Developmental maturation of inhibitory control circuitry in a high-risk sample: A longitudinal fMRI study

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ARTICLE INFO

Keywords:
- Go/no-go
- Functional magnetic resonance imaging
- Sandwich estimator
- Neuroimaging

ABSTRACT

Background: The goal of this work was to characterize the maturation of inhibitory control brain function from childhood to early adulthood using longitudinal data collected in two cohorts.

Methods: Functional MRI during a go/no-go task was conducted in 290 participants, with 88 % undergoing repeated scanning at 1- to 2-year intervals. One group entered the study at age 7–13 years (n = 117); the other entered at age 18–23 years (n = 173). 33.1 % of the sample had two parents with a substance use disorder (SUD), 43.8 % had one parent with an SUD, and 23.1 % had no parents with an SUD. 1162 scans were completed, covering ages 7–28, with longitudinal data from the cohorts overlapping across ages 16–21. A marginal model with sandwich estimator standard errors was used to characterize voxel-wise age-related changes in hemodynamic response associated with successful inhibitory control.

Results: There was significant positive linear activation associated with age in the frontal, temporal, parietal, and occipital cortices. No clusters survived thresholding with negative linear, positive or negative quadratic, or positive or negative cubic contrasts.

Conclusions: These findings extend previous cross-sectional and small-scale longitudinal studies that have observed positive linear developmental trajectories of brain function during inhibitory control.

1. Introduction

Inhibitory control is the ability to voluntarily suppress goal- or task-irrelevant information. It is key to the control of attention and provides the flexibility needed to guide behavior based on task goals. Inhibitory control is often assessed with tasks that require withholding a prepotent response, such as the go/no-go paradigm, in which individuals respond to frequent “go” stimuli but must inhibit responses to infrequent “no-go” stimuli. The ability to successfully inhibit a response increases from childhood to adulthood using cognitive control abilities mature and goal-directed behaviors develop (Dempster, 1992; Harms & Bjorklund, 1993; Luna et al., 2004, 2001). During adolescence, a protracted development in top-down self-regulation including inhibitory control is believed to be associated with increased risk-taking behaviors (Casey, 2015; Geier, 2013), such as substance use, which escalates during adolescence and peaks in young adulthood (Schulenberg et al., 2018).

Early functional magnetic resonance imaging (fMRI) studies investigating maturation of inhibitory control circuitry used cross-sectional designs and reported both activation decreases and increases with age. Specifically, significant activation increases with age have been reported in orbitofrontal cortex (Rubia et al., 2006; Tamm et al., 2002), anterior cingulate (Rubia et al., 2006), and inferior frontal gyrus extending into insula (Tamm et al., 2002) during response inhibition in go/no-go tasks. Similarly, during other inhibitory control tasks (i.e., flanker and stop tasks), activation increases with age have been found in inferior frontal cortex (Bunge et al., 2002; Rubia et al., 2007) and anterior cingulate (Bunge et al., 2002), as well as temporal and parietal areas (Bunge et al., 2002; Rubia et al., 2007) that were not reported in the go/no-study tasks.
Significant activation decreases with maturation have been reported in the superior frontal gyrus (Booth et al., 2003; Tamm et al., 2002), portions of anterior, middle, and posterior cingulate (Booth et al., 2003; Tamm et al., 2002), and dorsolateral prefrontal cortex (Durston et al., 2006), as well as subcortical areas (e.g., caudate and thalamus (Booth et al., 2003)) during go/no-go tasks. A stop-signal task (Cohen et al., 2010) found similar activation decreases with age in the medial prefrontal cortex extending into anterior cingulate.

These studies have not converged on definitive developmental changes in inhibitory control circuitry, likely due to a number of methodological factors. One may be the variable developmental periods during which participants were scanned. For example, some studies have investigated age-related changes cross-sectionally by comparing groups of early or middle adolescents with young adults (Adleman et al., 2002; Booth et al., 2003; Bunge et al., 2002; Casey et al., 1997; Durston et al., 2002b), whereas other studies have used linear regression to identify positive or negative age-related changes (Adleman et al., 2002; Luna et al., 2001; Marsh et al., 2006; Rubia et al., 2000, 2007; Rubia et al., 2006; Schulte et al., 2019; Tamm et al., 2002; Velanova et al., 2008). Gaps between measurement groups (e.g., comparing 12-16 year-olds with 18-21 year-olds) or limiting the age range of participants (e.g., 13-17 years) excludes important developmental time periods and can present an incomplete picture. Additionally, developmental changes are difficult to characterize with cross-sectional studies, as these types of designs are unable to fully capture change over time.

Only a few studies have examined maturation of inhibitory control circuitry using longitudinal designs. Using an accelerated longitudinal design, Ordaz and colleagues demonstrated decreasing activation across ages 9–26 years in the right prefrontal cortex, as well as increasing activation to inhibitory errors in the anterior cingulate during an anti-saccade task (Ordaz et al., 2013). More recently, a similar design was used to investigate age-related change in brain activation during an incentivized anti-saccade task. Particularly relevant here are the findings observed during non-incentivized trials of decreasing activation with age in the prefrontal cortex and a U-shaped developmental trajectory in the posterior parietal cortex (Paulsen et al., 2015). These longitudinal studies converge on a common finding of decreasing prefrontal activation during the inhibition of saccades across adolescence. However, to our knowledge, this has not been investigated in a longitudinal design during the more widely used go/no-go task of motor inhibition. Furthermore, these studies focused on regions of interest (ROI), which restricts the search for maturational changes to a priori regions, thereby potentially missing critical age-related effects outside of these regions.

Here we sought to characterize the development of neural circuitry involved in successful inhibitory control across ages 7–28 years using a go/no-go task during fMRI scanning in a longitudinal design. The development of successful inhibitory control is relevant for elucidating aberrant inhibitory control, which is known to occur in substance use and other disorders. However, most developmental studies have investigated primarily healthy samples that are free from risky behaviors (such as substance use) and disorders (such as depression and ADHD) that are common during childhood, adolescence, and young adulthood. Here, we investigate the development of inhibitory control in a sample that includes youth who display these high risk behaviors and disorders. We used a recently developed toolbox for whole-brain analysis of longitudinal neuroimaging designs—the Sandwich Estimator Toolbox (SwE) (Guillaume, 2015; Guillaume et al., 2014; Guillaume and Nichols, 2015)—to test linear, quadratic, and cubic patterns of activation increases and decreases across age. Based on prior longitudinal work, we expected to see linear decreases in activation with age in the prefrontal cortex.

2. Materials and methods

2.1. Participants

Participants were 290 individuals (111 female) from two cohorts: 117 children and early adolescents aged 7.6–12.9 years at study entry and 173 adolescents and young adults aged 16.1–24.2 years at study entry. Thirty-five participants contributed one scan and 255 participants (87.9 %) contributed between two and eight scans, for a total of 1162 scans (497 scans from the younger cohort and 665 scans from the older cohort) covering the ages of 7.6–28.5 years (with cohort-overlap from 16.1 to 21.7 years of age). Repeat scans took place at approximately 1- to 2-year intervals. See Table 1 for sample size and age by cohort and scan number; see Fig. 1 for a graphical depiction of longitudinal scans by age and cohort.

Participants were offspring from the Michigan Longitudinal Study (MLS; (Zucker et al., 1996, 2000)), a prospective study consisting of a community sample of families with at least one parent with an alcohol use disorder (AUD) and at least one child (approximately two-thirds of the sample) as well as a control sample of families from the same neighborhoods, also with at least one child but where neither parent had a substance use disorder (SUD). Due to initial MLS recruitment strategies, the majority of the present sample was male (61.7 %) and White (80.7 %). Families were excluded if the target child displayed signs of fetal alcohol syndrome or the mother reported drinking during pregnancy. Full details on assessment and data collection in the MLS can be found elsewhere (Zucker et al., 2000).

Participants included in the present analyses are those who participated in the MLS’s neuroimaging sub-study and therefore represent a subset of the larger MLS sample. Participants were excluded if they were left-handed or ambidextrous or had any of the following: neurological, acute, uncorrected, or chronic medical illness; use of centrally active medications either currently or within the past 6 months; a history of psychosis or schizophrenia in first-degree relatives; an IQ less than 70 (as determined by the Wechsler Adult Intelligence Scale (Wechsler, 1981, 1997) or Wechsler Intelligence Scale for Children (Wechsler, 1974, 1991)); or MRI contraindications such as metal implants or claustrophobia. The presence of Axis I psychiatric or developmental disorders other than past or current conduct disorder, attention

Table 1

| Sample Size and Age by Scan Number and Cohort. | Adolescents/Young Adults | Full Sample |
|-----------------------------------------------|---------------------------|-------------|
| n Mean Age (SD) Age Range | n Mean Age (SD) Age Range | n |
| Scan 1 117 10.2 (1.2) 7.6–12.9 | 173 19.7 (1.7) 16.1–24.2 | 290 |
| Scan 2 104 12.3 (1.6) 9.0–16.5 | 151 21.8 (1.8) 19.0–27.0 | 255 |
| Scan 3 88 14.2 (1.8) 10.4–18.1 | 129 23.3 (1.8) 20.0–27.1 | 217 |
| Scan 4 73 15.6 (1.8) 11.8–19.1 | 98 24.3 (1.6) 21.1–28.1 | 171 |
| Scan 5 56 16.9 (1.4) 13.6–19.6 | 60 25.2 (1.2) 22.5–28.2 | 116 |
| Scan 6 39 18.1 (1.3) 16.0–20.6 | 37 26.0 (0.9) 24.1–28.5 | 76 |
| Scan 7 16 19.1 (0.9) 17.6–20.7 | 16 26.5 (0.7) 25.1–27.8 | 32 |
| Scan 8 4 20.1 (1.4) 18.7–21.7 | 1 26.3 (...) | 5 |

Note. SD, standard deviation.
deficit/hyperactivity disorder (ADHD), and substance use disorder, as well as unmedicated depression or anxiety was exclusionary. Participants who were taking medication for ADHD were asked to abstain from alcohol and all other substances for at least 48 h prior to the scan session. In participants aged 15 years and older, urine drug screens were conducted immediately before the scan; those who tested positive were rescheduled. Participants under the age of 15 provided verbal confirmation on the day of the scan of drug and alcohol abstinence. Pregnancy was exclusionary: Standard screening for MRI involved asking all female participants if they might be pregnant, and females aged 15 years and older completed a urine pregnancy test immediately before the scan. All participants provided written informed consent (for those 18 and older) or assent (with parental consent, for those 17 and younger) that was approved by the University of Michigan Medical School Institutional Review Board.

2.2. Stimuli and task

An event-related go/no-go task (Durston et al., 2002a; Hardee et al., 2014; Heitzeg et al., 2014, 2010) was used to assess brain activity during successful inhibitory control (i.e., withholding a prepotent response). Participants were instructed to respond via button press to target stimuli (all letters except for “X”; 75% of stimuli) but withhold their response to nontarget stimuli (the letter “X”; 25% of stimuli). Stimulus duration was 500 ms, with a 3500 ms inter-stimulus interval consisting of a black screen with a white fixation cross. Participants completed five 3.5-min runs of 49 trials each. Rates of false alarms (pressing the button for nontarget stimuli), hits (pressing the button for target stimuli), misses (not pressing the button for target stimuli), and correct rejections (not pressing the button for a nontarget stimuli) were recorded. Reaction times to false alarms and hits, measured from the beginning of stimulus presentation, were also recorded. All participants practiced the task on a desktop computer prior to scanning.

2.3. Other measures

2.3.1. Psychopathology

Axis I disorders were assessed by a clinical psychologist based on DSM-IV disorders (American Psychiatric Association (1994)) criteria utilizing the Diagnostic Interview Schedule-Version 4 (Robins et al., 2000) for participants aged 18 years and older and the Diagnostic Interview Schedule-Child-Version 4 (Shaffer et al., 2000) for participants under 18 years old.

2.3.2. Family history

Family history of SUD was defined as the number of parents (zero, one, or two) with a lifetime diagnosis of drug or alcohol abuse or dependence, according to DSM-IV criteria.

2.4. fMRI data acquisition

Whole-brain blood oxygen level-dependent (BOLD) functional images were acquired on a 3.0 T GE Signa scanner (Milwaukee, WI, USA) using T2*-weighted single-shot combined spiral in/out sequences (Glover and Law, 2001) with the following parameters: TR = 2000 ms; TE = 30 ms; flip angle = 90 degrees; field-of-view = 200 mm; 64 × 64 matrix; slice thickness = 4 mm, 29 slices. High-resolution anatomical T1 scans were also obtained for spatial normalization. Foam padding around the head and instructions to participants on the importance of keeping still were used to minimize motion.

2.5. Data analysis

2.5.1. fMRI data: preprocessing

An iterative algorithm was used to reconstruct functional images (Noll et al., 2005; Sutton et al., 2003). Motion correction was performed using FSL v5.0.2.2 (FMRIB, Oxford, UK). Runs exceeding 3 mm translation or 3° rotation were excluded. Statistical Parametric Mapping (SPM8; Wellcome Institute of Cognitive Neurology, Oxford, UK) was used to preprocess images. Functional images were first slice-time corrected, spatially normalized to the Montreal Neurological Institute (MNI) template using SPM defaults, and then smoothed with a 6-mm full-width half-maximum smoothing kernel. A high-pass filter (128 s) was used to remove low-frequency noise.

2.5.2. fMRI data: individual level

SPM8 was used to process images at the individual level with a general linear model. Go trials, correct rejections, and false alarms were modeled separately with the standard hemodynamic response function (event duration 4000 ms from stimulus onset); six realignment parameters and white matter signal intensity were also modeled as nuisance variables. Because our primary contrast of interest was activation associated with successful inhibitory control, images that represented the hemodynamic response associated with correct rejections versus implicit baseline were computed for each participant. The implicit baseline was comprised of the 3500 ms fixation only. Because of the high frequency of target trials relative to other event types, an implicit baseline was used as opposed to target stimuli (i.e., “go” stimuli) (DeVito et al., 2013).

2.5.3. fMRI data: group level

Group-level analyses used SPM12 and the Sandwich Estimator Toolbox for Longitudinal and Repeated Measures Data v2.1.0 (SwE; Guillaume, 2015; Guillaume et al., 2014; Guillaume and Nichols, 2015) to investigate the development of brain activity associated with successful response inhibition. The SwE toolbox is useful for
longitudinal and repeated-measure neuroimaging data, as it fits a marginal model that avoids the need for per-subject dummy variables. Instead of iteratively computing variance components, it uses the non-iterative “sandwich estimator” to find standard errors. The approach used by the SwE toolbox has a number of advantages compared to traditional linear mixed effect models. First, no random effects (e.g., random slopes) need to be specified; only the population model is specified. Second, the use of an unstructured error covariance allows for all possible random effects to be accounted for. Third, a balanced design is not necessary, and even subjects with single data points can be modeled and will contribute to the fitting of cross-sectional effects. Finally, ordinary least squares is used to estimate the population model, which means that the method is non-iterative and avoids convergence failures that can occur in complex mixed-effects models. In accordance with the toolbox’s documentation, the following non-default options were selected: SwE type = classic (no pooling of covariance over subjects, recommended when N is large); degrees of freedom type = naïve; and non-parametric wild bootstrap = yes, with type C2 small-sample adjustments for WB resampling, and 999 bootstraps.

Three different models were used to test the linear, quadratic, and cubic patterns of longitudinal activation change, respectively. In each model, age was decomposed into its between-subject and within-subject components, following Guillaume and colleagues (Guillaume et al., 2014), to avoid an assumption of identical cross-sectional and longitudinal effects. Correct rejection rate was included as a nuisance variable to account for improvements in task performance with age and was similarly decomposed into its between- and within-subject components. We chose to control for task performance so that the interpretation of any differences in brain activation over time would not be confounded by differences in performance. However, for completeness, models that did not include task performance were also run (see Supplemental Material). Because this is a high-risk sample, we also controlled for substance use in supplemental linear mixed models (see Supplemental Material). For each of the three models, both positive and negative associations with age were assessed. Between-subject age was the covariate of interest, and contrast weights were entered accordingly. Correction for multiple comparisons was achieved with a cluster-wise family-wise error (FWE) level of $p < .05$ (cluster-defining threshold of $p < .001$).

### 2.5.4. Task performance

Linear mixed models run in SPSS v24 were used to evaluate the association between age and the following task performance measures: correct rejection rate, false alarm reaction time, hit rate, and hit reaction time. Scan number was entered as a repeated effect, subject as a random factor, and age as a fixed-effect covariate. A first-order autoregressive covariance matrix was chosen due to the presence of repeated measures.

![Fig. 2. Scatterplots of Task Performance by Age.](image)

**A)** Reaction time for hits (in milliseconds) by scan age in years. **B)** Correct rejection rate by scan age. In both plots, the linear regression line has been overlaid.

### Table 2

**Diagnostic Data by Cohort.**

|                      | Children and Early Adolescents (n = 117) | Adolescents and Young Adults (n = 173) | Full Sample (N = 290)$^*$ |
|----------------------|-----------------------------------------|---------------------------------------|---------------------------|
| Parents with an SUD  | 27.4/38.5/34.2                          | 20.2/47.4/32.4                       | 23.1/43.8/33.1            |
| (％: zero/one/two)   |                                         |                                       |                           |
| Lifetime DSM-IV Diagnosis (%)$^*$ |                             |                                       |                           |
| Generalized Anxiety Disorder | 2.2                                     | 5.2                                   | 0.0/6.0/4.6               |
| Major Depression     | 2.2                                     | 21.4                                  | 8.3/17.1/16.1            |
| ADHD                 | 12.1                                    | 17.6                                  | 11.7/15.7/18.6           |
| Conduct Disorder     | 2.2                                     | 9.4                                   | 5.0/6.1/9.3              |
| Alcohol Abuse or Dep.| 1.1                                     | 30.0                                  | 11.7/21.4/24.1           |
| Cannabis Abuse or Dep.| 1.1                                     | 16.8                                  | 5.0/12.0/14.9            |
| Nicotine Dep.        | 0.0                                     | 8.7                                   | 5.0/4.3/8.0              |
| Other Drug Abuse or Dep.| 0.0                                     | 3.5                                   | 1.7/3.4/1.1              |

*Note. SUD, substance use disorder; DSM, Diagnostic and Statistical Manual of Mental Disorders; ADHD, attention deficit/hyperactivity disorder; Dep., Dependence.
$^*$Diagnosis data for the full sample are reported by family history of SUD status: zero/one/two.
$^*$Lifetime diagnosis data were missing in 26 participants for all disorders except ADHD and conduct disorder, for which there were missing data in 29 participants.
whereas participants who had two parents with an SUD had the highest rates of disorder.

3.2. Task performance

As expected, there was a significant effect of age on all four task performance measures: correct rejection rate ($F_{1,401} = 123.2, p < .001$), false alarm reaction time ($F_{1,243} = 96.4, p < .001$), hit rate ($F_{1,313} = 29.9, p < .001$), and hit reaction time ($F_{1,324} = 127.0, p < .001$). Specifically, reaction times decreased and correct inhibitions increased with age. See Fig. 2 for scatterplots of hit reaction time and correct rejection rate by age.

3.3. Longitudinal imaging results

3.3.1. Linear

For the model that tested positive linear activation changes associated with age during correct rejections (Table 3, Fig. 3), there were significant increases in areas that included frontal (medial frontal gyrus, inferior frontal gyrus, and middle frontal gyrus), temporal (superior temporal gyrus), parietal (superior parietal lobule), and occipital (fusiform gyrus, lingual gyrus, and cuneus) cortex. There were no clusters that survived thresholding with the negative linear contrast.

3.3.2. Quadratic

There were no clusters that survived thresholding with the positive or negative quadratic contrasts.

3.3.3. Cubic

There were no clusters that survived thresholding with the positive or negative cubic contrasts.  

4. Discussion

The goal of this large longitudinal study was to characterize age-related changes in brain function related to successful inhibitory control. We tested linear, quadratic, and cubic effects of age for both positive and negative contrasts. We found that activation in primarily frontal and occipital regions, including bilateral orbital frontal cortex (BA 11), bilateral inferior frontal gyrus (BA 47), and bilateral occipital cortex (BA 18/19), increased linearly with age. There were no areas with significantly increasing quadratic or cubic activation or decreasing linear, quadratic, or cubic activation.

Functional MRI studies characterizing age-related activation differences in key inhibitory control circuits have primarily reported prefrontal cortex effects (for review, see (Cron and Dahl, 2012)). Prefrontal cortex also undergoes structural changes through early adulthood (e.g., (Gotay et al., 2004; Shaw et al., 2008; Sowell et al., 2003, 1999)), concomitant with the development of cognitive control abilities (for review, see (Cron and Dahl, 2012)). Developmental effects (both increases and decreases) in the prefrontal cortex—in particular lateral prefrontal cortex—have been reported in other studies across a variety of inhibitory control tasks, such as the go/no-go, stop signal, flanker, anti-saccade, and Stroop tasks. We find a number of these studies are in agreement with the findings reported here, including the right dorsolateral prefrontal cortex (dIPFC; BA 9/46) (Adleman et al., 2002; Bunge et al., 2002; Marsh et al., 2006; Rubia et al., 2006) and bilateral ventrolateral prefrontal cortex (vIPFC; BA 44/45/47) (Adleman et al., 2002; Bunge et al., 2002; Marsh et al., 2006; Rubia et al., 2000, 2007). It has been argued that the vIPFC and dIPFC have distinct, dissociable roles in preparing to inhibit a response; the dIPFC is thought to represent task rules and goal representation in working memory while the vIPFC is thought to implement action control via motor control suppression (Swann et al., 2013). In particular, the inferior frontal gyrus, where the vIPFC is located, plays a crucial role in inhibitory control (for review, see (Aron et al., 2014)). We also found increasing linear activation in the orbital frontal cortex (OFC), consistent with Rubia and colleagues (Rubia et al., 2006). Neuroimaging studies show that OFC activity is increased in tasks requiring participants to inhibit behavior (Casey et al., 1997; Chikazoe et al., 2009; Horn et al., 2003; Majid et al., 2013; Rubia et al., 2005), demonstrating its involvement in the inhibition of unwanted actions.

Activation in the medial frontal gyrus (BA 6), which includes the supplementary motor area (SMA) and pre-supplementary motor area (pre-SMA), was also found to increase across development—in agreement with another developmental study of inhibitory control (Adleman et al., 2002). The medial frontal gyrus, and particularly the pre-SMA, is consistently activated in inhibitory control tasks (Aron, 2011; Chambers et al., 2009; Meyer and Bucci, 2016). The area of activation reported here covers both SMA and pre-SMA regions (Mayka et al., 2006; Nachev et al., 2008), which are involved in motor sequence processing, planning, and execution (Cona et al., 2017; Hoshi and Tanji, 2004; Hupfeld et al., 2017), as well as the mediation of motor inhibition (Li et al., 2006; Toma et al., 1999). The pre-SMA specifically has been shown to play an important role in switching from an automatic, habitual response to a controlled response (Isoda and Hikosaka, 2007), as well as motor response preparation and selection (Balle et al., 1999; Barber and Carter, 2005). The pre-SMA, along with the inferior frontal gyrus, are key regions for motor preparation (Aron et al., 2003; Eagle et al., 2008; Floden and Stuss, 2006). The inferior frontal gyrus is thought to first detect stimuli indicating a change in action is needed (i.e., no-go stimuli); it then sends a stop signal to the pre-SMA and subcortical regions (Duann et al., 2009; Sharp et al., 2010; Zandbelt et al., 2013). This is supported by evidence of corticocortical interactions between the pre-SMA and inferior frontal gyrus (Zandbelt et al., 2013), as well as connections between the pre-SMA and subcortical regions such as the caudate (Alexander et al., 1986; Duann et al., 2009).

The largest area showing linear increases in activation with age was comprised of the fusiform gyrus, lingual gyrus, and cuneus (BA 18/19), where activation increases have also been reported in other developmental studies of inhibitory control in adolescents (Adleman et al., 2002; Ordaz et al., 2013). These regions have also been reported in response inhibition studies in adults (Kelly et al., 2004; Liddle et al., 2001; Mathalon et al., 2003; Steele et al., 2013; Tian and Yao, 2008), but are not discussed in detail. However, neuroimaging studies on attentional control indicate that activation in extra-striate regions such as the fusiform and lingual gyri are enhanced when target stimuli fall within the attentional spotlight (Bretzczynski and DeYoe, 1999; Heinze et al., 1994; Mangan et al., 1998, 1997; Martinez et al., 1999; Toottell et al., 1998). During tasks like the go/no-go, the no-go stimulus is salient because it appears less frequently, is behaviorally relevant, and demands a change of response. It most likely drives attention in two ways: from a bottom-up involuntary manner, which is stimulus-driven and depends on the physical salience of the object, and from a top-down manner, which depends on the behavioral goals of the individual. It has been suggested that the inferior frontal gyrus, through its connections with the supplementary motor area (SMA) and pre-supplementary motor area (pre-SMA), was also found to increase across development—in agreement with another developmental study of inhibitory control (Adleman et al., 2002). The medial frontal gyrus, and particularly the pre-SMA, is consistently activated in inhibitory control tasks (Aron, 2011; Chambers et al., 2009; Meyer and Bucci, 2016). The area of activation reported here covers both SMA and pre-SMA regions (Mayka et al., 2006; Nachev et al., 2008), which are involved in motor sequence processing, planning, and execution (Cona et al., 2017; Hoshi and Tanji, 2004; Hupfeld et al., 2017), as well as the mediation of motor inhibition (Li et al., 2006; Toma et al., 1999). The pre-SMA specifically has been shown to play an important role in switching from an automatic, habitual response to a controlled response (Isoda and Hikosaka, 2007), as well as motor response preparation and selection (Balle et al., 1999; Barber and Carter, 2005). The pre-SMA, along with the inferior frontal gyrus, are key regions for motor preparation (Aron et al., 2003; Eagle et al., 2008; Floden and Stuss, 2006). The inferior frontal gyrus is thought to first detect stimuli indicating a change in action is needed (i.e., no-go stimuli); it then sends a stop signal to the pre-SMA and subcortical regions (Duann et al., 2009; Sharp et al., 2010; Zandbelt et al., 2013). This is supported by evidence of corticocortical interactions between the pre-SMA and inferior frontal gyrus (Zandbelt et al., 2013), as well as connections between the pre-SMA and subcortical regions such as the caudate (Alexander et al., 1986; Duann et al., 2009).
activation in the cuneus could reflect modulatory feedback from higher order regions, such as the prefrontal cortex, regarding the behavioral salience of no-go stimuli and the adaptive facilitation of goal-directed behavior.

Together, these results indicate that key components of the response inhibition network, including the prefrontal cortex, pre-SMA, and lingual/fusiform gyrus are increasing linearly in activation across age. This could reflect the view that younger subjects have more diffuse or attenuated patterns of activation across a number of different regions that shifts to focal activation in regions critical to task performance across development (Casey et al., 1997; Durston et al., 2006; Durston et al., 2002; Schroeter et al., 2004; Velanova et al., 2009). Previous neurodevelopmental studies have reported age-related behavioral improvements that correlated with increases in neural activation magnitude in a number of executive control tasks, including response inhibition tasks (Durston et al., 2006; Marsh et al., 2006; Rubia et al., 2013; Vink et al., 2014).

We did not find maturational effects in several brain regions reported in prior studies of inhibitory control development. For example, cross-sectional developmental studies have identified the anterior cingulate as showing greater activation in adults relative to children or adolescents during incongruent trials of the Stroop task (Adleman et al., 2002), correct no-go trials during a Flanker task (Bunge et al., 2002), and correct no-go trials during a go/no-go task (Rubia et al., 2006). However, longitudinal work using an anti-saccade task has found increased anterior cingulate activation with age only during inhibitory errors but

Table 3
Correct Rejections vs. Baseline: Increasing Linear Activation Changes Associated with Age.

| Cluster | Cluster Name | Cluster Hemi | Peak Label | BA | k | x | y | z | z-value |
|---------|--------------|--------------|------------|----|---|---|---|---|---------|
| 1       | Occipital    | B            | Fusiform Gyrus | 19 | 15,522 | -24 | -68 | -14 | 6.16    |
|         |              |              | Lingual Gyrus  | 18 |       | -22 | -76 | -16 | 5.99    |
|         |              |              | Cuneus        | 18 |       | -24 | -80 | 14  | 5.90    |
| 2       | Orbital Frontal | B            | Medial Frontal Gyrus | 11 | 1152 | 6  | 26  | -14 | 5.36    |
|         |              |              | Subcallosal Gyrus | 11 |       | -10 | 24  | -14 | 5.25    |
|         |              |              | Medial Frontal Gyrus | 11 |       | 8   | 34  | -16 | 5.14    |
| 3       | Inferior Frontal/ Temporal Pole | L          | Inferior Frontal Gyrus | 45 | 919  | -46 | 26  | 10  | 4.94    |
|         |              |              | Superior Temporal Gyrus | 38 |       | -50 | 22  | -16 | 4.60    |
|         |              |              | Inferior Frontal Gyrus | 47 |       | -42 | 24  | -12 | 4.28    |
| 4       | Middle Frontal | R            | Middle Frontal Gyrus | 46 | 1864 | 50  | 20  | 24  | 4.81    |
|         |              |              | Medial Frontal Gyrus | 46 |       | 52  | 28  | 22  | 4.54    |
|         |              |              | Postcentral Gyrus | 3  |       | 28  | -28 | 46  | 4.39    |
| 5       | Inferior Frontal | R            | Inferior Frontal Gyrus | 47 | 776  | 38  | 32  | -8  | 4.81    |
|         |              |              | Inferior Frontal Gyrus | 47 |       | 50  | 22  | -10  | 4.68   |
|         |              |              | Inferior Frontal Gyrus | 47 |       | 50  | 40  | -8  | 4.47    |
| 6       | Superior Parietal | L            | Superior Parietal Lobule | 7  | 312  | -28 | -62 | 54  | 4.00    |
|         |              |              | Superior Parietal Lobule | 7  |       | -30 | -54 | 54  | 3.97    |
| 7       | Medial Frontal | B            | Medial Frontal Gyrus | 6  | 449  | 6   | -22 | 64  | 4.00    |
|         |              |              | Medial Frontal Gyrus | 6  |       | 10  | -32 | 68  | 3.64    |
|         |              |              | Postcentral Gyrus | 5  |       | 10  | -48 | 72  | 3.56    |

Note. Hemi, hemisphere; R, right; L, left; B, bilateral; BA, Brodmann area; k, cluster size in voxels. Coordinates are in Montreal Neurological Institute (MNI) space. Correction for multiple comparisons was achieved with a cluster-wise family-wise error (FWE) level of $p < .05$ (cluster-defining threshold of $p < .001$). Statistics can be found in Table 3.
not during correct inhibition (Ordaz et al., 2013). This latter finding is consistent with the current findings and with the role of the anterior cingulate in error processing and performance adjustment (Alexander and Brown, 2010; Botvinick et al., 2001; Carter et al., 1998; Ridderinkhof et al., 2004). We also did not find activation changes in subcortical regions such as the thalamus and striatum, which have been reported previously in developmental studies of inhibitory control, but with mixed directionality. Some studies have reported greater thalamic and/or basal ganglia activation for children/adolescents relative to adults (caudate: Booth et al., 2003; Rubia et al., 2000, 2007; Rubia et al., 2006); thalamus: Rubia et al., 2007), while others have reported greater activation for adults compared to children/adolescents (caudate: (Rubia et al., 2007); thalamus: (Luna et al., 2001; Rubia et al., 2006)).

The basal ganglia has direct connections to primary motor cortex and is thought to suppress planned or ongoing movements during inhibitory control tasks (Vink et al., 2005). It has been shown to be reliably recruited during motor inhibition tasks (e.g., (Aron and Poldrack, 2006; Boehler et al., 2010; Kelly et al., 2004; Padmala and Pessoa, 2010; Rubia et al., 2005; Vink et al., 2005)). One potential explanation for not finding changes across time in these regions is that activations there are associated with fundamental processes that develop relatively early (Sussman et al., 2016; Velanova et al., 2008), and the use of a wide age-range that included late adolescents and young adults may have “washed out” any such effects.

Contrary to our hypotheses, we did not see significant activation decreases over time in any regions. Although some previous cross-sectional studies did not find any regions that were significantly more active in children relative to adults (e.g., (Adleman et al., 2002; Bunge et al., 2002)), prior longitudinal work found decreasing prefrontal activation during inhibition with age (Ordaz et al., 2013; Paulsen et al., 2015). Differences between the findings from this study and those of previous longitudinal studies could be due to methodological differences, including task type (go/no-go vs. anti-saccade), neural contrast (correct rejections > implicit baseline vs. anti-saccade correct > fixation baseline), and analytic approach (e.g., SwE vs. ROIs). In addition, the majority of participants in the present study were scanned four times, resulting in a more robust longitudinal dataset than in other longitudinal studies. Furthermore, sample characteristics such as age range (e.g., 7–28 vs. 10–22 years-old) and risk status (high-risk for substance use vs. non-high-risk) differed between this and previous studies. Inconsistencies between this study and previous longitudinal studies (Ordaz et al., 2013; Paulsen et al., 2015) are unlikely to be due to our decision to include task performance in the analysis, as we found that results from analyses performed both with and without task performance are similar.

With regard to risk status and substance use, findings may not generalize to populations that are free from substance use and psychiatric disorders (e.g., depressed, ADHD). The relevancy of these findings is considerable for those youth at highest risk for the development of these problems as they move into adulthood.

To our knowledge, this study is the largest-scale (i.e., over 1000 observations), widest age-range longitudinal study to assess developmental changes in inhibitory control. As such, it builds on the findings of previous cross-sectional and smaller-scale longitudinal studies and interrogated linear, quadratic, and cubic patterns of age-related changes in inhibitory control activation from age 7 to 28. We also controlled for task performance, which accounts for age-related behavioral improvements in inhibitory control. Finally, use of the Sandwich Estimator is a strength because of its advantages over traditional methods. Specifically, the method enables a whole-brain search for developmental effects by allowing subjects with single data points to be modeled along with subjects with multiple data points. In addition, ordinary least squares is used to estimate the population model, which means the method is non-iterative and avoids convergence failures that can occur in complex mixed-effects models.

In conclusion, the findings presented here are an extension of previous cross-sectional and small-scale longitudinal studies aimed at identifying the developmental correlates of successful inhibitory control. Results indicate linear increases in activation with age in frontal, temporal, parietal, and occipital areas. These results are relevant for understanding how the brain changes functionally over time and matures to support the development of successful inhibitory control.

Declarations of Competing Interest

None.

Acknowledgments

This work was supported by the National Institutes of Health (grant numbers K01 DA044270, K01 AA024804, T32 AA007477, R01 AA07065, and R01 AA025790) and the Wellcome Trust (100309/Z/12/Z).

The authors would like to thank Bennet Fauber for his essential help with implementing the Sandwich Estimator Toolbox.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.dcn.2020.100781.

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