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Review article

Sex differences in brain and behavior in adolescence: Findings from the Philadelphia Neurodevelopmental Cohort

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ABSTRACT

Sex differences in brain and behavior were investigated across the lifespan. Parameters include neurobehavioral measures linkable to neuroanatomic and neurophysiologic indicators of brain structure and function. Sexual differentiation of behavior has been related to organizational factors during sensitive periods of development, with adolescence and puberty gaining increased attention. Adolescence is a critical developmental period where transition to adulthood is impacted by multiple factors that can enhance vulnerability to brain dysfunction.

Here we highlight sex differences in neurobehavioral measures in adolescence that are linked to brain function. We summarize neuroimaging studies examining brain structure, connectivity and perfusion, underscoring the relationship to sex differences in behavioral measures and commenting on hormonal findings. We focus on relevant data from the Philadelphia Neurodevelopmental Cohort (PNC), a community-based sample of nearly 10,000 clinically and neurocognitively phenotyped youths age 8–21 of whom 1600 have received multimodal neuroimaging. These data indicate early and pervasive sexual differentiation in neurocognitive measures that is linkable to brain parameters. We conclude by describing possible clinical implications.

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1. Introduction

An extensive literature on brain and behavior has documented sex differences in cognitive, affective and brain imaging parameters. Such measures have been informative in evaluating aberrations in neurodevelopmental disorders where sex differences are prominent, including attention deficit, learning dis-

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abilities and autism spectrum disorder. Sexual differentiation of behavior has been related to organizational factors during sensitive periods of development, with the prenatal period most investigated across species. There is growing evidence that puberty is another organizational period with long lasting effects on brain and behavior. Adolescence presents an especially informative and dynamic period as brain maturation is accelerated, hormonal changes associated with puberty emerge and social factors increase their impact. The transition to adulthood is influenced by complex interactions where the effects of this critical period may differ for males and females with implications for healthy functioning and psychopathology.

We will begin this review by highlighting sex differences in neurobehavioral measures in adolescence that are linked to brain function. We will then summarize neuroimaging studies examining brain structure, connectivity and perfusion. We will conclude by summarizing literature on the role of hormonal measures and discuss clinical implications.

2. Behavior linked to brain function

The developmental course of specific behavioral domains has been well documented. Executive-control (e.g., Conklin et al., 2007; Goldberg et al., 2001; Pickering, 2001), language and reasoning (e.g., Friederici and Wartenburger, 2010; Kuhl, 2010) and, more recently, social cognition (e.g., Burnett et al., 2011; Shaw et al., 2012) show improved performance from childhood to young adulthood, especially pronounced during adolescence for executive domains of attention and working memory (Ang and Lee, 2010). Neural substrates for such age-related differences are being examined extensively with structural and functional neuroimaging, initially in cross-sectional studies and more recently expanding to longitudinal investigations. Results highlight childhood and adolescence as periods during which important age-related differences are observed in parameters of neural structure and function (Casey et al., 2010; Giedd et al., 1999; Matsuzawa et al., 2001; Shaw et al., 2008). Integrating neuroimaging with behavioral findings, Jung and Haier (2007) identified a central role for frontal and parietal regions in the neurodevelopment of cognition, and this hypothesis has received support in large-scale studies (Deary et al., 2010).

Sex differences have been extensively documented in behavioral measures (e.g., Halpern et al., 2007; Hines, 2010). Males perform better than females on spatial (Linn and Petersen, 1985; Voyer et al., 1995) and motor tasks (e.g., Moreno-Briseno et al., 2010; Thomas and French, 1985), while females perform better than males on some verbal and memory tasks (e.g., Hedges and Nowell, 1995; Hyde and Linn, 1988; Saykin et al., 1995) as well as measures of social cognition (Erwin et al., 1992; Gur et al., 2010, 2012; Moore et al., 2015; Williams et al., 2008). Some sex differences have been related to structural neuroimaging (e.g., De Bellis et al., 2001; Goldstein et al., 2001; Gur et al., 1999; Lenroot et al., 2007) and functional imaging measures (e.g., Gur et al., 1982, 1995, 2000; Lenroot and Giedd, 2010), including volumetric differences in executive and memory related areas, supporting neural substrates for sex differences in cognition. However, the developmental course of sex differences in brain-behavior relationship, especially in adolescence and across neurobehavioral domains, remains to be elucidated, particularly with longitudinal studies.

Shortcomings of most cognitive measures currently used limit their applicability in establishing further links between brain function and behavioral domains. Most are broadly defined and load heavily on the "g factor" (Salthouse, 2004) without separating accuracy from speed. This feature precludes rigorous testing of hypotheses on the effects of brain connectivity on performance, which is expected to differentially influence processing speed. Additionally, the paper-and pencil administration format of many tests precludes their use in large-scale neuroimaging genomic studies. More narrowly defined behavioral tasks, used in functional neuroimaging, have been adapted as computerized tests to obtain rapid and efficient quantification of individual differences (Gur et al., 1992; Gur et al., 2010). The literature is especially limited in the application of an identical neurocognitive test battery across a population ranging from childhood through puberty and young adulthood.

The Philadelphia Neurodevelopmental Cohort (PNC) includes a large well-characterized community sample of youths, age 8–21 years. The PNC received a computerized neurocognitive battery (CNB; Gur et al., 2010, 2012; Roalf et al., 2014a) that is based on functional neuroimaging studies (Roalf et al., 2014b), has established validity (Moore et al., 2015) and heritability (Calkins et al., 2010; Greenwood et al., 2007; Gur et al., 2007). The age range from childhood to young adulthood enables to examine the pattern of performance, both accuracy and speed, during adolescence. The cross sectional sample was obtained between 2009 and 2011 and a subsample of about 500 is followed longitudinally with clinical, neurocognitive and neuroimaging measures.

Performance scores on each neurocognitive domain at baseline were standardized to the average of the entire sample (n = 9122: 4405 males, 4717 females). The z-scores were entered into a repeated-measures ANOVA in SAS (SAS Institute Inc., Cary, NC, operating on Linux LIN 64 platform), using PROC GLM separately on the 12 Accuracy measures and the 14 Speed measures with Age group (7 levels, 2-year spans from 8 to 21) and Sex as grouping factors and Test as a repeated measures (within–group) factor. The Age group, Sex, and Test effects and their interactions for each test are presented in Table 1.

Fig. 1 shows performance scores on each domain. As can be seen, there is overwhelming age associated improvement in performance across multiple neurobehavioral domains. Against that background, there is some variability among domains and between accuracy and speed measures and, most importantly, sex differences modulate these effects in a manner related to adolescence.

Several effects are notable in Fig. 1. Among the Executive domain measures (A), abstraction and mental flexibility shows the least age related improvement in accuracy and speed shows a trend toward decline post pubescence. Attention shows the greatest improvement in both accuracy and speed while working memory has intermediate age-related effect sizes. Sex differences are not prominent in executive functions except for higher accuracy in females for attention and greater working memory speed for males. Both effects emerge after age 11. For Episodic Memory tests (B), effect sizes are considerably smaller than for attention; memory is apparently a major strength of the developing brain already in childhood. Age-related improvement is most pronounced for verbal memory speed and for face memory, two domains in which females outperform males across the age range. As with sex differences in the Executive domain, the magnitude of the sex difference increases in post pubescence age bands. For the Complex Cognition domain (C), age-related improvement is seen primarily in accuracy where the effect sizes are large as well as in verbal reasoning speed. Sex differences appear again after age 11, where males begin to show improved accuracy while females begin to show better speed. For Social Cognition (D), females outperform males from childhood onward in both accuracy and speed across all three measures. Nonetheless, this difference seems accentuated in post pubescent years, especially for speed. The opposite sex difference is observed for motor speed, where males outperform females across the age range. Here too, however, these differences become greater in the post pubescent age groups. Thus, while most age-related trajectories flatten after age 18, both the rate of age-related differences and the magnitude of the sex differences increase after age 11.