Age-related differences in the neural correlates of trial-to-trial variations of reaction time

Nancy E. Adleman a,b,*, Gang Chen c, Richard C. Reynolds c, Anna Frackman b,1, Varun Razdan b,2, Daniel H. Weissman d, Daniel S. Pine b, Ellen Leibenluft b

a Department of Psychology, The Catholic University of America, 620 Michigan Ave., NE, Washington, DC 20064, USA
b Emotion and Development Branch, National Institute of Mental Health, National Institutes of Health, 9000 Rockville Pike, Bethesda, MD 20892, USA
c Scientific and Statistical Computing Core, National Institute of Mental Health, National Institutes of Health, 9000 Rockville Pike, Bethesda, MD 20892, USA
d Department of Psychology, University of Michigan, 530 Church St, Ann Arbor, MI 48109, USA

A R T I C L E   I N F O

Article history:
Received 10 August 2015
Received in revised form 6 May 2016
Accepted 8 May 2016
Available online 12 May 2016

Keywords:
Reaction time
Variation
fMRI
Displaying RT-BOLD

A B S T R A C T

Intra-subject variation in reaction time (ISVRT) is a developmentally-important phenomenon that decreases from childhood through young adulthood in parallel with the development of executive functions and networks. Prior work has shown a significant association between trial-by-trial variations in reaction time (RT) and trial-by-trial variations in brain activity as measured by the blood-oxygenated level-dependent (BOLD) response in functional magnetic resonance imaging (fMRI) studies. It remains unclear, however, whether such “RT-BOLD” relationships vary with age. Here, we determined whether such trial-by-trial relationships vary with age in a cross-sectional design. We observed an association between age and RT-BOLD relationships in 11 clusters located in visual/occipital regions, frontal and parietal association cortex, precentral/postcentral gyrus, and thalamus. Some of these relationships were negative, reflecting increased BOLD associated with decreased RT, manifesting around the time of stimulus presentation and positive several seconds later. Critically for present purposes, all RT-BOLD relationships increased with age. Thus, RT-BOLD relationships may reflect robust, measurable changes in the brain-behavior relationship across development.

© 2016 The Authors. Published by Elsevier Ltd. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

1. Introduction

Intra-subject variation in reaction time (ISVRT) is a measure of a subject’s consistency in responding to stimuli across a task, often quantified as the standard deviation of RT across a task epoch; higher ISVRT, reflected in larger standard deviations, is associated with greater variability, or inconsistency, of responses. ISVRT is a developmentally-important phenomenon; it decreases from childhood through young adulthood (Williams et al., 2005, 2007; Dykert et al., 2012; Li et al., 2009, 2004; Tamnes et al., 2012), paralleling the behavioral development of executive functions such as attention and self-regulation (Gomez-Guerrero et al., 2011), as well as structural brain development within the frontal lobes (Marshall et al., 2008; Giedd, 2004; Gogtay et al., 2004). Further, atypical ISVRT is associated with developmental disorders of executive control linked to atypical brain development (Bora et al., 2006; Leth-Steenensen et al., 2000; Kaiser et al., 2008; Adleman et al., 2014, 2012; Brotman et al., 2009; Castellanos et al., 2005; Epstein et al., 2011). Thus, determining how the relationship between ISVRT and brain activity supporting executive functions varies with age may ultimately inform our understanding of both normal and atypical cognitive development.

To elucidate the development of neural mechanisms mediating age-related changes in behavior, it is important to map brain-behavior associations across age (Pfeifer and Allen, 2012). Poldrack has emphasized the importance of quantifying such associations precisely (Poldrack, 2014). However, most developmental studies examine the relationship between activation and neural responses...
averaged over time (Poldrack, 2014), rather than at the level of specific trials. ISVRT is a particularly well-suited construct with which to delineate the development of brain-behavior associations in a precise fashion because 1) ISVRT has been shown to change with age, 2) RT varies at the level of specific trials, and 3) RT can be measured easily.

One approach to directly mapping brain-behavior relationships employs functional magnetic resonance imaging (fMRI) to link trial-specific changes in RT to trial-specific changes in the BOLD signal (Weissman et al., 2006). Using this approach in adults, several researchers have reported robust “RT-BOLD relationships” in frontal and parietal regions during executive function tasks (Weissman et al., 2006; Chee and Tan, 2010; Prado and Weissman, 2011; Yarkoni et al., 2009). Moreover, some researchers have reported that the size of the RT-BOLD relationship varies across populations who differ in their attentional abilities. For example, in frontal and parietal regions crucial for attention, stronger RT-BOLD relationships manifest in individuals who exhibit minimal, relative to marked, effects of sleep deprivation on attention (Chee and Tan, 2010; Chee et al., 2008). Similarly, investigating developmental differences in the RT-BOLD relationship may help to reveal which neural processes underlie developmental differences in executive functioning (Plude et al., 1994; Anderson et al., 2001; Rueda et al., 2004; Ridderinkhof and van der Stelt, 2000).

Along these lines, it is presently unclear whether children and adolescents show similar RT-BOLD relationships to adults. Carp and colleagues found weak or absent RT-BOLD associations in a relatively small sample of children and adolescents (n = 18) as compared to a group of young adults (n = 21) (Carp et al., 2012). Analogous to the above-noted findings on sleep deprivation, weaker RT-BOLD associations in children and adolescents compared to adults could reflect reduced attentional capacity early in development (Plude et al., 1994; Rueda et al., 2004; Ridderinkhof and van der Stelt, 2000). However, Kim and colleagues identified strong, linear RT-BOLD relationships in a larger (n = 28) sample of children (Kim et al., 2013), thereby raising the possibility that the first study was underpowered. Further, neither study employed age as a continuous variable to investigate more specifically how the RT-BOLD relationship varies cross-sectionally with age. Finally, both studies modeled RT-BOLD relationships using a canonical hemodynamic response function, which precludes the ability to distinguish between RT-BOLD relationships that occur “early” versus “late” in the average time-locked BOLD response to a trial type. Nonetheless, these “early” and “late” relationships can be quite different, possibly in ways that relate to early lapses of attention and later compensatory effects (Weissman et al., 2006). For all of these reasons, it remains unclear whether and when in the course of a neural response the RT-BOLD relationship differs between children and adults.

The goal of the present study was to answer these questions using methods that characterize RT-BOLD relationships throughout the course of each trial during the performance of a selective attention task that requires the engagement of executive function (Weissman et al., 2006). To this end, we used a finite impulse response (FIR) model to derive empirically the average event-related BOLD response to target stimuli in a selective attention task (Ollinger et al., 2001). We then compared both “early” and “late” time points of the RT-BOLD relationship in healthy children and adults. Finally, we employed age as a continuous variable to investigate more specifically how the RT-BOLD relationship varies across development.

Finally, initial studies examining the relationship between ISVRT and brain activation correlated overall subject ISVRT measures with task-related average neural responses across individuals (e.g., Bellgrove et al., 2004). While these studies shed light on the overall relationship between a subject’s level of variability and his/her brain activity as compared to other subjects, they could not isolate the relationships between RT variability and BOLD response at the level of a single trial. One of the first experiments to include a measure of RT as a regressor in fMRI analysis, and thus to examine parametric modulation of the BOLD response by RT was by Gilbert and colleagues (Gilbert et al., 2006). This study used log(RT) during low-demand tasks as a regressor in the fMRI general linear model. Other studies have utilized mean and, in some cases, standard deviations of RTs to calculate and standardize individual trial RT either within (Yarkoni et al., 2009) or across (Hahn et al., 2007) subjects. These standardized trial RTs are included as regressors in the general linear model, often using a standard HRF function (e.g., Carp et al., 2012; Kim et al., 2013; Gilbert et al., 2006; Hahn et al., 2007).

However, as stated by Yarkoni and colleagues (Yarkoni et al., 2009), differences in RT may not only be related to changes in the amplitude of the BOLD signal and thus, some studies utilize a FIR model to estimate the RT-BOLD relationship (Weissman et al., 2006; Yarkoni et al., 2009) to avoid making assumptions about its shape. The analysis in the present study was modeled after that of Weissman et al. (2006), and hence we employed similar techniques for RT standardization and modeling the RT-BOLD relationship. However, this study is the first to examine age differences in the RT-BOLD relationship using a FIR model and including age as a continuous variable.

2. Materials and methods

2.1. Participants

The protocol was approved by the National Institutes of Health Intramural Research Program Combined Neuroscience Institutional Review Board, which is accredited by the Association for the Accreditation of Human Research Protection Programs, Inc. Fifty-seven individuals participated in the study. Data were excluded from seven: two individuals were excluded for excessive head motion during the fMRI scan (average motion per TR before censoring >0.25 mm or more than 8% of TRs censored for motion) and five individuals were excluded for poor task performance (accuracy below 70% on any single run). Thus, fifty healthy participants (33 female, 17 male), ranging in age from 9.5 to 42.9 years (mean: 21.9 ± 7.0), were included in the final analyses (see Supplemental Fig. 1 for age histogram). Written consent and assent were acquired before the experiment began. Semi-structured psychiatric interviews by trained clinicians confirmed that participants had no history of psychiatric illness or psychotropic medication use, and no first-degree relative with a mood or anxiety disorder. Participants were in good physical health as indicated by medical history and physical exam. Participants were excluded for IQ < 70 on the Wechsler Abbreviated Scale of Intelligence (Clements, 1965), history of substance abuse within 2 months, head trauma, neurological disorder, pervasive developmental disorder, or contraindications to MRI.

2.2. In-scanner behavioral paradigm

Participants performed a modified global-local selective attention task (Weissman et al., 2006) programmed in E-prime and projected onto a screen viewed via a mirror mounted on the head coil. There were four stimuli that appeared equally often. Each stimulus was a large letter (“H” or “S”) made up of several identical smaller letters (“Hs” or “Ss”; see Supplemental Fig. 2). Half the stimuli were congruent (e.g., a large H made up of small H) while the other half were incongruent (e.g., a large S made up of small Hs). All stimuli appeared centered on a red fixation point. Moreover, each stimulus appeared for 200 ms and was followed by 2300 ms of fixation.
In alternating runs, participants were asked to identify the large
global letter (H or S) or the small local letters (Hs or Ss) that
appeared in each trial. They did so by pressing one of two but-
tons on a two-button response device using either the left thumb
or the right thumb. Stimulus presentation and jitter orders were
created with AFNI’s make_random_timing.py program. Thus, the
maximum inter-stimulus interval varied across run orders, as opti-
mized by this program. The inter-stimulus interval was jittered
in units of the TR (1250 ms) and ranged from 2.5 s to 12.5–16.25 s
(mean inter-stimulus interval: 3.98 s). Participants were pseudo-
randomly assigned to one of 80 run orders selected from 10,000
iterations. We included six runs, each of which contained 96 trials:
48 congruent and 48 incongruent. At the end of each run, the over-
all number of correct responses, errors, and percent correct were
displayed. Further details about the task and scan parameters are
available in (Chen et al., 2014).

2.3. Imaging acquisition

Neuroimaging data were collected on a 3-T General Electric
Signa scanner and 32-channel head coil. After acquisition of a sagi-
tal localizer scan, an automated shim calibrated the magnetic field
to reduce signal dropout due to susceptibility artifact. Six functional
runs of 304 time points each were acquired using 24 contiguous
5-mm interleaved axial slices covering the entire brain. These scans
used a 64 × 64 matrix with echoplanar single shot gradient
echo T2* weighting (TR = 1250 ms; TE = 25 ms; FOV = 240 mm; flip
angle = 35°), yielding 3.75 × 3.75 × 5 mm voxels. To reach longitudi-
nal magnetization equilibrium, the six initial images from each run
were discarded. A high-resolution structural MPRAGE scan (1-mm
interleaved sagittal slices; TE = min full; TI = 425; FOV = 256; f tag x
phase = 256 × 256; flip angle = 7°; 1 mm³ voxels) was also acquired
during the same session for coregistration with the functional
data. Because of the inhomogeneity introduced by a 32-channel
head coil, an ASSET calibration scan followed by a proton-density
weighted (PDW) scan with similar parameters to the MPRAGE scan
were conducted immediately prior to acquisition of the structural
scan, and the PDW scan was used to correct the MPRAGE before pre-
processing steps were conducted (in 7 subjects, the uncorrected
MPRAGE was used in pre-processing due lack of alignment between
the PDW and MPRAGE).

2.4. Behavioral data analysis

Trials were considered errors if a response occurred in less
than 100 ms from the onset on the stimulus, no response was
made within 2500 ms, or the response was incorrect. Five par-
ticipants whose accuracy fell below 70% for at least a single run
were excluded. For the remaining 50 participants, we calculated
mean reaction times for correct trials. As a behavioral measure of
ISVRT, we used each participant’s coefficient of variation of RT
(standard deviation of RT divided by mean RT). We employed this
measure because the mean and standard deviation of RT may be
highly correlated (Wagenmakers and Brown, 2007). Nonparamet-
ric correlational analyses were run between age and the following
measures: mean accuracy for all trials, mean RT for all trials and
for each trial type independently, and coefficient of variation of RT
across all trials and for each trial type independently.

2.5. Imaging analysis

Functional magnetic resonance imaging imaging data were analyzed
using Analysis of Functional NeuroImages (AFNI; http://afni.nimh.
nih.gov/afni; (Cox, 1996)) using standard preprocessing including slice-timing alignment, alignment of all volumes to base volume
and registration to Talairach template, spatial smoothing (6-mm
FWHM kernel), masking, and intensity scaling. TRs n and n + 1
were censored if the normed motion vector between time points
was greater than 1 mm. Participants were excluded if the average
motion per TR before censoring was >0.25 mm or if more than 8% of
TRs were censored for motion. There was no correlation between
age and average motion per TR before censoring (p’s > 0.44). Finally,
motion parameters were included as covariates in the regression
analysis.

Mean standardized RT was calculated for each trial by using the
RT for that individual trial and subtracting from it that partici-
pant’s mean RT value for that trial type (congruent or incongruent)
in the same run (Weissman et al., 2006). Therefore, trial-specific
mean-standardized RT gauged participant’s RT for each individual
trial, referenced to his or her overall performance in that condi-
tion: lower mean-standardized RT indicated faster relative RT and
higher mean-standardized RT indicated slower relative RT.

To avoid prior assumptions about the expected BOLD response
shape and to quantify precisely the chronometry of variation in
the RT-BOLD relationship, we analyzed the fMRI data using a finite
impulse response (FIR) linear regression model. Each trial was mod-
eled with 13 basis functions (i.e., tents), each of which spanned 1 TR.
In other words, each trial was modeled with a 13 TR (15 s) time win-

dow starting 2.5 s before stimulus onset and continuing for a total
of 15 s (i.e., final tent at 12.5 s after stimulus onset), resulting in 13
regressors per stimulus type (i.e., condition).

For each condition (i.e., congruent, incongruent), we created
26 regressors as follows. First, we modeled the hemodynamic
response associated with average RT across trials with 13 TENT
basis functions (or linear splines) that capture the BOLD response
over a period of 15 s with a TR of 1.25 s. In addition, to obtain
the RT-modulated effect per condition, we used the de-meaned
mean-standardized RT values at all the trials of the condition and
then multiplied those 13 TENT basis functions, creating another
13 regressors (i.e., 13 TENT basis functions and 13 RT-modulated
functions). The de-meaning step allowed us to obtain the response
shape and magnitude through the first set of 13 basis functions.
Finally, a third-order Legendre polynomial modeling baseline drift,
incorrect trials, and 6 head motion parameters were included in
each participant’s model to control for potential confounding
effects.

For each participant, two effects of interest were estimated for
each trial type: 1) the average stimulus-locked BOLD response
(i.e., the BOLD response across time associated with the average
RT) and 2) the RT-BOLD relationship (i.e., the change in the BOLD
response associated with a 1 s increase in RT, as measured by mean-
standardized RT) (Weissman et al., 2006). The mean–standardized
RT value for each trial was used to represent trial RT in order to con-
trol for differences in overall RT within a subject across trial types
or blocks, or across subjects. Specifically, we estimated the follow-
ing: the average BOLD response to congruent trials across 13 TRs
(average congruent), the average BOLD response to incongruent
trials across 13 TRs (average incongruent), the average RT-BOLD
relationship for congruent trials across 13 TRs (RT-BOLD congru-
ent), and the average RT-BOLD relationship for incongruent trials
across 13 TRs (RT-BOLD incongruent).

2.5.1. Developmental changes in trial-to-trial RT-BOLD
relationships

For all group analyses, we employed AFNI’s 3dClustSim (using a
70% group mask and averaged error terms from all subjects) to cal-
culate the cluster extent (k = 38) needed to obtain FWE-correction
across the brain at p < 0.05 with an initial height threshold of
p < 0.005.

For group analyses, beta estimates were entered into a multi-
variate model (Chen et al., 2014) using 3dMVMM in AFNI. In
these models, condition (congruent, incongruent) and tent (or TR,
referred to as time point from here on) served as within-participant variables while participant age served as a quantitative, continuous variable. Thus, no grouping by age was included in the model; instead, age was a continuous variable.

Separate models were created to examine the relationship between age as a continuous variable and 1) the average BOLD response regressors and 2) the RT-BOLD relationship regressors. The average response regressor analysis and results will not be discussed further (the results of this analysis are available in Supplemental information). Indeed, the model for the RT-BOLD relationship was of primary interest as it determines whether brain activity varies with trial-specific RT and, most importantly, whether such RT-BOLD relationships are related to age.

In clusters wherein a significant age x time point (i.e., TR) interaction was revealed, percent signal change values for each condition x time point combination were extracted separately for each participant. Since age was included as a continuous variable in the model, the significant interaction indicated that the RT-BOLD relationship varied across the full age distribution in the sample in these clusters. However, it did not indicate the direction of the relationship. Therefore, to visualize the direction of the relationship, we created “representative images.” These images, generated for display purposes only, averaged values in groups of subjects from specific age bands (see Fig. 1). While the RT-BOLD associations varied continuously across all ages, in these figures we depict the findings using three groups, each consisting of 16 subjects (this number was arbitrarily determined). These three groups were selected to represent RT-BOLD associations across the entire age range. Specifically, the first group included the sixteen youngest participants (youngest), the second was generated from sixteen subjects around the overall sample median age (middle), and the third included the sixteen oldest participants (oldest). The average RT-BOLD associations from each of these representative groups were plotted to illustrate the responses across all 13 time points (or TRs) in each significant cluster resulting from the multivariate models. Again, the model included age as a continuous variable and these graphs are for illustrative purposes only. Scatterplots of age by RT-BOLD relationship across all subjects in each significant TR in each of the regions in which there was a significant age x time point interaction are available in Supplemental Fig. 5.

2.5.2. Presence of RT-BOLD relationships in children and adolescents

The results of our primary analyses indicated the presence of developmental differences in RT-BOLD relationships, which were driven by increasing RT-BOLD relationships with age. However, an absence of RT-BOLD associations in younger subjects might produce similar findings. Indeed, results from two previous studies of children and adolescents were contradictory about the presence of RT-BOLD associations in this population. The first study found weak RT-BOLD associations manifesting only in the lateral parietal cortex in children and adolescents (Carp et al., 2012). The second study (Kim et al., 2013) reported several regions with linear RT-BOLD relationships in a sample of children and adolescents, but did not directly compare this sample to an adult group (of note, this study only tested for positive RT-BOLD relationships).

To clarify these findings and our own, we conducted analyses designed to determine whether RT-BOLD relationships were indeed present and measurable in children and adolescents. First, we identified regions in which there was a main effect of time point (i.e., tent) in our overall group RT-BOLD analysis, indicating a significant RT-BOLD relationship across all 50 participants, regardless of age. Second, to eliminate findings that might be driven by particularly strong RT-BOLD relationships in older participants, we then masked out all clusters in which there was an effect of age on RT-BOLD relationships (i.e., the clusters exhibiting a significant age x time point interaction with regard to the RT-BOLD relationship as reported in Table 2; in this analysis, we employed a FWE-correction across the entire brain at p < 0.05 with an initial height threshold of p < 0.005). A whole brain analysis of regions in which there was a significant RT-BOLD relationship across all 50 participants revealed widespread significant results. Thus, to illustrate the RT-BOLD relationships that we observed, we defined spherical ROIs with a 5 mm radius around the top five peak voxels from the whole brain results, located in left and right insula, left and right inferior parietal cortex, and right medial frontal gyrus (BA 32) (Fig. 2A). RT-BOLD values in each spherical ROI were extracted from each subject. We then mapped the RT-BOLD curves from these ROIs in children/adolescents (<18 years old; n = 21) and young adults (as defined in (Carp et al., 2012), >23 years old; n = 21), to provide direct comparisons with prior work (Carp et al., 2012).

3. Results

3.1. Behavioral data

Participants performed the task well (average of mean accuracy across all 6 runs: 94.4% ± 4.1%). There was no correlation between age and performance as measured by the average of a subject’s percentage accuracy over the 6 runs (r_s = 0.19, P = 0.20). However, compared to males, females were slightly younger (t(22.969) = 1.72, P = 0.10); Levene’s test indicated unequal variances (F = 4.94, P = 0.03), so degrees of freedom were adjusted from 48 to 22.969) and performed slightly better (t(21.565) = −1.73, P = 0.10; Levene’s test indicated unequal variances (F = 10.52, P = 0.002), so degrees of freedom were adjusted from 48 to 21.565). Moreover, as expected, mean RT was longer in incongruent (M = 888.2 ms, SD = 145.9) than congruent (M = 864.4 ms, SD = 138.6) trials (t(49) = −8.75, P < 0.001). There were, however, no correlations between age and either mean RT or coefficient of variation of RT across all conditions (congruent and incongruent), or for either condition independently (all |r_s| < 0.10, all P > 0.50). Note that age and IQ were not correlated within the sample (Pearson’s r = 0.09, P = 0.54), and controlling for IQ did not affect the results. See Table 1 for subject means, standard deviations, and ranges for behavioral measures.

3.2. Imaging data

3.2.1. Developmental changes in trial-to-trial RT-BOLD relationships

No interactions involving condition (incongruent, congruent) reached significance in the main RT-BOLD analysis; all significant findings, therefore, are averaged across conditions. Significant age by time point interactions indicated clusters where the RT-BOLD relationship differed with age across the modeled 15-s window (FWE-corrected level of p < 0.05 across the entire brain). There were eleven such clusters; these included bilateral clusters in visual cortex/precuneus/cuneus, precentral/postcentral gyrus, inferior frontal gyrus, middle/superior frontal gyrus, and thalamus. These also included unilateral clusters in left inferior parietal lobule and paracentral lobe/cingulate gyrus (Table 2). Scatterplots of RT-BOLD relationship by age across all subjects in each TR in which a significant interaction within these 11 clusters was present are presented in Supplemental Fig. 5. (Graphs of RT-BOLD averaged across all 50 subjects in each of these 11 clusters are presented in Supplemental Fig. 6).

We identified two main patterns of age x time point interaction among these clusters (i.e., how the RT-BOLD response changed with age). In the first pattern, RT-BOLD became increas-
Fig. 1. Representative clusters from the RT-BOLD age x time point interaction. Sample clusters in which there was a significant age x time point interaction in the RT-BOLD analysis. Brain slices show F-statistics according to the color bar; only voxels that surpass a height threshold of P<0.005 and are within a cluster of at least 38 voxels (FWE-correction across whole brain at P<0.05) are displayed. In these clusters, there was a developmental difference in the time course of the RT-BOLD relationship (i.e., the relationship between percent change in BOLD response per second increase in mean-standardized reaction time). A) Cluster in the right precentral/postcentral gyrus (k = 58; crosshairs at peak, coordinates: 23, −29, 69) and representative graph of the RT-BOLD relationship across the cluster in the 16 youngest, 16 middle, and 16 oldest participants. Note that the statistical model included age as a continuous variable. This graph is for illustrative purposes only and is not representative of the analysis, thus no error bars are included. Y-axis represents the percent change in BOLD response per each second change in mean-standardized RT; thus, for example, a positive y-value would indicate an increase in BOLD signal with an increase in mean-standardized RT. Time points at which there was a significant correlation between age and the RT-BOLD relationship (Pearson’s correlation; p < 0.05) are shaded in purple; the mean RT-BOLD relationship across 21 adults (age ≥ 23) was significantly different from 0 (one-sample t-test; p < 0.05) at these time points. The dotted line arrow indicates the approximate location within the time window of the group sample mean of correct RT across both conditions (sample mean = 876 ±142 ms). B) Cluster in the right IFG (k = 58; crosshairs at peak, coordinates: 47, 24, −1) and representative graph of the RT-BOLD relationship across the cluster in the 16 youngest, 16 middle, and 16 oldest subjects. Note that the statistical model included age as a continuous variable. This graph is for illustrative purposes only and is not representative of the analysis, thus no error bars are included. Y-axis represents the percent change in BOLD response per each second change in mean-standardized RT; accordingly, for example, a positive y-value would indicate an increase in BOLD signal with an increase in mean-standardized RT. Time points at which there was a significant correlation between age and the RT-BOLD relationship (Pearson’s correlation; p < 0.05) are shaded in purple; the mean RT-BOLD relationship across 21 adults (age ≥ 23) was significantly different from 0 (one-sample t-test; p < 0.05) at these time points. The dotted line arrow indicates the approximate location within the time window of the group sample mean of correct RT across both conditions (sample mean = 876 ±142 ms). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

ingly positive with age in the later portion of the modeled time window (TR range: 3.75–11.25, most around 6.25; see example in Fig. 1A). This pattern was evident in the following clusters: bilateral occipital/fusiform/precuneus/posterior cingulate, left precentral/postcentral gyrus, left middle/superior frontal gyrus, right precentral/postcentral gyrus, right middle/superior frontal gyrus, and left paracentral lobule/medial frontal gyrus/cingulate gyrus (clusters 1, 2, 3, 7, 8, and 10 in Table 2). In the other pattern, an increasing positive RT-BOLD response with age was also observed in the later portion of the modeled time window while, additionally, early in the modeled time window (TR range: −2.5–3.75), there was an increasing negative RT-BOLD relationship with age (see exam-
Fig. 2. RT-BOLD relationships are present in children and adolescents. Spherical ROIs were created with a 5 mm radius around the top 5 peak voxels in which we observed a main effect of time point in the RT-BOLD relationship across all participants (n = 50; P < 0.005); regions in which there was an effect of age on RT-BOLD relationships were masked out. A) Locations of the five spherical ROIs, each represented by a different color. Clockwise from top: orange: right medial frontal gyrus (5, 10, 45); gold: left inferior parietal lobe (-30, -46, 38); red: right inferior parietal lobe (33, -46, 41); yellow: left insula (-30, 17, 10); green: right insula (30, 17, 10). B) Plots of average RT-BOLD curves across child (n = 21) and adult (n = 21) age groups, as defined by (Carp et al., 2012) in two representative spherical ROIs located in the right insula and right inferior parietal lobule (patterns are similar in all 5 ROIs). Graph axes as in Fig. 1. The RT-BOLD relationship did not differ statistically between groups at any time point (all P > 0.1).

| Table 1 | Behavioral results. |
|---------|----------------------|
|         | Subject Mean ± SD    | Range Min–Max | Regression slope |
| Percent Accuracy | 94.4 ± 4.1 | 81.5 – 98.9 | -0.04 |
| Average RT all correct trials (ms) | 876.3 ± 141.9 | 671.6 – 1330.4 | 0.93 |
| Average RT correct congruent trials (ms)* | 864.4 ± 138.6 | 657.2 – 1314.5 | 0.71 |
| Average RT correct incongruent trials (ms)* | 888.2 ± 145.9 | 682.7 – 1346.3 | 1.15 |
| SD RT all correct trials (ms) | 173.5 ± 65.9 | 65.5–371.6 |  |
| SD RT correct congruent trials (ms) | 173.9 ± 66.7 | 68.2–366.4 |  |
| SD RT correct incongruent trials (ms) | 173.1 ± 67.0 | 62.9–386.3 |  |
| Coefficient of variation of RT all correct trials | 0.19 ± 0.05 | 0.08–0.32 | 0.001 |
| Coefficient of variation of RT correct congruent trials* | 0.20 ± 0.05 | 0.09–0.33 | 0.001 |
| Coefficient of variation of RT correct incongruent trials* | 0.15 ± 0.05 | 0.08–0.31 | 0.001 |

* Subject RT slower on incongruent than congruent trials P < 0.001.
* Coefficient of variation of RT higher for congruent than incongruent trials at trend level (P = 0.06).

This pattern was evident in clusters in the following regions: left inferior frontal gyrus/superior temporal gyrus, bilateral thalamus, right IFG, left inferior parietal lobule/postcentral gyrus, left middle frontal gyrus (clusters 4, 5, 6, 9, and 11 in Table 2).

Further examination of these clusters revealed that, compared to younger participants, older participants exhibited stronger RT-BOLD relationships in several brain regions (see Fig. 1 for examples from two clusters). The nature of this developmental difference was twofold. In clusters exhibiting the first pattern, in which RT-BOLD became increasingly positive with age in the later portion of the modeled time window (closer to the time of the peak BOLD response), older participants exhibited a more positive RT-BOLD relationship than younger participants (Fig. 1A). In clusters exhibiting the second pattern, this increase in positive RT-BOLD response with age later in the modeled window was still evident, but RT-BOLD association became more negative with age early in the modeled event window (i.e., before the peak of the BOLD response); specifically, older participants exhibited a more negative RT-BOLD relationship than younger participants (Fig. 1B; green line represents 16 oldest participants). Negative RT-BOLD associa-
tions indicate less activation on trials with relatively slow RTs than on trials with relatively fast RTs. Positive RT-BOLD associations indicate more activation on trials with relatively slow RTs than on trials with relatively fast RTs. The age-related increases of negative RT-BOLD relationships early in the modeled window and/or positive RT-BOLD relationships late in the modeled window were evident in all 11 significant clusters. However, both the timing of the effects (e.g., compare the timing of the early effect in Fig. 1A to B) and the significance of the simple effects varied across clusters.

### 3.2.2. RT-BOLD relationships are present in children and adolescents

We observed strong, widely-distributed RT-BOLD associations at all ages. In many regions, these strong RT-BOLD relationships in children and adolescents did not differ from those of the young adults. RT-BOLD responses of children and adolescents (n = 21) extracted from spherical ROIs drawn around the top five peak voxels in left and right insula, left and right inferior parietal cortex, and right medial frontal gyrus (Fig. 2A) did not differ in these regions from those of the young adults (n = 21; for representative graphs see Fig. 2B). Moreover, in all 5 spherical ROIs, there were <8TRs (out of 13) at which the RT-BOLD relationship in the child/adolescent group was significantly different than zero (all P<0.05).

### 4. Discussion

This study is important because it is the first to examine the development of the brain-behavior relationship on a trial-by-trial basis as a function of age. We observed strong RT-BOLD relationships in many brain regions, including fronto-parietal association cortex and thalamus, all of which manifested more powerfully with age. These RT-BOLD associations may provide a useful cross-task tool for elucidating brain-behavior associations across development and pathological states. Below we discuss these findings, and their relevance to the broader literature, in greater detail.

#### 4.1. Age-related differences in trial-to-trial RT-BOLD relationships

The strongest RT-BOLD associations were evident in the oldest participants. The data therefore suggest that these relationships develop throughout childhood and adolescence. Notably, the increase in the strength of RT-BOLD relationships was not limited to the time of the peak response (Carp et al., 2012) or to positive relationships between RT and the BOLD signal (i.e., regions in which the BOLD signal increases with RT) (Kim et al., 2013). Rather, such age-related variation manifested both early and late in the modified window. In addition, condition did not influence the model in this RT-BOLD analysis, indicating that task difficulty did not affect the age by time point interaction of the RT-BOLD relationship. Further, while RT-BOLD relationships became stronger with age, they could still be detected in early adolescence, unlike in some prior research (Carp et al., 2012). Finally, while robust RT-BOLD relationships were found at all ages, our data suggest that development involves region-specific changes in these relationships.

#### 4.2. Neural regions exhibiting age-related RT-BOLD relationship differences

Several global-local tasks with stimuli similar to those used in the present study have been used to study selective attention. These studies have identified task-related responses in similar regions to those showing developmental RT-BOLD relationships here, including frontal areas, precentral gyrus, inferior parietal lobe, thalamus, and visual regions such as the precuneus and fusiform (Weissman et al., 2002). Other methodologies also support the role of these regions in the performance of a global-local selective attention task: e.g., “virtual lesions” of the intraparietal sulcus (IPS) with TMS stimulation disrupt performance of a global Navon task (i.e., identification of the global letter) (Whitney et al., 2012), and TMS stimulation of the right intraparietal sulcus at different frequencies differentially affects global and local processing (Romei et al., 2011). Notably, in the present study, no age-related differences were identified in the anterior cingulate cortex, a region that is often identified in similar tasks and has been proposed to detect task-related response conflict (Weissman et al., 2002, 2003, 2009; Lux et al., 2004). It is important to note, however, that no interactions involving condition (incongruent, congruent) reached significance in the main RT-BOLD analysis and therefore, all significant findings are averaged across conditions. Thus, there were no developmental results specific to conflict (i.e., incongruent versus congruent stimuli).

The regions identified as showing age-dependent variation in RT-BOLD relationships include several core attention network areas. These regions constitute components of both the dorsal and ventral attention networks, and have been shown to be active in adults during attentional tasks and have been strongly implicated in RT-variability in prior studies with adults (e.g., Weissman et al., 2006). In addition, the strong results in visual processing regions are consistent with the biased competition model of visual attention (Desimone, 1998), in which top-down regions amplify the response of task- and/or goal-relevant perceptual processing areas. Age-related differences in RT-BOLD identified in these dorsal, ventral,
and visual regions are likely related to developmental changes in attention processes. Interestingly, a recent resting state analysis in a dichotomous sample (i.e., children versus adults) found an asymmetric pattern of development in the two attentional networks (dorsal and ventral) as measured by intrinsic connectivity (Farrant and Uddin, 2015). In this study, the authors found between-group differences in functional connectivity between dorsal and ventral attention network ROI seeds and several regions identified in our main analysis, including the left postcentral gyrus, bilateral posterior cingulate gyrus, and left thalamus.

4.3. Relevance of the present findings to prior work

The current study maps precisely the chronometry of brain-behavior relationships that correspond to RT variations, reporting significant age differences in the strength of such brain-behavior relationships. Our methods allowed us to model brain-behavior relationships in children and adolescents with greater temporal precision than prior work (Carp et al., 2012; Kim et al., 2013). Specifically, our statistical techniques parsed brain-behavior associations on a trial-by-trial basis, facilitated by an approach to data acquisition and analysis that allowed modeling of fluctuating brain-behavior associations within a trial. Thus, these methods charted the precisely orchestrated chronometry of healthy brain-network deployment during, and in response to, an individual’s reaction to a stimulus.

These methods also revealed the subtle ways in which brain-behavior relationships differ between children/adolescents and adults. Such subtleties can be obscured unless brain-behavior associations are probed with considerable temporal precision. In particular, the use of standard fMRI analysis techniques, which impose a standard HRF function and average BOLD responses to large, diverse stimuli, have only identified differences between children and adults during the peak of the BOLD response (Carp et al., 2012). Here, using a FIR model and trial-by-trial modulation analysis, we added to this literature by showing that the immature RT-BOLD relationship differs from the adult one at both early and late time points within a trial. As such, these findings add to a prior cross-sectional study of developmental differences in the RT-BOLD relationship (Carp et al., 2012) by showing that such developmental differences also occur in the early time period of a BOLD time course, not just at the peak of the BOLD response. Importantly, this age-related pattern is more complex than simply becoming “more positive” with age, showing increased negative and positive RT-BOLD associations distributed across the modeled time window. Notably, the “early negative” and “late positive” RT-BOLD relationships in older participants resemble those previously reported in a similarly aged group of adults (Weissman et al., 2006). These findings help to specify neural differences across the course of development associated with ISVRT, but the precise interpretation of the relationship between differences in the early and late epochs and changes in ISVRT require further work.

4.4. Psychological processes underlying variation in RT

Variation in RT has been hypothesized to reflect several different psychological processes including attention regulation, sustained attention, the detection of response conflict, effort, and arousal (Li et al., 2009; Gomez-Guerrero et al., 2011; Bora et al., 2006; Weissman et al., 2006; Prado and Weissman, 2011; Chee et al., 2008; Whyte et al., 1995). It is also important to note that several studies have shown a relationship between time spent on task and activation, particularly in the posterior/dorsal medial frontal cortex (Grinband et al., 2011; Weissman and Carp, 2013). However, in the current sample, there was no relationship between age and mean RT, nor were there any interactions between age, mean RT, and time point in any of the 11 clusters identified in the age x time interaction. Because ISVRT typically decreases over development (Williams et al., 2005, 2007; Dykier et al., 2012; Li et al., 2009, 2004; Tannes et al., 2012), and the developmental differences in RT-BOLD relationships that we observed were located in executive control, regulatory, and attention network regions, we speculate that ISVRT likely relates to attention modulation, consistent with the view that trials with slow RT represent lapses of attention (Weissman et al., 2006). Critically, our findings indicate that, relative to older individuals, younger individuals exhibit a reduction of both early, negative and late, positive RT-BOLD effects. This result may indicate that the attention systems of the adolescent brain remain immature relative to those of the adult brain. Decreased activation in control regions along with a more diffuse pattern of activation during attentional tasks in children, compared to adults, has been reported previously (Konrad et al., 2005). Several researchers have suggested that maturation across childhood and adolescence is associated with qualitative differences in processes underlying executive functions (Luna et al., 2004). Neuromevelopmental changes associated with maturation that result in qualitative differences in function may include increases in 1) focalization of networks (Konrad et al., 2005), 2) long-range connections that support top-down modulation (Luna et al., 2010), 3) top-down effective connectivity (Hwang et al., 2010), and 4) synaptic connectivity (Edin et al., 2007). Luna and colleagues (Luna et al., 2010) have noted that developmental qualitative differences in neural function might be best observed through a comparison of the BOLD time courses, as differences in BOLD response, representative of qualitative differences, might be obscured in standard group analyses. The FIR methods employed in the present study identify such developmental differences precisely by comparing the time course of the RT-BOLD relationship. Alternatively, it is possible that a different paradigm is needed to explore RT-BOLD relationships more thoroughly in children, as this task and paradigm were originally designed for use in adults. This alternative, though conceivable, is less likely because we did observe regions in which there were equally robust RT-BOLD relationships in all subjects.

One potential explanation for the current results could be an age-related shift in the latency of the peak BOLD response. However, the pattern of the findings did not support this possibility as age-related differences in the mean BOLD response generally reflected reductions in peak magnitude of the response (as shown in Supplemental Figs. 7 and 8), rather than an age-related shift in magnitude. Moreover, the average BOLD response and the BOLD-RT correlation analyses generally revealed different brain regions. The presence of latency differences in peak responses would be expected to generate overlapping clusters for average BOLD response and BOLD-RT correlations analyses.

In spite of the observation of age-related differences in neural function, we did not detect any age-related variation in ISVRT in our participant sample. While the reasons for this null finding remain unclear, several fMRI studies have not found significant between-subject behavioral differences inside the scanner that elicit behavioral differences outside of the scanner (McClure et al., 2007; Fani et al., 2012; Monkt et al., 2008; Solomon et al., 2015; Finger et al., 2008). All of these studies, however, do identify between-subject neural differences despite the lack of behavioral differences. Moreover, age-related differences in behavior are sometimes smaller than age-related differences in brain function (Deleeley et al., 2008). Thus, methodological and statistical factors may explain the lack of an age effect in ISVRT. Despite the lack of age-related variation in ISVRT in the current sample, decreases in ISVRT from childhood through young adulthood have been demonstrated consistently in behavioral studies across several task paradigms (Williams et al., 2005, 2007; Dykier et al., 2012; Li et al., 2009, 2004; Tannse et al., 2012), paralleling the normal developmental pattern of
both executive functions (Waber et al., 2007) and structural brain development (Giedd, 2004; Gogtay et al., 2004). Future studies employing more difficult or effortful tasks, and/or larger samples, might better reveal age-related decreases in ISVRT.

Our findings suggest that there are, in fact, age-related neural differences related to trial-by-trial variation in RT, regardless of whether behavioral differences are measurable. In fact, the lack of age-related differences in RT suggests that the results of the present study are likely to reflect variation-related neural differences with age and not spurious findings resulting from reaction time latency differences. Thus, we think that the present findings are important in elucidating differences in neural response with age.

5. Conclusions: understanding development of RT-BOLD relationship may help elucidate normal and abnormal brain development

In addition to potentially serving as a measure of brain-behavior associations related to attentional regulatory processing, the RT-BOLD relationship, both early and late in the BOLD response, may reflect brain development related to executive functioning. The results of this and future studies of the phenomenon may be of particular use in understanding disorders associated with abnormal development of executive functions, such as ADHD (Shaw et al., 2007, 2012). On a related front, increased ISVRT has also been associated with many developmental neurological and psychiatric disorders (Bora et al., 2006; Leth-Steenssen et al., 2000; Kaiser et al., 2008; Brotman et al., 2009; Castellanos et al., 2005; Epstein et al., 2011), and has even been observed in healthy people at increased familial risk for such disorders (i.e., first-degree relatives: Adleman et al., 2014; Brotman et al., 2009; Nigg et al., 2004; Bidwell et al., 2007). Therefore, understanding the brain mechanisms underlying ISVRT (i.e., RT-BOLD associations), is an important next step for the field. By beginning to delineate the healthy development of RT-BOLD associations throughout the brain, the present study has helped lay the groundwork for future research in psychopathological populations.

Acknowledgements

This research was supported by the Intramural Program of the National Institute of Mental Health (NIMH), National Institutes of Health (NIH). The authors gratefully acknowledge the work of the staff of the Section on Bipolar Spectrum Disorders and the NIH functional magnetic resonance imaging facility. Most importantly, they thank the children and families who participated in this research and made it possible.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.dcn.2016.05.001.

References

Adleman, N.E., et al., 2012. Cross-sectional and longitudinal abnormalities in brain structure in children with severe mood dysregulation or bipolar disorder. J. Child Psychol. Psychiatry, http://dx.doi.org/10.1111/j.1469-7610.2012.02568.x.
Adleman, N.E., et al., 2014. Increased intraindividual variability in response time in unaffected preschoolers at familial risk for bipolar disorder. Psychiatry Res. 219 (3), 687–689.
Anderson, V.A., et al., 2001. Development of executive functions through childhood and adolescence in an Australian sample. Dev. Neuropsychol. 20 (1), 385–406.
Belgrand, M.A., Hester, R., Garavan, H., 2004. The functional neuroanatomical correlates of response variability: evidence from a response inhibition task. Neuropsychologia 42 (14), 1910–1916.
Bidwell, L.C., et al., 2007. Testing for neuropsychological endophenotypes in siblings discordant for attention-deficit/hyperactivity disorder. Biol. Psychiatry 62 (9), 991–998.
Bora, E., Yahiy, S., Aldeniz, F., 2006. Sustained attention deficits in manic and euthymic patients with bipolar disorder. Prog. Neuropsychopharmacol. Biol. Psychiatry 30 (6), 1097–1102.
Brotman, M.A., et al., 2009. Increased intraindividual variability in response time in youth with bipolar disorder and at-risk family members. J. Am. Acad. Child Adolesc. Psychiatry 48 (6), 628–635.
Carp, J., et al., 2012. Removing the effect of response time on brain activity reveals developmental differences in conflict processing in the posterior medial prefrontal cortex. Neurolmage 59 (1), 853–860.
Casalam, F.X., et al., 2005. Varieties of attention-deficit/hyperactivity disorder-related intra-individual variability. Biol. Psychiatry 57 (11), 1416–1423.
Chee, M.W., Tan, J.C., 2010. Lapsing when sleep deprived: neural activation characteristics of resistant and vulnerable individuals. Neurolmage 51 (2), 835–843.
Chee, M.W., et al., 2008. Lapsing during sleep deprivation is associated with disrupted changes in brain activation. J. Neurosci. 28 (21), 5519–5528.
Chen, C., et al., 2014. Applications of multivariate modeling to neuroimaging group analysis: a comprehensive alternative to univariate general linear model. Neurolmage 99, 571–588.
Clements, G.R., 1985. An abbreviated form of the wechsler intelligence scale for children. J. Consult. Psychol. 29, 92.
Cox, R.W., 1996. AFNI: software for analysis and visualization of functional magnetic resonance neuroimages. Comput. Biomed. Res. 29 (3), 162–173.
Deleu, K., et al., 2008. Changes in male brain responses to emotional faces from adolescence to middle age. Neurolmage 40 (1), 389–397.
Desimone, R., 1998. Visual attention mediated by biased competition in extrastriate visual cortex. Philos. Trans. R. Soc. Lond. B Biol. Sci. 353 (1373), 1277–1255.
Dykert, D., et al., 2012. Sex differences in reaction time mean and intraindividual variability across the life span. Dev. Psychol. 48 (5), 1262–1276.
Edin, F., et al., 2007. Stronger synaptic connectivity as a mechanism behind development of working memory-related brain activity during childhood. J. Cognitive Neurosci. 19 (5), 750–760.
Epstein, J.N., et al., 2011. Evidence for higher reaction time variability for children with ADHD on a range of cognitive tasks including reward and event rate manipulations. Neuropsychology 25 (4), 427–441.
Fani, N., et al., 2012. Neural correlates of attention bias to threat in post-traumatic stress disorder. Biol. Psychol. 90 (2), 134–142.
Farb, R., Tadin, D., 2015. Asymmetric development of dorsal and ventral attention networks in the human brain. Dev. Cogn. Neurosci. 12, 165–174.
Finger, E.C., et al., 2008. Abnormal ventromedial prefrontal cortex function in children with psychopathic traits during reversal learning. Arch Gen. Psychiatry 65 (5), 586–594.
Giedd, J.N., 2004. Structural magnetic resonance imaging of the adolescent brain. Ann. N. Y. Acad. Sci. 1021, 77–85.
Gilbert, S.J., et al., 2006. Performance-related activity in medial rostral prefrontal cortex (area 10) during low-demand tasks. J. Exp. Psychol. Hum. Percept. Perform. 32 (1), 45–58.
Gogtay, N., et al., 2004. Dynamic mapping of human cortical development during childhood through early adulthood. Proc. Natl. Acad. Sci. U. S. A. 101 (21), 8174–8179.
Gomez-Guerrero, L., et al., 2011. Response-time variability is related to parent ratings of inattentiveness: hyperactivity, and executive function. J. Atten. Disord. 15 (7), 572–592.
Grinband, J., et al., 2011. The dorsal medial frontal cortex is sensitive to time on task: not response conflict or error likelihood. Neurolmage 57 (2), 303–311.
Hahn, B., Ross, T.J., Stein, E.A., 2007. Cingulate activation increases dynamically with response speed under stimulus unpredictability. Cereb. Cortex 17 (7), 1664–1671.
Hwang, K., Velanova, K., Luna, B., 2010. Strengthening of top-down frontal cognitive control networks underlying the development of inhibitory control: a functional magnetic resonance imaging effective connectivity study. J. Neurosci. 30 (46), 15535–15545.
Kaiser, S., et al., 2008. Intra-individual reaction time variability in schizophrenia: depression and borderline personality disorder. Brain Cogn. 66 (1), 73–82.
Kim, K., et al., 2013. Neural concurrency effects in the multi-source interference task vanish in healthy youth after controlling for conditional differences in mean RT. PLoS One 8 (4), e60710.
Konrad, K., et al., 2005. Development of attentional networks: an fMRI study with children and adults. Neurolmage 28 (2), 429–439.
Leth-Steenssen, C., Elbaz, Z.K., Douglas, V.I., 2000. Mean response times, variability, and skew in the responding ADHD children: a response time distributional approach. Acta Psychol. (Amst.) 104 (2), 167–190.
Li, S.C., et al., 2004. Transformations in the couplings among intellectual abilities and constituent cognitive processes across the life span. Psychol. Sci. 15 (3), 155–163.
Li, S.C., et al., 2009. Lifespan development of stimulus–response conflict cost: similarities and differences between maturation and senescence. Psychol. Res. 73 (6), 777–785.
Luna, B., et al., 2004. Maturation of cognitive processes from late childhood to adulthood. Child Dev. 75 (5), 1357–1372.
Luna, B., Padmanabhan, A., O’Hearn, K., 2010. What has fMRI told us about the development of cognitive control through adolescence? Brain Cogn. 72 (1), 101–113.

Lux, S., et al., 2004. A functional magnetic resonance imaging study of local/global processing with stimulus presentation in the peripheral visual hemifields. Neuroscience 124 (1), 113–120.

Marsh, R., Gerber, A.J., Peterson, B.S., 2008. Neuroimaging studies of normal brain development and their relevance for understanding childhood neuropsychiatric disorders. J. Am. Acad. Child Adolesc. Psychiatry 47 (11), 1231–1251.

McClure, E.B., et al., 2007. Abnormal attention modulation of fear circuit function in pediatric generalized anxiety disorder. Arch Gen. Psychiatry 64 (1), 97–106.

Monk, C.S., et al., 2008. Amygdala and ventrolateral prefrontal cortex activation to masked angry faces in children and adolescents with generalized anxiety disorder. Arch Gen. Psychiatry 65 (5), 568–576.

Nigg, J.T., et al., 2004. Evaluating the endophenotype model of ADHD neuropsychological deficit: results for parents and siblings of children with ADHD combined and inattentive subtypes. J. Abnorm. Psychol. 113 (4), 614–625.

Ollinger, J.M., Corbetta, M., Shulman, G.L., 2001. Separating processes within a trial in event-related functional MRI. Neuroimage 13 (1), 218–229.

Pfeifer, J.H., Allen, N.B., 2012. Arrested development? Reconsidering dual-systems models of brain function in adolescence and disorders. Trends Cogn. Sci. 16 (6), 322–329.

Plude, D.J., Enns, J.T., Brodeur, D., 1994. The development of selective attention: a life-span overview. Acta Psychol. (Amst.) 86 (2–3), 227–272.

Poldrack, R.A., 2014. Is efficiency a useful concept in cognitive neuroscience? Dev. Cogn. Neurosci.

Prado, J., Weissman, D.H., 2011. Spatial attention influences trial-by-trial relationships between response time and functional connectivity in the visual cortex. Neuroimage 54 (1), 465–473.

Riddertshof, K.R., van der Stelt, O., 2000. Attention and selection in the growing child: views derived from developmental psychophysiology. Biol. Psychol. 54 (1–3), 55–106.

Rornei, V., et al., 2011. Rhythmic TMS over parietal cortex links distinct brain frequencies to global versus local visual processing. Curr. Biol. 21 (4), 334–337.

Rueda, M.R., et al., 2004. Development of attentional networks in childhood. Neuropsychologia 42 (8), 1029–1040.

Shaw, P., et al., 2007. Attention-deficit/hyperactivity disorder is characterized by a delay in cortical maturation. Proc. Natl. Acad. Sci. U. S. A. 104 (49), 19649–19654.

Shaw, P., et al., 2012. Development of cortical surface area and gyrification in attention-deficit/hyperactivity disorder. Biol. Psychiatry 72 (3), 191–197.

Solomon, M., et al., 2013. Atypical learning in autism spectrum disorders: a functional magnetic resonance imaging study of transitive inference. J. Am. Acad. Child Adolesc. Psychiatry 54 (11), 947–955.

Tamnes, C.K., et al., 2012. Becoming consistent: developmental reductions in intraindividual variability in reaction time are related to white matter integrity. J. Neurosci. 32 (3), 972–982.

Waber, D.P., et al., 2007. The NIH MRI study of normal brain development: performance of a population based sample of healthy children aged 6–18 years on a neuropsychological battery. J. Int. Neuropsychol. Soc. 13 (5), 729–746.

Wagenmakers, E.J., Brown, S., 2007. On the linear relation between the mean and the standard deviation of a response time distribution. Psychol. Rev. 114 (3), 830–841.

Weissman, D.H., Carp, J., 2013. The congruency effect in the posterior medial frontal cortex is more consistent with time on task than with response conflict. PloS One 8 (4), e62405.

Weissman, D.H., Mangun, G.R., Woldorff, M.G., 2002. A role for top-down attentional orienting during interference between global and local aspects of hierarchical stimuli. Neuroimage 17 (3), 1266–1276.

Weissman, D.H., et al., 2003. Conflict monitoring in the human anterior cingulate cortex during selective attention to global and local object features. Neuroimage 19 (4), 1361–1368.

Weissman, D.H., et al., 2006. The neural bases of momentary lapses in attention. Nat. Neurosci. 9 (7), 971–978.

Weissman, D.H., Warner, L.M., Woldorff, M.G., 2009. Momentary reductions of attention permit greater processing of irrelevant stimuli. Neuroimage 48 (3), 609–615.

Whitney, C., et al., 2012. Executive semantic processing is underpinned by a large-scale neural network: revealing the contribution of left prefrontal, posterior temporal, and parietal cortex to controlled retrieval and selection using TMS. J. Cogn. Neurosci. 24 (1), 133–147.

Whyte, J., et al., 1995. Sustained arousal and attention after traumatic brain injury. Neuropsychologia 33 (7), 797–813.

Williams, B.R., et al., 2005. Inconsistency in reaction time across the life span. Neuropsychology 19 (1), 88–96.

Williams, B.R., et al., 2007. Reaction time inconsistency in a spatial stroop task: age-related differences through childhood and adulthood. Neuropsychol. Dev. Cogn. B Aging Neuropsychol. Cogn. 14 (4), 417–439.

Yarkoni, T., et al., 2009. BOLD correlates of trial-by-trial reaction time variability in gray and white matter: a multi-study fMRI analysis. PloS One 4 (1), e4257.