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In vivo evidence of neurophysiological maturation of the human adolescent striatum

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ABSTRACT

Maturation of the striatum has been posited to play a primary role in observed increases in adolescent sensation-seeking. However, evidence of neurophysiological maturation in the human adolescent striatum is limited. We applied T2*-weighted imaging, reflecting indices of tissue–iron concentration, to provide direct in vivo evidence of neurophysiological development of the human adolescent striatum. Multivariate pattern analysis (MVPA) of striatal T2*-weighted signal generated age predictions that accounted for over 60% of the sample variance in 10–25 year olds, using both task-related and resting state fMRI. Dorsal and ventral striatum showed age related increases and decreases respectively of striatal neurophysiology suggesting qualitative differences in the maturation of limbic and executive striatal systems. In particular, the ventral striatum was found to show the greatest developmental differences and contribute most heavily to the multivariate age predictor. The relationship of the T2*-weighted signal to the striatal dopamine system is discussed. Together, results provide evidence for protracted maturation of the striatum through adolescence.

1. Introduction

Adolescent behavior is characterized by increases in sensation-seeking that can lead to maladaptive risk-taking, resulting in increased likelihood of death or serious injury (Eaton et al., 2006). Thus, there is an impetus to understand the neurodevelopmental changes in the motivational system that may contribute to this behavioral profile. The striatum is of particular interest in this context because of its involvement in motivation and reward processing as well as learning, motor control, and cognition (Haber and Knutson, 2010; McClure et al., 2003; Middleton and Strick, 2000; Vo et al., 2011).

Rodent and non-human primate models provide evidence indicating continued striatal synaptogenesis in early adolescence, peaks in dopamine receptor expression and dopamine projections from the striatum to prefrontal cortex, and synaptic pruning in late adolescence (Crews et al., 2007; Kalsbeek et al., 1988; Rosenberg and Lewis, 1995; Tarazi et al., 1998; Teicher et al., 1995). This line of evidence has led to the hypothesis that similar neurophysiological changes are occurring in adolescent humans (Casey et al., 2008; Spear, 2000). Initial functional magnetic resonance imaging (fMRI) studies have found compelling evidence suggesting peak sensitivity of the adolescent striatum to reward stimuli relative to adults and children (Ernst et al., 2005; Galvan et al., 2006, 2007; Geier et al., 2010; Leijenhorst et al., 2010; Padmanabhan et al., 2011), though

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this finding has not been consistent (Bjork et al., 2004; Eshel et al., 2007) and likely depends on the reward context investigated (Crone and Dahl, 2012). For example, recent work has suggested that striatal reactivity to reward anticipation increases into adulthood while reactivity to reward receipt decreases (Hoogendam et al., 2013). Currently there is a lack of in vivo measures with which to assess age-related differences in human striatal neurophysiology which limits our ability to understand neural mechanisms underlying differences in adolescent striatal function. Understanding the development of striatal neurophysiology is of particular significance given that abnormal striatal neurophysiology and function are implicated in a range of neuropsychological disorders that emerge during childhood and adolescence (Bradshaw and Sheppard, 2000; Chambers et al., 2003). An improved understanding of normative neurophysiological maturation of the striatum can thus inform models of normal and abnormal adolescent behavior.

Tissue–iron concentration is predominant in the striatum (Haacke et al., 2005; Schenck, 2003) and has been found to support dopamine D2 receptor and dopamine transporter (DAT) densities in studies of iron deficiency, ADHD, and restless leg syndrome, which are related to abnormalities in DA processing, (Adisetiyo et al., 2014; Connor et al., 2009; Erikson et al., 2000; Wiesinger et al., 2007), as well as the function and regulation of dopamine neurons (Beard, 2003; Jellen et al., 2013). As such, differences in striatal tissue iron concentration, which can be measured using MRI, can potentially serve as an indicator of dopaminergic differences in adolescence. Tissue–iron is paramagnetic and thus strongly influences the T2*-weighted MRI signal (Langkammer et al., 2010, 2012; Schenck, 2003), which can be non-invasively collected in vivo throughout the lifespan (Aquino et al., 2009; Haacke et al., 2005; Wang et al., 2012). The influence of iron on the T2* signal has been used to quantify iron in a variety of MR measures, including susceptibility weighted imaging (SWI) (Haacke et al., 2004), R2* (Haacke et al., 2010), and R2′ (Sedlacik et al., 2014). In this study, we make use of a large T2*-weighted echo-planar imaging (EPI) dataset, most akin to SWI. Initial studies have used similar data in conjunction with multivariate pattern analysis to investigate the striatal processes underlying learning (Vo et al., 2011).

Here we use T2*-weighted EPI (T2*) to characterize age-related differences in the neurophysiology of the human adolescent striatum in vivo using a multivariate pattern analysis approach. Specifically we use spatial patterns of striatal T2* to generate highly significant age predictions from both task-related and resting state T2*-weighted EPI (fMRI) acquisitions, demonstrating the strong and robust relationship between this measure and development. Furthermore, we identify the ventral striatum, a central hub of dopamine reward pathways hypothesized to underlie adolescent risk-taking (Blum et al., 2000; Casey et al., 2008; Spear, 2000), as a critical component of adolescent striatal maturation. This work highlights the dynamic nature of normative adolescent striatal development, informing models of the maturation of motivational systems during adolescence.

2. Materials and methods

2.1. Sample

One hundred and sixty adolescents and young adults participated in this study (ages 10–25, $M = 16.56$, $SD = 3.62$). Eighteen participants were excluded due to excess head movement (described below), yielding a final sample of 142 (ages 10–25, $M = 16.41$, $SD = 3.71$, 71 male). A subset of these were also included in a replication analysis using resting-state data (described below). All subjects had medical histories that revealed no neurological disease, brain injury, and no history of personal or first-degree relative with major psychiatric illness. All experimental procedures in this study complied with the Code of Ethics of the World Medical Association (1964 Declaration of Helsinki) and the Institutional Review Board at the University of Pittsburgh. Participants were paid for their participation in the study. These data were initially collected for a project investigating reward processing and resting state functional connectivity and subsets of this dataset were included in previously published studies of resting state network development (Hwang et al., 2013) and incentive processing (Paulsen et al., 2014).

2.2. Imaging procedure

Imaging data were collected using a 3.0 Tesla Trio (Siemens) scanner at the Magnetic Resonance Research Center (MRRC), Presbyterian University Hospital, Pittsburgh, PA. The acquisition parameters were: TR = 1.5 s; TE = 25 ms; flip angle = 70°; single shot; full *k*-space; 64×64 acquisition matrix with FOV = 20 cm × 20 cm. Twenty-nine 4 mm-thick axial slices with no gap were collected, aligned to the anterior and posterior commissure (AC–PC line), generating 3.125 mm × 3.125 mm × 4 mm voxels, which covered the entire cortex and most of the cerebellum. We collected four runs of 302 TRs during the antisaccade task ($4 \times 302 = 1208$) and one run of 200 TRs during the resting-state scan. A three-dimensional volume magnetization prepared rapid acquisition gradient echo (MPRAGE) pulse sequence with 192 slices (1 mm slice thickness) was used to acquire the structural images in the sagittal plane.

T2*-weighted data were collected as part of a separate study investigating reward processing. Briefly, subjects participated in a reward modulated antisaccade task, in which they were instructed to make saccades to the mirror locations of peripherally presented stimuli. At the start of each trial, subjects were presented with either a reward, loss, or neutral cue that indicated the possibility of reward dependent on performance. Performance was evaluated using eye-tracking and participants received auditory feedback for correct and incorrect trials.

2.3. Resting-state dataset

One hundred subjects also participated in a resting state scan. Eleven were excluded due to motion artifacts and thus 89 subjects were included in this analysis (ages 10–25, $M = 16.2$, $SD = 3.77$; 43 male). We collected a 5 min