

UC San Diego

UC San Diego Previously Published Works

Title

Cortical morphology of the pars opercularis and its relationship to motor-inhibitory performance in a longitudinal, developing cohort.

Permalink

<https://escholarship.org/uc/item/4tp5g2wr>

Journal

Brain structure & function, 223(1)

ISSN

1863-2653

Authors

Curley, Lauren B
Newman, Erik
Thompson, Wesley K
[et al.](#)

Publication Date

2018

DOI

10.1007/s00429-017-1480-5

Peer reviewed

Cortical morphology of the pars opercularis and its relationship to motor-inhibitory performance in a longitudinal, developing cohort

Lauren B. Curley¹ · Erik Newman² · Wesley K. Thompson^{2,3} · Timothy T. Brown^{2,4,5} · Donald J. Hagler Jr.^{4,6} · Natacha Akshoomoff^{2,3} · Chase Reuter³ · Anders M. Dale^{1,3,4,5,6} · Terry L. Jernigan^{1,2,3,6}

Received: 27 January 2017 / Accepted: 18 July 2017 / Published online: 29 July 2017
© The Author(s) 2017. This article is an open access publication

Abstract This study investigates the relationship between variability in cortical surface area and thickness of the pars opercularis of the inferior frontal gyrus and motor-inhibitory performance on a stop-signal task in a longitudinal, typically developing cohort of children and adolescents. Linear mixed-effects models were used to investigate the hypotheses that (1) cortical thinning and (2) a relatively larger cortical surface area of the bilateral pars opercularis of the inferior frontal gyrus would predict better performance on the stop-signal task in a cohort of 110 children and adolescents 4–13 years of age, with one to four observations (totaling 232 observations). Cortical thickness of the bilateral opercular region was not related to inhibitory performance. However, independent of age, gender, and total cortical surface area, relatively larger cortical surface area of the bilateral opercular region of the inferior frontal gyrus was associated with better motor-inhibitory performance. Follow-up analyses showed a

significant effect of surface area of the right pars opercularis, but no evidence for an effect of area of left pars opercularis, on motor-inhibitory performance. These findings are consistent with the previous work in adults showing that cortical morphology of the pars opercularis is related to inhibitory functioning. It also expands upon this literature by showing that, in contrast to earlier work highlighting the importance of cortical thickness of this region in adults, relative cortical surface area of the pars opercularis may be related to developing motor-inhibitory functions during childhood and adolescence. Relationships between cortical phenotypes and individual differences in behavioral measures may vary across the lifespan.

Keywords Motor inhibition · Cortical surface area · Cortical thickness · Magnetic resonance imaging · Brain development · Inferior frontal gyrus

✉ Terry L. Jernigan
tjernigan@ucsd.edu

Lauren B. Curley
lcurley@ucsd.edu

Erik Newman
newmanerik@gmail.com

Wesley K. Thompson
wkthompson@ucsd.edu

Timothy T. Brown
ttbrown@ucsd.edu

Donald J. Hagler Jr.
dhagler@ucsd.edu

Natacha Akshoomoff
nakshoomoff@ucsd.edu

Chase Reuter
creuter@ucsd.edu

Anders M. Dale
amdale@ucsd.edu

¹ Department of Cognitive Science, University of California, San Diego, La Jolla, USA

² Center for Human Development, University of California, San Diego, 9500 Gilman Drive, La Jolla, CA 92093-0115, USA

³ Department of Psychiatry, University of California, San Diego School of Medicine, La Jolla, USA

⁴ Center for Multimodal Imaging and Genetics, University of California, San Diego School of Medicine, La Jolla, USA

⁵ Department of Neurosciences, University of California, San Diego School of Medicine, La Jolla, USA

⁶ Department of Radiology, University of California, San Diego School of Medicine, La Jolla, USA

Abbreviations

| | |
|------|--|
| ADHD | Attention deficit hyperactivity disorder |
| GNG | Go/no-go |
| IFG | Inferior frontal gyrus |
| fMRI | Function magnetic resonance imaging |
| SSRT | Stop-signal reaction time |
| SSD | Stop-signal delay |
| MRI | Magnetic resonance imaging |

Introduction

Research has long focused on the neural substrates of psychiatric disorders. However, in recent years, there has been a greater shift toward identifying neurobiological correlates of basic behavioral phenotypes that can be measured dimensionally and cut across disorders (Insel et al. 2010). One behavioral phenotype that has received attention is response inhibition (Casey et al. 1997; Liddle et al. 2001; Johnstone et al. 2007; Forstmann et al. 2008; Tamm et al. 2002; Newman et al. 2015a; Madsen et al. 2010). Motor response inhibition is typically defined as the ability to withhold a planned motor response to a stimulus or to stop an ongoing response (Aron et al. 2004). Impairment in this basic process has been most commonly associated with attention-deficit/hyperactivity disorder (ADHD) (Barkley 1997), though it has been associated with other psychiatric disorders as well, such as anxiety and mood disorders (Wright et al. 2014), and schizophrenia (Ethridge et al. 2014).

Response inhibition is most often measured using standardized, continuous-performance tasks such as the stop-signal paradigm (Logan and Cowan 1984) or a variant of the go/no-go task (GNG) (Conners et al. 2003; Rosvold et al. 1956). The ability to inhibit a preplanned motor response has been linked to a highly interconnected, predominantly right-lateralized circuit involving frontal, motor, and striatal regions (Chambers et al. 2009). According to one model, the inferior frontal gyrus (IFG) is thought to be the origin of a “stop” signal, inhibiting the motor response via direct stimulation of the subthalamic nucleus and resulting in inhibition of motor output of the thalamus (Chambers et al. 2009). This description of the neural system underlying response inhibition is supported by functional magnetic resonance imaging (fMRI) studies. Functional studies, both in adults and in clinical populations, implicate the IFG as a region involved in successful response inhibition (Aron and Poldrack 2006; Eagle et al. 2008). Some previous investigations into the functional correlates of cognitive control and response inhibition suggest gender differences in regional activation (Bell et al. 2006; Garavan et al. 2006; Liu et al. 2012; Weiss et al.

2003) and age by gender interactions during adolescence (Rubia et al. 2010, 2013).

Despite the extensive work on brain functional correlates of response inhibition in healthy populations, research on the relationship between response inhibition and cortical morphology is limited, particularly in developing children and adolescents. Several studies have addressed this indirectly by examining neuroanatomical differences between children with ADHD and comparison groups. The previous studies comparing children and adolescents with and without ADHD symptoms found thinner cortex in ADHD and a relationship between increased rate of cortical thinning and the severity of ADHD symptoms (Shaw et al. 2011, 2013; Batty et al. 2010; Proal et al. 2011). Shaw and colleagues argued their findings supported a dimensional approach to ADHD, where the disorder is considered one extreme of a continuum of a behavioral phenotype. In other words, rather than simply investigating binary groups of participants with or without a diagnosis, a better approach to studying typical development and the development of clinical disorders would be examining the entire range of cognitive and behavioral performance.

Madsen et al. (2010) used diffusion-weighted imaging to examine associations between stop-signal reaction time (SSRT) performance, which is operationally defined as the ability to withhold or cancel an initiated motor response, and white matter microstructure in children. They found that after controlling for age, better response inhibition was associated with higher fractional anisotropy in the white matter underlying the IFG. However, no studies have examined relationships of SSRT to both thickness and surface area of the IFG in this age group. In a study of young adults with or without a childhood diagnosis of ADHD, our group found that thinner cortex in the opercular region was related to better performance on a Go/No-go task, independent of ADHD status (Newman et al. 2015a, b). However, cortical surface area of the same region was unrelated to performance.

The relationships among surface area, thickness, and response inhibition observed in adults may not translate directly to brain–behavior relationships in children. Cortical surface area and cortical thickness show distinct developmental trajectories, which may be mediated by distinct developmental processes and distinct genetic influences (Panizzon et al. 2009; Brown et al. 2012; Jernigan et al. 2011; Chen et al. 2012). It is, therefore, also necessary to begin to investigate differences in these relationships as a function of age (Casey et al. 2014). Our group recently took this approach to determine neural architectural correlates of anxiety in typically developing children and adolescents (Newman et al. 2015b). We found that higher anxiety was associated with thinner cortex

globally and decreased relative surface area of the ventromedial prefrontal cortex, but that the strength of these associations diminished with age. It is, therefore, reasonable to consider whether a similar age interaction may be present in any association between response inhibition and cortical morphology. In addition, our group found that relatively larger surface area of the anterior cingulate was positively related to better performance on a flanker task in children less than 12 years of age, but this relationship was not present in older adolescents examined in the same study (Fjell et al. 2012). Thus, it is reasonable to hypothesize that in our younger developing cohort, there may be a relationship between regional surface area and motor-inhibitory performance.

The current project aims to build on and extend our previous findings in adults (Newman et al. 2015a) by examining the relationship between both cortical thickness and cortical surface area and motor-inhibitory performance in typically developing children and adolescents. Due to the distinct developmental trajectories of cortical surface area and thickness (Brown et al. 2012; Wierenga et al. 2014), we may observe a different pattern of results relative to adults. Our primary hypotheses were (1) that apparent thinning of the pars opercularis of the inferior frontal gyrus would correspond to better performance, independent of age and gender, and (2) that a relatively larger surface area of the same region would correspond to better response inhibition, independent of age and gender. Given the inconsistent laterality of previous findings, we did not have strong hypotheses about laterality, and so for both primary hypotheses, we examined the bilateral pars opercularis. Contingent upon finding significant effects in the bilateral region of interest and in light of previous findings suggesting that these associations may differ as a function of age and/or gender, follow-up analyses examined age and gender interactions. Finally, we examined associations with the right and left pars opercularis separately.

Methods

Participants

Participants were part of the Pediatric Longitudinal Imaging, Neurocognition, and Genetics study at the University of California, San Diego. Prior to participation, participants under 7 years old provided verbal assent, participants over 7 years old provided written assent, and parents or guardians provided written consent after an oral description of the study was provided. Participants were required to understand directions presented in English and have normal or corrected-to-normal hearing and vision. Potential

participants with neurological disorders, significantly preterm birth, a diagnosis of autism spectrum disorder, mental retardation, and/or head trauma with loss of consciousness lasting more than 30 min, or daily drug or alcohol use by the mother during pregnancy, were excluded.

The sample consisted of 110 typically developing children (59 male) between the ages of 4 and 13 years. Of these 110 participants, 82 had complete measurements for two visits, 32 had three visits, and 8 had four visits taken at approximately 1-year intervals, for a total of 232 visits. The average age of participants at the first visit was 6.9 years (SD 1.57 years, $n = 110$). At the second visit, the average age was 7.90 years (SD 1.45 years, $n = 82$), at the third visit 9.07 years (SD 1.31 years, $n = 32$), and the fourth visit 9.71 years (SD 1.30 years, $n = 8$) (see Table 1; Fig. 1).

Stop-signal reaction time (SSRT)

We administered the stop-signal task from the Cambridge Neuropsychological Test Automated Battery (CANTAB, Cambridge Cognition Ltd., Cambridge, UK; Fray et al. 1996). While seated at a computer, participants rested the index finger of each hand on left and right response buttons. A fixation circle was presented for 500 ms, after which an arrow appeared in the center pointing either right or left. The participant was instructed to respond with the relevant response key (right or left) corresponding to the direction of the arrow, as quickly as possible. The stop-signal task is made up of ‘go’ trials (75%) and ‘stop’ trials (25%) presented over five blocks of 64 trials each. On the ‘stop’ trials, a tone is presented at a variable delay after the ‘go’ signal, indicating that the participant should withhold the response. A participant’s stop-signal delay (SSD) is the delay at which he/she can successfully withhold his/her response 50% of the time. The stop-signal reaction time (SSRT) is calculated for each participant by subtracting the SSD from the median reaction time on ‘go’ trials. This measure indicates the time each individual participant needs to refrain from executing a preplanned motor action upon presentation of a stop signal, with lower reaction times indicating better performance. For all behavioral and structural analyses, the logarithm of stop-signal reaction time was used as a variance stabilizing transformation. The $\log(SSRT)$ measure was then inverted, so that higher scores correspond to better performance allowing for more intuitive interpretation of results (see Fig. 2a, b).

Neuroimaging

All neuroimaging data were collected at UC San Diego using the PING protocol (see Jernigan et al. 2016b for details). This is a multiple modality, high-resolution

Table 1 Summary of demographic and repeated-measures data

| Demographics | Total | Male | Female |
|---|-----------------|-----------------|-----------------|
| Number of participants | 110 | 59 | 51 |
| Age [mean (SD) in years] | | | |
| Baseline ($N = 110$) | 6.9 (1.57) | 6.92 (1.41) | 6.87 (1.76) |
| Time point 2 ($N = 82$) | 7.90 (1.45) | 7.95 (1.29) | 7.85 (1.63) |
| Time point 3 ($N = 32$) | 9.07 (1.31) | 9.26 (1.27) | 8.90 (1.37) |
| Time point 4 ($N = 8$) | 9.71 (1.30) | 9.83 (0.00) | 9.69 (1.41) |
| Stop-signal reaction time [mean (SD) in ms] | | | |
| Baseline ($N = 110$) | 298.62 (114.33) | 316.06 (129.68) | 278.45 (90.64) |
| Time point 2 ($N = 82$) | 258.50 (95.04) | 267.00 (99.84) | 248.65 (89.46) |
| Time point 3 ($N = 32$) | 232.77 (98.38) | 241.52 (121.76) | 225.05 (75.13) |
| Time point 4 ($N = 8$) | 232.47 (112.52) | 238.80 (0.00) | 231.56 (121.51) |
| Handedness (R/L/Amb/NA) ^a | 83/14/9/4 | | |
| Race/ethnicity ^b | | | |
| Caucasian | 54 | | |
| African American | 5 | | |
| Hispanic/Latino | 36 | | |
| Asian | 13 | | |
| Pacific Islander | 1 | | |
| American Indian | 1 | | |
| Mixed race | 22 | | |
| Other | 3 | | |

Number of participants, age, and stop-signal reaction time are outlined for the overall sample and also by male/female subgroups. Age and stop-signal reaction time means and standard deviations (SD) are given for each time point for the overall sample and by male/female subgroups. Handedness is reported for the overall sample (*R* right handed, *L* left handed, *Amb* ambidextrous, *NA* not reported). Race and ethnicity are reported for the overall sample

^a Four participants did not identify handedness

^b Participants were free to mark whichever race/ethnicity options they chose: if multiple races were checked, s/he was categorized as “Mixed race”; if none was selected, s/he was categorized as “Other”. Some participants marked only “Hispanic/Latino”, while others marked “Hispanic/Latino” in addition to a race. Therefore, the total number reported in each category does not sum to the total number of participants

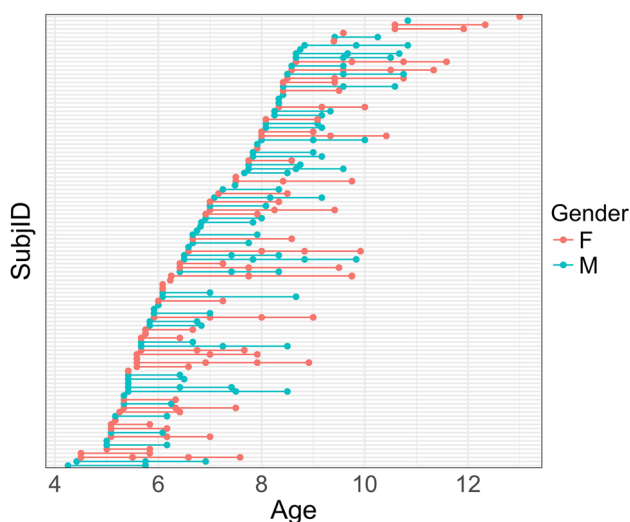


Fig. 1 Summary of repeated-measures. Age is plotted on the *x*-axis, grouped by subject on the *y*-axis. Female participants are shown in red; male participants in light blue

magnetic resonance imaging (MRI) protocol during which participants underwent a 1-h imaging session including acquisition of T1, T2, and diffusion-weighted images. All data were evaluated for quality at multiple stages during processing, including registration, motion correction, and removal of artifacts. Automated protocols available in Freesurfer (Fischl 2004) in addition to analyses developed at UC San Diego Multimodal Imaging Laboratory were used for processing and morphometric analysis. The right and left pars opercularis were extracted using the Desikan atlas available in Freesurfer (Desikan et al. 2006). To create the bilateral pars opercularis thickness region of interest, the right and left pars opercularis measures were averaged. To create the bilateral pars opercularis surface area region of interest, the right and left pars opercularis areas were added together (see Fig. 3). Post hoc cortical surface-based mapping analyses relied upon nonlinear, surface-based registration constrained by cortical folding patterns (Fischl et al. 1999), and used surface-constrained,

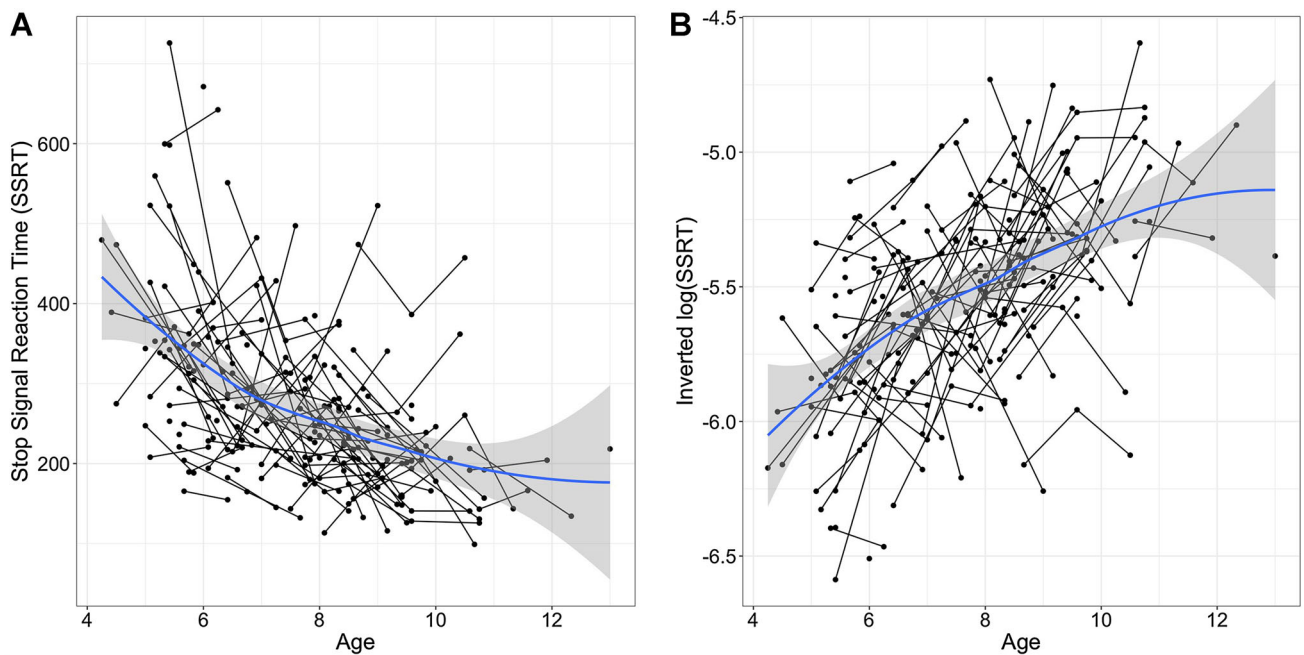


Fig. 2 **a** Stop-signal reaction time (SSRT) as a function of age. Lower SSRT scores indicate better performance (i.e., faster reaction times). The *blue line* is smooth loess fit to the raw data, with *shaded* 95% confidence intervals around the mean at each point. **b** Inverted

$\log(\text{SSRT})$ scores as a function of age, where higher scores indicate better performance. Inverted $\log(\text{SSRT})$ scores were used as the dependent measure in all models

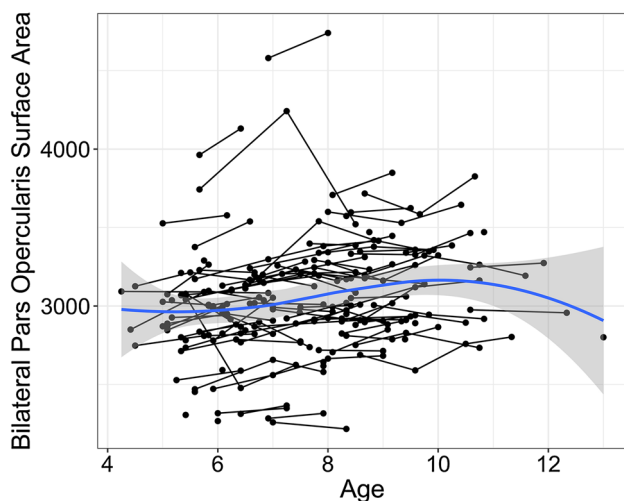


Fig. 3 Bilateral pars opercularis surface area is shown on the y-axis and age is shown on the x-axis. The *blue line* is smooth loess fit to the raw data, with *shaded* 95% confidence intervals for the mean at each point

iterative smoothing with 705 iterations, equivalent to ~ 33 mm full width at half maximum (Hagler et al. 2006).

Analysis

We tested the primary hypotheses with two separate region-of-interest analyses using longitudinal mixed-

effects regression models to predict inverted $\log(\text{SSRT})$ scores from cortical thickness and surface area of the pars opercularis. Analyses were carried out using the nlme package in R with a covariance structure of AR(1). Bilateral pars opercularis thickness and surface area were both centered (demeaned) prior to analysis and entered as fixed effects. Preliminary analyses investigating age and gender effects on stop-signal performance indicated an effect of gender, which was then included in all primary models investigating region-of-interest effects. Age and gender were centered (with female coded as negative and male as positive) and entered as fixed effects in the model, while subject ID was entered as a random effect. Total cortical surface area was centered and also included as a covariate in the surface area model to estimate the effect of relative surface area of the pars opercularis. Scanner was included as a covariate of no interest. For each of the two main hypotheses, a Bonferroni-corrected p value of 0.025 was used as the threshold for significance.

If either of the primary models examining bilateral pars opercularis was significant, interactions between age, gender, and the bilateral pars opercularis were included in a later model to determine if significant interactions were present. Finally, the left and right pars opercularis were examined in separate models.

Table 2 Inverted log(SSRT) scores were predicted using a linear mixed-effects model

| Fixed effects | B value | t value | p value |
|---|---------|---------|-----------|
| Age ^a | 0.10 | 7.62 | 0.0000*** |
| Gender ^a | −0.11 | −2.09 | 0.0389* |
| Bilateral pars opercularis thickness ^a | −0.27 | −1.33 | 0.1853 |
| Scanner | 0.12 | 1.37 | 0.1682 |

Predictors included bilateral pars opercularis thickness and covariates were age, gender, and scanner. Where noted, predictors were centered (demeaned)

Random effect: subject

^a Predictor has been centered (demeaned), * $p < .05$, *** $p < .001$

Results

The average stop-signal reaction time (SSRT) for all participants at baseline was 298.62 ms (SD 114.33 ms, $n = 110$). At the second visit, the average score was 258.50 ms (SD 95.04 ms, $n = 82$), at the third visit, the average score was 232.77 ms (SD 98.38 ms, $n = 32$), and at the fourth visit, the average score was 232.47 ms (SD 112.52 ms, $n = 8$) (see Table 1).

The hypothesis that cortical thickness in the bilateral pars opercularis would significantly predict inverted log(SSRT) scores was tested using a linear mixed-effects model covarying for age and gender (Table 2). Age and gender were both significant predictors of inverted log(SSRT) scores, with older participants ($t = 7.62$, $p < 0.001$) and females ($t = -2.09$, $p = 0.04$) performing better. However, there was no significant relationship between bilateral pars opercularis thickness and inverted log(SSRT) scores ($t = -1.33$, $p = 0.19$).

The hypothesis that relative surface area in the bilateral pars opercularis would significantly predict inverted log(SSRT) scores was tested with a similar linear mixed-effects model with total surface area as an additional covariate (Table 3). We found a significant, positive relationship between bilateral pars opercularis surface area and

inverted log(SSRT) scores ($t = 2.53$, $p = 0.01$), where larger surface area was associated with better performance on the stop-signal reaction time task. Consistent with the thickness model, older participants ($t = 7.76$, $p < 0.001$) performed better. Total cortical surface area was not related to inverted log(SSRT) scores.

Because the model examining bilateral pars opercularis surface area was significant, an additional follow-up analysis examined interactions between age, gender, and bilateral pars opercularis surface area (Table 4). In a model including all interactions between age, gender, and bilateral pars opercularis surface area, there were no significant interaction terms. We then performed follow-up analyses investigating left and right pars opercularis surface area separately (Table 5). Right pars opercularis surface area was positively related to better SSRT performance ($t = 2.60$, $p = 0.01$), but the effect of left pars opercularis surface area was not significant ($t = 1.21$, $p = 0.23$). Of note, we had two main a priori hypotheses regarding both bilateral pars opercularis surface area and thickness, and thus, we corrected for two statistical tests (see “Analysis”, above). The additional models exploring interactions between age, gender, and bilateral pars opercularis surface area and then left and right pars opercularis were not corrected for multiple comparisons as they were post hoc tests contingent upon prior significant effects.

To visualize the relationship between age and surface area, we created post hoc, vertex-wise maps of (uncorrected) t -statistics for the surface area effects on inverted log(SSRT) scores, controlling for age, gender, total cortical surface area (which were all demeaned, as above), and scanner. For this visualization, we used the baseline observations only ($N = 110$). The color scale codes t -statistic values, ranging from -5 to 5 with the boundary between warm and cool colors at zero. As reported above, there appears to be an association between relative surface area of the pars opercularis and SSRT performance. In addition, the visualization suggests that there may be modest positive and negative associations across both the left and right cortical surfaces in other regions (see Fig. 4).

Table 3 Inverted log(SSRT) scores were predicted using a linear mixed-effects model

| Fixed effects | B value | t value | p value |
|--|---------|---------|-----------|
| Age ^a | 0.10 | 7.76 | 0.0000*** |
| Gender ^a | −0.11 | −1.94 | 0.0553 |
| Bilateral pars opercularis surface area ^a | 0.00 | 2.53 | 0.0127* |
| Total cortical surface area ^a | −0.00 | −0.84 | 0.4049 |
| Scanner | 0.10 | 1.15 | 0.2535 |

Predictors included bilateral pars opercularis surface area, and covariates were age, gender, total cortical surface area, and scanner. Where noted, predictors were centered (demeaned)

Random effect: subject

^a Predictor has been centered (demeaned), * $p < .05$, *** $p < .001$

Table 4 Inverted log(SSRT) scores were predicted using a linear mixed-effects model

| Fixed effects | <i>B</i> value | <i>t</i> value | <i>p</i> value |
|--|----------------|----------------|----------------|
| Age ^a | 0.10 | 7.20 | 0.0000*** |
| Gender ^a | −0.11 | −1.97 | 0.0516 |
| Bilateral pars opercularis surface area ^a | 0.00 | 2.27 | 0.0250* |
| Total cortical surface area ^a | −0.00 | −0.91 | 0.3664 |
| Age ^a × gender ^a | 0.04 | 1.53 | 0.1289 |
| Age ^a × bilateral pars operc ^a | −0.00 | −0.56 | 0.5780 |
| Gender ^a × bilateral pars operc ^a | 0.00 | 0.81 | 0.4191 |
| Age ^a × gender ^a × bilateral pars operc ^a | 0.00 | 1.49 | 0.1384 |
| Scanner | 0.10 | 1.14 | 0.2574 |

Predictors included bilateral pars opercularis surface area and covariates were age, gender, total cortical surface area, and scanner. All interaction terms for age, gender, and bilateral pars opercularis surface area were included. Where noted, predictors were centered (demeaned)

Random effect: subject

^a Predictor has been centered (demeaned), * $p < .05$, *** $p < .001$

Table 5 Inverted log(SSRT) scores were predicted using linear mixed-effects models

| | <i>B</i> value | <i>t</i> value | <i>p</i> value |
|--|----------------|----------------|----------------|
| (a) Left pars opercularis model | | | |
| Age ^a | 0.11 | 7.92 | 0.0000*** |
| Gender ^a | −0.12 | −1.98 | 0.0505 |
| Left pars opercularis surface area ^a | 0.00 | 1.21 | 0.2295 |
| Total cortical surface area ^a | 0.00 | 0.10 | 0.9196 |
| Scanner | 0.11 | 1.18 | 0.2399 |
| (b) Right pars opercularis model | | | |
| Age ^a | 0.10 | 7.75 | 0.0000*** |
| Gender ^a | −0.10 | −1.62 | 0.1084 |
| Right pars opercularis surface area ^a | 0.00 | 2.60 | 0.0106* |
| Total cortical surface area ^a | −0.00 | −0.73 | 0.4659 |
| Scanner | 0.11 | 1.23 | 0.2214 |

(a) Surface area of the left pars opercularis with covariates age, gender, total cortical surface area, and scanner. (b) Surface area of the right pars opercularis with covariates age, gender, total cortical surface area, and scanner. Where noted, predictors were centered (demeaned)

Random effect: subject

^a Predictor has been centered (demeaned), * $p < .05$, *** $p < .001$

Discussion

This study investigated the relationship between variation in regional cortical morphology and performance variability on a response-inhibition task in a longitudinal, typically developing cohort. Based on the previous work, we focused our analyses on the pars opercularis of the inferior frontal gyrus (Aron and Poldrack 2006; Chambers et al. 2009; Eagle et al. 2008; Newman et al. 2015a). The primary finding from this study was that greater relative

cortical surface area in the bilateral pars opercularis was associated with better response inhibition. Thickness in this region showed no significant relationship with inhibitory functioning.

These results stand in contrast to a recent study in an adult sample showing that cortical thickness in this region, but not surface area, was associated with response inhibition. Specifically, better inhibitory functioning was associated with thinner cortex in the IFG. A number of methodological differences could contribute to the differences observed in these two studies. First, the previous study used percentage of commission errors on a go/no-go task to measure response inhibition, whereas the current study used an estimate of time needed to successfully inhibit a response on a stop-signal task. Second, the previous sample was comprised entirely of young adults, whereas the current sample was comprised of children ranging in age from 4 to 13. Third, the sample in the previous study was comprised of individuals diagnosed with ADHD as well as comparison participants, and, therefore, reflected wide variability in inhibitory functioning. The current sample was of typically developing children.

While there are differences in task demands between the go/no-go and stop-signal tasks, functional studies have linked both to the function of the IFG (Chikazoe et al. 2007; Chikazoe 2010; Aron et al. 2015). It may be that age plays a larger role in the different relationships observed between the pars opercularis and performance observed in these two studies. In a recent cross-sectional study linking anxiety to regional cortical morphology in children and adolescents, our group found that regional surface area, but not regional thickness, predicted behavior (Newman et al. 2015b). Specifically, greater relative surface area expansion of the ventromedial prefrontal cortex was associated with lower self-reported anxiety.

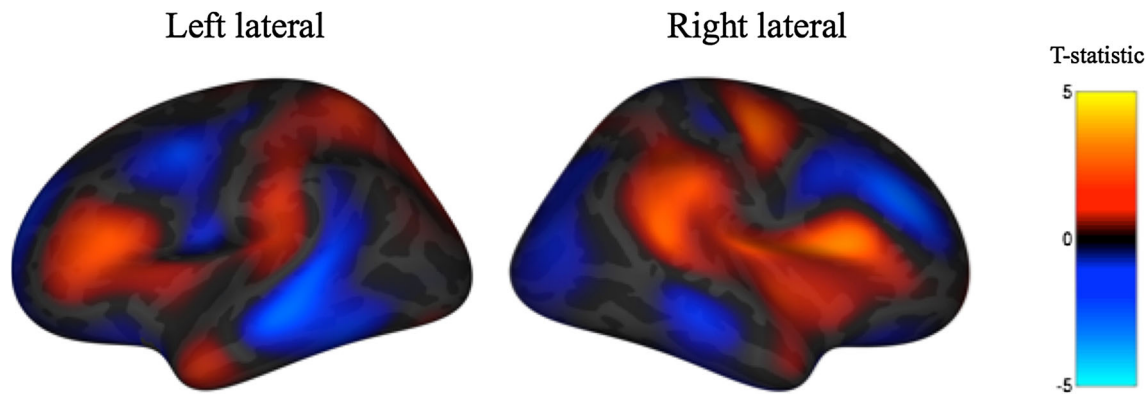


Fig. 4 Post hoc exploratory vertex-wise maps depicting effect of inverted $\log(\text{SSRT})$ on cortical surface area. Covariates include demeaned age and gender, and scanner. Heat maps reflect the t -statistic values on a scale from -5 to 5

Recent studies have shown that there is very little overlap between the genetic factors that influence surface area and thickness, although they are both highly heritable (Chen et al. 2011, 2012; Panizzon et al. 2009), and their developmental trajectories are markedly different (Brown et al. 2012; Jernigan et al. 2016a). On average, surface area increases steadily until middle childhood and begins to taper off in adolescence and early adulthood, and these changes occur at different rates in different regions of the cortex. In contrast, cortical thickness decreases consistently and continuously over the course of development (Brown et al. 2012; Walhovd et al. 2016). Therefore, future work should aim to assess the differential contributions of regional surface area and thickness to cognitive performance in developing cohorts.

The exploratory vertex-wise surface maps of the relationship between regional surface area and response inhibition show the predicted bilateral effect in the pars opercularis. These maps provide additional information to readers about the degree of variability across the cortical surface in the direction and magnitude of the relationship between relative surface area expansion and SSRT performance.

Conclusions and limitations

In this study, we examined a large number of typically developing children in a longitudinal cohort to determine whether we could confirm an association between regional morphology of the inferior frontal gyrus and performance on the stop-signal task. The results suggested a relationship between regional cortical surface area of the pars opercularis and performance on this motor-inhibitory task. In contrast to our group's earlier work highlighting the relationship between the cortical thickness of this region and inhibitory control task performance in adults (Newman et al. 2015a), it appears that the relative cortical surface area of the pars opercularis may be especially

important for the development of inhibitory control, although directly assessing this relationship requires further examination. This highlights the possibility that different cortical phenotypes may show differential or unique relationships to behavioral functions at different points during development. However, among the many possible influences on developing brain structure and response inhibition, this study evaluated only age and gender as covariates. In addition to age and gender, there is evidence that genetics, experience, socioeconomic status, and many other factors could affect both measures of brain structure and cognitive performance (Chen et al. 2012; Noble et al. 2015). Future analyses should also evaluate other covariates thought to relate to both structural brain development and response inhibition to form a more complete picture of the factors influencing these relationships.

Acknowledgements The authors want to thank the volunteer research participants and parents who participated in this study. In addition, the authors want to thank the staff of the Center for Human Development (CHD) at UC San Diego and the Center for Multimodal Imaging and Genetics (CMIG) at UC San Diego for their work in gathering and processing the behavioral and imaging data.

Author contributions LC conducted the analyses included in the paper with assistance from EN and CR, created the table and figures, and did the majority of the writing. EN and TJ assisted in interpretation of results and contributed a significant amount of writing and editing. WT aided in method selection and statistical interpretation of the results. TJ, NA, and TB were involved at different stages of the design and execution of the PLING study and provided oral and written feedback on the results and discussion. AM developed and DH executed the multimodal imaging protocol for image acquisition and processing. DH created the t -statistic maps.

Compliance with ethical standards

Funding sources Pediatric Imaging, Neurocognition and Genetics (PING): RC2DA029475. Pediatric (Longitudinal) Imaging, Neurocognition and Genetics (PLING): R01HD061414. Role of Emotion and Choice in Learning (REaCH): R24HD075489.

Ethics approval and consent to participate All procedures performed were approved by the Institutional Review Board of the University of California, San Diego. Verbal assent was obtained for all participants under 7 years, and written assent was obtained for all participants 7 years and older. Parents or guardians provided written consent.

Availability of data and materials The baseline imaging data for a small portion of participants included in the current study are available from the Pediatric Imaging, Neurocognition, and Genomics (PING) data set through the NIMH Data Archive (<https://data-archive.nimh.nih.gov>). Additional data are available by request from the senior author (TLJ).

Conflict of interest Anders M. Dale is a founder of and holds equity interest in Cortechs Labs, La Jolla, CA, USA, and serves on its scientific advisory board. The terms of this arrangement have been reviewed and approved by UCSD in accordance with its conflict of interest policies. The other co-authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Open Access This article is distributed under the terms of the Creative Commons Attribution 4.0 International License (<http://creativecommons.org/licenses/by/4.0/>), which permits unrestricted use, distribution, and reproduction in any medium, provided you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made.

References

- Aron AR, Poldrack RA (2006) Cortical and subcortical contributions to stop signal response inhibition: role of the subthalamic nucleus. *J Neurosci* 26:2424–2433. doi:10.1523/jneurosci.4682-05.2006
- Aron AR, Robbins TW, Poldrack RA (2004) Inhibition and the right inferior frontal cortex. *Trends Cogn Sci* 8(4):170–177. doi:10.1016/j.tics.2004.02.010
- Aron AR, Cai W, Badre D, Robbins TW (2015) Evidence supports specific braking function for inferior PFC. *Trends Cogn Sci* 19(12):711–712. doi:10.1016/j.tics.2015.09.001
- Barkley RA (1997) Behavioral inhibition, sustained attention, and executive functions: constructing a unifying theory of ADHD. *Psychol Bull* 121(1):65–94. doi:10.1037/0033-2909.121.1.65
- Batty MJ, Liddle EB, Pitiot A, Toro R, Groom MJ (2010) Cortical gray matter in attention-deficit/hyperactivity disorder: a structural magnetic resonance imaging study. *J Am Acad Child Adolesc Psychiatry* 49(3):229–238. doi:10.1097/00004583-201003000-00006
- Bell EC, Willson MC, Wilman AH, Dave S, Silverstone PH (2006) Males and females differ in brain activation during cognitive tasks. *Neuroimage* 30:529–538. doi:10.1016/j.neuroimage.2005.09.049
- Brown TT, Kuperman JM, Chung Y, Erhart M, McCabe C, Hagler DJ, Venkatraman VK, Akshoomoff N, Amaral DG, Bloss CS, Casey BJ, Chang L, Ernst, TM, Frazier JA, Gruen JR, Kaufmann WE, Kenet T, Kennedy DN, Murray SS, Sowell ER, Jernigan TL, Dale AM (2012) Neuroanatomical assessment of biological maturity. *Curr Biol* 22(18):1693–1698. doi:10.1016/j.cub.2012.07.002
- Casey BJ, Trainor RJ, Orendi JL, Schubert AB, Nystrom LE, Giedd JN, Castellanos X, Haxby JV, Noll DC, Cohen JD, Forman SD, Dahl RE, Rapoport JL (1997) A developmental functional MRI study of prefrontal activation during performance of a Go-No-Go task. *J Cogn Neurosci* 9(6):835–847. doi:10.1162/jocn.1997.9.6.835
- Casey BJ, Oliveri ME, Insel T (2014) A neurodevelopmental perspective on the research domain criteria (RDoC) framework. *Biol Psychiatry* 76:350–353. doi:10.1016/j.biopsych.2014.01.006
- Chambers CD, Garavan H, Bellgrove MA (2009) Insights into the neural basis of response inhibition from cognitive and clinical neuroscience. *Neurosci Biobehav Rev* 33(5):631–646. doi:10.1016/j.neubiorev.2008.08.016
- Chen CH, Panizzon MS, Eyer LT, Jernigan TL, Thompson W, Fennema-Notestine C, Jak AJ, Neale MC, Franz CE, Hamza S, Lyons MJ, Grant MD, Fischl B, Seidman LJ, Tsuang MT, Kremen WS. (2011) Genetic influences on cortical regionalization in the human brain. *Neuron* 72(4):537–544. doi:10.1016/j.neuron.2011.08.021
- Chen C-H, Gutierrez ED, Thompson W, Panizzon MS, Jernigan TL, Eyer LT, Fennema-Notestine C (2012) Hierarchical genetic organization of human cortical surface area. *Science* 335(6076):1634–1636. doi:10.1126/science.1215330
- Chikazoe J (2010) Localizing performance of go/no-go tasks to prefrontal cortical subregions. *Curr Opin Psychiatry* 23(3):267–272. doi:10.1097/ycp.0b013e3283387a9f
- Chikazoe J, Konishi S, Asari T, Jimura K, Miyashita Y (2007) Activation of right inferior frontal gyrus during response inhibition across response modalities. *J Cogn Neurosci* 19(1):69–80. doi:10.1162/jocn.2007.19.1.69
- Conners C, Epstein J, Angold A, Klaric J (2003) Continuous performance test performance in a normative epidemiological sample. *J Abnorm Child Psychol* 31(5):555–562. doi:10.1023/a:1025457300409
- Desikan RS, Ségonne F, Fischl B, Quinn BT, Dickerson BC, Blacker D, Buckner RL, Dale AM, Maguire RP, Hyman BT, Albert MS, Killiany RJ (2006) An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. *NeuroImage* 31(3):968–980. doi:10.1016/j.neuroimage.2006.01.021
- Eagle DM, Baunez C, Hutcheson DM, Lehmann O, Shah AP, Robbins TW (2008) Stop-signal reaction-time task performance: role of prefrontal cortex and subthalamic nucleus. *Cereb Cortex* 18(1):178–188. doi:10.1093/cercor/bhm044
- Ethridge LE, Soilleux M, Nakonezny PA, Reilly JL, Kristian Hill S, Keefe RSE et al (2014) Behavioral response inhibition in psychotic disorders: diagnostic specificity, familiarity and relation to generalized cognitive deficit. *Schizophr Res* 159(2–3):491–498. doi:10.1016/j.schres.2014.08.025
- Fischl B (2004) Automatically parcellating the human cerebral cortex. *Cereb Cortex* 14(1):11–22. doi:10.1093/cercor/bhg087
- Fischl B, Sereno MI, Tootell RBH, Dale AM (1999) High-resolution intersubject averaging and a coordinate system for the cortical surface. *Hum Brain Mapp* 8:272–284. doi:10.1002/(sici)1097-0193(1999)8:4<272:aid-hbm10>3.0.co;2-4
- Fjell AM, Walhovd KB, Brown TT, Kuperman JM, Chung Y, Hagler DJ, Venkatraman V, Roddey JC, Erhart M, McCabe C, Akshoomoff N, Amaral DG, Bloss CS, Libiger O, Darst BF, Schork NJ, Casey BJ, Chang L, Ernst TM, Gruen JR, Kaufmann WE, Kenet T, Frazier J, Murray SS, Sowell ER, van Zijl P, Mostofsky S, Jernigan TL, Dale AM (2012) Multimodal imaging of the self-regulating developing brain. *Proc Natl Acad Sci* 109(48):19620–19625. doi:10.1073/pnas.1208243109
- Forstmann BU, Jahfari S, Scholte HS, Wolfensteller U, van den Wildenberg WPM, Ridderinkhof KR (2008) Function and structure of the right inferior frontal cortex predict individual differences in response inhibition: a model-based approach. *J Neurosci* 28(39):9790–9796. doi:10.1523/jneurosci.1465-08.2008

- Fray PJ, Robbins TW, Sahakian BJ (1996) Neuropsychiatric applications of CANTAB. *Int J Geriatr Psychiatry* 11:329–336. doi:[10.1002/\(sici\)1099-1166\(199604\)11:4<329:aid-gps453>3.0.co;2-6](https://doi.org/10.1002/(sici)1099-1166(199604)11:4<329:aid-gps453>3.0.co;2-6)
- Garavan H, Hester R, Murphy K, Fassbender C, Kelly C (2006) Individual differences in the functional neuroanatomy of inhibitory control. *Brain Res* 1105(1):130–142. doi:[10.1016/j.brainres.2006.03.029](https://doi.org/10.1016/j.brainres.2006.03.029)
- Hagler DJ, Saygin AP, Sereno MI (2006) Smoothing and cluster thresholding for cortical surface-based group analysis of fMRI data. *NeuroImage* 33(4):1093–1103. doi:[10.1016/j.neuroimage.2006.07.036](https://doi.org/10.1016/j.neuroimage.2006.07.036)
- Insel T, Cuthbert B, Garvey M, Heinssen R, Pine DS, Quinn K et al (2010) Research domain criteria (RDoC): toward a new classification framework for research on mental disorders. *Am J Psychiatry* 167(7):748–751. doi:[10.1176/appi.ajp.2010.09091379](https://doi.org/10.1176/appi.ajp.2010.09091379)
- Jernigan Terry L, Baaré William FC, Stiles Joan, Madsen Kathrine Skak (2011) Postnatal brain development: structural imaging of dynamic neurodevelopmental processes. *Brain Res* 189:77–92. doi:[10.1016/b978-0-444-53884-0.00019-1](https://doi.org/10.1016/b978-0-444-53884-0.00019-1)
- Jernigan TL, Brown TT, Bartsch H, Dale AM (2016a) Toward an integrative science of the developing human mind and brain: focus on the developing cortex. *Dev Cogn Neurosci* 18:2–11. doi:[10.1016/j.dcn.2015.07.008](https://doi.org/10.1016/j.dcn.2015.07.008)
- Jernigan TL, Brown TT, Hagler DJ, Akshoomoff N, Bartsch H, Newman E, Thompson WK, Bloss CS, Murray SS, Schork N, Kennedy DN, Kuperman JM, McCabe C, Chung Y, Libiger O, Maddox M, Casey BJ, Chang L, Ernst TM, Frazier JA, Gruen JR, Sowell ER, Kenet T, Kaufmann WE, Mostofsky S, Amaral DG, Dale AM (2016b) The pediatric imaging, neurocognition, and genetics (PING) data repository. *NeuroImage* 124:1149–1154. doi:[10.1016/j.neuroimage.2015.04.05](https://doi.org/10.1016/j.neuroimage.2015.04.05)
- Johnstone SJ, Dimoska A, Smith JL, Barry RJ, Pleffer CB, Chiswick D, Clarke AR (2007) The development of stop-signal and go/no go response inhibition in children aged 7–12 years: performance and event-related potential indices. *Int J Psychophysiol* 63(1):25–38. doi:[10.1016/j.ijpsycho.2006.07.001](https://doi.org/10.1016/j.ijpsycho.2006.07.001)
- Liddle PF, Kiehl KA, Smith AM (2001) Event related fMRI study of response inhibition. *Hum Brain Mapp* 12(2):100–109. doi:[10.1002/1097-0193\(200102\)12:2<100:AID-HBM1007>0.CO;2-6](https://doi.org/10.1002/1097-0193(200102)12:2<100:AID-HBM1007>0.CO;2-6)
- Liu J, Zubieta JK, Heitzeg M (2012) Sex differences in anterior cingulate cortex activation during impulse inhibition and behavioral correlates. *Psychiatry Res Neuroimaging* 201(1):54–62. doi:[10.1016/j.psychres.2011.05.008](https://doi.org/10.1016/j.psychres.2011.05.008)
- Logan GD, Cowan WB (1984) On the ability to inhibit thought and action: a theory of an act of control. *Psychol Rev* 91:295–327. doi:[10.1037//0033-295x.91.3.295](https://doi.org/10.1037//0033-295x.91.3.295)
- Madsen KS, Baaré WFC, Vestergaard M, Skimminge A, Ejersbo LR, Ramsøy TZ, Gerlach C, Åkeson P, Paulson OB, Jernigan TL (2010) Response inhibition is associated with white matter microstructure in children. *Neuropsychologia* 48(4):854–862. doi:[10.1016/j.neuropsychologia.2009.11.001](https://doi.org/10.1016/j.neuropsychologia.2009.11.001)
- Newman E, Jernigan TL, Lisdahl KM, Tamm L, Tapert SF, Potkin SG, Mathalon D, Molina B, Bjork J, Castellanos FX, Swanson J, Kuperman JM, Bartsch H, Chen CH, Dale AM, Epstein JN (2015a) Go/no go task performance predicts cortical thickness in the caudal inferior frontal gyrus in young adults with and without ADHD. *Brain Imaging Behav* 10(3):880–892. doi:[10.1007/s11682-015-9453-x](https://doi.org/10.1007/s11682-015-9453-x)
- Newman E, Thompson WK, Bartsch H, Hagler DJ, Chen CH, Brown TT, Kuperman JM, McCabe C, Chung Y, Libiger O, Akshoomoff N, Bloss CS, Casey BJ, Chang L, Ernst TM, Frazier JA, Gruen JR, Kennedy DN, Murray SS, Sowell ER, Schork N, Kenet T, Kaufmann WE, Mostofsky S, Amaral DG, Dale AM, Jernigan TL (2015b) Anxiety is related to indices of cortical maturation in typically developing children and adolescents. *Brain Struct Funct* 221(6):3013–3025. doi:[10.1007/s00429-015-1085-9](https://doi.org/10.1007/s00429-015-1085-9)
- Noble KG, Houston SM, Brito NH, Bartsch H, Kan E, Kuperman JM, Akshoomoff N, Amaral DG, Bloss CS, Libiger O, Schork NJ, Murray SS, Casey BJ, Chang L, Ernst TM, Frazier JA, Gruen JR, Kennedy DN, Van Zijl P, Mostofsky S, Kaufmann WE, Keating B, Kenet T, Dale AM, Jernigan TL, Sowell ER, For the Pediatric Imaging, Neurocognition, and Genetics Study (2015) Family income, parental education and brain structure in children and adolescents. *Nat Neurosci* 18(5):773–778. doi:[10.1038/nn.3983](https://doi.org/10.1038/nn.3983)
- Panizzon MS, Fennema-Notestine C, Eyler LT, Jernigan TL, Prom-Wormley E, Neale M, Jacobson K, Lyons MJ, Grant MD, Franz CE, Xian H, Tsuang M, Fischl B, Seidman L, Dale A, Kremen WS (2009) Distinct genetic influences on cortical surface area and cortical thickness. *Cereb Cortex* 19(11):2728–2735. doi:[10.1093/cercor/bhp026](https://doi.org/10.1093/cercor/bhp026)
- Proal E, Reiss PT, Klein RG, Mannuzza S, Gotimer K, Ramos-Olazagasti MA et al (2011) Brain gray matter deficits at 33-year follow-up in adults with attention-deficit/hyperactivity disorder established in childhood. *Arch Gen Psychiatry* 68(11):1122–1134. doi:[10.1001/archgenpsychiatry.2011.117](https://doi.org/10.1001/archgenpsychiatry.2011.117)
- Rosvold HE, Mirsky AF, Sarason I, Bransome ED, Beck LH (1956) A continuous performance test of brain damage. *J Consult Psychol* 20(5):343–350. doi:[10.1037/h0043220](https://doi.org/10.1037/h0043220)
- Rubia K, Hyde Z, Giampietro V, Smith A (2010) Effects of age and sex on developmental neural networks of visual–spatial attention allocation. *NeuroImage* 51:817–827. doi:[10.1016/j.neuroimage.2010.02.058](https://doi.org/10.1016/j.neuroimage.2010.02.058)
- Rubia K, Lim L, Ecker C, Halarai R, Giampietro V, Simmons A, Brammer M, Smith A (2013) Effects of age and gender on neural networks of motor response inhibition: from adolescence to mid-adulthood. *NeuroImage* 83:690–703. doi:[10.1016/j.neuroimage.2013.06.078](https://doi.org/10.1016/j.neuroimage.2013.06.078)
- Shaw P, Gilliam M, Liverpool M, Weddle C, Malek M, Sharp W, Greenstein D, Evans A, Rapoport J, Giedd J (2011) Cortical development in typically developing children with symptoms of hyperactivity and impulsivity: support for a dimensional view of attention deficit hyperactivity disorder. *Am J Psychiatry* 168(2):143–151. doi:[10.1176/appi.ajp.2010.10030385](https://doi.org/10.1176/appi.ajp.2010.10030385)
- Shaw P, Malek M, Watson B, Greenstein D, de Rossi P, Sharp W (2013) Trajectories of cerebral cortical development in childhood and adolescence and adult attention-deficit/hyperactivity disorder. *Biol Psychiatry* 74(8):599–606. doi:[10.1016/j.biopsych.2013.04.007](https://doi.org/10.1016/j.biopsych.2013.04.007)
- Tamm L, Menon V, Reiss AL (2002) Maturation of brain function associated with response inhibition. *J Am Acad Child Adolesc Psychiatry* 41(10):1231–1238. doi:[10.1097/00004583-200210000-0001](https://doi.org/10.1097/00004583-200210000-0001)
- Walhovd KB, Fjell AM, Giedd J, Dale AM, Brown TT (2016) Through thick and thin: a need to reconcile contradictory results on trajectories in human cortical development. *Cereb Cortex*. doi:[10.1093/cercor/bhv301](https://doi.org/10.1093/cercor/bhv301)
- Weiss E, Siedentopf CM, Hofer A, Deisenhammer EA, Hoptman MJ, Kremser C, Golaszewski S, Felber S, Fleischhacker WW, Delazer M (2003) Sex differences in brain activation pattern during a visuospatial cognitive task: a functional magnetic resonance imaging study in healthy volunteers. *Neurosci Lett* 344(3):169–172. doi:[10.1016/s0304-3940\(03\)00406-3](https://doi.org/10.1016/s0304-3940(03)00406-3)
- Wierenga Lara M, Langen Marieke, Oranje Bob, Durston Sarah (2014) Unique developmental trajectories of cortical thickness and surface area. *NeuroImage* 87:120–126. doi:[10.1016/j.neuroimage.2013.11.010](https://doi.org/10.1016/j.neuroimage.2013.11.010)
- Wright L, Lipszyc J, Dupuis A, Thayapararajah SW, Schachar R (2014) Response inhibition and psychopathology: a meta-analysis of go/no-go task performance. *J Abnorm Psychol* 123(2):429–439. doi:[10.1037/a0036295](https://doi.org/10.1037/a0036295)