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

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ABSTRACT

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.

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; Dykiert 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 (Marsh 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-Steensen 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

Abbreviations: ISVRT, Intra-subject variation in reaction time; RT-BOLD relationship, change in the Blood Oxygenation Level Dependent signal associated with 1 s increase in reaction time.

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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.