Moore et al., 2017). Specifically, better working memory performance was associated with greater gray matter volume in right Crus I and II and right lobule VIIb; better set shifting was associated with greater gray matter in bilateral lobules VIIb and VIIIa and left Crus II. In addition, a moderating effect of age was observed. The older children in this study demonstrated better working memory performance and more gray matter in right lobule VIIIa/b, whereas this relationship was weaker in younger children. These results are consistent with the protracted maturation of the cerebellum and improving performance of working memory in adolescence. No similar studies have yet been completed using functional neuroimaging, which naturally follows structural imaging studies. While it would be expected that function of posterior lobules would predict cognition (Guell et al., 2018; Stoodley & Schmahmann, 2009), it is unclear whether the same patterns observed in structural data will also be observed in functional data. The activation and functional connectivity studies thus far suggest that cerebello-cortical connectivity will increase throughout adolescence, predicting EF performance more strongly with increasing age.

In summary, evidence thus far suggests that overall developmental changes in functional network organization and connectivity strength likely coincide with, and may even drive, changes in cognitive abilities (Grayson & Fair, 2017; Kundu et al., 2018). The posterior cerebellum is active along with the fronto-parietal network during EF tasks in childhood and adolescence. There is also evidence that cerebellar regions become more strongly functionally connected to cortical regions throughout childhood and adolescence, and that EF performance improves across this age span. While methods used in developmental functional connectivity studies thus far vary widely, most demonstrate remarkably similar findings. However, more work is needed to map developmental trajectories of cerebello-cortical functional connectivity and their relationships with cognition. Because no studies have focused on developmental cerebellar connectivity specifically, it is unclear how age, EF performance, and cerebello-cortical functional connectivity are all related to each other, and a piece of neurodevelopmental models of executive functioning may be currently missing. We therefore investigated relationships among cerebello-cortical functional connectivity, EF performance, and age, in a large, population-based data set, to elucidate these typical neurodevelopmental trajectories.

2 AIM 1: RELATIONSHIPS BETWEEN AGE AND FUNCTIONAL NETWORK CONNECTIVITY

2.1 Aim and hypotheses

The first aim of this study was to investigate how age predicts patterns of cerebello-cortical resting-state functional connectivity in children and adolescents. Linear and quadratic effects of age were tested, as it is currently unclear what relationship age has with cerebello-cortical functional connectivity. However, as Dosenbach et al.'s (2010) brain maturation model of connectivity demonstrated an asymptote at age 22, it was predicted that connectivity would increase linearly in our sample of 8 – 21-year-olds.

Hypothesis 1a: Age will predict connectivity between the nodes of cortical executive networks (FPN, CON) in a positive linear fashion.

Hypothesis 1b: Age will predict connectivity between the posterior cerebellum and prefrontal nodes of cortical executive networks in a positive linear fashion.

Hypothesis 1c: Age will predict connectivity between the anterior cerebellum and motor cortex in a quadratic fashion.

2.2 Methods

2.2.1 Participants: The Philadelphia Neurodevelopmental Cohort

The Philadelphia Neurodevelopmental Cohort (PNC) is a population-based sample of children and adolescents ages eight to 21. The PNC is a collaboration between Children's Hospital of Philadelphia (CHOP), the Center for Applied Genomics, and the University of Pennsylvania (Penn). Procedures were reviewed and approved by the institutional review boards at CHOP and Penn. Please see previous publications about the characteristics of the PNC for greater detail on study methods (Satterthwaite et al., 2014, 2016). Dr. Turner received permission to download and use the data for this project through the National Center for Biotechnology Information (NCBI) database of Genotypes and Phenotypes (dbGaP). The data and analyses presented in the current project are based on the use of study data downloaded from the dbGaP web site, under phs000607.v2.p2 (https://www.ncbi.nlm.nih.gov/projects/gap/cgi-bin/study.cgi?study_id=phs000607.v2.p2).

The PNC includes 1,445 children and adolescents recruited at their pediatric visits to the CHOP network who completed clinical, cognitive, and neuroimaging measures. All participants completed the GOASSESS computerized assessment for psychopathology; collateral informants provided information for participants under the age of 18. The Penn Computerized Neurocognitive Battery (CNB) was utilized to measure cognitive function. Both resting-state functional magnetic resonance imaging (fMRI) and valid neurocognitive data were available for 1397 participants. Participants were excluded for the following reasons: medical condition with probable central nervous system involvement ($n = 338$), no information about medical conditions ($n = 50$), inpatient psychiatric hospitalization ($n = 35$), use of drugs or alcohol resulting in adverse effects ($n = 74$), and invalid neuropsychological performance ($n = 57$). Participants were also excluded for unusable imaging data ($n = 7$), high in-scanner head motion (mean framewise displacement (FD) > 0.5 mm; $n = 109$), and inadequate coverage of the cerebellum ($n = 173$). Thus, 554 participants were included in this study. Participant demographic details are presented in Table 1.

Table 1 Participant demographic information.

Variable	Mean	Standard Deviation	Minimum	Maximum
Age	14.10	3.18	8	21
Years of Education	7.77	3.13	1	15
Mother's Years of Education	14.22	2.47	2*	20
Father's Years of Education	13.88	2.65	5	20
Estimated IQ (WRAT)	103.03	17.03	70	145
Mean Framewise Displacement (mm)	0.180	0.106	0.033	0.498

Gender		Race		
Male	Female	Caucasian	African American	Other/Mixed
216	338	221	271	62

N = 554; WRAT, Wide Range Achievement Test.
*This is the number reported in the original data; the modal value is 12 so it is possible this is an error, but removing this value does not change the mean

2.2.2 Neuroimaging

2.2.2.1 Image acquisition

Neuroimaging was acquired on a single scanner, a 3T Siemens TIM Trio whole-body scanner located in the hospital of the University of Pennsylvania operating under the VB17 revision of the Siemens software. Signal excitation and reception were obtained using a quadrature body coil for transmit and a 32-channel head coil for receive.

Participants completed a mock scanning session prior to MRI acquisition to acclimate to the MRI environment and learn to remain still during scanning. Mock scanning included recorded scanner noise. Feedback regarding head motion was provided by the MoTrack motion tracking system (Psychology Software Tools, Inc, Sharpsburg, PA). Six different scans were performed: structural MRI, three functional MRI (resting-state, fractal N-back, and emotion identification), diffusion-weighted MRI, and perfusion MRI. Resting-state fMRI and structural MRI scans were utilized for this study.

Structural images were obtained using a magnetization prepared, rapid-acquisition gradient-echo (MPRAGE) sequence. Resting-state BOLD scans were acquired with a single-shot, interleaved multi-slice, gradient-echo, echo planar imaging (GE-EPI) sequence. Scanning parameters were as follows: TR = 3000 ms, voxel resolution 3 × 3× 3 mm, 46 interleaved slices. Total scanning time was 6.2 minutes. During the resting-state scan, participants were instructed to stay awake, keep their eyes open, fixate on a cross hair, and remain still. For further neuroimaging details please see Satterthwaite et al. (2014).

2.2.2.2 Image preprocessing

Images were preprocessed using a standard pipeline implemented in the Data Processing Assistant for fMRI, Advanced Edition (DPARSFA; Yan & Zang, 2010) and SPM12 (https://www.fil.ion.ucl.ac.uk/spm/software/spm12/). Preprocessing steps included the following: removal of the first five timepoints to account for scanner stabilization, slice timing correction with the middle slice as a reference, realignment, co-registration to T1, normalization to the Montreal Neurological Institute (MNI) template using the unified segmentation algorithm, and smoothing with a 6 mm full width half maximum Gaussian kernel. Images were inspected manually for full cerebellar coverage and participants whose cerebellum was not included or had mean FD > 0.5 were excluded (*n* = 173).

ICA-AROMA (Pruim et al., 2015) was then utilized to minimize the effects of head motion on each participant’s imaging data. ICA-AROMA uses independent components analysis (ICA) via MELODIC to identify signal that is consistent with head motion, white matter, and cerebrospinal fluid. These components that are identified as noise are then regressed out of the images to create denoised images. These denoised images were used in all further analyses.

2.2.2.3 Independent components analysis

The Group ICA of fMRI Toolbox (GIFT; http://mialab.mrn.org/software/gift/index.html) version 4.0b was used to compute group independent components analysis (GICA) for all participants using the Infomax algorithm and 20 ICASSO permutations. The number of independent components (ICs) was set to 100, as previous studies have shown that 100 components provides effective parcellation of known functional networks without creating extreme parcellations of visual and cerebellar areas (Nomi et al., 2017; Wu et al., 2018).

Following GICA, all independent components were visually inspected to determine which ICs represented brain signal (Allen et al., 2011). Based on previously identified cortical networks associated with cognitive processing (Allen et al., 2011), ICs corresponding to the nodes of fronto-parietal and cingulo-opercular networks, as well as posterior cerebellum were selected for further analysis (see Figure 2 for visual representation of selected components and Table 2 for a description of component regions). FPN components included bilateral middle frontal gyrus (BA 9/46; IC82), left inferior parietal lobule (IC73), and right inferior parietal lobule (IC68). CON components included dorsal anterior cingulate (ACC; IC54) and bilateral anterior insula (IC16). Cerebellar components included left (IC83) and right (IC19) Crus I/II and left (IC57) and right (IC59) lobule VI/Crus I/Crus II/lobule VIIb/lobule VIII (these components will be hereafter labelled as left or right VI/VII/VIII for brevity, as Crus I and II are part of lobule VII). An anterior cerebellum component (bilateral lobule IV/V; IC12) and primary motor cortex (IC62) were also selected as control regions, as anterior cerebellar components are not expected to correlate with EFs. Figure 2 shows the components selected to represent specific networks. IC57 and IC59 were chosen for analysis with the cingulo-opercular network components and IC83 and IC19 were chosen for analysis with the fronto-parietal components because past work has shown more anterior/medial parts of the cerebellum to be connected to the CON and more posterior/lateral parts of the cerebellum to be connected to the FPN (Buckner et al., 2011; Marek et al., 2018; Seitzman et al., 2020).

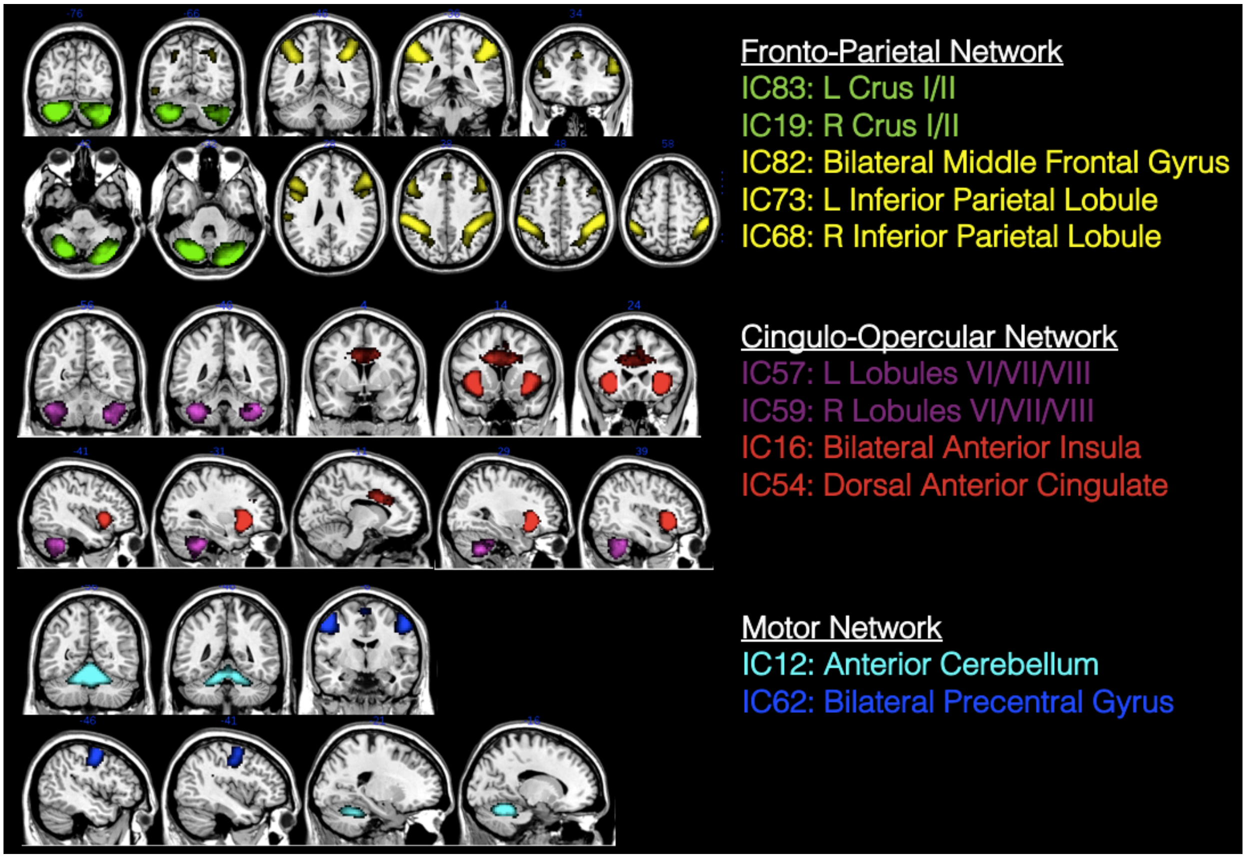

Figure 2 Selected Components. Components were plotted on the Single Subject T1 brain template in MRICron.

Table 2 Selected Components. Bolded components were utilized in Aims 2 and 3.

Component	Label	Network	Brain Regions
IC12	Anterior Cerebellum	Motor	Bilateral lobules IV, V, VI, vermis VI-V
IC62	Motor Cortex	Motor	Bilateral precentral gyrus, postcentral gyrus, supplementary motor area
IC57	**L VI/VII/VIII**	**CB**	**Left lobules VI, VIIb, VIIIa/b, Crus I, Crus II**
IC59	R VI/VII/VIII	CB	Right lobules VI, VIIb, VIIIa/b, Crus I, Crus II
IC16	**Anterior Insula**	**CON**	**Bilateral anterior insula, inferior frontal gyrus**
IC54	**Anterior Cingulate**	**CON**	**Dorsal anterior cingulate, middle cingulate cortex**
IC83	**L Crus I/II**	**CB**	**Left Crus I, Crus II (lateral/posterior)**
IC19	R Crus I/II	CB	Right Crus I, Crus II (lateral/posterior)
IC73	L Inferior Parietal	FPN	Left inferior parietal lobule
IC68	**R Inferior Parietal**	**FPN**	**Right inferior parietal lobule**
IC82	**Middle Frontal Gyrus**	**FPN**	**Bilateral middle frontal gyrus, frontal inferior triangle, frontal inferior operculum**

CB, Cerebellum; CON, Cingulo-Opercular Network; FPN, Fronto-Parietal Network

2.2.3 Statistical analyses

Functional network connectivity (FNC) between these ICs of interest was computed within the MANCOVAN toolbox in GIFT. MANCOVAN calculates Pearson's correlations between timecourses of components, computes the Fisher's Z transformation, and generates a matrix of FNC values. These FNC values were extracted for use in regression analyses. We extracted FNC between cortical nodes of the FPN (left: IC82 – IC73, right: IC82 – IC68) and CON (IC54 – IC16) and between posterior cerebellum and prefrontal cortex nodes of FPN (IC19 – IC82, IC83 – IC82) and CON (IC59 – IC54, IC57 – IC54). We also extracted FNC between anterior cerebellum and motor cortex (IC12 – IC62).

Multiple linear regression models were run in SPSS Version 25 to compute relationships between age and extracted FNC correlations. Gender was entered as a covariate, age was entered as the predictor, and FNC was entered as the outcome. Quadratic effects were also examined in separate regression models by adding age (centered) and age^2 as predictors, with gender as a covariate. We computed FDR-corrected significance for an α-value of .05 for each set of analyses using the Benjamini-Hochberg method (Benjamini & Hochberg, 1995).

We also followed up these analyses by running models including mean framewise displacement as a covariate at the group level. While we used conservative motion correction methods at the subject level and our sample has a low average FD, it is recommended to investigate the influence of head motion (Satterthwaite et al., 2019). However, head motion is usually correlated with age in developmental samples, so including FD in models runs the risk of reducing power and over-correcting for artifacts. Therefore, we did not include FD in our original models but still assessed whether its inclusion substantially changed our findings.

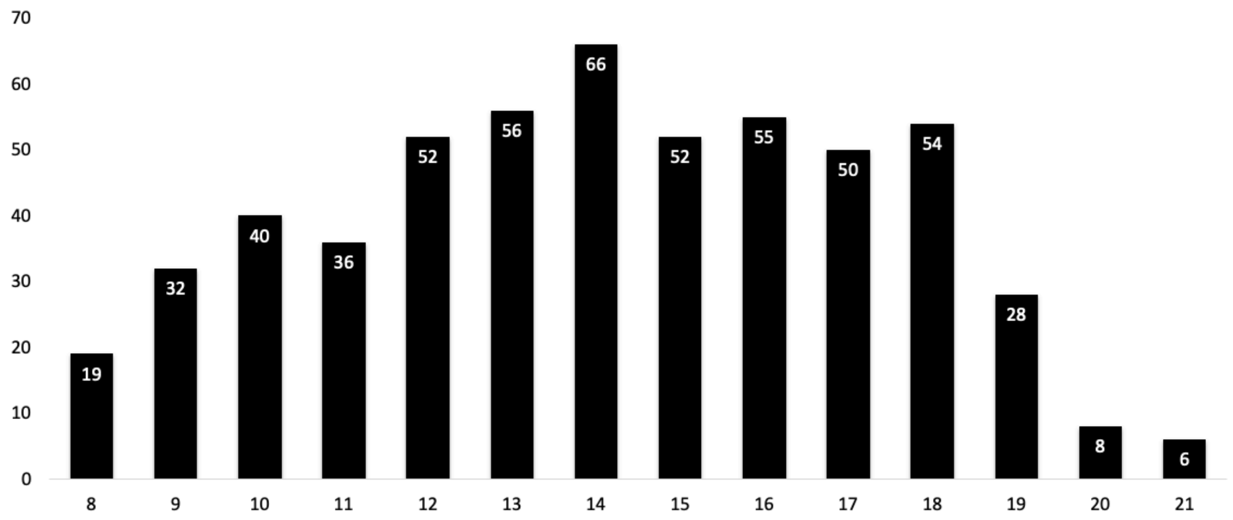

Figure 3 Age distribution in the current sample.

2.3 Results

A summary of results is presented in Table 3 and Figures 4 and 5. Age showed a significant positive linear relationship with connectivity between right (*B* = 0.009, *p* = .004) and left (*B* = 0.014, *p* < .001) VI/VII/VIII and ACC, between left Crus I/II and MFG (*B* = 0.009, *p* = .002), and between cortical nodes of left FPN (*B* = 0.008, *p* = .009). A trend level linear relationship was present for right FPN (*B* = 0.005, *p* = .098). The only nonlinear relationship observed was a quadratic relationship between age and CON connectivity (*B* = 0.003, *p* = .005). Gender was also significantly related to left FPN connectivity; males showed stronger connectivity than females. When FD was included in these regression models, we observed the same trends, but strength of relationships was reduced. CON (*B* = 0.003, *p* = .002) was still associated with age squared, and left FPN (*B* = 0.007, *p* = .032) and left VI/VII/VIII – ACC (*B* = 0.008, *p* = .014) connectivity were still associated with age. Age no longer predicted right VI/VII/VIII – ACC connectivity (*B* = 0.003, *p* = .291), and left Crus I/II – MFG connectivity only showed a trend (*B* = 0.006, *p* = .061).

Thus, as predicted, age was positively linearly related to posterior cerebellum – prefrontal cortex connectivity within some of the networks of interest. Based on these findings, we chose to compute further analyses with selected networks. We chose right FPN (MFG and right IPL) and left Crus I/II for fronto-parietal network analyses because left Crus I/II showed a relationship with age, but right Crus I/II – MFG did not, and right FPN showed a trend-level relationship with age. Also, Reineberg et al. (2015) found that connectivity between left Crus I/II and right FPN predicted general EF ability. We also chose CON components and left VI/VII/VIII – ACC for the cingulo-opercular network analyses for consistency. There is no literature to suggest there should be lateralized differences in these cerebello-cortical networks, and the PFC components are bilateral, so these specific components were chosen to reduce multiple comparisons.

Table 3 Multiple linear regression results for Aim 1. Gender was entered as a covariate, age was entered as the predictor, and functional network connectivity was entered as the outcome. The table presents statistics for age. Bolded outcomes show a significant relationship with age at a false discovery rate corrected significance level.

Outcome (*Y*)	Model F (*p*)	*B*	β	*95CI*	ΔR^2 (*p*)
Left FPN*	**7.50 (.001)**	**0.008**	**.111**	**0.002 – 0.014**	**.012 (.009)**
Right FPN	1.67 (.190)	0.005	.071	-0.001 – 0.011	.005 (.098)
CON	1.08 (.339)	0.004	.057	-0.002 – 0.011	.003 (.179)
CON^	**3.35 (.019)**	**0.003**	**.119**	**0.001 – 0.005**	**.014 (.005)**
Left VI/VII/VIII – ACC	**11.22 (<.001)**	**0.014**	**.181**	**0.008 – 0.020**	**.033 (<.001)**
Right VI/VII/VIII – ACC	**4.97 (.007)**	**0.009**	**.123**	**0.003 – 0.016**	**.015 (.004)**
Left Crus I/II – MFG	**5.64 (.004)**	**0.009**	**.134**	**0.004 – 0.015**	**.018 (.002)**
Right Crus I/II – MFG	1.40 (.247)	<0.001	.003	-0.005 – 0.005	<.001 (.947)
Anterior CB – Motor	1.41 (.245)	0.004	.059	-0.002 – 0.011	.003 (.170)
Anterior CB – Motor^	1.37 (.251)	0.001	.048	-0.001 – 0.003	.002 (.256)

*Gender was a significant predictor of connectivity

^Age^2 was entered as a predictor

FPN, fronto-parietal network; CON, cingulo-opercular network; ACC, anterior cingulate cortex; MFG, middle frontal gyrus; CB, Cerebellum

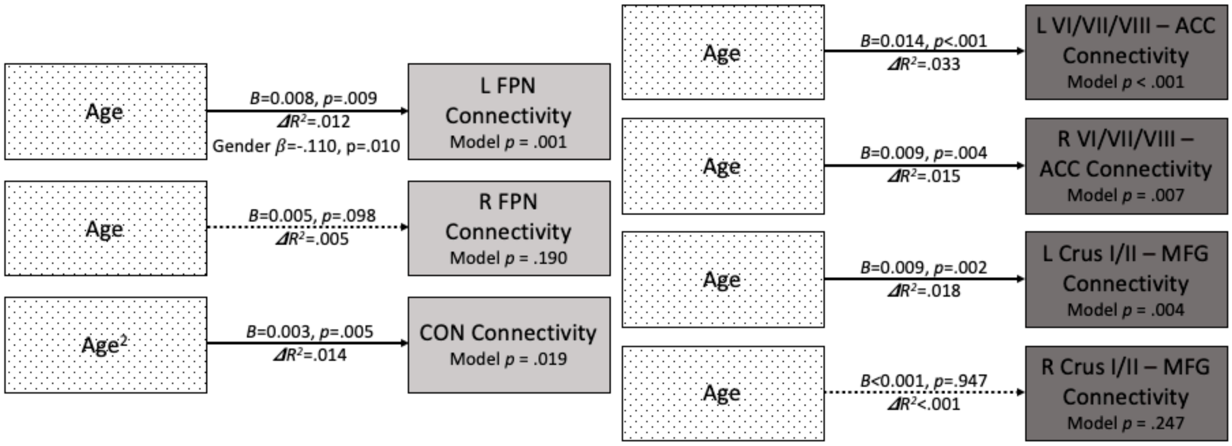

Figure 4 Multiple linear regression results for Aim 1. Gender was entered as a covariate, age was entered as the predictor, and functional network connectivity was entered as the outcome. Solid arrows represent significant relationships at a false discovery rate-corrected α and dotted arrows represent nonsignificant relationships.

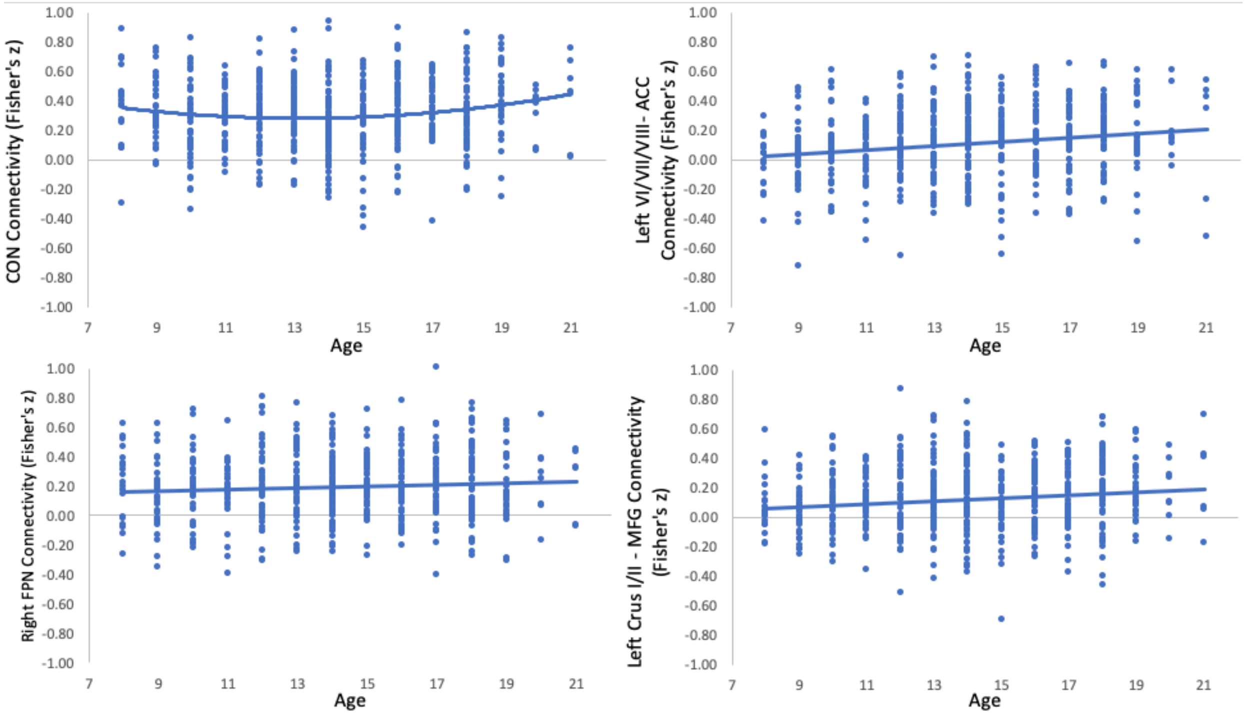

Figure 5 Relationships between age and functional connectivity for brain regions utilized in Aims 2 and 3. CON, cingulo-opercular network; FPN, fronto-parietal network

3 AIM 2: RELATIONSHIPS BETWEEN FUNCTIONAL NETWORK CONNECTIVITY AND EXECUTIVE FUNCTIONS

3.1 Aim and hypotheses

The second aim of this study was to investigate how cerebello-cortical rsFC is associated with executive functions in children and adolescents. Cerebello-cortical connectivity was also investigated as a mediator of the relationship between FPN/CON connectivity and EF because its function is to modulate information originating in the cortex (Ito, 2008). Thus, theoretically, it should serve to increase performance of EFs by predicting outcomes and helping the PFC to coordinate and automate behavior (Koziol & Lutz, 2013).

Hypothesis 2a: Connectivity between nodes of FPN and CON will positively predict performance on each EF task.

Hypothesis 2b: Connectivity between the posterior cerebellum and prefrontal nodes of FPN and CON will positively predict performance on each EF task.

Hypothesis 2c: Posterior cerebellum – PFC connectivity will mediate the relationship between executive network connectivity and performance on each EF task.

Hypothesis 2d: Connectivity between anterior cerebellum and motor cortex will predict finger tapping speed but will have only a weak relationship with EF performance.

3.2 Methods

3.2.1 Neuropsychological Testing

Participants completed the Penn CNB, which consists of 14 computerized neuropsychological tests presented in a fixed order; it takes approximately one hour to administer (Moore et al., 2015). The CNB was developed by a collaboration of experimental and clinical investigators (Gur et al., 2010, 2012). Because the original CNB was developed for use in healthy adult populations, measures were adapted for use with children and adolescents (i.e. simplifying instructions, reducing number of trials on some measures; Gur et al., 2012). The broad domains assessed include executive control, episodic memory, complex cognition, social cognition, and sensorimotor and motor speed. Moore et al. (2015) described the measures of the CNB as loading onto three factors, with Executive Control and Complex Cognition loading onto a single factor, likely related to the role that EF plays in complex cognition such as verbal and visuospatial reasoning. Each CNB test provides measures of both accuracy and speed except for the sensorimotor and motor speed measures (speed only). Most studies using these data thus far have utilized measures separately rather than broad factors, as each measure was chosen to tap into a specific neurocognitive function (Gur et al., 2012; Satterthwaite, Wolf, et al., 2015; White et al., 2017).

Three individual tests from the Executive Control factor were utilized for this study: the Penn Continuous Performance Test (PCPT), a measure of attention, the Letter N-Back (LNB), a measure of working memory, and the Penn Conditional Exclusion Test (PCET), a measure of abstraction and cognitive flexibility. The three tests were treated separately in these analyses because studies of executive function in children and adolescents show only modest correlations between flexibility and working memory domains and the factor structure of EFs changes over the course of adolescence (Huizinga et al., 2006; Lee et al., 2013; Miyake et al., 2000).

The PCPT includes two 1.5-minute segments of trials in which the participant responds to sets of seven different line segments presented at one stimulus per second. In the first block, participants press the space bar if the segments form a number; in the second block, they press the space bar if the segments form a letter. Number of correct and incorrect responses and median speed of correct and incorrect responses were recorded. The LNB presents letters for 500 ms and the participant is instructed to press the spacebar when they see an “X” (0-back), when the current letter is the same as the previous one (1-back), or when the current letter is the same as the one before the previous letter (2-back). There is an inter-stimulus interval of 2500 ms. Participants are first presented with a training period, then 135 trials, in three blocks of each condition (45 trials per condition) with a pre-determined order of trials. The number of correct and incorrect responses and the median response time for correct and incorrect responses (for each condition) were recorded. For this study, we exclusively used 2-back data, as the 2-back is the condition during which working memory is used. On the PCET, participants use the computer mouse to choose which one of four objects does not belong with the others based on one of three sorting principles. Feedback is given after each trial, and the rule changes after 10 successive correct sorts. Speed of correct and incorrect responses, number of correct and incorrect responses, and an accuracy score [(correct responses/total trials)/(number of categories attained + 1)] were recorded.

Motor speed on a finger tapping task was utilized as a control measure, as the cerebellum is highly involved in motor speed and coordination but it is only expected to correlate with anterior cerebellum – motor cortex connectivity (Caligiore et al., 2017). For this task, participants completed five 10-second trials per hand in which they pressed the space bar with their index finger as quickly as possible. Total taps with each hand was recorded. Penn CNB measures are presented in Table 4, and correlations among variables are presented in Appendix A.

Table 4 Penn Computerized Neurocognitive Battery performance.

Measure	Mean	Standard Deviation	Minimum	Maximum
PCPT Number of True Positives	51.64	7.55	11	60
PCPT Median RT for True Positives (ms)	489	64	370	788
Attention Efficiency	0	1.59	-6.30	2.71
Attention Accuracy (*d'*)*	0	1.51	-5.97	2.24
LNB Total Correct 2-Back Responses	8.31	1.58	2	10
LNB Median RT for Correct 2-Back Responses (ms)*	563	167	305	1760
Working Memory Efficiency*	0	1.47	-9.27	2.50
Working Memory Accuracy (*d'*)	0	1.58	-11.21	1.48
PCET Accuracy	1.93	0.69	0.04	3.27
PCET Median RT for Correct Responses (ms)	2424	896	1196	9256
Flexibility Efficiency	0	1.62	-7.88	2.93
Finger Tapping Speed (Both Hands; Total Number of Taps)	97.73	13.30	50	157

*Significant difference between males and females (two sample t-test)
PCPT, Penn Continuous Performance Test; LNB, Letter N-Back; PCET, Penn Conditional Exclusion Test; RT, reaction time

Accuracy and speed scores on executive control measures were combined into an efficiency score for this study, as in Moore et al. (2015). This was achieved by computing standardized (*z*) scores for accuracy and speed based on the entire sample, multiplying the speed *z*-score by -1 (so that higher scores meant faster responses, to align with accuracy), and summing *z*(accuracy) and -*z*(speed). Generalized additive models (GAMs) were run using the R software (R Core Team, 2016) implemented in R Studio (RStudio Team, 2019) to investigate nonlinear effects of age on EF efficiency (Baum et al., 2017) and to test for replication of previous work with the PNC. These models use penalized splines to compute the best fitting polynomial model to the data, and utilize the restricted maximum likelihood method to avoid overfitting. For the GAM analyses, gender was entered as a covariate, age was entered as the predictor, and efficiency was entered as the outcome.

Consistent with Gur et al.'s (2012) findings, efficiency of EF measures increases with age (Figure 6). Attention efficiency has the sharpest increase and GAM analysis indicated a quadratic curve was the best fit ($p < .001$). Working memory efficiency also showed a quadratic relationship with age ($p < .001$), and flexibility efficiency showed a slight linear increase with age ($p = .003$).

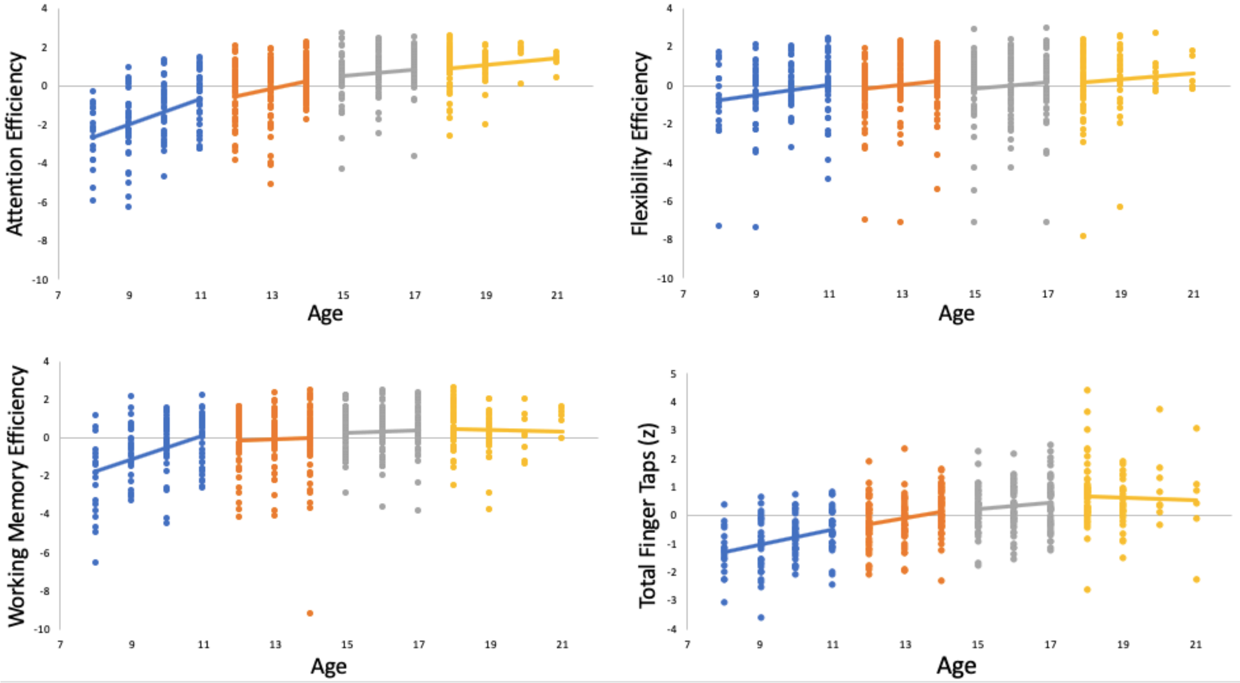

Figure 6 Developmental trajectories of cognitive functions in the current sample, split into age groups of approximately equal *n*.

3.2.2 Statistical analyses

The FNC values extracted from GIFT (described above in section 2.2.3) were entered into multiple linear regression models in SPSS. Gender was entered as a covariate, FNC was included as the predictor, and EF efficiency was entered as the outcome (Hypotheses 2a and 2b). As control measures to specify that the hypothesized effects are specific to our networks of interest, the relationships between anterior cerebellum – motor cortex connectivity and EF performance were tested, as well, as we predicted that these relationships would be only weakly significant or nonsignificant (Hypothesis 2d).

With regard to Hypothesis 2c, a simple mediational model was specified using the PROCESS macro in SPSS (Model 4). The models included executive network connectivity (FPN and CON) as the predictor, posterior cerebellum – PFC connectivity as a mediator, and EF efficiency as the outcome. For the cingulo-opercular network, the predictor was CON, and the mediator was left VI/VII/VIII – ACC connectivity. For the fronto-parietal network, the predictor was right FPN and the mediator was left Crus I/II – MFG connectivity. Gender was included as a covariate in the mediational models, as well. PROCESS computed all direct and indirect effects and bootstrapping with 5000 iterations was utilized to compute indirect effect confidence intervals. We computed FDR-corrected significance for an α-value of .05 for each set of analyses using the Benjamini-Hochberg method (Benjamini & Hochberg, 1995).

3.3 Results

Table 5 and Figure 7 present results of regression analyses. Left VI/VII/VIII – ACC connectivity significantly predicted attention efficiency at an FDR-corrected q-value ($B = 0.945$, $p = .001$), and the relationship between left VI/VII/VIII – ACC connectivity and working memory efficiency was only slightly above an FDR-corrected q-value ($B = 0.671$, $p = .009$). At an uncorrected p-value, left Crus I/II – MFG connectivity predicted working memory efficiency ($B = 0.612$, $p = .029$). Though the overall models did not reach significance, at an uncorrected p-value, right FPN connectivity showed a relationship with attention efficiency ($B = 0.641$, $p = .033$), left Crus I/II – MFG connectivity showed a relationship with attention efficiency ($B = 0.691$, $p = .023$), and CON connectivity showed a relationship with flexibility efficiency ($B = 0.567$, $p = .049$).

When FD was included as a covariate, right FPN predicted attention efficiency (*B* = 0.623, *p* = .036) and left VI/VII/VIII – ACC connectivity still predicted attention (*B* = 0.699, *p* = .017) and working memory (*B* = 0.564, *p* = .037) efficiency at uncorrected *p*-values. Again, the strength of relationships was reduced.

Table 5 Multiple linear regression results for Aim 2. Gender was entered as a covariate, functional network connectivity was entered as the predictor, and executive function efficiency was entered as the outcome. Bolded outcomes show a significant relationship with age at a false discovery rate corrected significance level.

Outcome	Model *F* (*p*)	*B*	*β*	*95CI*	ΔR^2 (*p*)
Predictor: Right Fronto-Parietal Network					
Attention Efficiency	2.59 (.076)	0.641	.091	0.05 – 1.23	.008 (.033)
Working Memory Efficiency*	6.09 (.002)	0.537	.082	-0.02 – 1.08	.007 (.051)
Flexibility Efficiency	0.97 (.380)	0.123	.017	-0.48 – .72	<.001 (.688)
Predictor: Cingulo-Opercular Network					
Attention Efficiency	1.84 (.160)	0.495	.075	-0.06 – 1.05	.006 (.080)
Working Memory Efficiency*	5.11 (.006)	0.357	.058	-0.15 – 0.87	.003 (.169)
Flexibility Efficiency	2.85 (.059)	0.567	.084	0.003 – 1.13	.007 (.049)
Predictor: Left Crus I/II – Middle Frontal Gyrus					
Attention Efficiency	2.88 (.057)	0.691	.096	0.09 – 1.29	.009 (.023)
Working Memory Efficiency*	6.59 (.001)	0.612	.092	0.06 – 1.16	.009 (.029)
Flexibility Efficiency	2.40 (.091)	0.539	.074	-0.07 – 1.15	.005 (.083)
Predictor: Left VI/VII/VIII – Anterior Cingulate Cortex					
Attention Efficiency	**6.11 (.002)**	**0.945**	**.144**	**0.40 – 1.50**	**.021 (.001)**
Working Memory Efficiency*	7.65 (.001)	0.671	.111	0.17 – 1.17	.012 (.009)
Flexibility Efficiency	1.93 (.147)	0.409	.061	-0.15 – 0.97	.004 (.151)
Predictor: Anterior Cerebellum – Motor Cortex					
Attention Efficiency	0.53 (.590)	0.196	.029	-0.37 – 0.76	.001 (.494)
Working Memory Efficiency*	4.31 (.014)	-0.149	-.024	-0.67 – 0.37	.001 (.571)
Flexibility Efficiency	1.80 (.166)	0.393	.057	-0.18 – 0.97	.003 (.177)
Finger Tapping Speed*	5.95 (.003)	0.066	.016	-0.28 – 0.42	<.001 (.711)

*Gender was a significant predictor

L, Left; R, Right; FPN, Fronto-Parietal Network; CON, Cingulo-Opercular Network; 95CI, 95% confidence interval

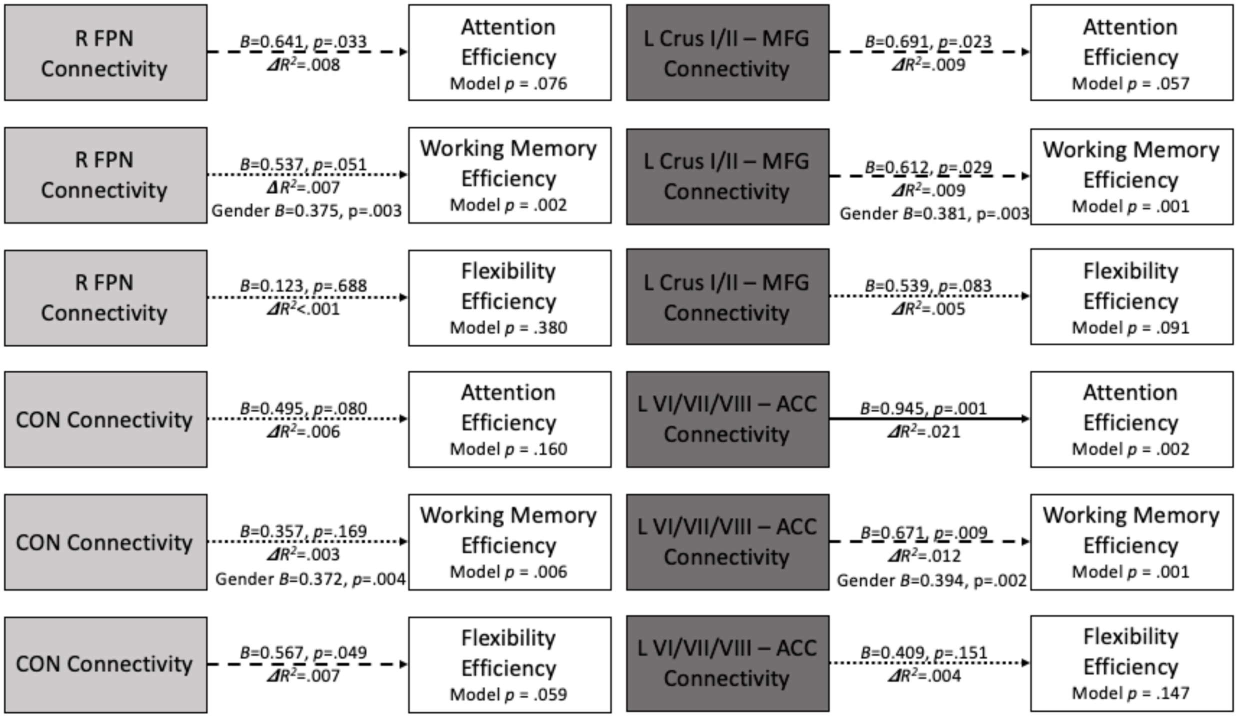

Figure 7 Multiple linear regression results for Aim 2. Gender was entered as a covariate, functional network connectivity was entered as the predictor, and executive function efficiency was entered as the outcome. Solid arrows represent significant relationships between connectivity and efficiency at a false discovery rate corrected *q*-value, dashed arrows represent significant relationships at an uncorrected *p*-value, and dotted arrows represent nonsignificant relationships.

Anterior cerebellum – motor cortex connectivity showed no significant or trend-level relationships with any CNB measures, including finger tapping. Although it is unexpected that there was no relationship with finger tapping, because there was also no relationship with executive function, we assume that significant results are not exclusively related to motor speed functions of the cerebellum.

Hayes (2013) argued that even though there may not be a relationship between each of the variables in a mediation model, that does not preclude mediation and/or moderation. It is possible that a mediator or moderator enhances the relationships between variables. Therefore, despite seeing few significant relationships between FNC and executive functions at a conservative threshold, we continued with mediation models.

Table 6 and Figure 8 present mediation results. First, for the cingulo-opercular network, bootstrapping revealed significant indirect effects for attention efficiency (*95CI* = 0.02 – 0.25) and working memory efficiency (*95CI* = 0.01 – 0.18), indicating that left VI/VII/VIII – ACC connectivity mediates the relationship between CON connectivity and attention and working memory performance. CON connectivity was significantly related to left VI/VII/VIII – ACC connectivity (*B* = 0.126, *p* = .003), and left VI/VII/VIII connectivity predicted both attention (*B* = 0.897, *p* = .001) and working memory (*B* = 0.637, *p* = .014) efficiency. Gender also significantly predicted working memory efficiency (*B* = 0.396, *p* = .002) but not connectivity. When FD was added to the models, left VI/VII/VIII – ACC connectivity still predicted working memory (*B* = 0.549, *p* = .043) and attention (*B* = 0.682, *p* = .020) efficiency at uncorrected *p*-values, but there was no longer a significant indirect effect (working memory *95CI* = -0.01 – 0.11; attention *95CI* = -0.02 – 0.13). Adding FD also made the relationship between left VI/VII/VIII – ACC connectivity and CON connectivity nonsignificant (*B* = 0.060, *p* = .147).

Second, for the fronto-parietal network, no indirect effects were significant and thus mediation was not observed. Right FPN connectivity was not significantly related to left Crus I/II connectivity. However, there was a direct effect of right FPN connectivity on attention efficiency at an uncorrected threshold (*B* = 0.633, *p* = .034). In addition, left Crus I/II connectivity predicted attention (*B* = 0.684, *p* = .024) and working memory (*B* = 0.606, *p* = .030) efficiency at uncorrected *p*-values. Gender also predicted working memory efficiency (*B* = 0.388, *p* = .002) but not connectivity in these models. Right FPN connectivity still predicted attention efficiency (*B* = 0.620, *p* = .037) after adding FD to the model but left Crus I/II – MFG connectivity did not predict attention or working memory efficiency (left Crus I/II – MFG predicted working memory efficiency at a trend level; *B* = 0.508, *p* = .075).

Table 6 Mediation results for Aim 2 using PROCESS Model 4. Gender was entered as a covariate, fronto-parietal or cingulo-opercular network connectivity was entered as the predictor, cerebellum – prefrontal cortex connectivity was entered as the mediator, and executive function efficiency was entered as the outcome. Indirect effect standard errors (*SE*) and confidence intervals (*95CI*) are bootstrapped. Bolded predictors show significant relationships at a false discovery rate corrected significance level or significant bootstrapped indirect effects.

Predictor	Standardized Coefficient	Unstandardized Coefficient	*SE*	*p*	*95CI*
Outcome: Left VI/VII/VIII – ACC, R^2 = .022, p = .002					
CON	**.125**	**0.126**	**0.04**	**.003**	**0.04 – 0.21**
Gender	-.078	-0.039	0.02	.066	-0.08 – 0.003
Outcome: Attention Efficiency, R^2 = .025, p = .003					
CON Direct Effect (Total Effect)	.058 (.075)	0.382 (0.495)	0.28	.176	-0.17 – 0.94
L VI/VII/VIIII – ACC	**.137**	**0.897**	**0.28**	**.001**	**0.35 – 1.45**
Gender	-.020	-0.066	0.14	.634	-0.34 – 0.21
Indirect Effect	**.017**	**0.113**	**0.06**		**0.02 – 0.25**
Outcome: Working Memory Efficiency, R^2 = .029, p = .001					
CON Direct Effect (Total Effect)	.045 (.058)	0.277 (0.357)	0.26	.288	-0.23 – 0.79
L VI/VII/VIII – ACC	.105	0.637	0.26	.014	0.13 – 1.14
Gender	.131	0.396	0.13	.002	0.15 – 0.65
Indirect Effect	**.013**	**0.081**	**0.04**		**0.01 – 0.18**
Outcome: Flexibility Efficiency, R^2 = .013, p = .069					
CON Direct Effect (Total Effect)	.077 (.084)	0.523 (0.57)	0.29	.071	-0.04 – 1.09
L VI/VII/VIII – ACC	.052	0.344	0.29	.229	-0.22 – 0.91
Gender	.063	0.209	0.14	.140	-0.07 – 0.49
Indirect Effect	.006	0.044	0.04		-0.02 – 0.13
Outcome: Left Crus I/II – MFG, R^2 = .002, p = .515					
R FPN	0.011	0.011	0.04	.788	-0.07 – 0.09
Gender	-0.047	-0.022	0.02	.267	-0.06 – 0.02
Outcome: Attention Efficiency, R^2 =.018, p = .017					
R FPN Direct Effect (Total Effect)	0.089 (0.091)	0.633 (0.641)	0.30	.034	0.05 – 1.22
L Crus I/II – MFG	0.095	0.684	0.30	.024	0.09 – 1.28
Gender	-0.025	-0.082	0.14	.552	-0.35 – 0.19
Indirect Effect	0.001	0.008	0.04		-0.07 – 0.08
Outcome: Working Memory Efficiency, R^2 =.030, p < .001					
R FPN Direct Effect (Total Effect)	0.081 (.082)	0.530 (.537)	0.27	.053	-0.01 – 1.07
L Crus I/II – MFG	0.092	0.606	0.28	.030	0.06 – 1.15
Gender	0.129	0.388	0.13	.002	0.14 – 0.64
Indirect Effect	0.001	0.007	0.03		-0.07 – 0.07
Outcome: Flexibility Efficiency, R^2 =.009, p = .177					
R FPN Direct Effect (Total Effect)	0.016 (0.017)	0.117 (0.123)	0.31	.702	-0.48 – 0.72
L Crus I/II – MFG	0.074	0.537	0.31	.083	-0.07 – 1.15
Gender	0.061	0.202	0.14	.154	-0.08 – 0.48
Indirect Effect	0.001	0.006	0.03		-0.06 – 0.06

L, Left; R, Right; FPN, Fronto-Parietal Network; CON, Cingulo-Opercular Network; SE, standard error; 95CI, 95% confidence interval

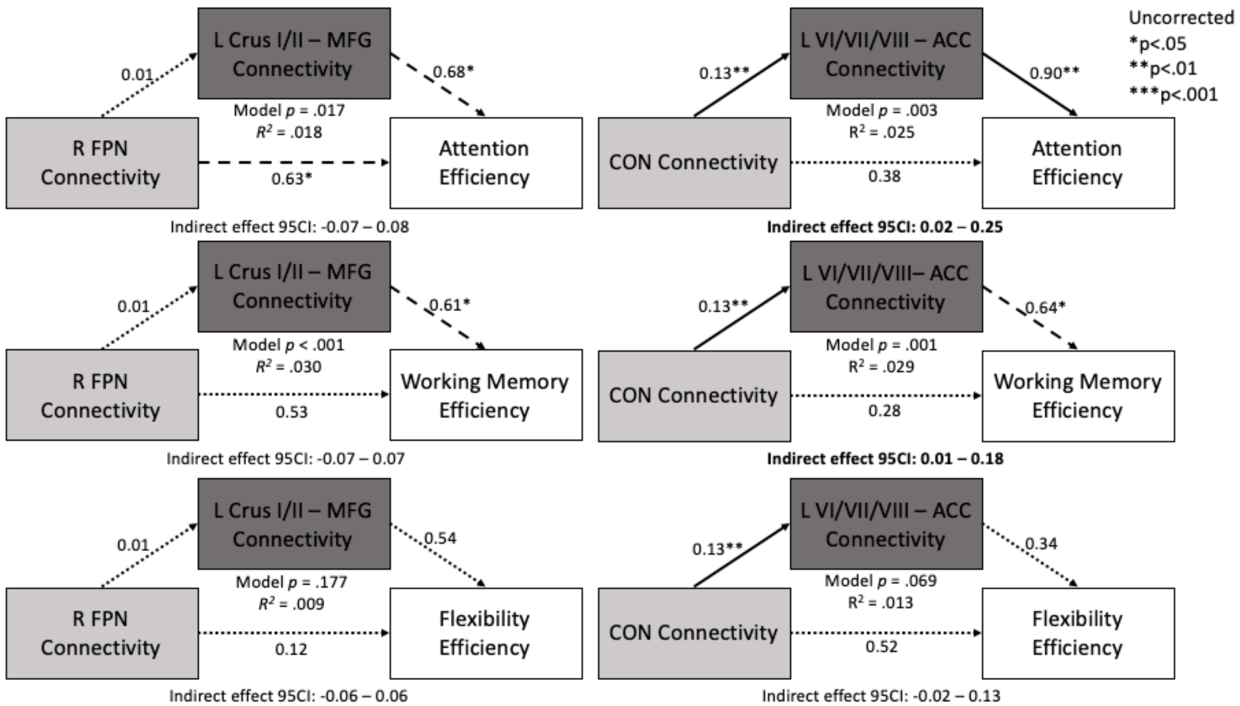

Figure 8 Mediation results for Aim 2 using PROCESS Model 4. Gender was entered as a covariate, fronto-parietal or cingulo-opercular network connectivity was entered as the predictor, cerebellum – prefrontal cortex connectivity was entered as the mediator, and executive function efficiency was entered as the outcome. Solid arrows represent significant relationships at a false discovery rate corrected α, dashed arrows represent significant relationships at an uncorrected *p*-value, and dotted arrows represent nonsignificant relationships. Unstandardized coefficients are reported.

To check whether significant relationships were accounted for solely by motor speed, *d'* was calculated for the EF measures, using signal detection theory (Stanislaw & Todorov, 1999). We chose to use *d'* instead of number of correct responses because many participants had a 100% hit rate on the LNB, resulting in a highly skewed distribution of scores. The loglinear transformation was used to calculate *d'*, as follows:

$$d' = z\frac{hits + 0.5}{target\ trials + 1} - z\frac{false\ alarms + 0.5}{foil\ trials + 1}$$

While *d'* for working memory was still skewed, it showed greater variability than raw true positive scores. There were no significant gender differences in working memory *d'* (*t*(552) = -1.06, *p* = .290), but females were more accurate than males on the PCPT (*t*(552) = 3.13, *p* =

.002). Qualitatively, left VI/VII/VIII – ACC connectivity showed a slightly stronger relationship with working memory accuracy ($B = 0.821$, $p = .003$) than efficiency ($B = 0.671$, $p = .009$), but a slightly weaker relationship with attention accuracy ($B = 0.697$, $p = .008$) than efficiency ($B = 0.945$, $p = .001$). Left Crus I/II – MFG connectivity had a weaker relationship with accuracy than efficiency for both attention (Accuracy $B = 0.412$, $p = .151$; Efficiency $B = 0.691$, $p = .023$) and working memory (Accuracy $B = 0.402$, $p = .183$; Efficiency $B = 0.612$, $p = .029$). CON showed a similar relationship with attention accuracy ($B = 0.506$, $p = .057$) and efficiency ($B = 0.495$, $p = .080$) and a stronger relationship with working memory accuracy ($B = 0.634$, $p = .023$) than efficiency ($B = 0.357$, $p = .169$). Right FPN showed a weaker relationship with attention accuracy ($B = 0.305$, $p = .280$) than efficiency ($B = 0.641$, $p = .091$) and no difference between working memory accuracy ($B = 0.564$, $p = .057$) and efficiency ($B = 0.537$, $p = .051$). Flexibility accuracy showed no significant relationships with connectivity.

Using *d'* in mediation models showed many of the same relationships among variables as using efficiency (Figure 9). With regard to attention and working memory, left VI/VII/VIII – ACC connectivity still mediated the relationship between CON connectivity and both working memory (*95CI* = 0.02 – 0.21) and attention (*95CI* = 0.01 – 0.18) accuracy. Thus, we infer that relationships between cerebellum – CON connectivity and working memory efficiency are not solely accounted for by speed and gender. Right FPN and left Crus I/II – MFG connectivity, in contrast, were not associated with attention or working memory accuracy in the mediation models. Flexibility accuracy again showed no significant relationships with connectivity.

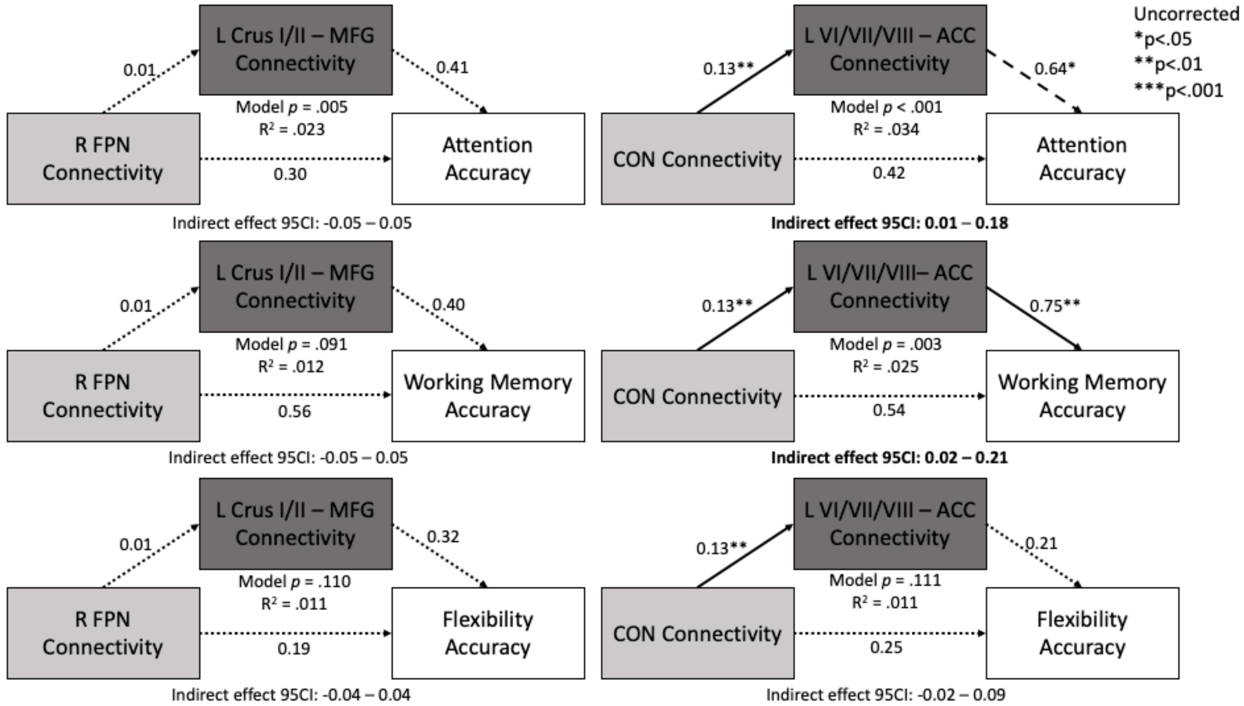

Figure 9 Mediation results with accuracy as the outcome. Gender was entered as a covariate, fronto-parietal or cingulo-opercular network connectivity was entered as the predictor, cerebellum – prefrontal cortex connectivity was entered as the mediator, and executive function accuracy (*d'*) was entered as the outcome. Solid arrows represent significant relationships at a false discovery rate corrected α, dashed arrows represent significant relationships at an uncorrected *p*-value, and dotted arrows represent nonsignificant relationships. Unstandardized coefficients are reported.

4 AIM 3: MODERATED MEDIATION

4.1 Aim and hypotheses

The final aim was to combine the previous findings into a single moderated mediation model to investigate effects of age on relationships between connectivity and EF efficiency. A multivariate PROCESS model (Hayes, 2013) was utilized to investigate age as a moderator of the mediation described in Hypothesis 2c, including posterior cerebellum – PFC connectivity, executive network connectivity, and age × connectivity interaction terms, with EF efficiency as the outcome variable (see Figures 10 and 11). This aim serves to extend previous work, as well, by combining age, connectivity, and EF performance in a single model. In this final model, age was investigated as a moderator because previous demonstrated that the relationship between EF performance and cerebellar structure/function is not consistent at all age groups (Kolskår et al., 2018; Moore et al., 2017; Satterthwaite et al., 2013; van den Bosch et al., 2014). Rather, age was predicted enhance the relationship between EF performance and functional connectivity. We hypothesized that age would affect all three paths of this model.

Hypothesis 3a: Age will moderate the mediation of EF performance by cerebello-cortical connectivity: cerebello-cortical connectivity will be stronger in older participants and posterior cerebellum – PFC connectivity will predict EF more strongly in older participants. The direct relationships between FPN/CON connectivity and EF performance will also become stronger with age.

4.2 Methods

The PROCESS macro in SPSS was used to investigate relationships among FNC, age, and EF performance in a single statistical model (Hayes, 2013). Gender was included as a covariate. A conditional process model was specified (Model 59), with connectivity between posterior cerebellum and PFC as a mediator of the relationship between FPN/CON connectivity, and age as a moderator of all three paths in the mediational model. In total, we ran six moderated mediational models to investigate EF efficiency. Indirect effects were bootstrapped with 5000 iterations. We computed FDR-corrected significance for an α-value of .05 using the Benjamini-Hochberg method (Benjamini & Hochberg, 1995).

4.3 Results

All conditional process models except for CON predicting flexibility efficiency showed a significant main effect of age, and there was also a significant main effect of gender on working memory efficiency (Table 7). No indirect effects or conditional indirect effects were significant in any model. Age moderated the relationship between CON and left VI/VII/VIII – ACC connectivity at an uncorrected *p*-value (*B* = 0.028, *p* = .030); connectivity was stronger in older participants (Figure 10b). In addition, age moderated the relationship between left VI/VII/VIII – ACC connectivity and attention efficiency at an FDR-corrected threshold (*B* = -0.199, *p* = .005). An interaction probe revealed that the focal relationship between left VI/VII/VIII – ACC connectivity and attention efficiency is positive for children, and the relationship is nonsignificant in adolescents and young adults (Figure 10d). We also observed a direct effect of left VI/VII/VIII – ACC connectivity on attention efficiency (*B* = 3.079, *p* = .005). No moderated mediation was observed for models predicting working memory or flexibility efficiency. Adding FD to the model reduced the strength of correlations but the same significant direct effects and interactions were observed, with one exception. CON connectivity showed a negative relationship with left VI/VII/VIII – ACC connectivity overall (*B* = -0.394, *p* = .031), and age still moderated this relationship (*B* = 0.032, *p* = .011) showing a negative correlation in younger children and a positive correlation in older participants.

Table 7 Moderated mediation results for Aim 3. The same mediation model was specified as in Aim 2, and age was entered as a moderator of all three paths of the mediational model. All values are bootstrapped with 5000 samples. Bolded outcomes show significant relationships at a false discovery rate corrected significance level.

Predictor	Unstandardized Coefficient	*SE*	*p*	*95CI*
Outcome: L VI/VII/VIII – ACC, $R^2 = .060, p < .001$				
CON	-0.286	0.189	.132	-0.66 – 0.09
Age	0.004	0.006	.516	-0.01 – 0.01
Gender	-0.031	0.021	.131	-0.07 – 0.01
CON × Age	0.028	0.013	.030	0.002 – 0.05
Outcome: Attention Efficiency, $R^2 = .364, p < .001$				
CON Direct Effect	1.188	1.032	.250	-0.84 – 3.22
L VI/VII/VIII – ACC	**3.079**	**1.033**	**.003**	**1.05 – 5.11**
Age	**0.335**	**0.030**	**<.001**	**0.28 – 0.39**
Gender	0.080	0.112	.479	-0.14 – 0.30
CON × Age	-0.062	0.072	.390	-0.20 – 0.08
L VI/VII/VIII – ACC × Age	**-0.199**	**0.071**	**.005**	**-0.34 – -0.06**
Outcome: Working Memory Efficiency, $R^2 = .111\ p < .001$				
CON Direct Effect	-0.558	1.127	.621	-2.77 – 1.66
L VI/VII/VIII – ACC	1.16	1.129	.305	-1.06 – 3.37
Age	**0.122**	**0.033**	**<.001**	**0.06 – 0.19**
Gender	0.461	0.122	<.001	0.22 – 0.70
CON × Age	0.056	0.078	.472	-0.10 – 0.21
L VI/VII/VIII – ACC × Age	-0.060	0.077	.442	-0.21 – 0.09
Outcome: Flexibility Efficiency, $R^2 = .028, p = .017$				
CON Direct Effect	-0.283	1.300	.828	-2.84 – 2.27
L VI/VII/VIII – ACC	0.286	1.302	.826	-2.27 – 2.84
Age	0.044	0.038	.243	-0.03 – 0.12
Gender	0.238	0.141	.093	-0.04 – 0.51
CON × Age	0.055	0.090	.540	-0.12 – 0.23
L VI/VII/VIII – ACC × Age	-0.007	0.089	.936	-0.18 – 0.17
Outcome: L Crus I/II – MFG, $R^2 = .024, p = .011$				
R FPN	0.250	0.183	.171	-0.11 – 0.61
Age	**0.013**	**0.004**	**<.001**	**0.01 – 0.02**
Gender	-0.017	0.019	.394	-0.05 – 0.02
R FPN × Age	-0.017	0.013	.164	-0.04 – 0.01
Outcome: Attention Efficiency, $R^2 = .356, p < .001$				
R FPN Direct Effect	-0.044	1.072	.967	-2.15 – 2.06
L Crus I/II – MFG	1.816	1.186	.126	-0.51 – 4.15
Age	**0.304**	**0.024**	**<.001**	**0.26 – 0.35**
Gender	0.070	0.113	.532	-0.15 – 0.29
R FPN × Age	0.026	0.073	.723	-0.12 – 0.17

Predictor	Unstandardized Coefficient	*SE*	*p*	*95CI*
L Crus I/II – MFG × Age	-0.117	0.081	.146	-0.28 – 0.04
Outcome: Working Memory Efficiency, $R^2 = .115, p < .001$				
R FPN Direct Effect	1.258	1.160	.279	-1.02 – 3.54
L Crus I/II – MFG	1.720	1.283	.181	-0.80 – 4.24
Age	**0.159**	**0.026**	**<.001**	**0.11 – 0.21**
Gender	0.461	0.122	<.001	0.22 – 0.70
R FPN × Age	-0.062	0.079	.438	-0.22 – 0.09
L Crus I/II – MFG × Age	-0.096	0.087	.271	-0.27 – 0.08
Outcome: Flexibility Efficiency, $R^2 = .026, p = .023$				
R FPN	1.633	1.341	.224	-1.00 – 4.27
L Crus I/II – MFG	-0.260	1.484	.861	-3.18 – 2.66
Age	**0.079**	**0.030**	**.009**	**0.02 – 0.14**
Gender	0.231	0.141	.102	-0.46 – 0.51
R FPN × Age	-0.110	0.092	.230	-0.29 – 0.07
L Crus I/II – MFG × Age	0.046	0.101	.651	-0.15 – 0.24

L, Left; R, Right; FPN, Fronto-Parietal Network; CON, Cingulo-Opercular Network; SE, standard error; 95CI 95% confidence interval

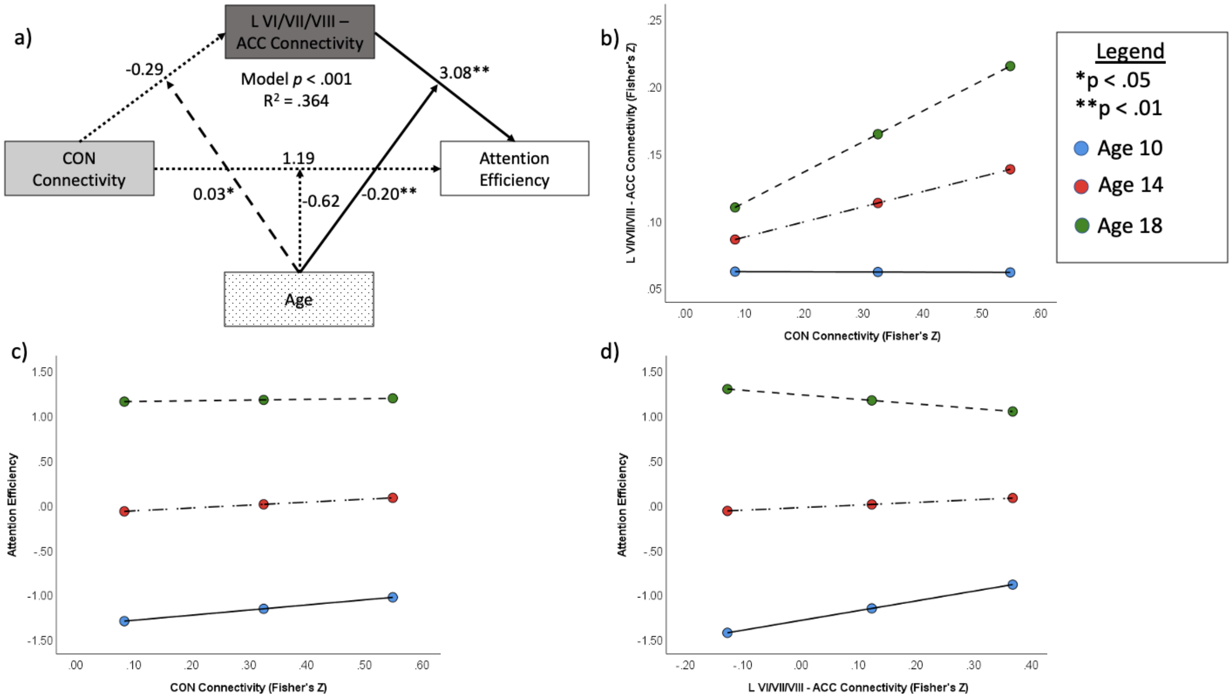

Figure 10 Significant moderated mediation results for Aim 3. The same mediation model was specified as in Aim 2, and age was entered as a moderator of all three paths of the mediational model. Solid arrows represent significant relationships at a false discovery rate corrected α, dashed arrows represent significant relationships at an uncorrected *p*-value, and dotted arrows represent nonsignificant relationships. Figure a) shows the theoretical model and significant relationships. Figures b, c, and d show conditional effects of the three paths in the mediational model. Figure b) shows the relationship between CON connectivity and left VI/VII/VIII – ACC connectivity at 16, 50, and 84% of the mean age; c) shows the relationship between CON connectivity and attention efficiency; and d) shows the relationship between left VI/VII/VIII – ACC connectivity and attention efficiency. Unstandardized coefficients are reported.

When we re-ran these conditional process models with *d'* instead of efficiency as the outcome, different results were observed. Age still moderated the relationship between CON and left VI/VII/VIII – ACC connectivity at an uncorrected *p*-value (*B* = -0.029, *p* = .030; Figure 11b). In contrast, there was a relationship between left VI/VII/VIII – ACC connectivity and working memory accuracy (*B* = 2.80, *p* = .021), and this relationship was moderated by age (*B* = -0.167, *p* = .045). However, these results were only significant at uncorrected *p*-values. The younger children showed a stronger relationship between left VI/VII/VIII – ACC connectivity and working memory accuracy than adolescents and young adults did, similar to results observed for attention efficiency. Right FPN and left Crus I/II – MFG connectivity were not associated with attention or working memory accuracy in the conditional process analysis; only age predicted connectivity and EF in these models.

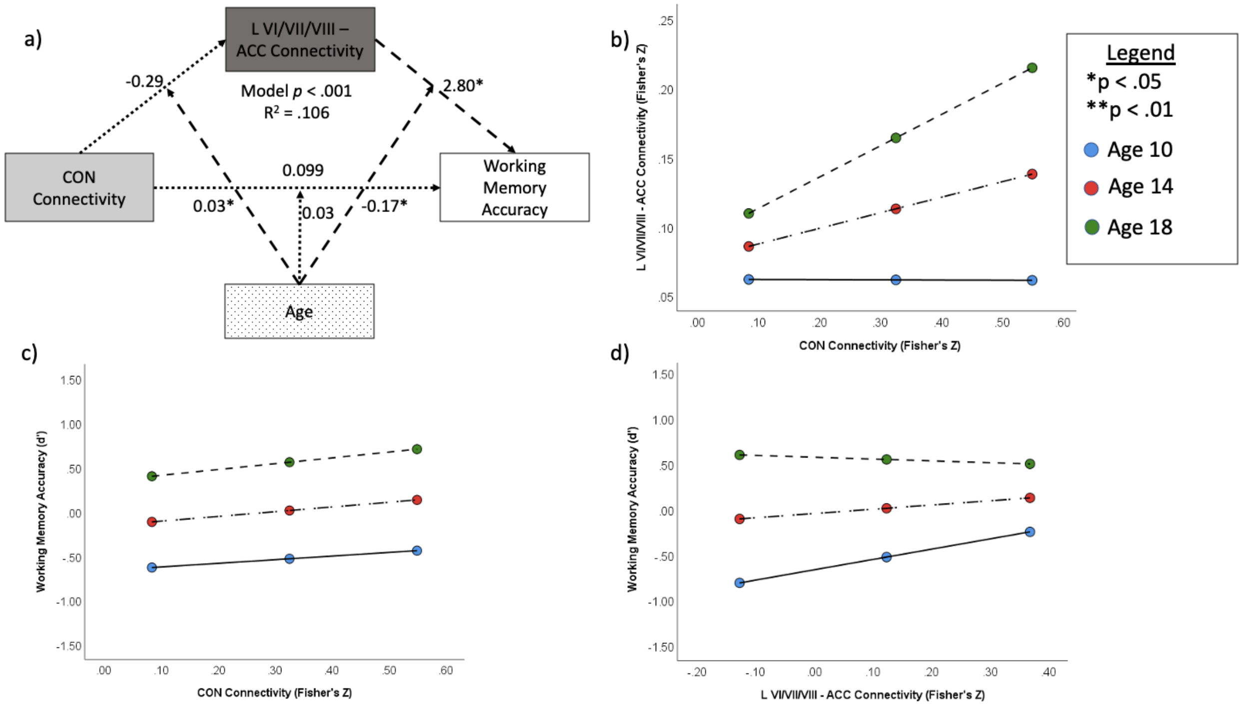

Figure 11 Significant moderated mediation results for Aim 3 predicting accuracy. The same mediation model was specified as in Aim 2, and age was entered as a moderator of all three paths of the mediational model. Solid arrows represent significant relationships at a false discovery rate corrected α, dashed arrows represent significant relationships at an uncorrected *p*-value, and dotted arrows represent nonsignificant relationships. Figure a) shows the theoretical model and significant relationships. Figures b, c, and d show conditional effects of the three paths in the mediational model. Figure b) shows the relationship between CON connectivity and left VI/VII/VIII – ACC connectivity at 16, 50, and 84% of the mean age; c) shows the relationship between CON connectivity and working memory accuracy; and d) shows the relationship between left VI/VII/VIII – ACC connectivity and working memory accuracy. Unstandardized coefficients are reported.

5 DISCUSSION AND CONCLUSIONS

5.1 Summary of findings

This is the first investigation of relationships between typically developing cerebello-cortical functional connectivity and executive functioning across childhood and adolescence. We observed several positive linear relationships between age and cerebello-cortical connectivity, as predicted. Thus, as children get older, connectivity between posterior cerebellum and prefrontal cortex (ACC and MFG) becomes stronger. With regard to executive functioning, left VI/VII/VIII – ACC connectivity positively predicted attention efficiency at a stringent threshold. At an uncorrected threshold, left VI/VII/VIII – ACC and left Crus I/II – MFG connectivity showed relationships with working memory efficiency.

Cerebello-cortical rsFC predicted attention and working memory efficiency more strongly than the right FPN and CON did, suggesting a possible role for the posterior cerebellum in increasing efficiency in these tasks that require both attention and speed. This notion was also supported by mediation analysis that showed left VI/VII/VIII – ACC connectivity mediated the relationship between CON connectivity and both attention and working memory. Thus, while CON did not show a strong direct effect on cognition, adding cerebellum – ACC connectivity to the model demonstrated a transmission of effect. In contrast, right FPN showed no indirect effect through Crus I/II – MFG. Thus, the posterior cerebellum may communicate more with the CON than the FPN in relation to executive functioning during this developmental period.

While direct and indirect effects of connectivity on attention and working memory were observed in this sample, age generally appears to have an omnibus effect on both cerebello-cortical connectivity and cognition from childhood to early adulthood. Overall, age predicted EFs more strongly than did connectivity. We did observe that cerebellum – CON connectivity became stronger with age, as predicted. However, the relationship between cerebellum – ACC connectivity and attention efficiency was only significant in younger children. No conditional direct or indirect effects were observed for the FPN. Thus, our hypotheses were partially supported.

5.2 Direct and indirect effects of cerebello-cortical connectivity on executive functions

Regression analyses demonstrated that cerebello-cortical rsFC predicted working memory and attention efficiency more strongly than cortical FPN and CON did, across all ages. The difference was more prominent for left VI/VII/VIII – ACC connectivity when we tested accuracy (*d'*), suggesting that cerebellum – ACC connectivity is not solely influencing performance through speed of processing or motor speed. Thus, this finding adds to the growing literature implicating the posterior cerebellum in cognitive processes of attention and working memory (Buckner et al., 2011; Caligiore et al., 2017; E et al., 2014; Guell et al., 2018; Ito, 2008; Stoodley & Schmahmann, 2009).

The most robust direct effects on cognition were present for left VI/VII/VIII – ACC connectivity predicting attention and working memory performance. In addition, there was a significant indirect effect of CON connectivity on both working memory and attention efficiency (and accuracy), mediated by left VI/VII/VIII – ACC connectivity, as predicted. These relationships indicate that in childhood and adolescence, the posterior cerebellum works with the cingulo-opercular network to facilitate both efficient and accurate responses on attention and working memory tasks.

Interestingly, this cerebellar component (IC57) was one of the largest cerebellar components that encompassed multiple lobules—most of left lobule VI, VIIb, and VIII, and the more anterior parts of left Crus I/II. Guell et al. (2018) saw activity in bilateral lobules VI and

VII (lobule VII includes Crus I/II, lobule VIIb) during working memory, in regions similar to our component. In addition, Moore et al. (2017) showed that increased gray matter in right lobule VIIb and Crus II was associated with better verbal working memory performance in children and adolescents, consistent with our connectivity findings and indicating that gray matter volume and connectivity are related to similar cognitive processes. Lobule VIII is most consistently shown to be a secondary motor lobule (Guell et al., 2018), but is often associated with working memory, as well (Brissenden et al., 2016; E et al., 2014). Its dual role may suggest that "motor cognition," or prediction of movement outcomes, is occurring within the secondary motor lobules through formation of forward internal models, possibly to facilitate accurate and efficient button presses (Fuentes & Bastian, 2007; Sokolov et al., 2017). Because our imaging analysis was data-driven and shows resting-state correlations between lobules VI, VII, and VIII, our results highlight the way movement and thought are likely intertwined during childhood via procedural learning and paired forward and inverse models (Koziol & Lutz, 2013; Wolpert & Kawato, 1998). Our results also still align with Guell and colleagues' because lobule VIII is often co-active with lobule VI and VII during working memory tasks that involve both cognitive processing and a motor response (E et al., 2014; Stoodley & Schmahmann, 2009).

Lobules VI and VII have also consistently been associated with the cingulo-opercular network, which has been identified as crucial for sustained task performance and tonic alertness (Buckner et al., 2011; Coste & Kleinschmidt, 2016; Dosenbach et al., 2006; Marek et al., 2018; Sadaghiani & D'Esposito, 2015; Seitzman et al., 2020). Posner, Rothbart, and Voelker (2016) refer to the CON as the "executive attention network," highlighting its role in attentional control, error and conflict detection, and performance monitoring in relation to goals. Dosenbach and colleagues (2006) showed that posterior cerebellar regions were active with the CON, especially during errors, and much work has demonstrated that both the cerebellum and ACC participate in conflict monitoring and error-based learning (Becerril & Barch, 2013; Botvinick et al., 2004; Dosenbach et al., 2006; Ide & Li, 2011; Ito, 2008; Sokolov et al., 2017). Becerril and Barch (2013) suggested that the dorsal ACC responds to errors, whereas the left lateral and inferior cerebellum are associated with conflict monitoring. Similarly, Ide and Li (2011) related the dorsal ACC to error occurrence and the inferior cerebellum to post-error slowing (i.e. performance monitoring and adjustment) on a stop signal task. The dorsal ACC has also been implicated in updating internal models of task performance, as it was active when participants were updating spatial predictions during a saccade task (Kolling et al., 2016; O'Reilly et al., 2013). Thus, the posterior cerebellum and ACC may be responsible for creating and updating internal models, respectively, for efficient performance on tasks that require "executive attention."

Notably, mediation effects were strongest for attention efficiency and working memory accuracy, which may reflect the nature of internal models—the goals of the PCPT and LNB 2-back are to respond quickly and accurately, but more emphasis is placed on speed in the PCPT because trials are shorter, and more emphasis is placed on accuracy in the LNB (Gur et al., 2010). Thus, while we cannot specifically show whether cerebellum – ACC connectivity in our study is related to error-based performance optimization, we speculate that the ACC and anterior insula store goals, the posterior cerebellum creates internal models of these goals to predict appropriate responses and their consequences, the ACC generates prediction errors based on outcomes to update the internal model, and the cerebellum and ACC work together to update internal models and adjust performance through error-based learning (Caligiore et al., 2017; Dosenbach et al., 2008; Ito, 2008; Koziol et al., 2009; O'Reilly et al., 2013; Sokolov et al., 2017). Koziol et al. (2009) posited that this process makes behavior more efficient, automatic, and coordinated with repeated trials.

Lesion studies have consistently indicated a role for the cerebellum in both attention and working memory; these are two fundamental domains of impairment in the cerebellar cognitive affective syndrome (Argyropoulos et al., 2020). Working memory and attention are also highly related—attention (to stimuli, task rules and goals) is required for encoding and manipulation that facilitates good working memory performance (Fougnie, 2008). Further, successful performance on the PCPT and LNB 2-back requires many of the same cognitive processes, including vigilance, sustained attention, performance monitoring, and error detection, which fall under Posner and colleagues' (2016) definition of executive attention. Nigg (2017) argued that executive attention is closely related to "low level" executive functions such as working memory and inhibitory control (Diamond, 2013), which also fall under the umbrella of cognitive control, referring to these more basic cognitive elements of executive function. Therefore, our findings that cerebellum – ACC connectivity is associated with performance on both attention and working memory tasks likely reflect the cerebellum's (and the ACC's) role in executive attention or cognitive control broadly, rather than a role in higher level facets of executive function (Botvinick et al., 2004; Kolling et al., 2016; Nee et al., 2013). This notion aligns with Schmahmann's "universal cerebellar transform" theory, which argues that the cerebellum performs the same operation on any information it receives, thus acting as a domain-general processor (Schmahmann et al., 2019). With regard to its role in executive functioning and within the cingulo-opercular network, its domain-general role may therefore be facilitating executive attention.

In contrast to the cingulo-opercular network, fronto-parietal network and Crus I/II – MFG connectivity showed direct relationships with attention and working memory, but cerebello-cortical mediation was not observed. Therefore, the posterior cerebellum may be specifically integrated into the CON to support executive functioning during childhood and adolescence. The FPN is associated with the cerebellum more often than the CON is in the adult literature, and appears to be functionally connected to more of the cerebellum than the CON is (Marek et al., 2018). Our findings seemingly contradict past work, but it is possible that Crus I/II – FPN connectivity strengthens earlier in childhood and then plateaus, rather than continuing to increase through adolescence (Kipping et al., 2017). Further, Dosenbach et al. (2006) related the FPN to flexible adjustment during tasks, as opposed to the CON's role in maintaining task set; therefore, our measures of task accuracy and efficiency and resting-state functional connectivity may tap into sustained, executive attention, more so than task updating.

Moreover, we did not see any significant relationships between connectivity and performance on the PCET, a measure of reasoning, problem-solving, and flexibility. The lack of findings with the PCET may be due to greater variability in performance across all age groups which may have reduced correlations; additionally, participants exhibited a greater accuracy-speed tradeoff on this task, which likely reduced efficiency. However, we also did not see significant relationships between connectivity and PCET accuracy. CON connectivity did predict flexibility efficiency at an uncorrected *p*-value of .049, which may be related to executive attention. Because our significant findings were specific to cerebellum – ACC connectivity, cingulo-opercular network connectivity, attention, and working memory, it is possible that this network is specifically associated with sustained task performance and executive attention more so than flexibility and problem-solving.

5.3 Age effects on connectivity and cognition—(lack of) moderated mediation

While we observed a mediational effect of cerebellum – ACC connectivity on the relationship between CON connectivity and executive attention, we did not observe the predicted age effects on all paths in the model. When age was added as a moderator to the mediational models, it reduced all direct and indirect effects, suggesting that age has a stronger influence over cognition than does connectivity. However, we did observe some interesting interactions between age and connectivity in conditional process models. First, the strength of the relationship between CON connectivity and left VI/VII/VIII – ACC connectivity increased with age, which we hypothesized. Second, the relationship between left VI/VII/VIII – ACC connectivity and attention efficiency was strongest in the younger participants and nonsignificant in older participants, in contrast to our hypotheses. This pattern was also present for working memory accuracy. These findings highlight some potentially interesting developmental processes.

Age showed significant relationships with both cerebello-cortical connectivity and executive functions. We replicated previous work with this cohort showing nonlinear relationships between age and both attention and working memory that increased until adolescence and then plateaued (Gur et al., 2012). Flexibility efficiency showed a slight linear relationship across the age group. Moreover, age demonstrated linear relationships with cerebello-cortical connectivity, as predicted, and in line with previous studies (Dosenbach et al., 2010; Fair et al., 2007, 2009, 2013; Kolskår et al., 2018; Kundu et al., 2018; Solé-Padullés et al., 2016). It is important to note, however, that age only accounted for a small amount of variance in cerebello-cortical connectivity and a much larger amount of variance in cognition.

This study revealed that age is a more robust predictor of executive functioning efficiency than cerebello-cortical connectivity is, demonstrated by differences in R^2 values from Aims 2 and 3. The mediational models in Aim 2 showed that connectivity accounted for approximately 1 – 3% of the variance in attention and working memory efficiency, whereas when age was added into the conditional process model, approximately 10 – 30% of the variance was accounted for. In addition, when age was added into the model, the mediation effect became nonsignificant, indicating that the robust age effects on cognition overshadow connectivity effects. Our findings contrast with Satterthwaite et al. (2013), who found that in-scanner performance on an N-back task was more strongly correlated with activation of FPN and CON regions than age, but that age mediated the relationship between activation and performance. Because their network was task-activated, they are likely seeing stronger relationships between the task and brain activity than we see for resting-state connectivity; rsFC is more of an indirect measure. The fact that we saw cerebellar mediation in our study, however, aligns with the network that Satterthwaite et al. observed during the N-back task, and suggests a framework from which future studies could address the interactions among regions within task-evoked executive networks. In addition, because age is correlated with both cerebellum – ACC connectivity and EF efficiency, it is likely we would see mediation if we tested the same model.

Nevertheless, the significant interactions we observed raise some interesting questions about developmental trajectories of cerebello-cortical connectivity and cognition. First, the relationship between the CON and posterior cerebellum – ACC connectivity was nonsignificant in younger children but significantly positive in adolescents and strongest in young adults. These results suggest that the posterior cerebellum becomes more integrated into the cingulo-opercular network across adolescence, which is in agreement with extant literature demonstrating that long-range functional connections strengthen with age and the cerebellum becomes integrated into functional networks (Dosenbach et al., 2010; Fair et al., 2007, 2009, 2013; Kundu et al., 2018). However, we saw this relationship only for the cingulo-opercular network and not the fronto-parietal network. While the interaction was not significant, the relationship between left Crus I/II – MFG connectivity and FPN connectivity is qualitatively stronger in younger children than adolescents and young adults. Stronger cerebellum – FPN connectivity in childhood compared to adulthood was also observed by Kipping et al. (2017), suggesting FPN cerebello-cortical connections strengthen earlier than the CON, which continues into adolescence and young adulthood.

The cingulo-opercular network has been identified as crucial for development of cognition, and particularly attention, into adolescence, whereas similar changes were not observed in the fronto-parietal network in past work (Kolskår et al., 2018; Marek et al., 2015; Posner et al., 2016). Our findings support Marek et al.'s (2015) hypothesis that major cortical networks may be relatively organized by adolescence, but the CON specifically continues to integrate with other brain regions, and particularly subcortical regions, which supports executive attention. We extend this hypothesis to include the cerebellum in cingulo-opercular network integration across adolescence.

Second, the relationships between left VI/VII/VIII – ACC connectivity and both attention efficiency and working memory accuracy were strongest in the younger participants. Similar trends were qualitatively present for working memory and flexibility efficiency, but these did not reach significance. Though relationships did not strengthen with age as predicted, findings are consistent with past work finding a plateau of prefrontal/cerebellar gray matter at approximately age 12 – 15 (Giedd et al., 1999; Gogtay et al., 2004; Tiemeier et al., 2010; Wierenga et al., 2014) and adult-level performance on basic EF tasks in childhood or early adolescence (Anderson, 2002; Lee et al., 2013; Luna et al., 2010). Thus, resting-state functional connectivity may be more consistent with frontal gray matter changes than we predicted. As discussed above regarding mediation, this interaction was significant with regard to attention efficiency and working memory accuracy, which we infer highlights the function of internal models in the cerebellum. We may be seeing the effect of cerebellar facilitation of the task goals through internal models, and this effect may be strongest in younger children because this is the period over which attention and working memory improve most robustly, both according our data and past work (Gur et al., 2012; Luna et al., 2010). While we hypothesized that the relationship between cerebello-cortical connectivity and EF efficiency would increase further into young adulthood, it is possible that executive attention relies more on the cerebellum as internal models are being formed and refined in childhood; in adulthood these processes may be more cortically- or subcortically-based with less reliance on the cerebellum. Ramnani argued that the cerebellum helps to transition neural systems from "controlled" to "automatic" processing (Koziol et al., 2014; Ramnani, 2014), which may be the reason it is more important in the younger children when the cerebellum is "teaching" the prefrontal cortex to anticipate outcomes through error-based learning (Caligiore et al., 2019; Koziol & Lutz, 2013).

In addition, because age was a stronger predictor of EF efficiency than was connectivity, there are likely important age-related aspects of working memory and attention that contribute to our findings. For example, using a paradigm in which they increased working memory load parametrically, Kharitonova et al. (2015) found that young children (ages 5 – 8) had a working memory capacity that was half that of adults. They activated a similar fronto-parietal brain network during the task, but children tended to specifically activate the ACC more than adults did, and children did not strongly recruit this network for loads that exceeded their working memory capacity. Thus, cerebellum – ACC connectivity may be more strongly associated with 2-back accuracy in younger children in our study because it challenges their working memory capacity and requires greater attentional resources, whereas adolescents and young adults are not as challenged by this task and thus this network is less associated with 2-back performance and attention efficiency. Our data suggest that this is the case with our sample, since variability in 2-back accuracy and efficiency was greater in younger children and many of the older participants achieved 100% correct responses (median = 90%, mode = 100%). Therefore, the ACC may play a general role in cognitive control development in childhood (Kharitonova et al., 2015), and our findings suggest that that the posterior cerebellum is part of this process as well. It is possible that with more cognitively demanding tasks, this effect would be present in older participants, as well (task limitations are discussed in section 5.5, below). Further, Luna and colleagues (2004) showed that generally accurate working memory performance was achieved by age 15, but subtle error- and performance monitoring processes that enhanced response precision continued to develop into the early 20s. These changes related to higher working memory loads, greater attentional demands, and response precision or variability would be good candidates to study with regard to internal models, and thus the ACC and cerebellum.

Taken together, cerebellum – prefrontal cortex connectivity is associated with attention and working memory efficiency, but age is a stronger predictor of attention and working memory performance than is resting-state functional connectivity. Even so, we did observe the predicted strengthening of the relationship between cerebellum – ACC and CON connectivity throughout adolescence. At the same time, cerebellum – ACC connectivity predicted attention efficiency and working memory accuracy more strongly in younger participants, so the cerebellum may influence executive attention more in childhood when there is the greatest increase in attention and working memory performance and the establishing of internal predictive models. Future work utilizing more sensitive measures of task variability, change over time, practice effects, and task-based fMRI would be helpful to probe how the cerebellum may or may not fit into development of the CON and executive functions.

5.4 Gender effects

While investigating gender was not an aim of this study, our results show some gender effects that both align with past work using the PNC dataset and suggest avenues for future research. Gur et al. (2012) showed gender differences in attention accuracy and speed, and working memory speed, which we replicated. Interestingly, the conditional process models that showed age × connectivity interactions did not show significant gender effects on cognition, which may indicate that when gender differences are present, the relationship between cerebello-cortical connectivity and executive attention is weaker and gender should be explored as a factor. It would be beneficial to probe item-level responses and non-responses, because there may be important differences in the way boys and girls respond, or how they sacrifice accuracy for speed. In addition, other PNC studies have shown significant gender effects on neuroimaging and executive functions, but they have not focused on the cerebellum (Gur & Gur, 2016; Satterthwaite, et al., 2015). While our results show patterns that are present while controlling for gender, it still may play an important role in neurodevelopment of cerebello-cortical connectivity as it does with cerebellar structure (Tiemeier et al., 2010; Wierenga et al., 2014), which has yet to be studied thoroughly.

5.5 Limitations

There are important limitations in this work that should be considered. The publicly available PNC dataset did not include item-level responses, which would be helpful for determining relevant measures such as intra-individual variability and non-responding to target stimuli. Intra-individual variability and subtle task differences may be especially relevant to study cerebellar function (Koziol et al., 2009). Roalf et al. (2014) showed a U-shaped curve for within-individual variability across Penn CNB tasks, showing high variability in childhood which decreased until mid-adolescence and then slightly increased in young adulthood. Thus, we may see reductions in variability within tasks, as well, and perhaps over multiple assessments.

The tasks utilized in this study also have some inherent limitations. All tasks were administered on a personal computer via a Web-based platform, often in participants' homes, which may result in inaccurate recording. However, the data were submitted to thorough quality assurance prior to upload into dbGAP, and we also performed our own quality assurance. The tasks were also designed to take as little time as possible because they were part of a large battery of tests and the original dataset included approximately 10,000 participants; therefore, some tasks had a small number of trials that may have not adequately captured the range of responses needed to tap into cerebellar function. In the development of the Penn CNB, the goal was to implement an efficient and reliable set of measures that utilize the smallest number of items needed in each test, can be implemented in large-scale studies, and generalized across many populations (Gur et al., 2010; Moore et al., 2015); thus, while the measures have been shown to be reliable and valid, they may not be sensitive enough to measure the nuance needed for studies of cerebellar function, particularly in older participants. Specifically, the letter N-back only has 10 correct trials for the 2-back condition, and most participants got perfect scores at older ages. Thus, we have little variability in accuracy. Calculating efficiency helped to make the distribution of this measure less skewed, but the task may not have been challenging or long enough to show variability in the older adolescents and thus we may not truly be measuring working memory. Because we saw similar results with regard to attention and working memory, and the working memory measure showed a ceiling effect, it may be beneficial to calculate a factor score for executive attention. Moore et al. (2015) investigated the psychometric properties of the Penn CNB in the PNC and showed that in a bifactor confirmatory factor analysis, attention and working memory loaded onto the same factor, whereas flexibility loaded onto a separate factor. In an analysis of speed measures, they also showed that attention, working memory, and finger tapping, the tasks requiring constant vigilance, loaded onto one factor. Thus, these factors may indeed measure executive attention and vigilance. To our knowledge, there has not been a study utilizing these factors along with neuroimaging, so it would be interesting to see whether we would observe a reliable and valid measure of executive attention and whether it relates to brain function. Similarly, because we saw that age does not uniformly correlate with connectivity or executive functions, future researchers may consider comparing younger versus older or pre- versus post-pubertal participants to shed light on these complex interactions as well as measurement validity in different age groups (Blakemore, 2012; Casey et al., 2010).

With regard to neuroimaging, data collected from children are notoriously noisy due to motion (Satterthwaite et al., 2012). We controlled for head motion using conservative measures at the subject level and excluded participants with excessive head motion, but we did not include mean FD in our statistical models because we did not want to over-correct for artifacts that are correlated with age (Satterthwaite et al., 2019). We did, however, test our models with FD included as a covariate to check for specificity of our findings, and our main findings remained the same. Including FD reduced the strength of observed relationships and also removed the mediation (Aim 2); however, because FD and age are correlated and they had similar effects when added to the mediation models, it is likely that we are seeing the effect of age when we add FD.

In addition, Marek et al. (2018) demonstrated that cerebellar rsFC is more variable than cortical networks, and this effect may be amplified in children and adolescents and thus impact cerebello-cortical connectivity. Inherent noise may have been especially problematic in the anterior cerebellar component, discussed further below. Finally, our interpretations are limited by the fact that we used resting-state instead of task-based fMRI. However, as discussed in the introduction, resting-state fMRI is particularly useful in children and is thought to show underlying neural architecture that correlates with task-evoked networks (Guell et al., 2018; Uddin et al., 2010). Our goal was to investigate how this network architecture relates to executive function, so using resting-state was appropriate for our aims. We infer that the posterior cerebellum and cingulo-opercular network influence executive attention and working memory performance, and future work can specify how these networks function during these tasks in greater detail.

Further, as predicted, we did not see a linear relationship between age and anterior cerebellum – precentral gyrus connectivity; however, a quadratic relationship was also not observed. We also saw no relationship between anterior cerebellum – precentral gyrus connectivity and finger tapping speed. It is possible that these unexpected results are due to excessive noise in the anterior cerebellum component, as it is located close to ventricles and may be contaminated by CSF signal. Despite our best efforts to get clean components, neuroimaging and preprocessing methods are still largely not optimized for the cerebellum (Schlerf et al., 2014). It is also possible that it is challenging to accurately measure finger tapping on a personal computer, and as Moore et al. (2015) mentioned, that task also requires constant vigilance so may actually be tapping into vigilance more than motor speed. Although these components or the finger tapping task may have been problematic, we also did not see relationships between anterior cerebellum – M1 connectivity and EF efficiency; therefore, we can be reasonably confident that our main findings are specific to the networks selected.

5.6 Conclusions and future directions

In summary, this study indicates that in childhood and adolescence, connectivity between the posterior cerebellum and prefrontal cortex regions slightly strengthens, and the posterior cerebellum mediates the relationship between the cingulo-opercular network and both attention and working memory efficiency. While these relationships were present when investigating the sample overall, we found that age has a stronger effect on attention and working memory performance than does connectivity over this developmental period, and cerebellum – ACC connectivity may have a greater impact on executive attention in childhood than in adolescence and young adulthood. In addition, the posterior cerebellum becomes more integrated into the cingulo-opercular network across adolescence and young adulthood. These findings raise numerous questions for future research.

First of all, longitudinal studies would be ideal to investigate developmental changes across adolescence. While this version of the PNC is cross-sectional, a subset of participants is being followed longitudinally, and there are other large-scale longitudinal studies that may help to investigate cerebello-cortical connectivity over time. For example, the Adolescent Brain Cognitive Development study, which has recently released data on approximately 10,000 9 – 10-year-olds will continue at multiple timepoints through early adulthood (Jernigan et al., 2018).

Similarly, it would be important to study change over time during a task to probe cerebellar (and ACC) function, as investigating variability, accuracy, and/or efficiency changes could tap into changes in internal models (Koziol & Lutz, 2013). As mentioned previously, using tasks with larger numbers of trials and multiple levels of difficulty could also provide more information about the cerebellum's role in automaticity and error-based learning. Studying practice effects in their own right has been generally neglected but may also shed more light on cerebellar function than simple accuracy or efficiency measures.

Interestingly, many articles referencing relationships between the cerebellum and cingulo-opercular network were investigating schizophrenia (e.g. Becerril & Barch, 2013). Therefore, our findings may be relevant for studies of schizophrenia or prodromal psychosis. Work with the PNC has already established a role for the CON and cerebellum in psychosis spectrum symptoms (Satterthwaite et al., 2015; Wolf et al., 2015), so our findings that cerebellum – CON connectivity is associated with attention and working memory in healthy participants may be relevant as a comparison in studies of psychosis. Numerous other developmental disorders affecting the structure of the cerebellum are associated with EF deficits, as well, such as Chiari malformation (Koziol & Barker, 2013) and posterior fossa tumor (Cantelmi et al., 2008; King et al., 2019). In addition, neurodevelopmental disorders such as autism, attention deficit/hyperactivity disorder (ADHD), and dyslexia have been associated with deficits in cerebellar structure and/or function (Stoodley, 2015). ADHD may be especially relevant, given our finding that cerebellum – ACC connectivity is related to executive attention. Thus, the cerebellum's role within the cingulo-opercular network might be important to study in these populations during sensitive periods in which disruption of cerebello-cortical circuitry makes individuals vulnerable (Fair et al., 2013; Wang et al., 2014). This study can contribute to the understanding of how cerebello-cortical functional connections are typically related to age and executive functioning and can help guide research questions regarding different clinical groups.

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APPENDICES

Appendix A

Correlations among Penn Computerized Neurocognitive Battery performance measures and age.

	Age	Attention Efficiency	Attention True Positives (z)	Attention Accuracy (d’)	Working Memory Efficiency	Working Memory True Positives (z)	Working Memory Accuracy (d’)	Flexibility Efficiency	Flexibility Accuracy (z)	Finger Tapping Speed (z)
Age	-	0.592	0.362	0.528	0.290	0.192	0.290	0.126	0.135	0.531
Attention Efficiency	0.592	-	0.797	0.618	0.399	0.262	0.278	0.227	0.177	0.497
Attention True Positives (z)	0.362	0.797	-	0.756	0.297	0.238	0.224	0.220	0.165	0.297
Attention Accuracy (d’)	0.528	0.618	0.756	-	0.250	0.310	0.390	0.211	0.214	0.341
Working Memory Efficiency	0.290	0.399	0.297	0.250	-	0.736	0.643	0.327	0.297	0.323
Working Memory True Positives (z)	0.192	0.262	0.238	0.310	0.736	-	0.789	0.299	0.299	0.197
Working Memory Accuracy (d’)	0.290	0.278	0.224	0.390	0.643	0.789	-	0.294	0.321	0.236
Flexibility Efficiency	0.126	0.227	0.220	0.211	0.327	0.299	0.294	-	0.812	0.154
Flexibility Accuracy (z)	0.135	0.177	0.165	0.214	0.297	0.299	0.321	0.812	-	0.125
Finger Tapping Speed (z)	0.531	0.497	0.297	0.341	0.323	0.197	0.236	0.154	0.125	-

Appendix B

Correlations with mean framewise displacement.

	Mean FD
Attention Efficiency	-0.150
Working Memory Efficiency	-0.079
Flexibility Efficiency	-0.028
Finger Tapping (*z*)	-0.169
CON	-0.209
L VI/VII/VIII – ACC	-0.329
L Crus – MFG	-0.225
R FPN	-0.019
Anterior CB – Motor	-0.188
Age	-0.264