Neuro-anatomic evidence for the maturational delay hypothesis of ADHD

Katya Rubia*

Department of Child Psychiatry/Medical Research Council Social, Genetic, and Developmental Psychiatry Research Center (SGDP), Institute of Psychiatry, 16 De Crespigny Park, SG DP PO46, London SE5 8AF, United Kingdom

Attention deficit hyperactivity disorder (ADHD) has been hypothesized to be related to a delay rather than a deviance of normal brain development before it was first defined by the DSM-III (1). The hypothesis was initially based on the behavioral observation that children with ADHD behave like younger children who are naturally more active, more impulsive, and have a shorter attention span than older children. This is well expressed in the definition of the disorder in the DSM-IV, where ADHD is characterized by an age-inappropriate display of inattention, hyperactivity, and impulsiveness. The behavioral observation is further supported by the cognitive profile of ADHD children: They show deficits in late developing higher cognitive functions of inhibitory self-control, attention, and temporal foresight (2, 3). The fact that ADHD symptoms tend to improve with age and up to 80% of children (depending on the follow-up length and definition of persistence) grow out of ADHD in adulthood (4) further supports the theory of a maturational lag that eventually normalizes in a considerable proportion of children. Indirect neurobiological support comes from cross-sectional structural imaging studies finding reduced size in cortico-striatal brain regions that are known to develop late in adolescence (5) and functional imaging studies showing reduced brain activation in ADHD compared with their age-matched peers in precisely those brain areas whose functions develop progressively with age between childhood and adulthood (6–10). Cross-sectional studies, however, are confounded by cohort effects; direct testing of the maturational delay hypothesis requires longitudinal imaging studies that map the developmental trajectories of brain maturation in healthy and ADHD children. In a recent issue of PNAS, Shaw *et al.* (11) study largely longitudinal data to provide direct neurobiological evidence for the maturational delay hypothesis of ADHD.

ADHD Is a Delay of Normal Brain Maturation

Previous mixed longitudinal and cross-sectional structural MRI studies of the same research group in >150 ADHD children scanned repeatedly between 5 and 20 years showed that ADHD children are characterized by a nonprogressive reduction in gray and white matter (2) and cortical thickness in cortical and cerebellar brain regions (11). Developmental growth curves in almost all cortical regions in ADHD children were lower but still parallel to those of controls. These findings can be interpreted as a maturational delay, because they suggest that ADHD children are "limping behind" normal development in a nonprogressive fashion. However, the relatively gross volumetric analyses of the cortical lobes in the first study (2) and the relative lack of power to investigate nonlinear changes in the second study (12) prevented the authors from detecting differences in developmental peaks within cortical brain areas. Shaw *et al.* (11) measured cortical thickness that can demonstrate considerable variability in timing of cortical maturation within each lobe in sufficiently large subject numbers to detect nonlinear changes. Cortical thickness was estimated in a mixed longitudinal and cross-sectional analysis from 223 children with ADHD and 223 healthy controls, scanned between two and five times within intervals of 2 or 3 years. Cortical thickness typically increases in childhood, reaches its peak in adolescence, and decreases again in adulthood, presumably reflecting dendritic, glial, and vasculature growth (thickness increase) as well as myelination and synaptic pruning (cortical thinning) (13). The authors found that the age of attaining peak cortical thickness was delayed in patients with ADHD for most of the cortical points by a substantial time window of ≈3 years. The most pronounced differences were in the frontal lobes, with the largest delay of 5 years in the middle frontal cortex and a delay of ≈2 years for the superior and medial prefrontal cortices. The second most pronounced delay was in the peak of cortical thickness in the bilateral middle and superior temporal cortex of ≈4 years. The only region in which ADHD children were 4 months ahead of the controls in their maturational peak was the motor cortex. The typical ontogenetic sequence, however, of earlier development of primary sensory and motor areas before higher-order association areas was similar in both groups, suggesting a delay rather than a deviance in cortical maturation. These important findings constitute the first neuro-anatomical documentation of the originally observation-based theory of a maturational delay of brain development in ADHD.

The findings of delayed structural brain maturation seem, thus far, to be specific to ADHD.

The findings that the most prominent delay in cortical thickness occurs in the frontal lobes fits well with the more specific hypothesis that ADHD is characterized by a delay in fronto-striatal systems that mediate the late developing cognitive control functions that are impaired in ADHD. The prefrontal regions that are delayed in structural maturation in the study of Shaw *et al.* (11) have consistently been found to be smaller in structure (5) and underactivated in ADHD children during tasks of cognitive control (7, 10, 14). They are also the same regions where function develops linearly with age between childhood and adulthood during the same cognitive control tasks in which ADHD children show underactivation (6, 8, 9).

The finding of a prominent delay in the structural development of the superior and medial temporal lobes was more unexpected; however, there is recent evidence for structural (5) and functional abnormalities in these temporal regions in ADHD adolescents during tasks of attention such as attentional

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*E-mail: k.rubia@iop.kcl.ac.uk.

switching, divided attention, and attention allocation (10, 15–17). The superior temporal together with the superior frontal lobes are association areas that develop latest in the life course (13). One could speculate that the functional significance of the findings of a delayed maturation of frontal and temporal regions in ADHD might be related to the observed age-inappropriate deficits in functions of self-control and attention, respectively. Appropriate and in-depth understanding of the functional, behavioral, and cognitive significance of this structural delay and of the complex interrelationship between these developing systems, however, will require longitudinal studies that combine structural and functional imaging data.

Implications, Clinical Relevance, and Future Directions

The cause for this delay in structural brain maturation is unknown. There is evidence that both genetic and environmental factors influence brain development. The authors postulate the involvement of neurotrophin polymorphisms that may differ in ADHD (11). One could also speculate that monoamine polymorphisms that have been shown to be involved in ADHD and to influence brain structure abnormalities (18) could influence brain development either directly (19) or via the regulation of neurotrophic factors (20).

Medication is a potential confounder of the developmental differences found in this and previous studies. Preliminary evidence has shown more pronounced white matter and no gray matter abnormalities in unmedicated compared with medicated ADHD children (2), making it unlikely that medication is the cause for the structural delay. However, replications are needed in medication-naïve patients to rule out medication effects. Future comparisons between the developmental trajectories of medication-naïve and medicated patients would help to understand the much debated and clinically relevant question of the impact of stimulant medication on the developing brain of ADHD children.

Of clinical interest is the relationship between clinical outcome and delay of cortical thickness in ADHD. If symptoms are associated or "caused" by a maturational delay, one might expect that patients who "catch" up in the maturation of their cortical thickness would show a better clinical outcome or grow out of their symptoms. Unfortunately, clinical outcome data were not available for the paper under discussion. However, initial evidence for a relationship between normalization of structural delay and improved clinical outcome is provided by earlier studies by the authors. Children with ADHD who in late adolescence showed normalization of the reduced cortical thickness of their parietal lobes and left cerebellar hemisphere showed a better clinical outcome and were more likely to grow out of the disorder (12, 21). Future comparisons of developmental trajectories of cortical thickness between persisters and nonpersisters of ADHD would shed light on the relationship between developmental delay, its normalization, and the clinical course of the disorder.

Also, clinically interesting would be an investigation of the impact of ADHD subtypes and of comorbidities on the developmental brain trajectories. The ADHD children scanned in this (and previous imaging studies) were mostly of the combined type of ADHD. Almost nothing is known on brain maturation in children with the predominantly inattentive subtype. It would be interesting to investigate whether comorbidities influence developmental trajectories. In one of the previous studies of the authors, children with ADHD who normalized in their left anterior cerebellar volume abnormalities by late adolescence were less comorbid than those who did not (21). It is conceivable that a more severe and prolonged structural developmental delay would make patients more susceptible to the development of other complications; alternatively, it is also conceivable that more complicated comorbid presentations of ADHD are associated with a more pronounced delay in brain maturation.

An important question is whether the delay of brain maturation is a specific characteristic of ADHD or is shared by other child psychiatric disorders. So far, none of the other major psychiatric disorders have been associated with a maturational delay of brain structure. However, to my knowledge, longitudinal structural studies have been conducted only in patients with ADHD, childhood-onset schizophrenia (COS), and autism, finding maturational deviance rather than delay. Adolescents with COS are characterized by a striking nonlinear, progressive acceleration of the normal gray matter and volume decrease in cortical regions that levels off in adulthood (22). In autism, there is an early left hemispheric overgrowth of gray and white matter at young toddler age with conflicting findings of either arrested growth or remaining brain enlargement in adolescence and adulthood (23). The findings of delayed structural brain maturation seem, thus far, to be specific to ADHD and may be an important neuroanatomic trait. However, further exploration of the developmental trajectories in other child psychiatric disorders is needed to establish the importance of a delay of brain maturation as a specific neuroanatomic marker for ADHD.

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