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Network specialization during adolescence: Hippocampal effective connectivity in boys and girls

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ABSTRACT

Adolescence is a complex period of concurrent mental and physical development that facilitates adult functioning at multiple levels. Despite the growing number of neuroimaging studies of cognitive development in adolescence focusing on regional activation patterns, there remains a paucity of information about the functional interactions across these participating regions that are critical for cognitive functioning, including memory. The current study used structural equation modeling (SEM) to determine how interactions among brain regions critical for memory change over the course of adolescence. We obtained functional MRI in 77 individuals aged 8–16 years old, divided into younger (ages 8–10) and older (ages > 11) cohorts, using an incidental encoding memory task to activate hippocampus formation and associated brain networks, as well as behavioral data on memory function. SEM was performed on the imaging data for four groups (younger girls, younger boys, older girls, and older boys) that were subsequently compared using a stacked model approach. Significant differences were seen between the models for these groups. Younger boys had a predominantly posterior distribution of connections originating in primary visual regions and terminating on multi-modal processing regions. In older boys, there was a relatively greater anterior connection distribution, with increased effective connectivity within association and multi-modal processing regions. Connection patterns in younger girls were similar to those of older boys, with a generally anterior-posterior distributed network among sensory, multi-modal, and limbic regions. In contrast, connections in older girls were widely distributed but relatively weaker. Memory performance increased with age, without a significant difference between the sexes. These findings suggest a progressive reorganization among brain regions, with a commensurate increase in efficiency of cognitive functioning, from younger to older individuals in both girls and boys, providing insight into the age- and gender-specific processes at play during this critical transition period.

Introduction

One of the most significant chapters in human development is the transition from childhood to adolescence (Blakemore et al., 2010; Paus et al., 2008). During this period, individuals show significant maturation of cognitive abilities, including processing speed, working memory, abstract reasoning, and response inhibition (Bunge and Wright, 2007; Luna et al., 2004), affording the ability to better attend to relevant information. Only recently have the neurophysiological mechanisms underlying these distinct behavioral changes begun to be uncovered. Human functional neuroimaging has provided a new avenue of study via the visualization and measurement of brain structure and function over the course of adolescent development (Blakemore, 2012; Casey et al., 2005).

The complexity of this transformative stage contains many avenues for disruption, and it is little wonder, therefore, that this period brings with it a surge of psychiatric illnesses, in particular disorders of mood (Paus et al., 2008). The groundwork for this process is actually laid perinatally, as a surge of gonadal hormones drives the initial organization

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of neural networks; a second surge of these hormones at puberty then serves to fully develop and activate these previously-constructed networks (Schulz et al., 2009). This time frame is therefore a critical window for the study of brain network reorganization.

Rapid adoption of neuroimaging techniques has generated a large and continually growing number of studies seeking to understand the changes occurring in the brain during adolescence (Bennett and Rypma, 2013; Ernst et al., 2015; Mills and Tamnes, 2014), and yet relatively few have focused on how brain regions work *in concert*, influencing one another, to perform these elaborate functions. This knowledge gap may be due to the enormous complexity of the task: the functional interactions among a broad set of brain regions are not only continually changing over time, but changes to one brain region cause changes to others, whether they are directly or indirectly connected (Bressler and Mcintosh, 2007). Formal functional network analyses are therefore invaluable to meet this challenge. Such analyses examine the brain as a network, defined as a set of elements (or nodes, which in the current context are brain regions) and the pairwise interaction between these elements (Stanley et al., 2013). Functional network analyses are a way to represent and interrogate the brain's complexity either at the whole level (e.g., whole brain graph analysis) (Bullmore and Sporns, 2009) or by focusing on a selected number of brain regions/nodes (e.g., Structural equation modeling (SEM) and dynamic causal modeling (DCM)) (Frässle et al., 2015; McIntosh and Gonzalez-Lima, 1994).

The formal interaction among nodes, generally quantified via covariance metrics, can be done with two types of assessment: "functional connectivity" and "effective connectivity". Whereas the former is based strictly on correlations among brain regions, the latter conveys information on directionality via the influence of one node over another (Friston, 2002, 2011, 1994). A well-established statistical method for evaluating effective connectivity is structural equation modeling (SEM), pioneered in neuroimaging by McIntosh and Gonzales-Lima (McIntosh and Gonzalez-Lima, 1994). SEM can be performed as a hypothesis-driven approach constrained by *a priori* structural anatomical knowledge (typically derived from macaque anatomy) to quantify the influence of brain regions on one another. The advantages of SEM lie in the fact that it uses statistical evidence from observed data, as well as residuals that are otherwise not measured, to test specific hypotheses (Friston, 2011); it does so by comparing observed and modeled variance-covariance data structures (Guye et al., 2008). Effective connectivity approaches thus provide a deeper understanding of the interactions within the brain than functional connectivity approaches, more effectively bridging the divide between network structure and function (Mashal et al., 2012; McIntosh, 2000). Indeed, SEM has previously been used to investigate a variety of aspects of adolescence, including the development of brain structure (Giedd et al., 2007), the interaction of executive function and risk taking (Romer et al., 2011), and the genetics of cortical variability, specifically cortical thickness (Schmitt et al., 2009).

Absent from studies of developmental effective connectivity is the investigation of brain networks central to learning, memory, and emotion. The hippocampal complex is particularly critical to these functions, serving as a core component within a hierarchy of processing centers, with information flowing to and from a wide array of cortical regions via the entorhinal cortex (Amaral et al., 2014; Canto et al., 2008; Schultz and Engelhardt, 2014). This extensive network of brain regions, the communication of which is centered around and converges upon the hippocampus (Mišić et al., 2014), is critical for the sensing, encoding, integrating, and storage of life experiences (Davachi, 2006). Mature cognitive processing, and in particular the formation of memories, is thought to be driven by the intricate coordination of brain rhythms among distributed neural regions (Colgin, 2016). The hippocampus may thus serve as a point of convergence, or functional hub (Mišić et al., 2014), that is involved in a wide array of cognitive functions, including the binding together of information from multiple brain areas to form coherent memories. Emerging evidence suggests that this process is driven by the coupling of different frequencies (Axmacher et al., 2010), which develops over the course of adolescence (Cho et al., 2015). The ability to effectively integrate experiential information into memory may in fact augment executive functioning (Murty et al., 2016), facilitating the transition from procedure-based to memory-based strategies for problem solving (Qin et al., 2014).

A persistent issue of concern for the interpretation of developmental neuroimaging results is the role of sexual dimorphism. The hippocampus is well-established as a brain region with distinctive sex-specific properties, and thus has been extensively studied in this context, particularly in animal models (Fester and Rune, 2015; McCarthy and Arnold, 2011). Furthermore, the hippocampus not only serves a critical role in memory, but is implicated as a potential point of vulnerability to disorders of mood and cognition, particularly in response to early life stress (Chen and Baram, 2015). Studies examining human hippocampal volumes have mixed results, with several early studies finding that the hippocampus is larger in females compared to males (when corrected for overall brain size) (Cahill, 2006), yet a meta-analysis in humans did not found any volumetric distinctions between sexes (Tan et al., 2016). In contrast, investigations of developmental *trajectories* can provide deeper understanding of this process, as hippocampal volumes significantly increase in females but not males over the course of puberty (Satterthwaite et al., 2014).

Furthermore, sex differences in the development of white matter connections among regions are also present, as boys show a steeper increase in white matter volumes than girls over the age range from 6 to 17 years (De Bellis, 2001), with evidence from myelin-transfer ratios suggesting that increases in white matter in males are predominantly due to increased axonal diameter whereas increases in girls are more likely due to increased myelin content (Perrin et al., 2009). These differences also extend to the network level, as previous work has found differences in intra- and inter-hemispheric white matter connectivity between young girls and boys (Ingalhalikar et al., 2014), with stronger intrahemispheric connections in boys and stronger interhemispheric connections in girls.

Taken together, these studies provide evidence that the structure of the hippocampus and its associated anatomical connections undergo significant remodeling during adolescence. The concomitant developmental changes of influences among functional connections within this brain network remain unknown. In this paper, we explore the nature of these changes, with particular emphasis on the maturation of the influences of individual regions on each other. Furthermore, as adolescence is a period typified by distinct trajectories based on gender, it is important to compare and contrast developmental changes of girls and boys. The goal of this study was therefore to determine potential sexual dimorphism in the effective connections associated with the hippocampal activation in boys and girls 8–16 years old. For this, we sought to determine the architecture of hippocampal directional connections, where we hypothesized, boys would show a delayed evolution of the network with respect to girls, given their later onset of adolescence neural development (Brenhouse and Andersen, 2011). In addition, given that previous work suggests that with maturation comes a posterior to anterior shift in the strength of connections, we hypothesized that boys would display characteristics of a more posteriorly distributed network compared to girls.

Methods

Subjects

The study included 77 participants aged 8–16 years old (33 females). In order to compare by groups, participants were divided into two cohorts based on the median distribution of age (age = 10.5) (Sowell et al., 1999): Younger (ages 8–10; N = 42 (19 Females, 23 Males; mean age 9.48 ± 0.59)) and older (age 11–16, N = 35 (14 Females, 21 Males; mean age 12.94 ± 1.39)). Pubertal age (adrenal (PDSA) and gonadal (PDSG)) was calculated based on the Tanner stages (Tanner and Whitehouse, 1976). The work described herein was done in accordance with The Code