CHARACTERIZING DEVELOPMENTAL GROWTH AND INDIVIDUAL DIFFERENCES IN BRAIN SYSTEMS SUPPORTING INHIBITORY CONTROL: A LONGITUDINAL FMRI STUDY

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Inhibitory control, the ability to voluntarily suppress responses to task-irrelevant stimuli, enables goal-directed behaviors and continues to develop through adolescence. Neuroimaging studies indicate that developmental improvements in inhibitory performance are supported by the maturation of brain systems, but these studies have not used longitudinal designs and continuous metrics of age to characterize the process of growth or individual differences in trajectories. This study used longitudinal fMRI data from over 312 visits from 129 participants aged 8 to 28 years to characterize growth curves of brain function. Mean growth curves revealed developmental increases in activity within an error monitoring region, the dorsal anterior cingulate cortex (dACC). DACC activity was uniquely associated with task performance, suggesting that late-maturing dACC activity may be a primary process underlying the maturation of inhibitory control. Activity in the right dorsolateral prefrontal cortex (dlPFC) declined from childhood to

adolescence, and may function as a scaffold to support immature networks. Growth curves across remaining areas of the inhibitory control circuitry did not show developmental changes, suggesting that the foundational inhibitory control system is available early in development. Investigating individual differences in trajectories revealed patterns of variability segregated according to function. Error monitoring evidenced the least variability, and executive control regions showed parallel trajectories, indicating a preservation of rank-order stability over development. Some motor response control regions showed a decline in variability with age, indicating individuals follow different paths to the same end point of maturity. Sex predicted slope variability in a set of motor response control regions and an executive control region, with females but not males showing developmental declines in reactivity. Taken together, these findings extend prior cross-sectional studies to indicate that primary to the development of inhibitory control is enhanced error monitoring and less reliance on supportive dlPFC control. Further, results highlight important variability in developmental pathways, including notable sex differences.

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PREFACE

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1.0 INTRODUCTION

Inhibitory control is defined as the ability to inhibit a task-irrelevant prepotent response in favor of a voluntary, goal-directed response, and it enables internally-represented goals to guide behavior rather than suboptimal or reflexive tendencies that may be less adaptive (Dempster, 1992). Studies of inhibitory control utilize paradigms requiring participants to suppress a reflexive or prepotent response (e.g., to look at a stimulus that appears) and to instead make a voluntary, goal-directed response (e.g., to look in the opposite direction of a stimulus that appears). Behavioral studies indicate that the capacity for inhibitory control is present in infants (Amso & Johnson, 2005; Diamond & Goldman-Rakic, 1989), but the ability to engage inhibitory control in a consistent manner continues to improve over the course of childhood and adolescence (Davidson, Amso, Anderson, & Diamond, 2006; Dempster, 1992; Evdokimidis et al., 2002; Fuster, 2002; Klein & Foerster, 2001; Luna, Velanova, & Geier, 2008; Ordaz, Davis, & Luna, 2010). Thus, the extended developmental maturation of inhibitory control in adolescence is relevant to understanding immaturities in adolescents' higher-level control of behavior (Spear, 2007). As limitations in inhibitory control characterize psychopathologies that emerge at high rates in adolescence, including schizophrenia (Everling & Fischer, 1998; Sweeney, Takarae, Macmillan, Luna, & Minshew, 2004), depression (Joormann, 2010; Joormann & Gotlib, 2010), and substance use disorders (Ivanov, Schulz, London, & Newcorn,

2008; Pardini, Lochman, & Wells, 2004), understanding individual differences in development can also clarify patterns and periods of risk for the emergence of psychopathology.

Studies characterizing trajectories of the *brain basis* of inhibitory control are particularly valuable because the development of inhibitory control is thought to be driven by structural brain maturation of white matter and cortical association areas supporting performance, both of which continue to mature through adolescence (Giedd et al., 1999; Gogtay et al., 2004; Sowell, Thompson, Holmes, Jernigan, & Toga, 1999; Sowell et al., 2004) (Asato, Terwilliger, Woo, & Luna, 2010; Huttenlocher, 1990; Klingberg, Vaidya, Gabrieli, Moseley, & Hedehus, 1999; Liston et al., 2006; Yakovlev & Lecours, 1967). Specifically, structural maturation is thought to affect brain function supporting inhibitory control by enhancing the capacity to recruit widely-distributed brain circuitries (Luna, et al., 2008). Indeed, increased structural connectivity with age is associated with improvements in inhibitory control (Liston, et al., 2006), and prefrontally-guided functional connectivity during inhibitory control is strengthened across development (Hwang, Velanova, & Luna, 2010; Stevens, Kiehl, Pearlson, & Calhoun, 2007). A focus on brain function is an approach that probes an underlying mechanism that supports cognitive performance (Luna, 2009; Spelke, 2002) and can provide a rich data set to enhance interpretations of behavior, particularly when examining brain activity supporting different behavioral outcomes (Best & Miller, 2010; Spelke, 2002).

Existing developmental functional neuroimaging studies of inhibitory control reveal developmental changes that persist into adolescence. Prior to elaborating on these findings, adult studies will be briefly reviewed to provide a context for interpreting development, because these studies rely on a framework whereby the circuitry recruited by adults is held as the standard of mature performance (Luna, 2009). Interpretations of the meaning of brain activity in certain

regions are guided by an empirical understanding acquired from functional neuroimaging studies of adults and single-unit recordings in primates. Various inhibitory control tasks engage a set of core regions (Swick, Ashley, & Turken, 2011), and these can be segregated into three main circuitries, sets of regions that support similar functions and work together to support IC. These include motor response control, executive control, and error processing circuitries. The motor response control circuitry prepares and guides an appropriately-timed, goal-directed response, and includes the supplementary motor area (SMA), and pre-supplementary motor areas (pre-SMA), posterior parietal cortex (pPC), and the putamen (Everling, Dorris, Klein, & Munoz, 1999; Rubia, Smith, Brammer, & Taylor, 2003). The executive control circuitry coordinates adaptive goal-directed behavior and includes the dorsolateral prefrontal cortex (dlPFC) and ventrolateral prefrontal cortex (vlPFC)(Aron, Robbins, & Poldrack, 2004; Badre & Wagner, 2004; Miller & Cohen, 2001). The error processing circuitry monitors performance and signals the executive control circuitry to adjust activity to improve performance on subsequent trials when errors are made (Carter, Botvinick, & Cohen, 1999; Carter et al., 1998; Kerns, 2006; Ridderinkhof, Ullsperger, Crone, & Nieuwenhuis, 2004). Error processing during inhibitory control is supported by activity in the dorsal anterior cingulate cortex (dACC) following errors (Menon, Adleman, White, Glover, & Reiss, 2001; Polli et al., 2005).

Existing developmental functional neuroimaging studies of inhibitory control, which have been almost exclusively cross-sectional, reveal that regions within these three functional circuitries are all recruited consistently across development (Rubia et al., 2006; Swick, et al., 2011; Velanova, Wheeler, & Luna, 2008), but the degree to which they are recruited varies across development. Through the use of cross-sectional, age group-based analyses, studies have provided an initial understanding of how magnitudes of brain activity change with development

(Adleman et al., 2002; Booth et al., 2003; Luna et al., 2001; R. Marsh et al., 2006; Rubia et al., 2000; Tamm, Menon, & Reiss, 2002). Further, event-related fMRI study designs enable characterization of developmental differences in brain function supporting equivalent performance, such as differences in activity supporting only correct trials. Such studies comparing two age groups have revealed that brain activity changes from childhood to adulthood and between adolescence and adulthood in both executive control and error monitoring regions (Bunge, Dudukovic, Thomason, Vaidya, & Gabrieli, 2002; Durston, Thomas, Worden, Yang, & Casey, 2002; Rubia, Smith, Taylor, & Brammer, 2007; Rubia, et al., 2006). Further, a set of cross-sectional studies examining differences across three age groups have had the added capacity to reveal that brain regions supporting different functions mature at different rates. First to mature are motor response control regions, which show no differences in magnitudes of activity across children, adolescents, and adults (Velanova, et al., 2008; Velanova, Wheeler, & Luna, 2009). Second to mature are the executive control regions, as magnitudes of dlPFC and vlPFC activity change from childhood to adolescence, but remain stable from adolescence into adulthood (Velanova, et al., 2008, 2009). Last to mature is activity in an area associated with error processing, which changes from adolescence to adulthood (Velanova, et al., 2008). Supporting this is evidence for continued change from adolescence to adulthood in a cross-sectional study examining error processing in only these two age groups (Rubia, et al., 2007). Though generally there is homogeneity of developmental timetables among regions supporting similar functions, some evidence for heterogeneity exists in the motor response control regions, as the pPC exhibits more delayed maturation from childhood to adolescence (Velanova, et al., 2008).

1.1 TRAJECTORIES FOR THE BRAIN BASIS OF INHIBITORY CONTROL NEED TO BE CHARACTERIZED

While research has revealed general patterns of development in the motor response control, executive control, and error-monitoring regions supporting inhibitory control, developmental trajectories (growth curves) have not yet been fully characterized, owing to a reliance on cross-sectional designs and comparisons of age groups rather than treating age as a continuous variable. This limits the capacity to explore (1) the nature (shape and rate) of developmental change and (2) individual differences in growth curves. In the following section, we will expand upon these goals and how they can advance understanding of the development of the brain basis of inhibitory control.

1.2 WHAT IS THE NATURE OF DEVELOPMENTAL CHANGE?

The process of growth reflects both the shape of the trajectory of activity and the slope of change. Understanding whether the shape of growth curves are linear (this term is used to refer to rectilinear change), asymptotic, or curvilinear can clarify how rates of maturation may vary over development. Linear and asymptotic growth curves reveal a gradual, unidirectional progression towards maturity, but while linear patterns indicate constant growth rates over development, asymptotic patterns reveal changing rates of growth. Periods of accelerated growth reflect sensitive periods during which certain mechanisms have a greater impact. In curvilinear growth there are also periods of decelerated growth followed by accelerated growth that are separated by a change in directionality of change midway through the developmental

process. In the context of equivalent performance, this may indicate a qualitative shift - for example, such patterns in trajectories of gray matter are thought to reflect synaptogenesis followed by synaptic pruning (Huttenlocher, 1990). Second, trajectories that follow the same shape may still differ in slopes, indicating that some brain regions mature at faster rates than others. Overall, characterizing the shape and slope of growth curves can suggest periods where change is particularly marked, reveal similarities and differences among brain regions, and can suggest possible mechanisms supporting such change.

1.3 ARE THERE INDIVIDUAL DIFFERENCES IN DEVELOPMENTAL TRAJECTORIES?

While the end point of mature, optimal inhibitory control is the target for all individuals, the pathway to maturity may differ. A cross-sectional fMRI study of attention allocation indicated that individual differences exist in youth (Rubia, Hyde, Halari, Giampietro, & Smith, 2010), and a longitudinal fMRI study of working memory activity showed different slopes of linear change across two time points in individuals with different genotypes (Dumontheil et al., 2011). Importantly, trajectories have been shown to be a particularly sensitive approach for examining individual differences, as developmental trajectories of cortical thinning (brain structure) differ between individuals (Raznahan, Shaw, et al., 2011; Shaw et al., 2006), who vary in rates and time to peak (Lenroot et al., 2007; Raznahan, Greenstein, et al., 2011; A. Raznahan et al., 2010; Armin Raznahan et al., 2010; Raznahan, Shaw, et al., 2011; Shaw, et al., 2006). The existence of individual differences in growth curves of brain function supporting inhibitory control could suggest that individuals follow different routes to converge at the same end point, or they may

follow the same path but with different slopes, with some individuals experiencing wider sensitive periods during which brain function supporting inhibitory control can be shaped by various factors including experience and gene expression.

The variability in trajectories may reflect a range of individual characteristics. Promising factors for initial investigation include sex and IQ because they have been shown to modulate executive function, brain function, and brain structure. Boys and girls show different slopes of frontal and parietal activity supporting attention allocation, (Rubia, et al., 2010), slopes of white matter growth (Asato, et al., 2010; Bava et al., 2011), and trajectories of cortical maturation (Lenroot, et al., 2007; Armin Raznahan, et al., 2010). Depending on the timing of divergences in trajectories, the existence of sex-modulated trajectories may point to the role of gonadal hormones in shaping how brain activation changes with development. In addition, IQ has been shown to modulate trajectories of brain maturation - high IQ individuals demonstrate a slower, more gradual cortical maturation compared to lower IQ individuals, although both eventually reach similar levels in adulthood (Shaw, et al., 2006). IQ has also been shown to modulate behavioral indices of inhibitory control in one (Evdokimidis, et al., 2002) study of adults, but not another (Michel & Anderson, 2009). Thus, it remains unclear whether inhibitory control-related brain function in higher IQ- individuals may exhibit a more protracted development similar to structural maturation. Understanding trajectories may highlight mechanistic relationships – for example, that a longer sensitive period may allow higher IQ individuals to eventually demonstrate better inhibitory control or that higher-IQ individuals may demonstrate better IC throughout development, irrespective of the time to peak. The maturation of inhibitory control may be affected differently by these factors as they may make different resources and brain processing approaches more readily available.

1.4 LONGITUDINAL STUDIES USING CONTINUOUS METRICS OF AGE CAN CHARACTERIZE GROWTH CURVES

Though initial event-related fMRI studies have begun to map out patterns of developmental change, this characterization is coarse because of a reliance on cross-sectional and age group-based samples. The only prior longitudinal study of brain function supporting inhibitory control utilized a longitudinal design (Durston & Casey, 2006), but relied on an age group comparison, meaning that no studies to date have mapped growth curved for the brain basis of inhibitory control. Age has often been treated as a categorical variable (children, adolescents, adults) to investigate qualitative differences across various stages of development. This approach provides important information regarding broad differences in well-defined developmental stages but limits sensitive characterization of trajectories and ages at which maturity is attained. Most studies attempt to model developmental change over a wide age range from childhood to adulthood (with age ranges spanning one and a half to two decades), but small sample sizes demand that participants be categorized into two or three developmental groups. As a result, age groups are either narrow (e.g., ages 10-12 years) so as to inadequately represent a period of developmental change, or wide (e.g., 13-17 years) so as to represent a heterogeneous period of as if it were homogeneous. Studies that only include two or three age groups are limited in the types of developmental change that they can detect, as they can only describe linear or V-shaped patterns of change, respectively.

Predetermined age ranges also undermine the ability to characterize interregional variability in maturation. For example, if adult-like behavior is reached at ages 15, 17, and 19 for three different regions, then in an age group analysis where 18 is the cutoff for the adult group, the first two regions to mature would be noted to follow the same developmental

timetable (adult-like in adolescence) that is qualitatively distinct from last region to mature, even though all three regions reach maturity in succession. Rather, the need to examine gradual change using age as a continuous variable and spanning a wide age range is informed by large developmental studies of brain structure (Giedd, et al., 1999; Gogtay, et al., 2004; Sowell, et al., 1999; Sowell, et al., 2004) and behavioral studies of inhibitory control (Evdokimidis, et al., 2002; C. Klein, 2001; C. Klein & Foerster, 2001) that consistently reveal gradual neurocognitive maturation characterized by varied rates of change and/or points of inflection over the course of late childhood, adolescence, and early adulthood. Taken together, this underscores the need to extend research investigating the brain basis of inhibitory control using a continuous metric of age and large sample sizes, which allows developmental change to be described more sensitively across the wide age span over which it occurs.

Further, cross-sectional study designs are limited in their ability to distinguish measurement error from true developmental change, and have less power for a comparable number of observations – problems that can be addressed with particular types of longitudinal analyses. First, whereas longitudinal studies can demonstrate true developmental change, cross-sectional studies can only describe differences among individuals differing in age because age-related differences are inseparable from cohort effects or systematic age-related measurement errors (e.g., developmental declines in motion while in the scanner, which can lead to false positive developmental findings (Church, Petersen, & Schlaggar, 2010; Poldrack, Pare-Blagoev, & Grant, 2002)). Longitudinal analyses can address these issues by explicitly modeling between- and within-subject variation separately so as to more sensitively describe true growth processes. Second, longitudinal studies have greater power to detect true developmental differences as compared to cross-sectional studies with the same number of observations because

estimates of age-related change are more reliable (Singer & Willett, 2003). Indeed, using a design in which the brain activity supporting inhibitory control in a small (n = 7) group of nine year-olds was compared to their own activity two years later or to a separate group of eleven-year olds, Durston et al. (2006) showed that longitudinal but not comparable cross-sectional analyses are capable of detecting developmental changes in frontal and cingulate cortices.

Not all longitudinal study designs are equivalent. The Durston et al. (2006) study – the sole longitudinal fMRI of inhibitory control - followed only seven individuals over only two time points and conducted a repeated-measures analysis of the data (Durston et al., 2006). Reliance on only two time points may produce exaggerated or minimized descriptions of change because of susceptibility to measurement error at either or both time points or due to learning effects (Brown, Petersen, & Schlaggar, 2006; Singer & Willett, 2003). For an accurate and thorough description of the shape and slope of developmental trajectories, data sets must include individuals with three or more waves of data, treat age continuously, and model curvilinear functions as well as linear and asymptotic functions. Hybrid cross-sectional/longitudinal designs, in which subjects who span a wide age range at time one and are followed longitudinally, provide results that are less biased by cohort effects and can extend models of developmental change over a wider age range. Growth curves can also be modeled for each participant, permitting comparisons of trajectories across individuals.

1.5 APPROACH, SPECIFIC AIMS, AND HYPOTHESES

The overarching aims of this study are twofold: (1) to describe developmental trajectories of brain systems supporting inhibitory control and (2) to examine individual differences in these trajectories. These aims were investigated by assessing: behavioral performance that provides a context for understanding the developmental changes in the brain, and activity in brain regions implicated in motor response control, executive control, and error monitoring.

This study utilized functional neuroimaging data of antisaccade task performance from a hybrid cross-sectional/longitudinal study of participants who were sampled at ages ranging from childhood to early adulthood in order to investigate the nature of developmental change in brain activity supporting inhibitory control. Regions of interest were selected a priori to encompass regions that are activated across a number of inhibitory control tasks rather than the antisaccade task alone to facilitate generalizability of results. Published results from the first wave of data collection guided hypotheses regarding mean patterns of developmental change (Hwang, et al., 2010; Velanova, et al., 2008, 2009).

An oculomotor inhibitory control task, the antisaccade task, was selected for its capacity to probe brain-behavior relationships over development, attributable to the following characteristics: first, it has a well-delineated neural system stemming from a combination of single-unit recordings in primates (Amador, Schlag-Rey, & Schlag, 2004; Everling, et al., 1999; Everling & Fischer, 1998; Everling & Munoz, 2000; Funahashi, Chafee, & Goldman-Rakic, 1993; Schlag-Rey, Amador, Sanchez, & Schlag, 1997) and fMRI studies in humans (Connolly, Goodale, Menon, & Munoz, 2002; Curtis & Connolly, 2008; Curtis & D'Esposito, 2003; DeSouza, Menon, & Everling, 2003); second, the simplicity of the task and the reflexive nature of the response to be suppressed obviates strategy use (Luna, et al., 2008); third, stimulus input

and response output are in the same domain so information does not need to be translated across modalities – an ability that may have a distinct maturational timeline that could confound developmental results; fourth, this task is sensitive to aspects of protracted development and it has been shown to be sensitive to adolescent development at both the behavioral and brain levels of analyses (Fischer, Biscaldi, & Gezeck, 1997; Fukushima, Hatta, & Fukushima, 2000; Klein, 2001; Klein & Foerster, 2001; Klein, Foerster, Hartnegg, & Fischer, 2005; Luna & Sweeney, 2004; Luna, et al., 2001; Munoz, Broughton, Goldring, & Armstrong, 1998; Nieuwenhuis, Ridderinkhof, van der Molen, & Kok, 1999; Ordaz, et al., 2010; Romine & Reynolds, 2005; Velanova, et al., 2008, 2009).

Statistical analyses of longitudinal data will rely on growth modeling, which allows extension of multiple regression for use with repeated-measures data (Singer & Willett, 2003). Hierarchical linear modeling (HLM), an approach that uses multi-level fixed effects and random effects analyses to account for nesting of data within individuals or groups were used because it uniquely enables flexible modeling of time, so that data collected at uneven intervals and from individuals with only a single time point can also be included in the model (Bryk & Raudenbush, 1987, 2002). In this framework, model-building approaches can be used to first model general patterns of developmental change, and then test for significant individual differences in intercepts and slopes of individual growth models, and finally to test predictors of the intercept and the slope that may explain individual differences.

Our first aim was to describe the nature of developmental trajectories, including shape of growth curves and their slopes. Based on prior cross-sectional studies using the antisaccade paradigm (reviewed in Luna, 2009), we hypothesized that behavioral performance will follow an inverse function, stabilizing to adult levels in adolescence. Based on cross-sectional studies

using a similar design with children and adolescents (Rubia, et al., 2007; Velanova, et al., 2008, 2009), we hypothesized that shapes of and slopes of growth curves for brain regions supporting similar functions (e.g., all motor response control regions) will be most similar to each other and differ from those supporting other functions. Specifically, motor response control regions will reach maturity prior to executive control regions, which in turn will mature prior to error processing regions.

Our second aim was to explore significant individual differences in slopes of growth curves and ages at which maturity is reached. Given evidence from longitudinal and cross-sectional studies of structural brain maturation and cross-sectional studies of inhibitory control performance, we predicted that significant individual differences will exist for growth curves for behavioral performance and brain activity in motor response control, executive control, and error processing circuitries. Further, on the basis of longitudinal and cross-sectional studies of structural brain maturation, cross-sectional studies of inhibitory control performance, and cross-sectional imaging studies of other executive functions showing that trajectories vary according to IQ or sex, we predict that these variables will also explain individual variability in growth curves of behavioral performance and brain activity in motor response control, executive control, and error processing circuitries. Specifically, females will show an earlier rapid growth spurt and earlier age of maturation while individuals with higher IQs will show a slower trajectory towards maturation.

2.0 METHODS

A hybrid cross-sectional/longitudinal study design was utilized to maximize the age range at each time point; therefore participants ranged from childhood to adulthood at across each study wave. Cross-sectional data from the first time point examining developmental changes in brain activity supporting antisaccade performance have previously been published (Hwang, et al., 2010; Velanova, et al., 2008, 2009).

2.1 PARTICIPANTS

Individuals were recruited through advertisements placed in newspapers, throughout the community and flyers sent to students enrolled in local public schools for participation in a longitudinal study of cognitive and brain development. Volunteers were native English speakers screened by phone for head injuries, eye movement problems (lazy eye, color blindness, altered vision), medications known to affect brain function and/or eye movements, major medical problems, history of neurological or psychiatric problems in themselves or a first degree relative. In addition, they were ruled out for nonremovable metal on the body, claustrophobia, weight greater than 300 lbs to ensure scanner eligibility. Studies were performed in accordance with University of Pittsburgh Institutional Review Board guidelines.

2.2 VISIT PROCEDURE

Data were collected each year during a set of two visits: a visit to the behavioral laboratory followed by a magnetic resonance imaging (MRI) scanning session within at least three months. During behavioral visits, participants completed an IQ test and questionnaires about their demographics. For the purposes of other studies, participants also completed various computerized and paper-and-pencil cognitive tasks and oculomotor tasks similar to those administered at the subsequent MRI visit. Oculomotor data were used for an analysis separate from those reported here, but this visit provided subjects with an opportunity to be acquainted with the paradigms used in the subsequent fMRI study and to ensure participants understood task instructions. Scan visits consisted of an hour and 15 minute-long scanning sequence and included the acquisition of behavioral data that will be reported here. Immediately prior to scanning, naïve participants spent approximately 10 minutes in a simulation scanner to acclimate to the size constraints and noise of the MR scanner environment (Rosenberg et al., 1997). Vision was normal or corrected to normal using magnet compatible glasses or contact lenses.

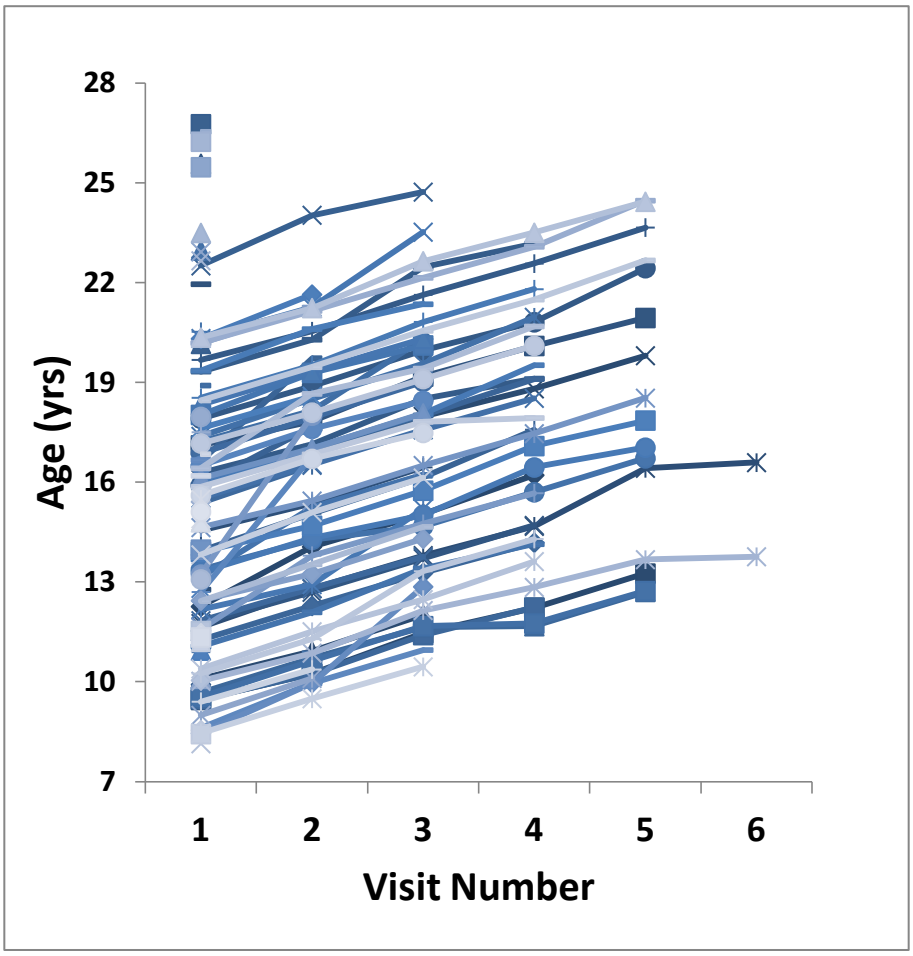

Figure 1: Age distribution according to number of study visits.

The hybrid cross-sectional/longitudinal nature of the study design is evident in this graph depicting age distribution of individuals with a given number of study visits. Visits are spaced one year apart, but not all individuals have the same number of study visits. Data reflect participant visits prior to exclusions related to data quality.

Study visits occurred at approximately twelve month intervals, and participants provided data ranging from one to six time points. Figure 1 illustrates the hybrid cross-sectional/longitudinal study design characterized by a wide age span of participants at each wave of the study. Over the course of the study, 24 individuals (14 F) did not return for follow-up due to obtaining braces, difficulty rescheduling or contacting, excessive movement in the scanner, loss of interest, and change of residence (listed in order of frequency). A total of 139 participants (75 F) completed a total of 356 visits (177 F). Of these, 21 visits (8 F) were not

included in subsequent data analyses because three scans of eye data and neuroimaging data could not be acquired for one of the following reasons: technical or administrative errors (11 visits), participants falling asleep (4 visits), participants asking to be removed from the scanner (5 visits), or the discovery of a brain abnormality (1 individual's first visit).

Therefore data from a total of 341 visits (173 F) representing 135 participants (72 F) were preprocessed. This reflected two individuals who completed six visits, twelve who completed five, 22 who completed four, 31 who completed three, 20 who completed two, and 48 who completed one visit. This study design including single visits has been found to be effective for characterizing longitudinal trajectories (Bryk & Raudenbush, 1987, 2002). Following preprocessing, additional visits were excluded due to lack of integrity in structural MRI images (four visits), excessive movement during functional MRI runs (20 visits), lack of at least three runs inclusive of usable functional and eye scoring data after accounting for movement (three visits), poor quality of eye tracking (one visit), and scanner inhomogeneities (one visit). As a result, a total of 312 visits from 129 individuals were included in initial statistical analyses (see Table 1). Participants ranged in age from 8.1 to 28.9 years of age. Final statistical models were limited to visits from participants between 9.0 and 26.0 years of age in order to ensure that data throughout the age range estimated was based on a similar number of estimates. The final reported regressions are based on a sample composed of 302 visits from 123 individuals (64 F).

Table 1: Number of individuals per frequency of study visit after accounting for excluded visits

# Visits	*# Individuals (# F)*
1	47 (28)
2	23 (10)
3	30 (14)
4	17 (8)
5	11 (7)
6	1 (1)
Total	129 (68)

2.3 IQ SCORES

The four-subtest Wechsler Abbreviated Scale of Intelligence (Wechsler, 1999) was administered to estimate an IQ score. Full-Scale IQ scores are conceptualized to be stable with age but were administered at years one, three, and five. The score obtained at the oldest age of testing was selected for use *a priori*, since scores are more reliable with increasing age (Wechsler, 1999). IQ, a level-2 variable, was missing from one female with a single time point. Mean IQ was 113.48 (SD = 11.648, range: 85 – 142), did not differ significantly between the sexes, $t(120) = 0.918$, $p = 0.361$.

2.4 FMRI DATA ACQUISITION

Data were acquired using a Siemens 3-Tesla MAGNETOM Allegra (Erlangen, Germany) fitted with a standard circularity-polarized head coil. Pillows and tape minimized head movement.

Earplugs dampened scanner noise. A PC (Dell Dimension 8200, Pentium 4, 2 GHz, Windows XP) running E-Prime (Psychology Software Tools, Pittsburgh, PA, USA) controlled stimulus display. Stimuli were projected onto a screen at the head of the scanner bore viewable via a mirror attached to the head coil.

Structural images were acquired first using a sagittal magnetization-prepared rapid gradient-echo (MP-RAGE) T1-weighted sequence (TR = 1570 msec, echo time [TE] = 3.04 ms, flip angle [a] = 8 degrees, inversion time [TI] = 800 ms, voxel size = .78125 x .78125 x 1 mm) and used for alignment of functional images. Functional images were acquired using an echo-planar sequence sensitive to blood oxygen level dependent (BOLD) contrast [T2*] (TR =1.5 s, TE = 25 ms, a = 70 deg, voxel size = 3.125 x 3.125 mm in-plane resolution), with 29 contiguous 4-mm thick axial images acquired parallel to the anterior-posterior commissure plane during each TR. Participants performed four functional runs (each, 6 min 15 s), followed by up to three runs of an unrelated experiment. The first six images in each run were discarded to allow stabilization of longitudinal magnetization.

2.5 ANTISACCADE PARADIGM

Run and task trial structures are depicted in Figure 2, which is reproduced from Velanova et al. (2008). Each run consisted of a two blocked periods of oculomotor task performance interspersed with three blocked periods of fixation. Oculomotor tasks were administered in a counterbalanced order and included the antisaccade (AS) task and the visually-guided saccade task (VGS), a reflexive task that served to enhance the inhibitory demands during AS trials. Each run began with 36 s of fixation (control), followed by a 114 s task block, a second block of

fixation (45 s), a second task block (114 s), and a final block of fixation (36 s). Participants performed the AS task during one task block, and the VGS task during the other.

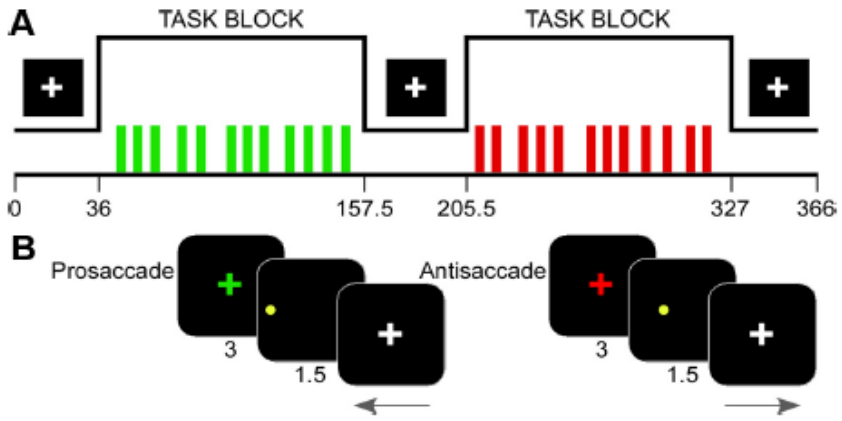

Figure 2: Experimental task design

Depiction of experimental (A) run structures and (B) task trial structures. From Velanova et al. (2008).

Task order was counterbalanced across runs (within participant) and across participants. Participants were explicitly told the task order prior to the start of each run.

Each task block was preceded by a 3 s cue informing participants about the nature of the upcoming trials (either "Start LOOK-AWAY game" for AS blocks, or "Start LOOK-TOWARD game" for VGS blocks). Twelve AS trials or twelve VGS trials were presented in each task block, such that, across four runs, participants performed 48 of each trial type. Intervals between trials during which a white fixation cross-hair was presented varied between 3 to 9 s, with a greater number of shorter intervals. This temporal jitter allowed separation of trial-related signal components and differed from trial to trial for each participant (Dale, 1999). Trial presentation was time-locked to the onset of successive whole-brain image acquisitions. Each task block ended with a 3 s "task end" cue, alerting participants that a long period of fixation would follow. Three additional MR frames (4.5 s) of fixation served to jitter the onset of the task block proper

(following cue presentation) and were arranged such that if three additional frames (4.5 s) of fixation followed the task onset cue, no additional fixation frames preceded the "task end" cue, else if two additional frames (3 s) of fixation followed the task onset cue, one frame (1.5 s) preceded the "task end" cue and so forth. Inclusion of these additional frames of fixation reduced noise in estimating responses associated with task start and end cues, and also modestly improved estimates of transient and sustained effects.

Each AS and VGS task trials began with a 3 s colored fixation cross-hair (subtending ~0.7 degrees of visual angle) instructing participants to make a visually-guided saccade (green) or an antisaccade (red). Participants were instructed to fixate on this instruction cue. Immediately following this, the saccade target stimulus, a yellow circle, appeared for 1.5 s. For VGS trials, participants' task was to look toward the saccade stimulus. For AS trials, participants were instructed to inhibit saccades toward the saccade stimulus and to look instead toward the empty location in its horizontal mirror location. The target stimulus subtended ~0.5 degrees an appeared at one of six horizontal eccentricities (at +/- 6, 3, or 0 degrees). Target location order was randomized within each task block. No "gap" was interposed between the instruction cue and saccade target stimulus to increase the probability of accurate performance in younger participants (Fischer, et al., 1997).

2.6 EYE TRACKING

Eye movement measurements were obtained during scanning using a long-range optics (LRO) eye-tracking system (Model R-LRO6, Applied Science Laboratories, Bedford, MA, USA) with a sampling rate of 60 Hz. Nine-point calibrations were performed at the beginning of the session

and between runs as necessary. Real-time monitoring also permitted immediate identification of head movement or gross inattention to the task, and experimenters redirected subjects immediately following the run.

2.7 FMRI DATA PREPROCESSING

Neuroimaging data were preprocessed to remove noise and motion artifacts and functional images will be aligned to structural images. Functional data were slice-time corrected and motion was corrected within and across runs using a rigid-body rotation and translation algorithm. Functional files were registered to a standardized atlas using a series of affine transforms to align each subject's T1-weighted image to a 3 mm MNI template brain. Data were then smoothed using a weighted 5 mm full width half-maximum Gaussian kernel, a 0.03 Hz high-pass temporal filter was applied, and the voxel time series was normalized and scaled to have a mean intensity of 100 so that regression coefficients can be interpreted as percent signal change. Structural images were visually inspected to ensure data integrity (e.g., ghosting, magnetic field inhomogeneities, wraparound); data from four visits were excluded as a result. As a result of visual inspection, data from one functional visit was excluded due to scanner inhomogeneities.

2.8 MOVEMENT ANALYSES

Measures of head movement during functional sequences were obtained using a rigid-body rotation and translation algorithm. Translations and rotations in the x, y, and z dimensions were averaged across frames and total root mean square linear and angular precision measures were calculated for each run. Runs in which total root mean square movement exceeded 1 mm (translations) or 1 degree (rotations) were excluded from further analysis, encompassing a total of 79 runs. As a result, 20 visits (9 F) were excluded because they no longer included at least three runs of functional neuroimaging data. Excluded visits encompassed individuals ranging in age from 8.5 to 18.4 years (mean = 13.2 yrs, s.d.= 2.9 yrs). Mean ages for excluded visits did not differ for males and females ($t(18) = -0.98$, $p = 0.923$).

After accounting for motion and eye data that was not acquired due to technical or administrative errors, three visits (but no individuals) were excluded because they did not have at least three runs with both functional MRI data and scoreable eye data.

2.9 EYE TRACKING DATA

Eye-movement data were analyzed and scored offline using ILAB (Gitelman et al., 1999) in conjunction with an in-house scoring suite written in MATLAB (MathWorks, Inc., Natick, MA) by trained raters. Saccades were identified using a velocity algorithm employing a 20 deg/s criterion and were presented graphically and numerically for inspection of measurements for each saccade. Raters reviewed the results generated by the algorithms to identify blink artifacts and occasional failures of the software to identify primary saccades, and to make modifications,

if necessary, using the editing features available in ILAB. Each eye movement trial was scored for performance accuracy (correct, corrected error, uncorrected error, or dropped because trial was unscorable due to blinks or signal loss). Errors were typically followed by a saccade to the correct location indicating that participants understood the instruction but were unable to inhibit the automatic response towards the cue. Express saccades, characterized by an initial saccadic latency of less than 67 ms reflecting anticipatory errors were also included as dropped trials (Fischer & Ramsperger, 1984). For these analyses, we compiled error rates as a metric of antisaccade performance; this was calculated as the number of corrected error trials divided by the total number trials excluding dropped trials. One visit had to be excluded because of the poor quality of eye tracking data resulted in the dropping of more than 75% of trials.

2.10 FMRI DATA ANALYSES

For each voxel, a general linear model that estimates the average hemodynamic response was generated using Analysis of Functional Neuro-Images (AFNI) (Cox, 1996). Correct, corrected error, and uncorrected error/dropped trials were modeled using the SPM gamma function, with baseline signal drift plus six motion parameters entered as covariates. For each region of interest (ROI) except the dACC, hemodynamic responses during correct trials were compared to the fixation baseline. This contrast was chosen because the imaging data from the antisaccade versus fixation contrast has higher test-retest reliability than the antisaccade versus VGS comparison (Raemaekers et al., 2007) and to maintain consistency with previous cross-sectional analyses of these data (Velanova, et al., 2008, 2009) that informed choice of ROIs and study

hypotheses. Given the dACC's role in error processing, activity in dACC was examined through the comparison of corrected error trials versus baseline.

Our analyses focused on *a priori* ROIs associated with inhibitory control not specific to the antisaccade task including regions associated with motor response control (SEF, preSMA, pPC (bilateral), putamen (bilateral), FEF (bilateral)), executive control (dlPFC (bilateral), vlPFC (bilateral)), and error monitoring (dACC) (Kenner et al., 2010; Munoz & Everling, 2004; Swick, et al., 2011). Central coordinates of these ROIs were identified using Neurosynth platform and database (www.Neurosynth.org, accessed March, 2010), an automated brain-mapping framework that combines meta-analysis, machine-learning, and text-mining approaches to generate statistical z-maps for a given search term or topic (Yarkoni, Poldrack, Nichols, Van Essen, & Wager, 2011). As topic maps are factor maps that summarize results from a larger set of studies associated with a related set of terms, topic maps were used when possible. Terms and topics were selected based on their having been implicated in inhibitory control and being inclusive of developmental studies. For term maps, we used the reverse inference maps associated with each term (rather than forward inference maps). These depict the voxelwise probability of each term given activation observed at each voxel coordinate assuming uniform priors (i.e., 50% probabilities of "term" and "no term"), and provide a statistical measure of the specificity of activation (to each relevant term) at each coordinate point across the hundreds of studies in the Neurosynth database associated with each term. Small corrections to central coordinates were made to ensure that final spheres overlapped with canonical eye movement regions. ROIs were defined as voxels within a given radius of each identified peak; a 10 mm radius was used for most cortical ROIs. However, a 7 mm radius was used for the SEF and preSMA to ensure that they did not overlap and a similarly-sized radius was used for the

putamen due to its smaller anatomical sixe, and 12 mm radius was used for the dlPFC to ensure full coverage. Table 2 summarizes the central coordinates and size of each ROI, which are depicted visually in Figure 3. Beta values reflecting response magnitudes for all voxels within each ROI were averaged for each subject visit to produce a mean percent signal change metric for each ROI per visit.

Table 2: Mean coordinates and cluster size for all regions of interest

	Center voxel coordinates				
	x	y	z	Radius (mm)	*n* voxels
SEF	0.0	-4.6	62.0	7	37
preSMA	0.0	5.0	52.1	7	37
FEF - L	-25.5	-1.5	56.0	10	107
FEF - R	26.5	-1.5	58.0	10	107
putamen - L	-26.0	4.0	6.0	7	37
putamen - R	26.0	2.0	4.0	7	37
pPC - L	-32.0	-48.0	50.0	10	107
pPC - R	32.0	-54.0	48.0	10	107
dlPFC - L	-41.0	19.0	41.0	12	185
dlPFC - R	42.0	18.0	42.0	12	183
vlPFC - L	-46.5	10.5	24.0	10	107
vlPFC - R	49.5	12.0	22.0	10	107
dACC	0.0	19.5	40.5	10	107

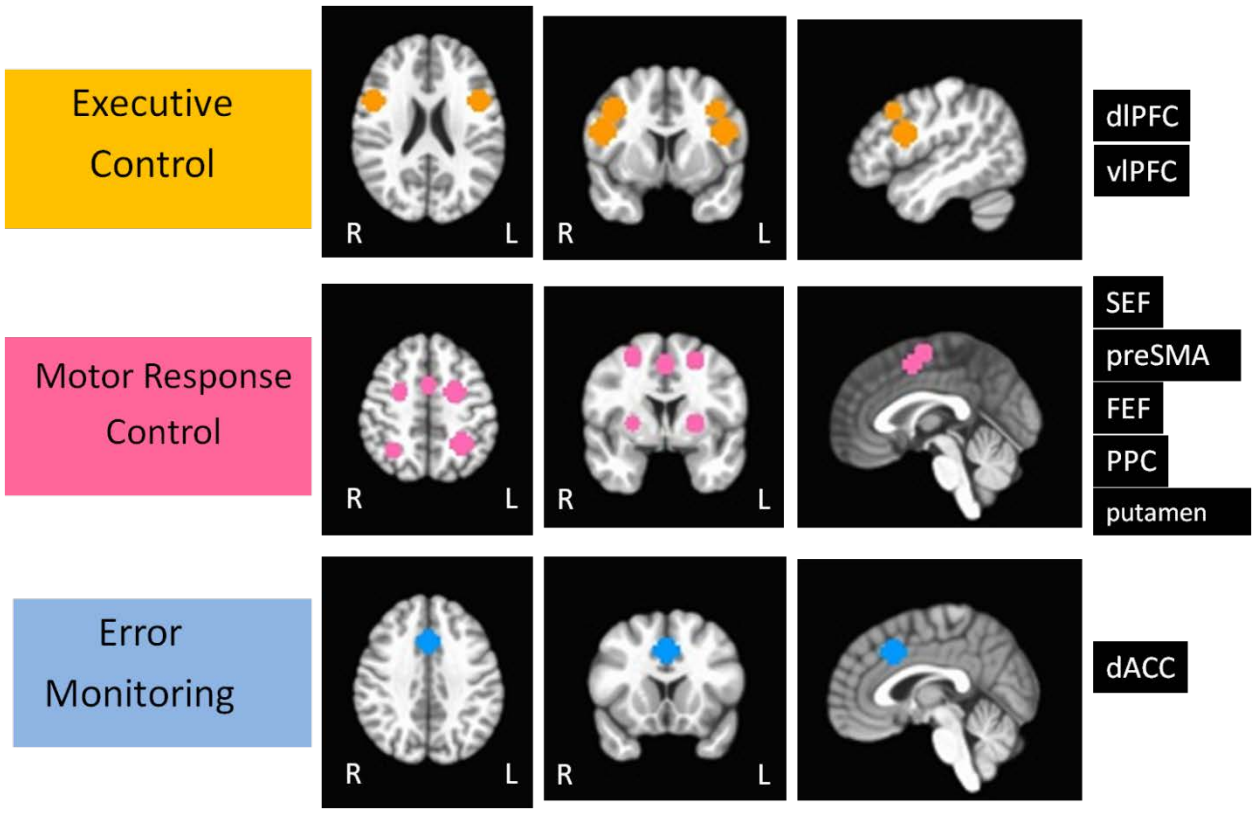

Figure 3: ***A priori r***egions of interest

A priori regions of interest for a priori executive control, motor response control, and error monitoring circuitries, as shown in (from left to right) axial, coronal, and sagittal slices. Images are shown in radiological view, as indicated by the letters denoting the right and left sides of the brain.

2.11 RELIABILITY OF FMRI DATA

First, test-retest reliability of fMRI measurements *across* sessions was established by examining change within subjects who provided two scans after the age of 20 (n=14), as change over time in this subsample should be reflective of data reliability and minimally related to developmental factors. Correlations between percent signal change estimates at the first and second scan were calculated for each subject on a voxelwise basis. As these adult participants demonstrated few error trials (see Figure 4), only reliabilities for correct trials are reported. Second, to index a sufficient amount of within-subject variability as a proportion of total variability, intra-class correlations (ICCs) were calculated using $\hat{\rho} = \frac{\hat{\tau}_{00}}{\hat{\tau}_{00}+\hat{\sigma}^2}$ (REML estimates) to determine the degree of within-subject clustering, ensuring the validity of nesting observations within individuals. Third, unequal sampling across the age range can produce variable data reliability across development, so we visually inspected the data to determine (a) whether spline models were superior to combining all individuals into a single model and (b) whether limiting the age range may minimize unequal sampling across the age range.

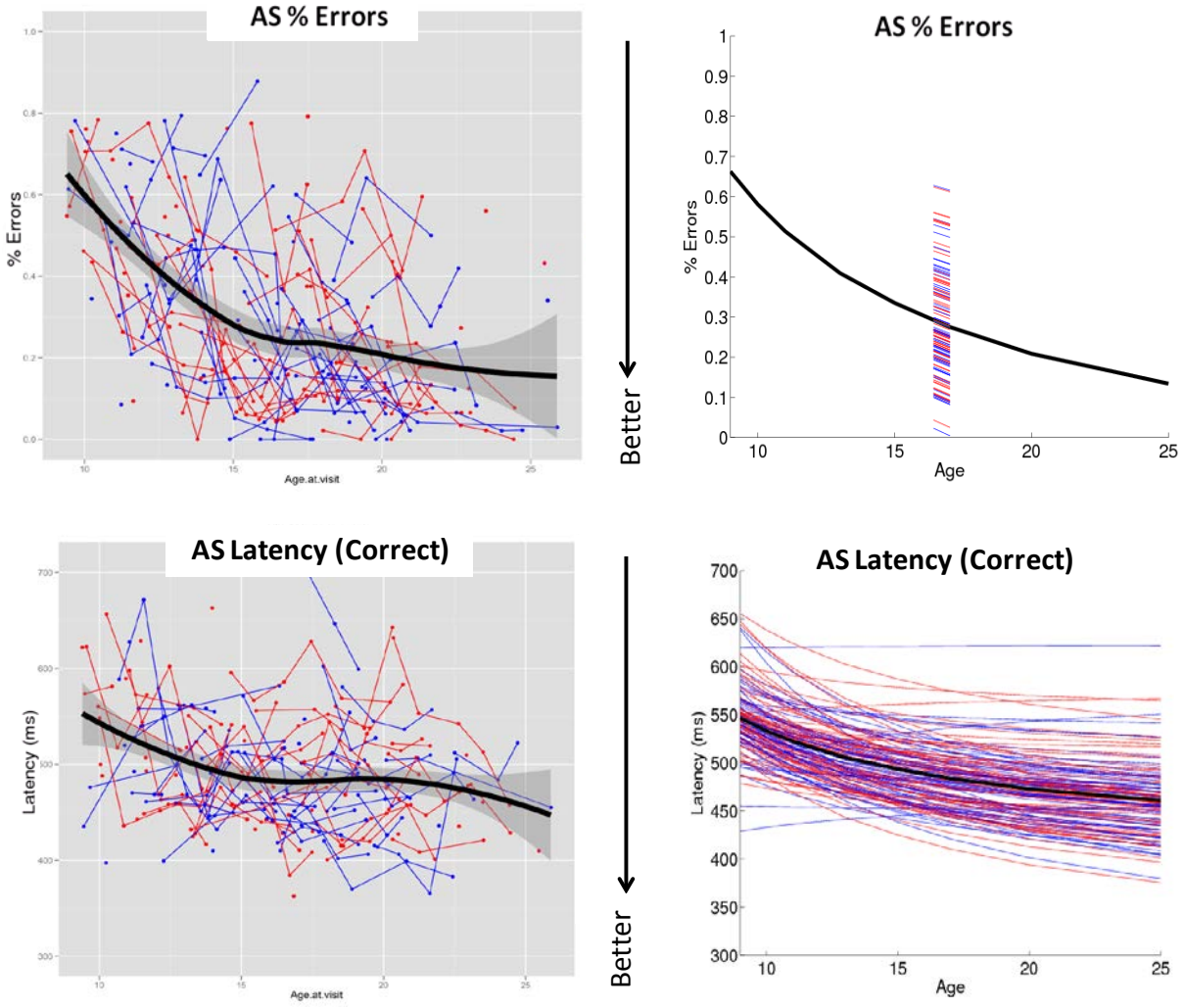

Figure 4: Raw behavioral data

Antisaccade (AS) error rates (in % errors) and latencies on correct trials (in ms). Raw data with superimposed loess lines (left) corroborate the model-fitting procedures suggesting an inverse function fits both models best (right). In all graphs, red lines denote females, and blue lines indicate males. For AS error rates, variance in intercepts but not slopes was significant, which is indicated by graphing a portion of each individual's estimated regression line. For latencies on correct trials, each regression line is plotted to underscore significant variability in both intercept and slope.

2.12 STATISTICAL ANALYSES

Hierarchical linear modeling (HLM) analyses (equivalent to random effects, mixed effects, or multilevel modeling) were used to model group-level trajectories and to test for significant individual variability in trajectories. This modeling approach allows nesting of multiple observations within an individual, and it is unique among other types of nested analyses in allowing for modeling individual regressions for each participant, and for flexible treatment of time (Raudenbush & Bryk, 2002). Analyses were conducted using the program HLM version 6 (Scientific Software International, Inc.).

The following analytic procedure was followed for each outcome variable, which include antisaccade corrected error rates and % signal change for each ROI. First, linear, quadratic, and inverse unconditional growth models were modeled. The optimally fitting model was selected for use as the unconditional growth model for subsequent model-building on the basis of the Akaike Information Criterion (AIC) model fit index, consistent with other developmental studies comparing shapes of developmental curves (Kail & Ferrer, 2007). AIC was selected for use because (1) it allows comparison of models that cannot be compared via model comparison tests (i.e., the linear and inverse age models) because they are not nested (i.e., do not have a different number of parameters), and (2) it is unique among other model fit indices in that it is a standardized value allowing comparison across models that have differing numbers of parameters (i.e. linear and quadratic age models). Lower (more negative) AIC values reflect better model fit to the data. To ensure validity of the AIC-informed selection of model shape, note that the final model (age, inverse age or quadratic age) was only selected if the relevant age term was also significant (e.g., if AIC indicates quadratic model is best-fitting, this model is only selected if the quadratic term is also significant).

The unconditional growth model is a base model from which to begin model-building procedures. In all cases, the age term was centered to facilitate meaningful interpretation of the intercept (for nonlinear transformations, inverse age values were centered around the inverse of the mean age of the sample). For example, an unconditional model using the inverse of age ("InvAgeC", centered) to predict antisaccade error rates ("ASerr") would be as follows:

Level 1:

$$ASerr_{ti} = \pi_{0i} + \pi_{1i}(InvAgeC)_{ti} + e_{ti} \qquad e_{ti} \sim N(0, \sigma^2)$$

Level 2:

$$\pi_{0i} = \beta_{00} + r_{0i}$$
$$\pi_{1i} = \beta_{10} + r_{1i}$$

$$\begin{bmatrix} r_{0i} \\ r_{1i} \end{bmatrix} \sim N\left(\begin{bmatrix} 0 \\ 0 \end{bmatrix}, \begin{bmatrix} \tau_{00} & \tau_{01} \\ \tau_{10} & \tau_{11} \end{bmatrix}\right)$$

In such a model, β_{00} reflects the grand mean antisaccade error rate at the mean age of the sample, and β_{10} reflects the grand mean slope of the trajectory. The random effect term for the intercept and slope are r_{0i} and r_{1i}, respectively; a significant r_{0i} term indicates individual differences in antisaccade error rates at the mean age of the sample, and a significant r_{1i} term indicates individual differences in trajectories of antisaccade error rates.

Second, model-building procedures were utilized to determine whether the random terms are indeed significant and, if so, to determine whether time-invariant predictors, sex and IQ (both terms centered to facilitate interpretation of coefficients in the model), at level two can explain the individual variability in the intercept and/or slope. Specifically, chi-square tests were used to test significant improvement in model fit between the unconditional growth model and nested models with random intercept and slope terms removed. If level two random intercept and/or slope terms were significant, indicating variability exists, then sex and IQ were added as level

two predictors to determine whether they were significant and whether significant intercept and/or slope variability remained. Finally, we removed any nonsignificant terms. Models were fit using (a) FIML estimates for the purposes of calculating deviance, degrees of freedom, and model comparison tests (AIC) and (b) REML estimates for reporting of fixed effect and variance component estimates as well as their significance tests.

To explore significant sex moderation of trajectories, follow-up analyses using a dummy coded variable with either females or males coded as the reference group were used to test the significance of intercepts and slopes for trajectories for each sex. To test sex differences in percent signal change values at other points along the estimated trajectories besides the mean age of the sample, regressions centered at ages 11 and 23 were tested for significant differences in intercepts. These ages were chosen because they reflect ages at the relative extremes of the ages sampled, but still have a high number of sample points to ensure reliability of estimates.

3.0 RESULTS

3.1 BEHAVIORAL PERFORMANCE

Table 3 lists AIC values used to guide the selection of unconditional models characterizing the shape of growth and the proportion of variance explained by the age term in this model. Table 4 lists estimates of fixed effects (intercept, slope), random effects (variance in intercepts, slopes, and level one variance), model fit indices (deviance, AIC), and the significance of all these terms (level one variance excepted) for all final behavioral models. AIC fit indices indicated that inverse models fit all variables best, indicating that rates of change decline over the adolescent years. Raw behavioral data with superimposed loess lines are depicted in Figure 4, which underscores the inverse trend in the data and highlight a lack of sex differences described below.

The antisaccade error rate at the mean age of the sample (16.7 years) was 0.283,and the a positive mean inverse age growth rate indicating a significant decline in error rates that levels off with age in late adolescence. At the mean age of the sample, latencies for correct antisaccade trials were slower (485.2 ms) than error trial latencies (353.8 ms). Both latencies significantly declined with age.

Table 3: Test-retest reliabilities, ICCs, and model fitting indices

	Test-retest reliability	ICC ‡	AIC value from unconditional growth model			Age model selected §	Pseudo-R^2, age term in unconditional model
	Mean (SD)^		inverse age	linear age	quadratic age		
Region of interest							
SEF	0.488 (0.239)	0.359	-1004.27	**-1004.96**	-1008.18	age	0.019
preSMA	0.282 (0.295)	0.382	**-1000.41**	-998.49	-1000.77	inverse	0.072
FEF (L)	0.662 (0.209)	0.383	-1254.19	-1250.68	**-1264.20**	quadratic	0.182
FEF (R)	0.472 (0.205)	0.273	**-1123.06**	-1119.10	-1128.13	inverse	0.104
putamen (L)	0.138 (0.187)	0.209	-1214.23	**-1214.85**	-1217.84	age	0.000
putamen (R)	0.143 (0.189)	0.228	-1258.72	**-1258.91**	-1260.88	age	0.039
pPC (L)	0.565 (0.237)	0.406	-1222.03	**-1222.46**	-1230.78	age	0.043
pPC (R)	0.600 (0.230)	0.355	**-1142.69**	-1137.84	-1146.84	inverse	0.103
dlPFC (L)	0.214 (0.300)	0.169	**-1277.61**	-1276.11	-1272.42	inverse	0.029
dlPFC (R)	0.280 (0.253)	0.428	**-1236.27**	-1234.63	-1231.18	inverse	0.031
vlPFC (L)	0.437 (0.263)	0.170	**-1222.83**	-1219.95	-1231.04	inverse	0.034
vlPFC (R)	0.440 (0.289)	0.291	**-1185.97**	-1185.16	-1189.69	inverse	0.033
dACC (error trials)	-	0.151	**-860.43**	-859.24	-860.21	inverse	0.070
Behavioral variable							
AS percent errors	0.763	0.650	**-249.79**	-236.37	-245.52	inverse	0.202
AS latency (correct)	0.533	0.606	**3198.73**	3204.29	3201.75	inverse	0.140
AS latency (error)	-	0.472	**2989.56**	2990.59	2990.42	inverse	0.000
VGS latency (correct)	0.716	0.564	**3018.84**	3020.59	3013.37	inverse	0.768

‡ All ICC values were statistically significant (2 SD CI did not overlap with zero)
§ Lower (more negative) AIC values are indicative of improved model fit. Note that in cases where AIC suggested selection of the quadratic model, this model was only chosen if the quadratic term was also significant. AIC values are bolded in the adjacent columns
^ Means and standard deviations are listed for brain regions to summarize r values calculated at the voxel level

Table 4: HLM model fitting outcomes for behavioral data

	AS percent errors	AS latency (correct)	AS latency (errors)	VGS latency (correct)
Fixed Effects (Robust SE)				
Model for Intercept, π_{0i}				
INTRCPT, β_{00}	0.283*** (0.016)	485.237 (4.795) ***	353.814 (3.348) ***	364.870 (3.389) ***
SEX‡ , β_{01}			-14.549 (6.688)	
IQ‡ , β_{02}			1.188 (0.308) ***	0.718 (0.288) *
Model for Age term slope, π_{1i}	inverse age	inverse age	inverse age	inverse age
INTRCPT, β_{10}	7.437*** (0.752)	1206.411 (271.808) ***	519.086 (200.997) *	613.915 (186.109) **
SEX‡ , β_{11}				
IQ‡ , $\beta 1_2$				
Random Effects (Variance Components)				
Var. in individual means, var(r_0) = $\hat{\tau}_{00}$	0.02 ****	1792.79 ***	738.88 **	852.692 ***
Var. in slopes, var(r_1) = $\hat{\tau}_{11}$	1.148 +	1765740.456 §	55336.595	634858.519 **
Var. in Age² slopes, var(r_2) = $\hat{\tau}_{22}$				
Var. within individuals, var(e_t) = $\hat{\sigma}^2$	0.013	1215.272	1144.160	712.995
No. of parameters	6	6	8	6
Deviance (FIML)	-261.792	3186.729	2956.481	3006.839
AIC	-249.792	3198.729	2972.481	3018.839
No. Fixed effect	2	2	4	2
No. Random effects	4	4	4	4

*** Significant at $p < 0.001$, ** Significant at $p < 0.01$, * Significant at $p < 0.05$, + Trend, significant at $p < 0.10$
‡ Predictor centered so that 0 reflects the grand mean; in the case of sex, a weight was created for each sex so that the sum of sex codes across all participants was zero

For antisaccade error rates, the variance in the intercept random effect term was significant, and there was a trend for the slope to be significant. Sex and IQ were added to the model to predict the significant intercept variability, but neither term was significant. For correct antisaccade trial latency, slope and intercept varied significantly across the sample, indicating slopes differed across individuals. Sex and IQ did not predict variability. For error trial latency, only intercepts varied, indicating parallel trajectories and this was predicted by both sex and IQ, with males and lower IQ individuals demonstrating the shortest error latencies.

3.2 RELIABILITY OF FMRI DATA

Visual inspection suggested that data points could be fit by continuous statistical functions and would not benefit from being modeled as a spline or discontinuous function. However, visual inspection of the data revealed only a few individuals at the youngest and oldest ages sampled. Since loess lines indicated that these visits may disproportionately skew regression results, and sex differences existed in the individuals samples (all eight- to nine-year old participants were male), only participants between the ages of 9 and 26 were included in subsequent analyses, resulting in a total of 302 visits contributed by 123 people.

Mean test-retest correlations for brain imaging data for each region of interest are listed in Table 3, and indicate moderate test-retest reliabilities, consistent with reliabilities reported for functional neuroimaging data during performance on the antisaccade task in adults (Raemaekers, et al., 2007).

Intra-class coefficients (ICCs,) for each ROI are reported in Table 2. ICCs greater than 0.10 suggest proper within-subject dependency needed for subsequent HLM analyses. Additionally the significance of the ICC value was statistically tested using a Wald test of

. Results indicated significant clustering effects, validating the need to use hierarchical linear modeling to model dependency within individuals. In all regions of interest for correct trial performance, ICCs was significantly different than zero. The ICC estimate for the single region of interest (dACC) for error trials was not significantly different from zero ($Z = 1.804$, $p = 0.071$). After removing points outside of 3 s.d. of the mean percent signal change (n=4) (visual inspection of the raw data indicated these were marked outliers), the ICC for the dACC was significant ($Z = 2.102$, $p = 0.036$). These visits were excluded from subsequent analyses of activity on error trials. As three of these data points were from individuals with at least three visits, removal of these data points were likely to minimize any findings of variability in individual means.

Due to developmental changes in the total number of correct ($B = 1.363$, $t(122) = 7.080$, $p = 0.000$) and error trials ($B = -1.070$, $t(122) = -7.759$, $p = 0.000$), the reliability of signal estimates from single-subject general linear models changed over development. Therefore, instead of calculating an average of all beta values, a weighted average beta estimates was calculated for each ROI that incorporated the standard errors of each voxel estimate as a weight. However, this minimally changed ICCs (mean = 0.244, SD = 0.086, range: [0.112, 0.335]), so HLM analyses proceeded with unweighted average betas.

3.3 MEAN GROWTH CURVES FOR BRAIN FUNCTION

Table 3 lists AIC values used to guide the selection of unconditional models characterizing the shape of growth and the proportion of variance explained by the age term in this model. Table 5 lists estimates of fixed effects (intercept, slope), random effects (variance in intercepts, slopes, and level one variance), model fit indices (deviance, AIC), and the significance of all these terms (level one variance excepted) for all final brain activation models. Mean growth curves for percent signal change in error monitoring regions, one executive control region, and motor response control regions are shown in Figure 5. A schematic summarizing patterns of significant growth curve findings (both mean growth curves and variability) is depicted in Figure 6.

Table 5: HLM model fitting outcomes for *a priori* regions of interest

(Table continued on the next 2 pgs)

	dlPFC (L)	dlPFC (R)	vlPFC (L)	vlPFC (R)	dACC (errors)
Fixed Effects (Robust SE)					
Model for Intercept, π0i					
INTRCPT, β00	-0.0083 (0.0018) ***	0.0048 (0.0027) +	0.0048 (0.0024)*	0.0285 (0.0024) ***	0.0517 (0.0041) ***
SEX‡ , β01				0.0030 (0.0048)	
IQ‡ , β02	-0.0004 (0.0002) *				0.0005 (0.0003) +
SEX*IQ‡ , β03					
Model for Age term slope, π1i	inverse age	inverse age	inverse age	inverse age	inverse age
INTRCPT, β10	0.0502 (0.1395)	0.3154 (0.1495) *	0.0980 (0.1220)	0.1935 (0.1557)	-0.7274 (0.1883) ***
SEX‡ , β11				-0.8186 (0.3113) *	
IQ‡ , β12					
SEX*IQ‡ , β13					
Model for Age² slope, π2i					
INTRCPT, β20					
Random Effects (Variance Components)					
Var. in individual means, var(r_0) = $\hat{\tau}_{00}$	0.00008 +	0.00044 ***	0.00023 ***	0.00027 **	0.00059 +
Var. in slopes, var(r_1) = $\hat{\tau}_{11}$	0.26576	0.46675	0.22957 +	0.13754 *	0.44370
Var. in Age² slopes, var(r_2) = $\hat{\tau}_{22}$					
Var. within individuals, var(e_t) = $\hat{\sigma}^2$	0.00068	0.00062	0.00085	0.00090	0.00251
No. of parameters	7	6	6	8	7
Deviance (FIML)	-1294.426	-1248.269	-1222.828	-1190.973	-862.987
AIC	-1280.426	-1236.269	-1210.828	-1174.973	-848.987
No. Fixed effect	3	2	2	4	3
No. Random effects	4	4	4	4	4

*** Significant at p < 0.001, ** Significant at p < 0.01, * Significant at p < 0.05, + Trend, significant at p < 0.10

‡ Predictor centered so that 0 reflects the grand mean; in the cae of sex, a weight was created for each sex so that the sum of all codes across all participants was zero

Table 5: (ctd) HLM model fitting outcomes for *a priori* regions of interest

	SEF	preSMA	FEF (L)	FEF (R)
Fixed Effects (Robust SE)				
Model for Intercept, π0i				
INTRCPT, β00	0.0501 (0.0034)***	0.0636 (0.0035) ***	0.0467 (0.0032) ***	0.0642 (0.0027) ***
SEX‡ , β01	-0.0052 (0.0068)	0.0078 (0.0071)		0.0001 (0.0055)
IQ‡ , β02				
Model for Age term slope, π1i	age	inverse age	age	inverse age
INTRCPT, β10	0.0001 (0.0008)	0.1034 (0.2456)	-0.0002 (0.0006)	0.2389 (0.1937)
SEX‡ , β11	0.0043 (0.0015) **	-1.0896 (0.4913) *		-1.011 (0.3875) *
IQ‡ , β12				
Model for Age² slope, π2i				
INTRCPT, β20			0.0003 (0.0001) *	
Random Effects (Variance Components)				
Var. in individual means, var(r_0) = $\hat{\tau}_{00}$	0.00074 ***	0.00064 ***	0.00055 ***	0.00030 **
Var. in slopes, var(r_1) = $\hat{\tau}_{11}$	0.00000 *	1.57311 **	0.00001	0.94294 *
Var. in Age² slopes, var(r_2) = $\hat{\tau}_{22}$			0.00000	
Var. within individuals, var(e_t) = $\hat{\sigma}^2$	0.00152	0.00143	0.00054	0.00103
No. of parameters	8	8	10	8
Deviance (FIML)	-1013.671	-1007.677	-1264.205	-1132.213
AIC	-997.671	-991.677	-1244.205	-1116.213
No. Fixed effects	4	4	3	4
No. Random effects	4	4	7	4

*** Significant at p < 0.001, ** Significant at p < 0.01, * Significant at p < 0.05, + Trend, significant at p < 0.10

‡ Predictor centered so that 0 reflects the grand mean; in the cae of sex, a weight was created for each sex so that the sum of all codes across all participants was zero

Table 5: (ctd) HLM model fitting outcomes for *a priori* regions of interest

	putamen (L)	putamen (R)	pPC (L)	pPC (R)
Fixed Effects (Robust SE)				
Model for Intercept, π0i				
INTRCPT, β00	0.0417 (0.0022) ***	0.0321 (0.0021) ***	0.0516 (0.0027) ***	0.0533 (0.0031) ***
SEX‡ , β01				
IQ‡ , β02			-0.0003 (0.0002)	-0.0006 (0.0002) *
Model for Age term slope, π1i	age	age	age	inverse age
INTRCPT, β10	0.0004 (0.0005)	-0.0001 (0.0005)	-0.0003 (0.0007)	0.1137 (0.1889)
SEX‡ , β11				
IQ‡ , β12			0.0001 (0.00005) +	
Model for Age² slope, π2i				
INTRCPT, β20				
Random Effects (Variance Components)				
Var. in individual means, var(r_0) = $\hat{\tau}_{00}$	0.00023 *	0.00020 *	0.00044 ***	0.00057 ***
Var. in slopes, var(r_1) = $\hat{\tau}_{11}$	0.00000 *	0.00000 +	0.00001 **	0.89928 ***
Var. in Age² slopes, var(r_2) = $\hat{\tau}_{22}$				
Var. within individuals, var(e_t) = $\hat{\sigma}^2$	0.00086	0.00074	0.00068	0.00086
No. of parameters	6	6	8	7
Deviance (FIML)	-1214.854	-1258.914	-1226.630	-1147.884
AIC	-1202.854	-1246.914	-1210.630	-1133.884
No. Fixed effect	2	2	4	3
No. Random effects	4	4	4	4

*** Significant at p < 0.001, ** Significant at p < 0.01, * Significant at p < 0.05, + Trend, significant at p < 0.10

‡ Predictor centered so that 0 reflects the grand mean; in the cae of sex, a weight was created for each sex so that the sum of all codes across all participants was zero

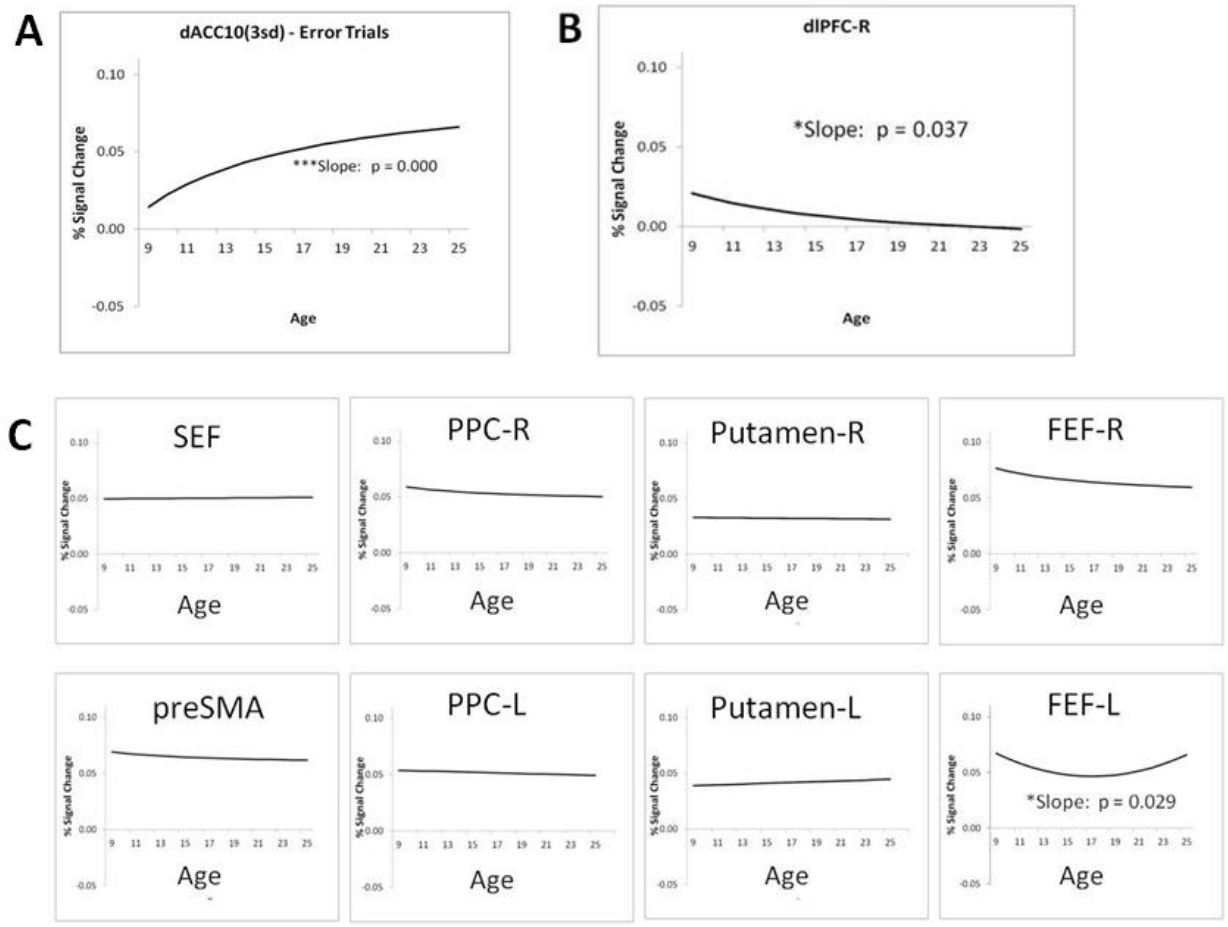

Figure 5: Mean growth curves depicting percent signal change in regions of interest

(A) Percent signal change increases significantly with age in a region associated with error monitoring –the dorsal anterior cingulate cortex (dACC) during error trials. (B) Among executive control regions during correct trials, only the right dorsolateral prefrontal cortex (dlPFC) demonstrates significant changes in activity with age. (C) Mean growth curve for all motor response control regions during correct trials. With one exception, these regions are engaged consistently throughout development.

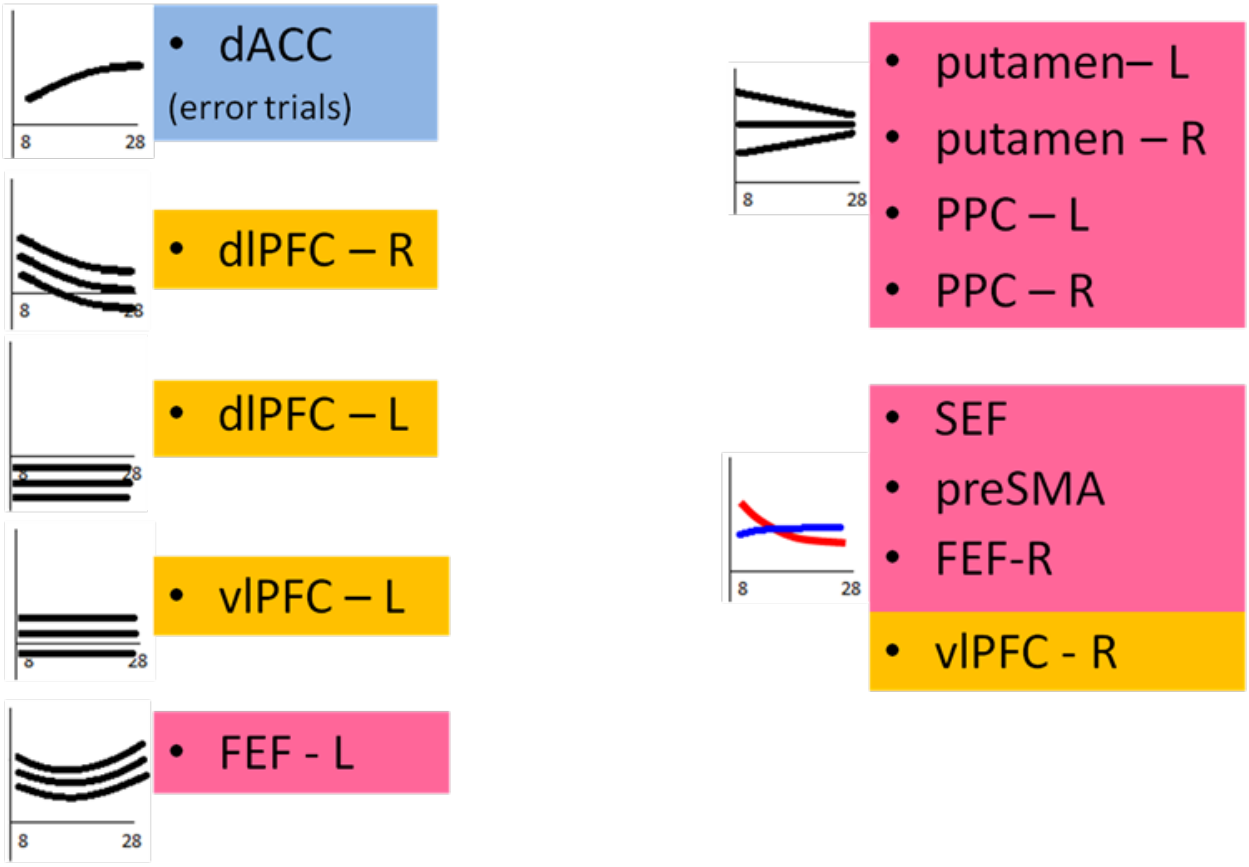

Figure 6: Schematic summariing patterns among growth curve findings across all regions of interest

Blue highlighting codes the error monitoring region, orange highlighting the executive control regions, and pink the motor response control regions. Each stylized graph conveys the best fitting model of developmental change (inverse age, age, or quadratic age), whether growth curve means are significantly different from the zero at the mean age of the sample (16.7 years), significance of the growth curve mean slope, significance of variability in intercepts, and significance of variability in slopes. Red and blue lines indicate models for females and males respectively in the cases where sex predicts variability in slopes.

Brain function in the dACC was best fit by an inverse function. A significant negative slope and a significant positive intercept (i.e., activity at the mean age of the sample, 16.7 years as well as in a regression coded at age 11) indicate activity in this region became more positive with age.

In the right dlPFC, a significant positive slope of inverse age indicated magnitudes of activity became less positive with age. While the intercept term for a model centered at age 11 was significantly different from zero ($B = 0.015$, $t(122) = 3.346$, $p = 0.001$), the intercept at the mean age of the sample was only a trend ($B = 0.005$, $t(122) = 1.800$, $p = 0.072$), and the intercept at age 23 was not significant ($B = -0.000$, $t(122) = -0.074$, $p = 0.942$), indicating magnitudes of activity in this ROI approach zero in adulthood. Given evidence from other studies indicating that error monitoring may signal dlPFC activity, we investigated whether error-related indices were related to dlPFC signal estimates on correct trials. The number of error trials did not predict right dlPFPC activity after accounting for the age term (inverse age), $t(122) = -1.635$, $p = 0.104$. However, dACC activity during error trials was positively associated with right dlPFC activity during correct trials, $B = 0.1175$, $t(120) = 3.123$, $p = 0.003$.

Age effects in the left dlPFC, left vlPFC, and right vlPFC were not significant, but different patterns of intercept and slope findings distinguish developmental patterns in these three regions. In the left dlPFC, a positive intercept indicated that activation in this region was positive throughout the sampled age range. In the left vlPFC, age effects were not significant, and a non-significant intercept indicated that activation in this region was minimal throughout development.

In the motor response control regions investigated (bilateral putamen, bilateral pPC, bilateral FEF, SEF, preSMA), all but one (left FEF), failed to show group mean developmental

change in magnitudes of brain activity. Intercepts in the first seven regions were significant and positive, indicating group mean activation in these regions was positive throughout. An inverse function best fit the data in the right pPC, right FEF, and pre-SMA, while a linear function best fit data in the putamen bilaterally, left pPC, and SEF. In the left FEF, AIC indices indicated the quadratic model best fit the data and the age squared term was significant. Intercept at mean age of the sample was significant, and a positive quadratic slope term indicated that magnitudes were lowest, but still significantly positive in this region during adolescence.

3.4 VARIABILITY IN GROWTH CURVES FOR BRAIN FUNCTION

For dACC activity during error trials, there was a trend for significant variability in intercepts of individual regressions, and even though IQ explained some of this variability at a trend level, there was still remaining trend level variability in intercepts. There was no significant variability in slopes.

In both bilateral dlPFC and vlPFC, variance at the intercept but not the slope was significant, indicating variability across individuals is manifested as parallel slopes. In the left dlPFC, variability in intercepts was significantly predicted by IQ, as higher-IQ individuals evidenced lower magnitudes of activity throughout development. The effect size for this predictor was 0.111 (pseudo-R^2 for τ_{00}), and variability in the intercept was only a trend after accounting for IQ. In the left vlPFC, intercepts but not slopes varied significantly, indicating that some individuals use this region to a small degree throughout the sampled age range, some do not, and others show small deactivations in this region. Figure 7 depicts the variability in intercepts in these three executive control regions.

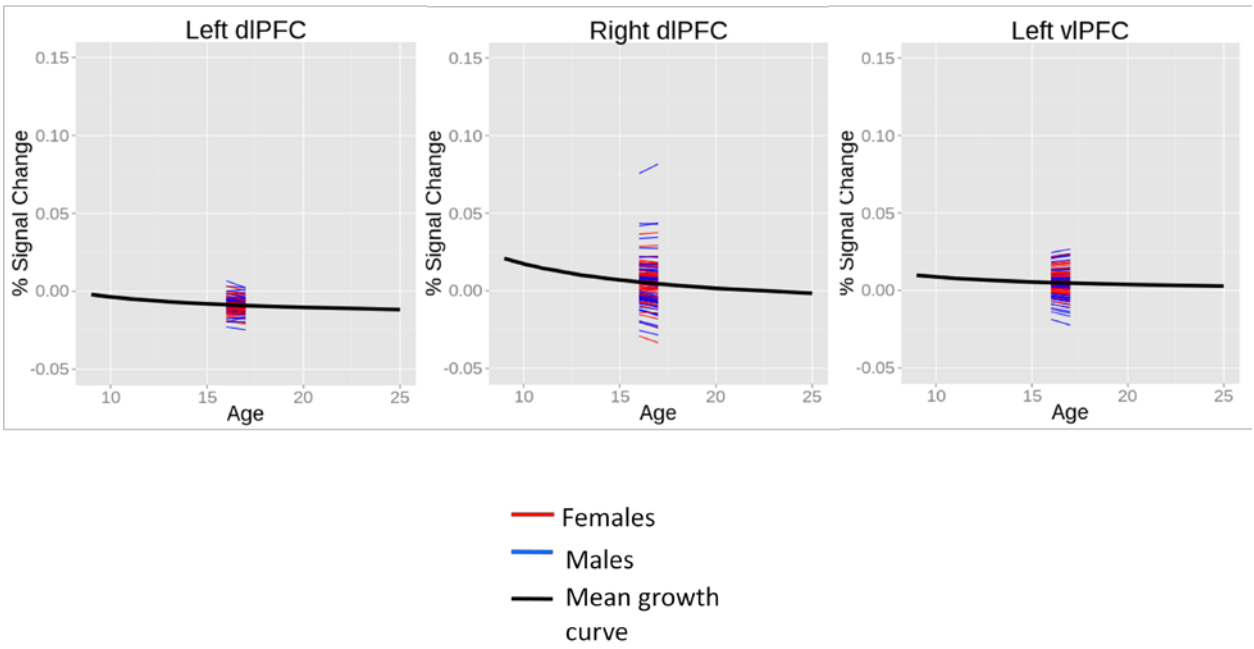

Figure 7: Parallel trajectories in executive control regions

In the right dlPFC, left dlPFC, left vlPFC, model-fitting indicates significant variability in intercepts but not slopes. This pattern is illustrated in the following figure, where the each dashed line depicts a small component of each individual's estimated trajectory in order to convey the range of parallel trajectories. Red lines denote female participants and blue lines denote male participants. The black line depicts the mean estimated growth curve across all individuals.

Lastly, despite the lack of main effects of age in the right vlPFC, findings revealed sex differences in trajectories. Trajectories varied in both intercepts and slopes, and findings revealed that females showed significant age-related declines (B = 0.568, t(120) = 2.801, p = 0.006), while males did not (B = -0.211, t(120) = -0.890, p = 0.375). After accounting for sex, significant variability in intercepts and slopes remained indicating that processes other than sex are also contributing to variability.

In all but one motor response control region, both intercepts and slopes varied significantly. A number of regions showed the same developmental pattern of declining variability with age, including the left and right putamen, left pPC, and SEF. This constituted the majority of motor response control regions whose variability in slopes was not explained by sex (with the exception of right pPC). This pattern is clear when estimated individual regression lines are plotted, as shown in Figure 8. This is further supported by data indicating τ_{00} values (intercept variance) in all these regions declined from ages 11, 16.7, and 23, and that correlations between intercept and slope are highly negative for regions where the age term was modeled and highly positive for regions where the inverse age term was modeled (left putamen: r = -0.937, right putamen: r = -0.982, left pPC: r = -0.295, SEF: r = 0.913). In the left FEF, intercepts but not slopes varied significantly between groups, indicating that all individuals follow the same U-shaped pathway.

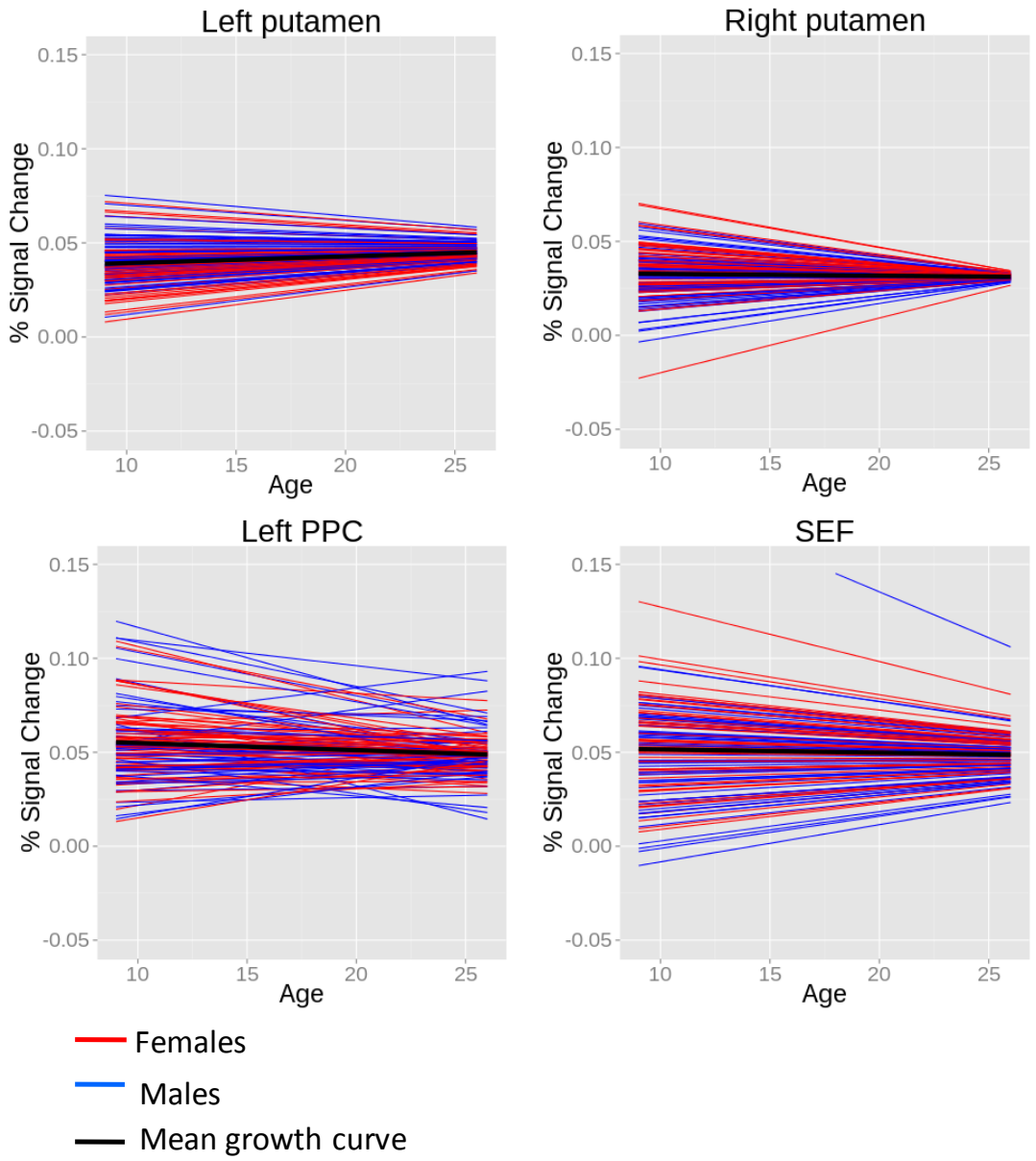

Figure 8: Equifinality in motor response control regions

Variability declines with age in a subset of motor response control regions, including the bilateral putamen, left pPC, and SEF. Red lines denote individual estimated growth curves for female participants and blue lines for male participants. The black line depicts the mean estimated growth curves across all individuals.

In both right and left putamen and pPC, neither IQ nor sex predicted variability in either intercept or slope. In the right FEF, SEF, and preSMA, sex but not IQ predicted variability in slopes, though significant variability remained after accounting for sex; neither sex nor IQ predicted variability in intercepts for these three regions. Planned follow-up simple effects analyses revealed females but not males showed significant developmental declines in all three regions, though trends were present for males in some regions (females: right FEF, B = 0.725, t = 3.139, p = 0.003; SEF, B = -0.002, t = -1.922, p = 0.057; preSMA, B = 0.602, t = 1.883, p = 0.062; males: right FEF, B = -0.270, t = -0.876, p = 0.383; SEF, B = 0.002, t = 1.880, p = 0.062; preSMA, B = -0.415, t = -1.094, p = 0.277). While there were no sex differences in intercepts at the mean age of the sample, analyses with predictors centered at age 11 indicated that females showed higher levels of activity in childhood in the SEF (B = -0.030, t = -2.520, p = 0.013) and right FEF (B = -0.031, t = -2.556, p = 0.012) and a trend for higher activity in the pre-SMA (B = -0.026, t = -1.666, p = 0.098). Regressions centered at age 23 indicated females showed trend levels of lower activity in the SEF (B = 0.022, t = 1.978, p = 0.050) and right FEF (B = 0.017, t = 1.824, p = 0.070), and significantly lower activity in the preSMA (B = 0.026, t = 2.207, p = 0.029). Taken together, these three regions are characterized by a pattern in which a negatively sloping female trajectory intersects with a stable male trajectory in adolescence and then continues to decline in the late adolescent/early adult years. Sex differences in trajectories for this region and the right vlPFC described earlier are depicted in Figure 9.

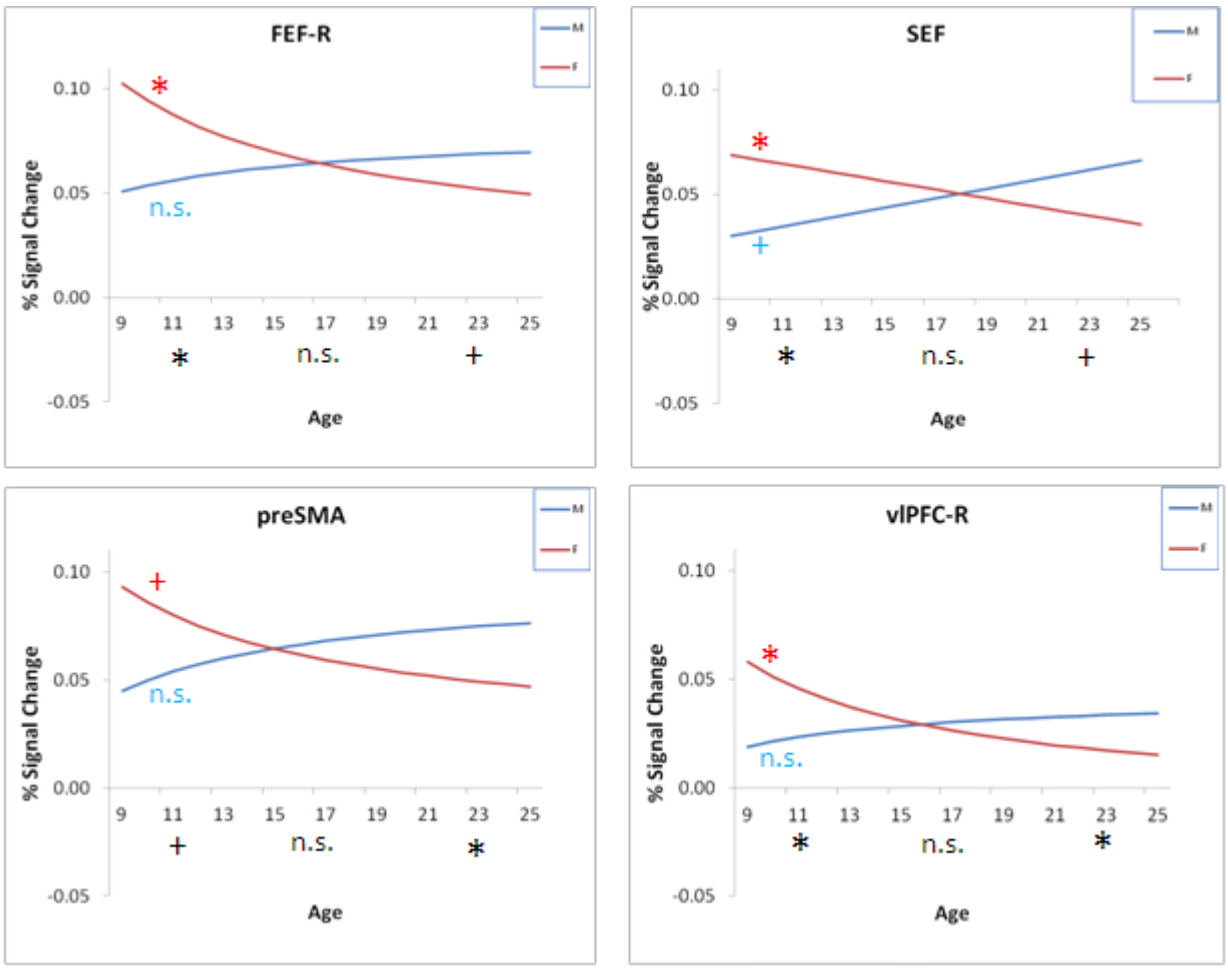

Figure 9: Sex effects

Significant sex effects are present in a set of regions, mostly those involved in motor response control (indicated by pink in the upper left corner; orange denotes executive control regions). Growth curves for each sex and symbols indicating significance are in red for females and blue for males. Black symbols indicate significance of sex differences at ages 11 and 23 years, arbitrarily chosen time points that were used probe simple effects of sex in childhood and adulthood (*** significant at $p < 0.001$, ** significant at $p < 0.01$, * significant at $p < 0.05$, + trend, significant at $p < 0.10$).

3.5 BRAIN-BEHAVIOR RELATIONSHIPS

To explore whether brain activity was associated with behavioral performance, antisaccade performance was regressed on magnitudes of brain activity for each region that showed developmental change in brain function: dACC during error trials and right dlPFC, left FEF, and bilateral visual cortical activity during correct trials. Two regressions were run for each region to account for the two metrics of behavioral performance: antisaccade error rates and latencies on correct trials. Each regression included a centered inverse age term as a covariate. Results indicated a significant negative association between dACC activity and antisaccade error rates ($B = -0.674$, $t = -4.735$, $p = 0.000$), with increased activity associated with a decline in error rates, as depicted in Figure 10. No significant relationships were found in right dlPFC ($B = -0.354$, $t = -1.276$, $p = 0.205$) or left FEF ($B = -0.014$, $t = -0.041$, $p = 0.967$). In addition, there was no significant relationship between any variable and antisaccade latencies on correct trials (dACC: $t(120) = -0.999$, $p = 0.320$; right dlPFC: $t(122) = -0.396$, $p = 0.692$; left FEF: $t(122) = 0.376$, $p = 0.707$; visual cortex: $t(122) = -1.301$, $p = 0.196$).

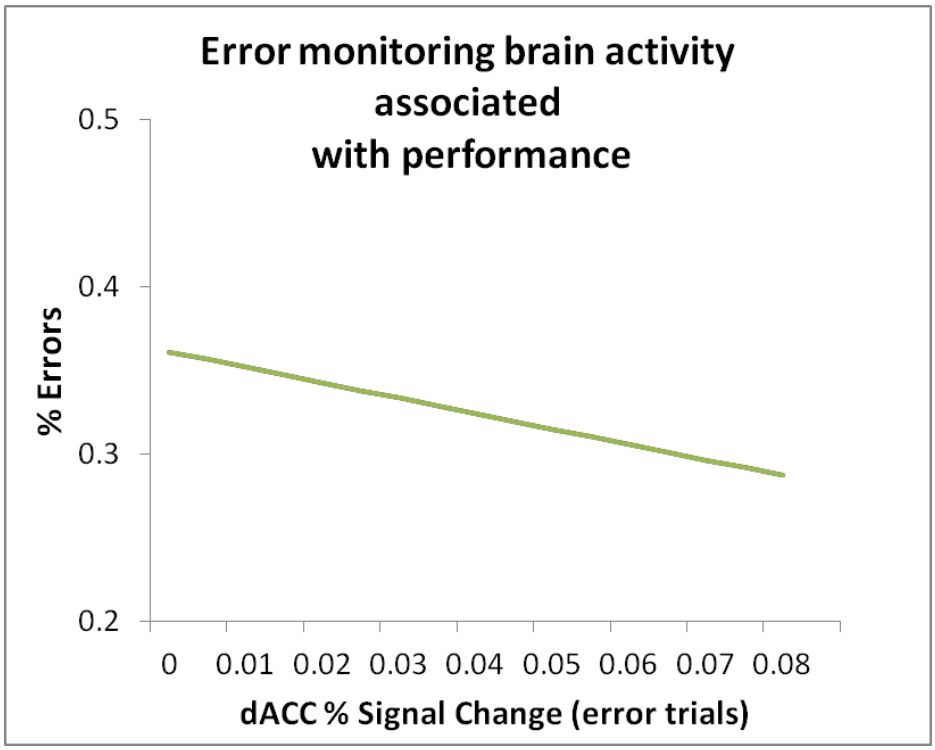

Figure 10: Relationship between brain activity and performance in an error monitoring region

Increased activity in the dACC during error trials is associated with better overall task performance, as indicated by lower antisaccade error rates.

Both behavior (error rates) and brain function in the dlPFC (left and right), left vlPFC, and left FEF showed significant inter-individual variability in intercepts but not slopes (parallel trajectories), so we investigated whether the individuals who performed best on the task throughout development were also the individuals that showed the least (or most) brain activity in these regions. This was achieved by using the centered intercept term (the Empirical Bayes coefficient) for each individual's regression of antisaccade error rates on the inverse of age; this value was then used as a level-2 predictor of intercept for each of the aforementioned regions of interest to investigate whether it significantly predicted intercept variability. Results indicated this variable indicative of relative behavioral performance did not predict brain function (right dlPFC: $t(121) = -0.729$, $p = 0.467$; left dlPFC: $t(121) = -0.727$, $p = 0.468$; left vlPFC: $t(121) = -0.191$, $p = 0.849$; left FEF: $t(121) = -0.251$, $p = 0.803$) suggesting that trait-like intrasubject variability in task performance is not associated with variability in brain function supporting correct responses.

4.0 DISCUSSION

The ability to voluntarily suppress a reflexive response in favor of a planned goal-directed response, is central to cognitive control of behavior and has been shown to improve through adolescence in tandem with changes in associated brain function. The aim of this study was to extend prior cross-sectional and two time-point studies functional neuroimaging studies of inhibitory control, with the goal to characterize normative growth curves of brain activity more sensitively, to explore variability in these trajectories, and to examine the role of sex and IQ in predicting such variability. By examining development in a priori regions of interest and organizing them into categories according to functional subcomponents of function needed for inhibitory control (error monitoring, executive control, and motor response control), we sought to highlight patterns within and between functional circuitries that can yield insights into patterns of maturation.

Behavioral results dovetail with cross-sectional findings indicating protracted, nonlinear, asymptotic patterns of development that varied across individuals, but were not explained by sex or IQ. Mean growth curves for brain activity revealed no developmental change in motor response control regions but developmental changes in dlPFC (executive control) and dACC (error monitoring). An examination of variability revealed that in most brain regions, individuals differed in the degree to which they recruited each brain region, and these patterns tended to be consistent within regions supporting similar functions. Motor response control regions showed

varied slopes across individuals, with most regions showing declines in variability with age. Executive control regions showed parallel trajectories over development reflective of preserved rank-order stability. Variability was least in the error monitoring region, with only a trend for parallel slopes. Importantly, key motor response control regions and an executive control region specific for inhibition showed sex differences in trajectories. Though on average (across the full sample) there was no developmental change in these regions, females but not males showed developmental declines in activity, resulting in greater female activity in late childhood.

4.1 DEVELOPMENTAL IMPROVEMENTS IN COGNITIVE CONTROL

This is also the only study, to our knowledge, to investigate the development of antisaccade performance with a longitudinal design, and our findings converge with existing cross-sectional behavioral studies showing age-related improvements in performance that continue through adolescence (Fischer, et al., 1997; Fukushima, et al., 2000; C. Klein, 2001; C. Klein & Foerster, 2001; Luna, Garver, Urban, Lazar, & Sweeney, 2004; Munoz, et al., 1998; Nieuwenhuis, et al., 1999; Ordaz, et al., 2010; Romine & Reynolds, 2005). Consistent with these studies, we found that the inverse function was the most optimal fit, indicating a rapid improvement from childhood through adolescence that subsequently stabilizes into adulthood.

Behavioral growth curves for error rates varied significantly across individuals, with variability in intercepts but not slopes indicating that individual differences are manifested as parallel trajectories. Such a pattern indicates that inhibitory control performance is a stable aptitude. That is, participants who demonstrate highest error rates in childhood will continue to demonstrate the worst inhibitory control throughout adolescence and early adulthood. Further,

this variability was not explained by sex or IQ. The lack of sex differences in performance fits with existing cross-sectional studies that consistently indicate no sex differences in antisaccade performance in samples of youth (Luna, et al., 2004; Ross, Radant, Young, & Hommer, 1994). Similarly, most studies using other metrics of inhibitory control such as the Simon task and Stroop task similarly do not find sex differences (Christakou et al., 2009; Daniel, Pelotte, & Lewis, 2000; R. Marsh, et al., 2006; Peterson et al., 2002), though exceptions exist (V. Anderson, 2001; V. A. Anderson, Anderson, Northam, Jacobs, & Catroppa, 2001). This study had the potential to reveal more difficult to detect age by sex interactions, but our findings suggest that these do not exist for antisaccade performance. That IQ does not modulate trajectories provides additional evidence in a conflicted literature where one study indicates a relationship exists between IQ scores and antisaccade performance over development (Evdokimidis, et al., 2002), but another does not (Michel & Anderson, 2009). This suggests that individual differences in processing speed or general cognitive processes do not influence the capacity to inhibit during development, nor does enhanced IQ seem to facilitate rapid development of inhibitory function, at least starting in late childhood.

4.2 MEAN GROWTH CURVES

4.2.1 Enhanced error monitoring supports developmental improvements in performance

Age related improvements in inhibitory control showing decelerating nonlinear growth could either be supported by (1) a gradual increase in the number of brain regions recruited to perform the task within key circuitries or (2) changes in a key brain region with co-occuring, similarly

nonlinear patterns of maturation (Kail & Ferrer, 2007). The first explanation is unlikely, as a comparable number (if not fewer due to minimized dlPFC use with age) of regions of interest were recruited over the course of development – though voxelwise analyses are necessary to draw a definitive conclusion. Rather, results support the latter explanation. This is based on evidence that dACC activity is uniquely correlated with performance, shows a nonlinear pattern of developmental change that parallels the decelerating rate of improvement in behavioral performance, and continues to mature throughout adolescence. These characteristics are unique to the dACC, distinguishing it from the other two regions of interest to demonstrate developmental change (right dlPFC and left FEF). Importantly, the finding that dACC activity increases with age in parallel with age-related declines in error rates fits with the direction of the brain-behavior association showing that *higher* levels of dACC activity during error trials are associated with decreased error rates (after accounting for variance explained by age). The dACC functions to monitor performance and its activity results in higher rates of correct performance (Carter, et al., 1999), making it a plausible candidate for supporting behavioral improvements in performance.

fMRI studies indicate that the dACC is consistently recruited during error trials preceding corrected performance (Menon, et al., 2001; Polli, et al., 2005) and electrophysiological studies suggest that it is the primary source of an error-related response occurring 80-180 ms following errors (Gehring, Goss, Coles, Meyer, & Donchin, 1993). While it has been debated whether the dACC is specifically involved in error monitoring per se (Garavan, Ross, Kaufman, & Stein, 2003; Garavan, Ross, Murphy, Roche, & Stein, 2002; Taylor, Stern, & Gehring, 2007) or monitoring of conflicting/incompatible responses (Botvinick, Nystrom, Fissell, Carter, & Cohen, 1999; Braver, Barch, Gray, Molfese, & Snyder, 2001; Carter, et al., 1999; Carter, et al., 1998),

the dACC is undoubtedly crucial for adjusting behavior following an unexpected response. In this mixed block/event-related task, antisaccade trials were presented in blocks, meaning that variability in task demands (e.g. set switching) did not require participants to regularly alter expectations to successfully complete the task. Rather, the only expected response was an antisaccade, and therefore the only unplanned response to be detected by the dACC was an erroneous reflexive saccade response. Because we examined brain activity during only the trials where errors were immediately corrected, we know that brain activity reflected an awareness of the error (hereafter we will refer to this as error monitoring). There is also some debate as to how the dACC monitors for unexpected responses - whether this is facilitated by general processes of arousal, by reactive detection of errors, or proactive evaluative cognitive functions (e.g., detecting situations where errors are likely to occur)(Carter, et al., 1998), or some combination of these processes (Paus, 2001). What is important is that dACC activity serves to facilitate improved performance on subsequent trials. Indeed, studies have shown that increase dACC activity predicts increases in dlPFC activity and associated response adjustments on the subsequent trial (Carter, et al., 1999; Kerns, 2006; Ladouceur, Dahl, & Carter, 2007).

Previous cross-sectional developmental fMRI studies that have also examined activity in the dACC during error trials have similarly reported increases with age (Rubia, et al., 2007; Velanova, et al., 2008). A study by Rubia et al. (2007) showed that adults showed greater dACC activity on error trials than a combined child/adolescent group and demonstrated a positive correlation between age and magnitudes of activity (Rubia, et al., 2007). Velanova et al. (2008), using the cross-sectional data from the first wave of this study, probed potentially more complex patterns of growth by dividing participants into three age groups to reveal that children and adolescents did not differ in activity levels, and both showed less activity than adults. The Rubia

et al. (2007) study was only able to identify rectilinear patterns of growth and Velanova et al. (2008) findings suggested either a shift from adolescence to adulthood or an accelerating pattern of change. With its substantially increased power and longitudinal design, this study was able to significantly detect nonlinear patterns of development, but results indicated decelerated growth rather than an accelerated pattern implied by Velanova et al. (2008). These findings are therefore novel because they indicate that the most rapid developmental changes in the dACC occur during the late childhood/early adolescent years rather than later in life as had previously been suggested. Early acceleration could be related to the stage of development when multiple distributed cortical regions are being connected (via a prefrontally-guided network) while late accelerations would imply processes of refinements that occur after prefrontally guided networks have been established (Hwang, et al., 2010; Luna, Padmanabhan, & O'Hearn, 2010). Our results suggest that the greatest growth is occurring during this period of the establishment of executive prefrontal connectivity. Importantly, our findings converge with a large developmental ERP study (n = 124) of error-related negativities during a different inhibitory control to indicate a nonlinear pattern of growth (Davies, Segalowitz, & Gavin, 2004) as well as a smaller group-based study indicating marked developmental change in the early adolescent years (Ladouceur, et al., 2007). These results depicting a relatively protracted development of the dACC suggest that even though the capacity to monitor performance and use this to inform subsequent behavior is available by early adolescence, this capacity continues to mature through early adulthood.

4.2.2 Right dlPFC may scaffold developmental change

One remarkable finding from our examination of activity supporting performance on correct trials is the constancy of activity across all the regions of interest examined. The motor

response control and most executive control brain regions used by the oldest participants in our sample were also used to the same degree by the youngest participants in our sample, implying a foundational network that supports access to the ability to generate an executive act of voluntarily inhibiting a response. The right dlPFC, however, showed changes with age as magnitudes declined at a decelerating rate from childhood to adolescence, at which point activity levels began to level off at adult levels, in which the dlPFC is minimally recruited, if at all. This parallels findings that functional networks are in place by adolescence, but are subsequently refined into adulthood (Boorman, O'Shea, Sebastian, Rushworth, & Johansen-Berg, 2007; Fair et al., 2009; Fair et al., 2007; Hwang, et al., 2010; Olesen, Nagy, Westerberg, & Klingberg, 2003). The dlPFC shows increased recruitment with increasing cognitive loads (Kirschen, Chen, Schraedley-Desmond, & Desmond, 2005), so less reliance on this region may reflect greater ease in engaging effective inhibitory control as the rest of the brain works in a collaborative fashion to support cognitive function. Instead, the role of the dlPFC may be to scaffold change when tasks are perceived as difficult and when first learning a new task. Function may subsequently be delegated to more specialized regions or networks as more experience with the task is acquired. This is supported by evidence that the dlPFC seems to be involved in general executive control processes rather than specific ones (e.g., inhibition, working memory)(Chaddock et al., 2012; Chein & Schneider, 2005; Jansma, Ramsey, Slagter, & Kahn, 2001). Further, experimental manipulations via training studies have shown that training in general skills that support successful completion of complex tasks (i.e., attend to important task features, manage task priorities) produce decreases in right dlPFC activation (Jolles & Crone, 2012; Kerns, 2006; Lee et al., 2012; Prakash et al., 2012). The development of inhibitory control may therefore progress

from a reliance upon prefrontal systems to scaffold challenging tasks to a more optimized network-wide processing that relieves reliance on more executive regions.

In light of evidence that error trials elicit the dACC to signal the right dlPFC to increase activity on the next trial decreasing overall error rates (Cavanagh, Cohen, & Allen, 2009; Kerns, 2006; Kerns et al., 2004), it stands to reason that developmental declines in dlPFC activity on correct trials may simply reflect developmental declines in the number of corrected error trials. Fewer errors may be associated with a fewer "requests" to the dlPFC for assistance. However, the number of error trials was not associated with levels of dlPFC performance. Intriguingly, dACC activity on error trials was positively associated with right dlPFC activity across all correct trials, providing preliminary evidence that in childhood and adolescence, the dlPFC may enhance its activity as a result of error detected by the dACC. This fits with the contention that dlPFC is generally recruited when faltering or immature function needs to be buttressed.

4.3 PATTERNS OF VARIABILITY ARE CONSISTENT WITHIN BRAIN CIRCUITRIES

Studies examining variability in developmental trajectories of brain function are exploratory as this has not yet been studied with regard to inhibitory control. Overall, our data indicate that patterns of variability are consistent within functional circuitries, with error monitoring regions showing minimal variability, most executive control regions showing parallel trajectories across individuals, and motor response control regions evidencing declining variability with age. That patterns of developmental change are similar within known functional circuitries may indicate

that regions within the same functional circuitries may mature according to similar developmental mechanisms.

4.3.1 Least variability in error monitoring function

The error monitoring region is the most developmentally invariant, the only region not to demonstrate statistically significant variability in either intercepts or slopes. In light of evidence for mean patterns of developmental increases in brain activity and the crucial role of brain activity in this region for performance, successful task performance may only occur if error-monitoring activity is modulated to fall within a narrow, developmentally specific range. That is, the lack of variability in the dACC during errors may reflect its central role in supporting developmental improvements in inhibitory control.

4.3.2 Parallel trajectories in most executive control regions

In most executive control regions of interest (bilateral dlPFC and left vlPFC), trajectories varied significantly in their intercepts but not slopes, suggesting interindividual variability is manifested as parallel trajectories. The implication of this finding is that rank order in percent signal change is preserved across individuals – the participants who show the greatest activation during correct trials in executive control regions (relative to other participants) during childhood also evidence the highest levels of activation in adolescence and adulthood. This pattern suggests that the underlying factors supporting this variability are traits, produce their effects by late childhood, and/or are variables that change on similar developmental timetables across all participants. When considering what might explain this variability, we considered behavioral performance

(error rates), because it also demonstrated this trait-like variability. That is, we explored whether the individuals who perform best on the task are also the ones who show the least (or potentially, most) activity on this task? Results indicating no correspondence between measures indicate that individual variability in executive control-related brain activity and behavior are not related. Thus, even though evidence suggests that dlPFC is used less in *situations* where performance is better across development, traits associated with strength of performance is not associated with more or less dlPFC usage. That is, the dlPFC may be "tuned" to the individual. Importantly, the better performers are not necessarily more "efficient" (use less brain activity) or use this network to a lesser or greater extent when they can successfully demonstrate inhibitory control.

Thus the question remains – what contributes to this interindividual variability in brain activity, and what are its implications? IQ and sex did not predict variability in intercepts for these executive control regions. Genetic variability may be a contributing factor. A two-time point longitudinal study of brain activity supporting working memory has shown that polymorphisms of the gene coding for the catechol-*O*-methyltransferase enzyme (COMT) was associated with different levels of lateral prefrontal cortex signal at different points in development (Dumontheil, et al., 2011), but was unable to probe whether this modulated the intercepts or slopes of individual differences. This suggests that dopamine levels that are known to affect cognitive processes could modulate overall levels of activity in brain regions during this period of development. Further, individual differences in environmental factors that tend to remain stable over the lifetime, such as levels of cognitive stimulation and socioeconomic status, are indices of the resources available to a developing brain. Variation in socioeconomic status has been shown to differentiate patterns of activation in frontostriatal regions in adults (Gianaros et al., 2011) and may similarly predict variability in brain activity among children.

4.3.3 Developmental changes in motor response control regions converge over development

Interestingly, a number of motor response control regions showed a consistent pattern of decreasing variability in activation levels with age. Such a pattern indicates that maturation reflects a stabilizing process of convergence. Early in development individuals begin at different levels but they all arrive at the same level of processing in adulthood. Interestingly our results show that even though all individuals show positive levels of activity with development, some individuals follow trajectories with negative slopes while other follow positively sloped ones. These findings underscore that what occurs over development is a convergence upon the mature "destination", which requires some individuals to increase and others to decrease activity levels to get to this point. This is distinct from a pattern where everyone needs to change activity in the same direction (e.g., reduce) but to varying degrees. Our findings imply that the pathway to development differs across individuals, but maturity is characterized by minimal variability across individuals as optimal processes are accessed. These results can help to guide future studies by highlighting that plausible developmental factors for explaining variability in motor response control regions should be expected to produce greater amounts of variability in childhood than in adulthood. Such factors would be characterized by their capacity to minimize variability across individuals, but also to increase activity in some individuals over development while decreasing activity in others. It warrants note that some of the motor response control regions did not show a unidirectional change in variability with development (preSMA, right FEF, right pPC), but much of this pattern was shaped by sex differences in trajectories that are described in the following section.

4.4 SEX DIFFERENCES IN GROWTH CURVES

Despite comparable task performance at all ages, this study revealed sex-specific patterns of developmental change in brain function. These were observed in the right vlPFC, an executive control region, and three motor response control regions, SEF, preSMA, and right FEF. Males did not change in levels of activity within the age range studied (late childhood to early adulthood), but females showed a nonlinear (decelerating) decline in magnitudes of activity in these regions. Trajectories crossed in late adolescence (between ages 15 and 18), with females showing greater magnitudes of activity in late childhood. That is, females may rely on increased activity of inhibitory and eye movement control regions early in development while males more similar engagement of these regions through development. In the context of evidence that both sexes show the same decreased recruitment of dACC, these findings may suggest that males and females may rely on different compensatory approaches in other areas of the network.

Sex differences are well-established for structural neurodevelopment and sex differences are similarly minimized during adolescence, but paradoxically, males exhibit steeper increases in white matter growth and steeper declines in gray matter than females (De Bellis et al., 2001; Giedd, 2004; Giedd, et al., 1999; Giedd, Castellanos, Rajapakse, Vaituzis, & Rapoport, 1997; Lenroot, et al., 2007; Perrin et al., 2008), who show earlier maturation of white matter microstructure (Asato, et al., 2010; Bava, et al., 2011). Earlier access to speeded connections in females may support the ready access of control regions during development. There is evidence that developmental changes in white matter microstructure are associated with magnitudes of brain function supporting executive function (Olesen, et al., 2003) via their effects on network integration (Stevens, Skudlarski, Pearlson, & Calhoun, 2009). Future studies examining the relationship between *trajectories* of white matter maturity (using DTI) and functional activity

within each sex can begin to highlight whether structural maturational processes may indeed support sex differences in brain function.

To our knowledge, only one other functional neuroimaging study of executive function has examined sex by age interactions in this age group. This study did find sex differences in regions crucial for inhibitory control task performance, with females showing age-related increases in left prefrontal regions and males showing age-related increases in right parietal regions (Christakou, et al., 2009). Though our findings also reveal prefrontal developmental changes among females, these changes are manifested as *declines* in prefrontal activity. Both sexes seem to rely on comparable circuitries, but the sexes differ in the degree to which levels of activity are modulated over development in frontal regions. While Christakou et al. (2010) also showed developmental modulation, their findings indicate that males and females rely on *different* circuitries, and activity in each circuitry is modulated over the course of development. As both studies relied on similar fMRI task designs (mixed block/event-related design), one possibility for these different findings is that Christakou's findings reflect sex differences in strategy use. The antisaccade task is less amenable to strategy use than the Simon and switch tasks used by Christakou et al. (2010), which has additional set-shifting demands. Thus, the sex difference recruitment of different circuitries in their study may reflect males' reliance on spatial strategies and females' reliance on more verbal strategies. As there were no main effects of sex or age in these regions, these findings underscore the importance of evaluating sex by age interactions in future studies, if power permits. Developmental neuroscience studies examining sex differences in domains known to demonstrate robust sex differences (e.g., language, spatial functioning) at the behavioral level have similarly shown that sex differences are not readily apparent as main effects, but rather as different patterns of development (Plante, Schmithorst,

Holland, & Byars, 2006; Roberts & Bell, 2000; Schmithorst & Holland, 2006). We have only sampled the late years of childhood and the early years of adulthood, but it would be valuable to explore when in childhood these sex differences emerge and whether they eventually converge in adulthood.

4.5 FUTURE DIRECTIONS

We examined brain activity controlling for performance (e.g., brain activity associated with only correct performance), but because performance changed with development, the reliability of our estimates of brain activity changed with development. This was particularly true for estimates of error-related brain activity, as error rates approached 20% in adulthood. While this did not seem to impact our results (as indicated by minimal change in ICCs for weighted and unweighted betas), this nonetheless may have resulted in a differing subjective experience (difficulty, frustration, reward) across development, as children's correct trials occurred in the context of more error trials. A follow-up study could extend our investigation of error performance by combining the event-related component of our fMRI paradigm with a task that titrates performance to be equivalent across all ages (Rubia, et al., 2003). This could provide a firm basis of support to our finding that variability during dACC errors is different that all other regions during correct trials. Our findings indicate that the most rapid period of developmental change occur during early adolescence, so this and other studies probing brain function associated with error monitoring may want to oversample participants in the early adolescent age range to most sensitively characterize the processes of change.

It would also be valuable to expand upon these initial sex difference findings by extending the age range sampled. Modeling developmental trajectories that begin at an earlier age could reveal whether males experience developmental changes at an earlier age than females, or whether they simply do not show developmental changes in these regions. In addition, future studies examining changes at the voxelwise level would allow us to explore whether female developmental declines in brain activity may be associated with developmental increase in brain activity in other regions within the brain. Understanding sex differences in inhibitory function has important implications for clarifying sex differences in rates of onset of psychopathology which emerges at this time (Hankin & Abramson, 2001).

Despite finding evidence for variability in trajectories, sex and IQ only explained a small proportion of the individual differences found. Future studies that investigate other predictors of brain function in this age group may investigate a range of genetic and environmental influence that can explain individual differences that are particularly strong in regions involved in executive control and motor response control circuits but not dorsal ACC. Such predictors should also be able to explain developmental change in patterns of variability as have been described. Twin research suggests both genetic and environmental factors contribute to variation in brain activity, as estimates of heritability supporting brain activity associated with executive function are around 40 – 65% in adults (Blokland et al., 2008). Potential genetic moderators of brain system function may include genotypes influencing dopamine availability in executive control and motor response control regions, including COMT and DAT1 (Congdon, Constable, Lesch, & Canli, 2009; Green, Kraemer, DeYoung, Fossella, & Gray, 2012; Mier, Kirsch, & Meyer-Lindenberg, 2010). Indeed, the aforementioned longitudinal study examining working memory – the only other known study examining moderators of brain function for any executive

function – found that COMT genotype interacted with age in the parietal and prefrontal cortices, and individuals with allele associated with poorer cognitive control showed developmental changes in activity (Dumontheil, et al., 2011). Relevant environmental variables may include socioeconomic status, a metric of the extent of resources available to an individual and a proxy for cognitive stimulation (McLoyd, 1998). Parenting style is another environmental variable that has known effects on inhibitory control abilities early in life (Moilanen, Shaw, Dishion, Gardner, & Wilson, 2009) and may affect trajectories of associated brain activity in more subtle ways.

We found some trends for IQ to moderate trajectories of inhibitory control, which merits further investigation in light of a research literature that exists showing that higher-IQ individuals rely on task circuitries that are more specialized for task performance (Neubauer & Fink, 2009; Schmithorst & Holland, 2006, 2007; van den Heuvel, Stam, Kahn, & Hulshoff Pol, 2009). Our results suggest that higher IQ individuals may show a greater reliance on regions that optimize performance (dACC) and less reliance on frontoparietal regions. Further, these patterns tend to be present throughout development, consistent with evidence from the structural neuroimaging literature that different trajectories of brain structure are present in early childhood. Future studies are needed to verify these results.

In this study we have examined transient brain activity associated with trial-by-trial performance in individual brain regions. To expand past these boundaries, functional connectivity approaches could be used to examine patterns of associations between individual brain regions. Developmental research examining functional connectivity has revealed system-wide patterns of network remodeling throughout the brain (Hwang, et al., 2010). Specifically, this has revealed that from childhood to adolescence, there is an increase in connectivity with parietal regions and the subsequent transition from adolescence to adulthood is marked by a

decrease in parietal connectivity and an increase in prefrontal connectivity. Longitudinal studies could highlight the most rapid periods of change in the network. Such studies could also reveal when, if at all, sex of IQ differences in patterns of connectivity supporting inhibitory control emerge, as both factors have been shown to support developmental changes in language processing (Schmithorst & Holland, 2006, 2007) and reveal whether there are sex differences in patterns of connectivity revealed. Future studies should also characterize trajectories of sustained activity supporting task performance. A specific network exists that controls goal-directed behavior by actively maintaining a configuration of cognitive processes for an extended period of time. This enables the availability of a set of "rules" that can quickly guide transient operations that must occur upon the appearance of stimuli (Dosenbach et al., 2006). A cross-sectional developmental study has revealed that sustained activity in regions supporting an inhibitory task set continues to improve from childhood to adulthood (Velanova, et al., 2009), and a subsequent longitudinal study could uncover exact patterns of development and highlight whether variability exists. As we found limited variability in the latest-maturing region, it would be valuable to explore whether a limited pattern of variability is also evident for another type of late-maturing activity.

Lastly, the antisaccade task has been demonstrated to be a useful endophenotype that can indicate risk for psychopathology, as relatives of individuals with psychopathology (e.g., schizophrenia) show impaired behavioral performance (Calkins, Curtis, Iacono, & Grove, 2004; Ettinger et al., 2006; Lennertz et al., 2012; Malone & Iacono, 2002; Mazhari et al., 2011; Radant et al., 2010; Radant et al., 2007) and performance on this task is heritable (Malone & Iacono, 2002; Radant, et al., 2010). Further, longitudinal studies of behavior and brains structure following healthy, at-risk, and disordered patients through childhood and adolescence have

demonstrated that such designs can reveal *how* trajectories of endophenotypes may go awry (Rachel Marsh, Gerber, & Peterson, 2008; Shaw et al., 2007; Shaw et al., 2009). By characterizing whether pathways are parallel throughout development (i.e., an early deficit that persists) or whether there is a sensitive period during which trajectories diverge, longitudinal studies of endophenotypes can reveal the process by which psychopathologies emerge. This study indicates that brain activity supporting *error monitoring* of inhibitory control performance may be a particularly sensitive endophenotype for characterizing risk for psychopathology during childhood and early adolescence. Thus, it would be valuable to prospectively follow healthy controls and individuals at high risk for developing schizophrenia (or other psychopathologies where inhibitory control is impaired) to explore when exactly and how trajectories of brain function supporting error monitoring diverge in adolescence.

4.6 IMPLICATIONS AND GENERALIZABILITY

One important perspective when considering the implications of these results is to consider their generalizability. We selected the antisaccade task because of its unique qualities that minimize its susceptibility to developmental confounds and its capacity to probe brain behavior relationships. While we recognize that this task is only a proxy for complex real-life situations, it is valuable for probing the integrity of the brain systems that are necessary to demonstrate inhibitory control in these real-life situations. In addition, these results are relevant for inhibitory control in general because we selected to analyze a priori regions of interest that previous meta-analyses and other developmental inhibitory studies have shown to be active across inhibitory control tasks (Swick, et al., 2011). Thus, while different inhibitory control tasks also elicit

distinct patterns of brain activation, the existence of a core set of inhibitory control brain regions supports our contention that these results can speak to general developmental changes in inhibitory control that are relevant to understanding behavior in complex, real-life situations.

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