

## OPINION

## Why do many psychiatric disorders emerge during adolescence?

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**Abstract** | The peak age of onset for many psychiatric disorders is adolescence, a time of remarkable physical and behavioural changes. The processes in the brain that underlie these behavioural changes have been the subject of recent investigations. What do we know about the maturation of the human brain during adolescence? Do structural changes in the cerebral cortex reflect synaptic pruning? Are increases in white-matter volume driven by myelination? Is the adolescent brain more or less sensitive to reward? Finding answers to these questions might enable us to further our understanding of mental health during adolescence.

Across cultures and centuries, adolescence has been noted as a time of dramatic changes in body and behaviour. Although most teenagers successfully navigate the transition from dependence on a caregiver to being a self-sufficient member of society, adolescence is also a time of increasing incidence of several classes of psychiatric illness, including anxiety and mood disorders, psychosis, eating disorders, personality disorders and substance abuse. The pathophysiology of these disorders is increasingly understood as arising from aberrations of the maturational changes that normally occur in the adolescent brain.

In this Perspective we address the neurobiological changes that occur during adolescence and discuss their possible relationship to the emergence of psychopathology. We focus on three major disorders, namely schizophrenia, substance-use disorders and affective/anxiety disorder, because our understanding of their developmental neurobiological basis has increased considerably in recent years.

### Typical development of the adolescent brain

In the past 15 years there has been an impressive accumulation of knowledge about the development of the structure and the function of the human brain. Studies carried out with MRI<sup>1–4</sup> in children and adolescents have allowed investigators to chart

trajectories of grey- and white-matter volumes, cortical thickness and, more recently, other structural properties of white matter, such as fractional anisotropy and magnetization-transfer ratio (MTR), as well as age-related changes in brain activity (BOX 1).

**Brain structure.** Most of the existing literature on age-related changes in brain structure has been reviewed in detail elsewhere<sup>5,6</sup>. Here we note only the most salient findings.

Volumes of cortical grey matter seem to increase during childhood, reaching peak levels at approximately the time of puberty onset, after which they gradually decline; this is the case for the frontal and parietal lobes but not for the temporal lobes<sup>7</sup>. Local volume of cortical grey matter declines during childhood and adolescence in most regions, with the slope of the decline varying from relatively gentle (for example, in the anterior portion of the superior temporal gyrus (STG)) to steep (for example, in the posterior portion of the STG) and, in some cases, displaying a nonlinear relationship with age; for example, between 10 and 20 years of age, an ‘inverted-U-shaped’ relationship between age and cortical grey matter has been found in the post-central gyrus, and a ‘U-shaped’ relationship has been found in the mid-dorsolateral frontal cortex<sup>8,9</sup> (FIG. 1).

Volumes of white matter show a rather clear linear increase throughout childhood and adolescence, with the maximum volumes often reached as late as the third decade of life<sup>10</sup>. It seems that the slope of the age-related increase is steeper in males than in females<sup>7,11</sup>. More recently, diffusion tensor imaging (DTI) has been used to assess white-matter changes in more detail in the human brain during childhood and adolescence. Overall, DTI studies reveal age-related decreases in the magnitude and increases in the directionality of water diffusion in a number of white-matter regions<sup>12–14</sup>, many of which are identical to those revealed by structural MRI studies, such as those of the arcuate fasciculus. Such changes in DTI-derived measures may indicate ongoing maturation of axons and/or their myelin sheaths (see below).

**Brain activity.** The overall picture to be gleaned from the existing descriptive studies of age-related changes in brain activity is less coherent than that for structural changes. This is due to the fact that functional MRI (fMRI) studies usually focus on a particular brain function, and to the fact that the behavioural paradigms used to assess that brain function often differ across laboratories. It is also more challenging to interpret fMRI data than structural measurements, owing to the indirect nature of the fMRI signal (BOX 1) and the large number of potential confounders, such as levels of anxiety and arousal during scanning, varying task performance across participants, and the use of different cognitive strategies by different participants in the same task — all of these might interact with the effects of age. We will touch here on two sets of fMRI studies of adolescents that respectively focused on cognitive control (or executive functions) and on experiencing gains and losses of various rewards.

A number of the initial studies that investigated how task-related brain activity changes during development focused on executive functions, such as working memory and response inhibition. But, as we reviewed previously<sup>6</sup>, many such executive abilities are fully developed by the time a child enters adolescence<sup>6</sup>. On the other hand, certain aspects of executive function, such as

## Box 1 | Neuroimaging

MRI has revolutionized the way we can study the structure and function of the brain in living human beings throughout the entire lifespan<sup>1</sup>. The principles of MRI are relatively straightforward: in most applications, the magnetic resonance signal results from the magnetic properties of hydrogen atoms, which form part of the most abundant substance in the human body, water. By placing the human body in a strong (0.5–7.0 T) static magnetic field ( $B_0$ ) and applying a brief pulse of electromagnetic energy, we can make the dipoles formed by the hydrogen nuclei rotate away from their axes and, in turn, measure the time it takes for the nuclei to ‘relax’ back to their original position. By slightly changing the static magnetic field at different positions along/across the  $B_0$ , we can establish the spatial origin of the signal and, eventually, create a three-dimensional image of the measurement. What is measured depends on the combination of various imaging parameters or, in the terminology of the MR physicists, on the acquisition sequence.

For imaging brain structure, the most common acquisition sequences include T1-weighted (T1W) and T2W images, diffusion-tensor images (DTI) and magnetization-transfer images (MT). The T1W and T2W images are typically used to quantify the volume of grey and white matter (global and regional) and to estimate the cortical thickness or other morphological properties of the cerebral cortex, such as its folding. Using DTI and MT imaging one can assess different properties of white matter, again in both a global and a regional manner. The various features of brain structure that can be extracted from these four types of images are described in the main text. In addition to the above sequences, less common but often even more informative acquisitions include T1 and T2 relaxometry (that is, measurement of the actual relaxation times<sup>2</sup>) and magnetic resonance spectroscopy<sup>3</sup>.

For imaging brain function, the most common MR parameter to measure is the so-called blood-oxygenation-level-dependent (BOLD) signal. The BOLD signal reflects the proportion of oxygenated and deoxygenated blood in a given brain region at a given moment. A strong correlation between the amount of synaptic activity and regional cerebral blood flow is the reason why the BOLD signal is a good, albeit indirect, measure of brain ‘function’ (REF. 4). In most functional MRI studies, one measures changes in BOLD signal in response to various sensory, motor or cognitive stimuli. Therefore, only brain regions that are likely to respond to such stimuli can be interrogated using a given paradigm.

planning time and delayed gratification, do improve significantly from mid-adolescence (~16 years of age) onward, as indicated by recent behavioural studies<sup>15</sup>. An fMRI study found age-related (between the ages of 7 and 22 years) increases in the blood-oxygenation-level-dependent (BOLD) signal in the prefrontal and parietal cortices during the performance of a working-memory task even after factoring out inter-individual differences in performance<sup>16</sup>. Similar BOLD increases were observed in these regions during the performance of a variety of tasks that involve some form of response inhibition, including the Stroop task<sup>17</sup>, the anti-saccade task<sup>18</sup>, the stop task<sup>19</sup> and, to a certain extent, the go/no-go task<sup>20</sup> and the Eriksen flanker task<sup>21</sup>.

Adolescence has traditionally been associated with risk-taking and sensation-seeking behaviour<sup>22</sup>. In this context, several investigators used fMRI to examine possible differences in brain activity between children, adolescents and young adults during the experience of gains or losses of various rewards. Owing to its role in reward and motivation<sup>23</sup>, the nucleus accumbens (or ventral striatum) was the focus of most of these studies. If adolescents were ‘driven’ by reward seeking, one would expect a heightened engagement of this structure

during tasks that involve reward seeking. This seemed to be the case in participants in some<sup>24,25</sup> but not other<sup>26</sup> studies. For example, one study<sup>26</sup> described an increase from early adolescence to young adulthood (12 to 28 years) in the BOLD signal in the nucleus accumbens during the anticipation of monetary gains; this was the case even when self-reported level of excitement in response to seeing anticipatory cues was taken into account. It is worthwhile to point out that in the same study, excitement correlated positively with the BOLD signal in the nucleus accumbens even when age was taken into account. This observation highlights the importance of considering various aspects of behaviour when interpreting fMRI findings.

Although functional imaging studies are beginning to illuminate the functional maturation of the neural circuits that are involved in, for example, executive functions and reward processing, future studies need to increase substantially sample sizes and enhance the behavioural characterization of subjects’ performance in the scanner in order to learn more about brain–behaviour relationships during adolescence.

#### Interpretation of underlying mechanisms

The age-related changes in brain structure and function during adolescence described

above have been interpreted using various conceptual frameworks. Changes in synaptic pruning and myelination have been the most popular explanations for the structural findings in the adolescent brain, whereas age-related alterations in neural connectivity and neurotransmission might underlie the functional changes associated with adolescence. We will now address, in a critical manner, such mechanistic interpretations.

*Does adolescence involve changes in pruning and myelination?* MRI-based estimates of the volume of cortical grey matter and cortical thickness seem to decrease during adolescence. This has often been interpreted as an indication of ‘synaptic pruning’, a process by which ‘redundant’ synapses that were overproduced in the early years of life are eliminated (see REF. 27 for a critical appraisal of “neural Darwinism”).

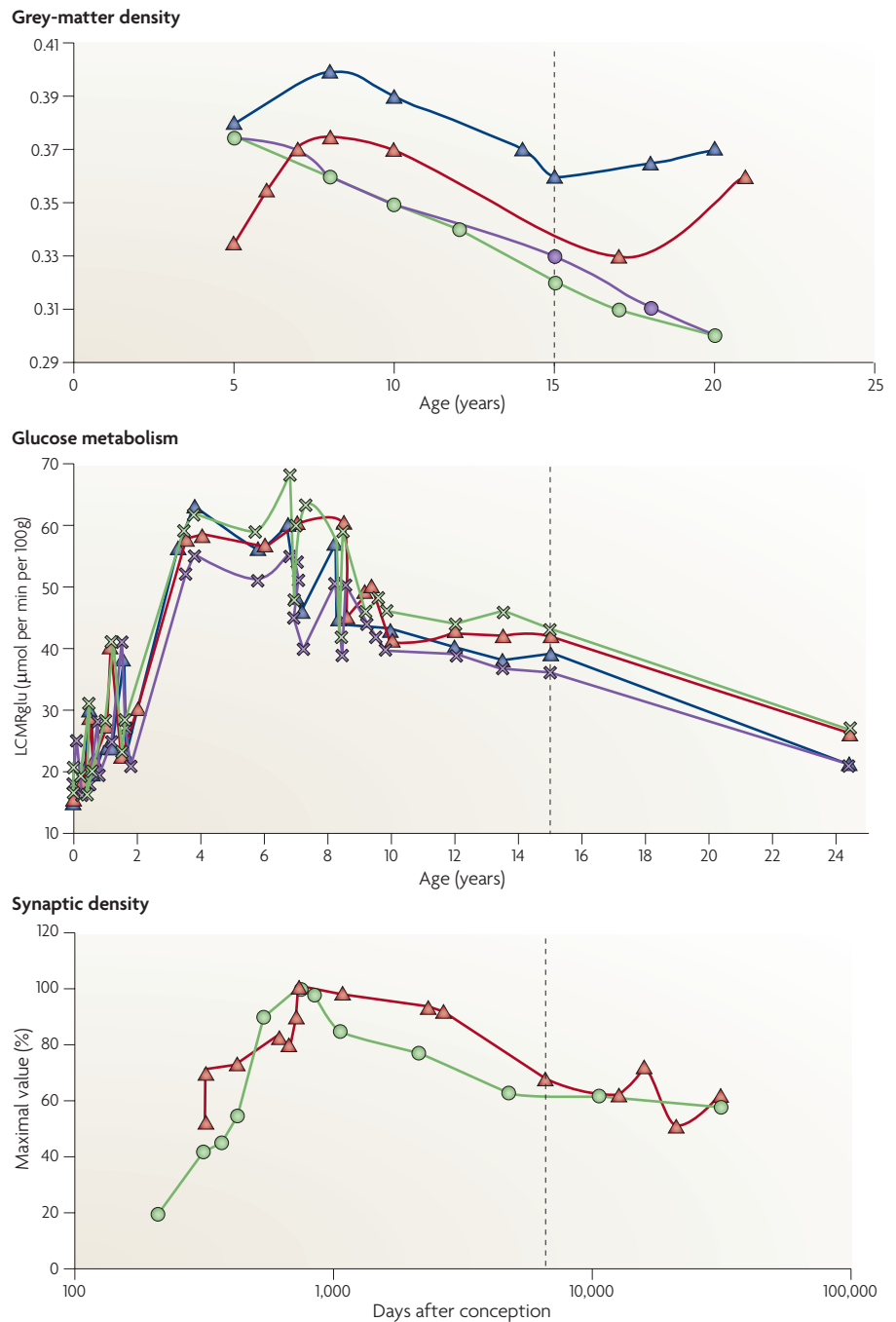
The initial evidence for accelerated synaptic pruning during development came from post-mortem studies by Huttenlocher and colleagues, who described a decrease in the number of synapses in the human cerebral cortex during childhood and adolescence<sup>28,29,30</sup>. It should be noted, however, that these studies were limited by the low number of specimens that were available for the different stages of human development, especially the adolescent period. Furthermore, most of the data do not actually indicate accelerated pruning of synapses during adolescence; rather, they indicate a gradual decrease in synapse number that begins (in several cortical regions) in childhood. More-definite evidence of synapse elimination during adolescence was provided by studies carried out by Rakic and colleagues in non-human primates<sup>31,32</sup>. Using electron microscopy, they observed a dramatic decrease in the number of synapses in the monkey visual cortex, as well as in other cortical areas, during puberty (that is, between the age of 2.5 and 5 years), whether the data were expressed as number of synapses per neuron or as number of synapses per 1 mm<sup>3</sup> of neuropil (~45% loss). But it is unlikely that this decrease in synaptic density translates into a decrease in cortical volume: Bourgeois and Rakic commented that “changes in the density of synapses affect very little either the volume or surface of the cortex because the total volume of synaptic boutons ... is only a very small fraction of the cortical volume” and concluded that “... a decline of synaptic number during puberty should have a rather small effect on the overall volume of the cortex” (REF. 32). Finally, it is often assumed that age-related

changes in cortical grey matter, glucose metabolism and synaptic density follow similar developmental trajectories from birth to adulthood and, hence, reflect the same cellular events; this is clearly not the case, especially during adolescence (FIG. 1).

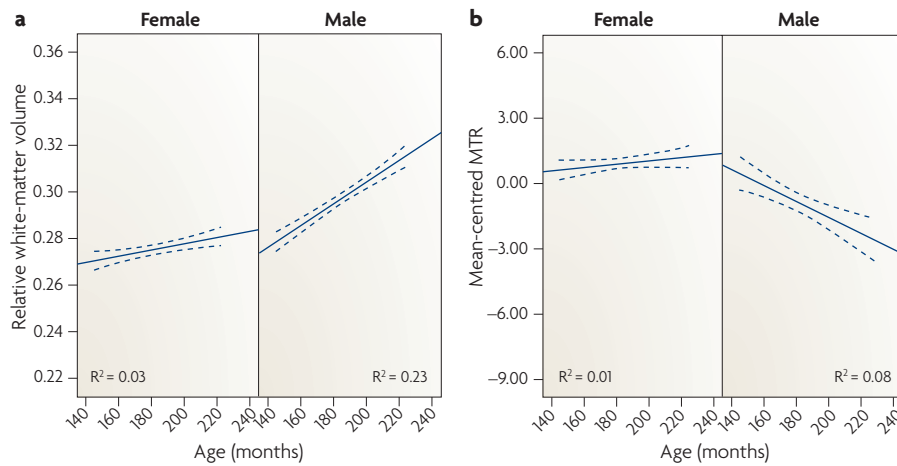
If the number of synapses *per se* is unlikely to change the cortical volume and/or thickness, then what other cellular elements could affect it? Approximately 10% of the (mouse) cortex is occupied by glial cells and approximately 60% is occupied by neuropil, which consists of dendritic and axonal processes<sup>33</sup>. It is conceivable that a reduced number of synapses, and a corresponding decrease in metabolic requirements, would be accompanied by a reduction in the number of glial cells, leading to a decrease in the regional volume and/or thickness of cortical grey matter. But it is perhaps even more likely that the apparent loss of grey matter reflects an increase in the degree of myelination of intra-cortical axons. Myelination of intra-cortical fibres progresses gradually from birth to adulthood<sup>34,35</sup>. The more myelinated the fibres are, the less 'grey' the cortex would appear on regular T1-weighted images. Such a 'partial-volume' effect could result in an apparent loss of cortical grey matter<sup>6</sup>.

Given the well-documented histology-based increase in the degree of myelination of white-matter pathways during the first two decades of human life<sup>36</sup>, it is perhaps not surprising that any changes in the volume or density of white matter, as revealed by computational analyses of T1-weighted images, are attributed to changes in myelination. Again, assumptions based on previous knowledge influence the interpretation of new data. Quite often we read articles that report age-related changes in myelination only to realize that what had actually been measured were volumes of white matter. Is it only a matter of semantics or could other, myelination-independent processes affect the volume and/or other features of white matter? In one of our large studies of human adolescence, we have observed a dissociation between age-related changes in the volume of white matter and changes in the MTR (an indirect index of the amount of myelin in white matter)<sup>37</sup>. Although white-matter volume increased with age during male adolescence, MTR values decreased, indicating a decrease in the amount of myelin per unit of volume (FIG. 2).

If myelin does not increase, what could be driving the observed increase in white-matter volume in males? Our tentative answer is a change in axonal calibre: the



**Figure 1 | Schematic representations of developmental trajectories in local volume of cortical grey matter, glucose metabolism and synaptic density.** Plots of grey-matter density (top graph) are based on data by Gogtay *et al.*<sup>8</sup> and illustrate the local grey-matter density in the mid-dorsolateral prefrontal cortex in red, in the angular gyrus of the parietal cortex in blue, in the posterior superior temporal sulcus of the temporal cortex in purple, and in the occipital pole in green. Plots of glucose metabolism (middle graph) are based on data by Chugani *et al.*<sup>109</sup> and provide information about the absolute values of local cerebral metabolic rate (LCMR) for glucose in the frontal (red), parietal (blue), temporal (purple) and occipital (green) cortices. Plots of synaptic density in the prefrontal (red) and visual (green) cortices (bottom graph) are based on data by Huttenlocher and de Courten<sup>28</sup> and Huttenlocher<sup>110</sup>, as re-plotted on a semi-logarithmic scale by Rakic *et al.*<sup>111</sup>. To facilitate the comparison across the different plots, the vertical line indicates age 15 years. Note the following features of the trajectories, especially between childhood and adulthood: for cortical grey matter, different trajectories are observed in different cortical regions; for glucose metabolism, the same trajectories are found in the four different lobes; the same trajectories are also found for synaptic density in the prefrontal and occipital cortices. Taken together, these plots indicate that it is unlikely that there is a direct relationship between the three sets of measures.



**Figure 2 | Sexual dimorphism in the maturation of white matter during adolescence.** **a** | Age-related changes in the relative (brain-size corrected) volume of white matter summed across the frontal, parietal, temporal and occipital lobes. **b** | Age-related changes in mean-centred values of magnetization transfer ratio (MTR) in the lobar white matter; the MTR provides an indirect index of myelination. Note that the opposite developmental trajectories in volume and MTR in males suggest that age-related increases in white-matter volume during male adolescence are not driven by myelination. Graphs are based on data from REF. 37.

larger the calibre, the fewer axons fit into the same unit of imaged volume, resulting in a relative decrease in the myelination index<sup>37</sup>. Although more work is needed to confirm this initial observation, it serves as a reminder that most of the MRI studies are not specific enough to allow one to interpret their findings as reflecting a single neurobiological process such as myelination.

Overall, as tempting as it might be to interpret descriptive findings obtained from structural MRI using mechanistic neurobiological processes, such as synaptic pruning or myelination, the evidence that supports such interpretations is limited. There is a pressing need to acquire direct evidence of the processes that underlie the observed changes in grey- and white-matter volume during adolescence using experimental models, in which investigators can combine *in vivo* and *ex vivo* methods to bring together descriptive and mechanistic levels of analysis. Until this happens, we suggest that a more cautious and open-minded approach is warranted.

**Neural connectivity.** Two key features characterize the functional organization of the mammalian brain: specialization and integration. Clearly, the structural and functional maturation of the neural pathways that connect a set of specialized brain regions is therefore essential for the successful development of cognitive, motor and sensory functions from infancy through childhood and adolescence and into adulthood. There are many different ‘connectivities’. Studies

of anatomical connectivity allow one to detect, using injection of radioactive tracers into the brain of experimental animals, the efferent and afferent projections of small populations of neurons. This is not the same as anatomical ‘connectivity’ assessed with DTI-based tractography, as this technique does not allow one to identify point-to-point (or cell-to-cell) connections between distinct neural populations. Functional connectivity captures the correlation between the neural activity of a set of brain regions that are ‘engaged’ during a particular task or measured at rest. But such correlations do not provide information regarding the causality or directionality of inter-regional interactions. Effective connectivity attempts to address this issue either by manipulating brain activity in one region and evaluating the effect of such manipulation elsewhere, or by using mathematical models<sup>38</sup>.

An example of a study that investigated functional connectivity during childhood and adolescence is an investigation of memory encoding in subjects between 11 and 19 years of age<sup>39</sup>. The study showed an age-related decrease in the fMRI signal in the left medial temporal lobe of subjects viewing photographs of natural outdoor scenes, whereas no age-related change was found in the control condition in which subjects viewed the same scene over and over. The authors used voxel-wise regression analysis to identify brain regions in which the fMRI signal correlated with that measured in two subregions of the left medial

temporal lobe, namely the hippocampus and the entorhinal cortex — structures that are known to participate in encoding new information. This analysis revealed an age-related increase in the correlation between activity in the left entorhinal cortex and activity in the left dorsolateral prefrontal cortex. This work nicely illustrates the importance of including analyses of functional connectivity in developmental studies: although the fMRI signal decreased with age in one of the memory-relevant structures (the entorhinal cortex), the proposed interaction between this structure and other brain regions (the prefrontal cortex) actually increased with age.

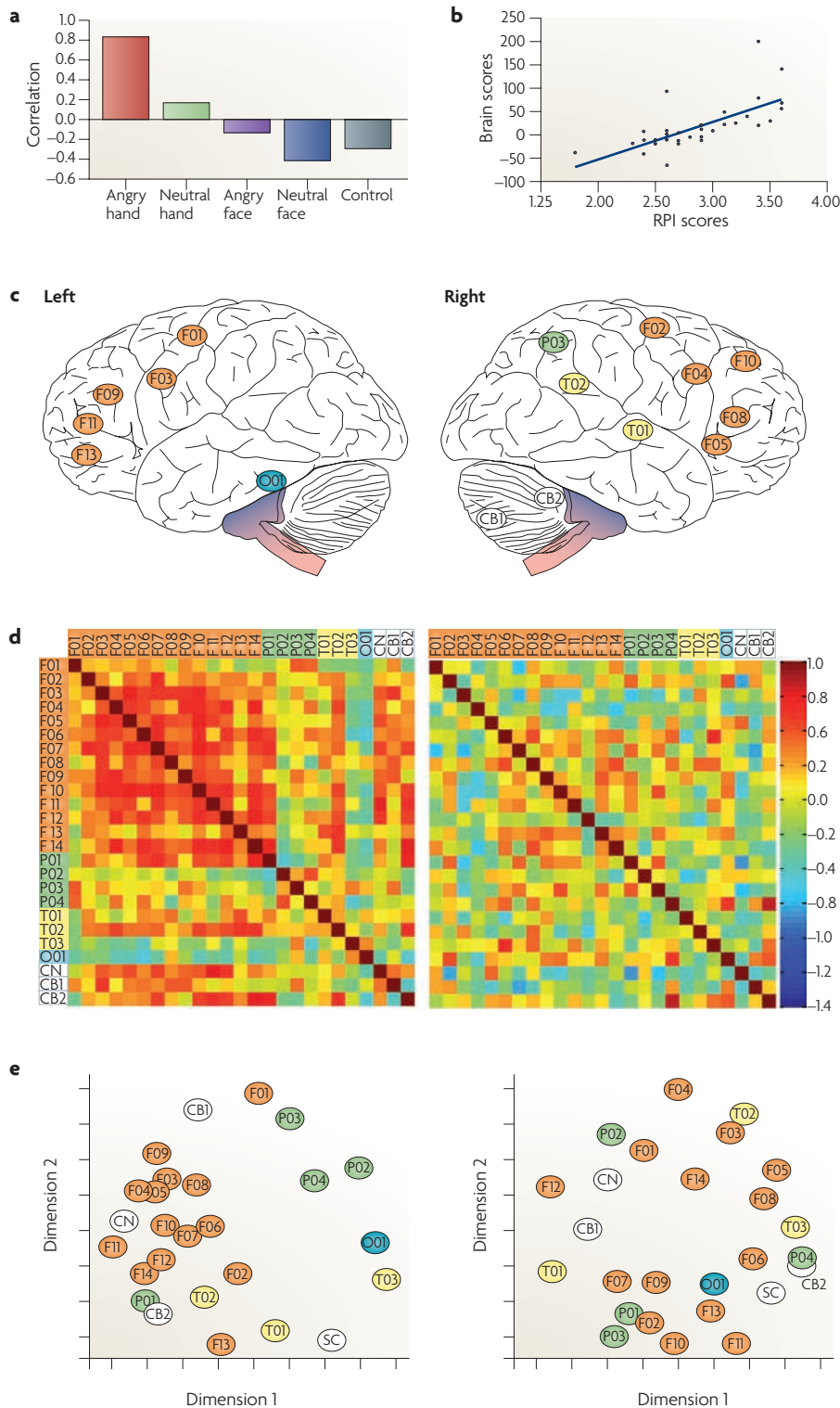
Another study investigated functional connectivity in the context of possible neural substrates of resistance to peer influences (RPI) in early adolescence (10-year-old children)<sup>40</sup>. This study aimed to determine whether the probability with which an adolescent follows the goals set by peers or those set by themselves might depend on the interplay between three neural systems. First, the action-observation network, which is considered by many to be the neural substrate of imitation<sup>41</sup>; it consists of frontal and parietal regions that are involved in the preparation and execution of actions. In this network, so-called ‘mirror neurons’ in the inferior pre-motor cortex, the inferior frontal gyrus and the anterior inferior parietal lobe are active both when subjects perform a specific action themselves and when they observe another individual performing the same action<sup>41</sup>. Second, the biological-motion processing network<sup>42</sup> (also known as the superior temporal sulcus (STS) network), which has an important role in extracting socially relevant cues, such as those imparted by the movements of eyes or hands. Neurons in the STS respond selectively to the presentation of dynamic bodies, body parts or faces<sup>42</sup>. Third, the executive network<sup>43</sup>, which supports a number of cognitive processes that underlie decision making, working memory and the suppression of alternative programmes that would otherwise interfere with planned actions; it consists of a set of regions in the lateral and medial prefrontal cortex<sup>43</sup>. In the study, subjects lying in an MRI scanner were asked to watch brief video clips containing face or hand/arm actions that were executed in neutral or angry ways, while changes in fMRI signals were measured. Outside the scanner, the subjects completed an RPI questionnaire<sup>44</sup>. Children with high RPI scores showed stronger inter-regional activity correlations in brain activity across the three networks while watching angry hand actions than the children who had low RPI scores (FIG. 3).

This method identified activity correlations between areas that included both regions involved in action observation (the fronto-parietal and temporo-occipital systems) and regions in the prefrontal cortex. Thus, what distinguished subjects with high and low resistance to peer influences was not the

magnitude of the BOLD response in individual brain regions but the degree of functional connectivity between regions.

**Neurochemistry.** The efficacy of communication across neuronal networks depends crucially on the state of the various

neurotransmitter systems (BOX 2). In adults, positron emission tomography (PET) is one of the *in vivo* techniques that is used to assess the state of neurotransmitter systems, such as the activity of the enzymes that are involved in the synthesis or metabolism of a given neurotransmitter or the number of



**Figure 3 | Functional connectivity correlates with resistance to peer influence.** This figure shows functional connectivity, indexed by inter-regional correlations in functional MRI (fMRI) signals, during the observation of angry hand movements in children who differ in their resistance to peer influences (RPI). **a** | Correlations between the fMRI signal in a combination of brain regions during observation of angry and neutral hand movements and facial expressions and scores on the RPI questionnaire. **b** | Brain activity (brain score) during angry hand movements correlated strongly with RPI scores. **c** | Locations of brain regions in which the fMRI signal correlated with the RPI score during the observation of angry hand movements; only regions that are visible on the lateral surface of the left and right hemispheres are shown. **d** | Correlation matrices depicting inter-regional correlations of fMRI signals measured during the observation of angry hand movements in subjects with high (left) and low (right) RPI scores (subjects with RPI scores above and below the group median, respectively). The degree of inter-regional correlation (that is, functional connectivity) is higher in children with high RPI scores than in children with low RPI scores. **e** | Multi-dimensional scaling representations of the inter-regional correlations of the 25-dimensional matrix depicted in part **d**. Brain regions between which the fMRI signals (during the observation of angry hand movements) were strongly correlated are placed close together. Functional connectivity between regions is greater in children with high RPI scores (left graph) than in children with low RPI scores (right graph). CB1, cerebellum, right; CB2, cerebellum, right; CN, caudate nucleus, right; F01, premotor cortex, dorsal, left; F02, premotor cortex, dorsal, right; F03, premotor cortex, ventral, left; F04, premotor cortex, ventral, right; F05, frontal operculum, right; F06, cingulate motor area, left; F07, insula, anterior, left; F08, prefrontal cortex, ventrolateral, right; F09, prefrontal cortex, dorsolateral, left; F10, prefrontal cortex, dorsolateral, right; F11, prefrontal cortex, ventrolateral, left; F12, anterior cingulate cortex, right; F13, orbitofrontal cortex, lateral, left; F14, prefrontal cortex, medial; O01, fusiform gyrus, left; P01, posterior cingulate cortex; P02, precuneus, left; P03, parietal cortex, dorsolateral, right; P04, parietal cortex, dorso-medial, right; SC, superior colliculus, right; T01, superior temporal sulcus, middle, right; T02, superior temporal sulcus, posterior, right; T03, hippocampus, right. Figure reproduced, with permission, from REF.40 © (2007) Society for Neuroscience.

## Box 2 | Basics of neurotransmission

Transmission of information from one neuron to the next involves several steps. Local excitatory and inhibitory postsynaptic potentials (EPSPs and IPSPs) are continuously being summed at the axonal hillock, and once a threshold value is reached an action potential is generated. The action potential then travels along the axon and, at the synapse, causes a release of neurotransmitters. The so-called conduction velocity is higher in myelinated axons than in non-myelinated axons and is also higher in large-diameter axons than in small-diameter axons<sup>104–106</sup>. Neurotransmitters are chemicals that either relay action potentials or modulate (for example, amplify) this process. Neurotransmitters include amino acids (for example, glutamate and GABA ( $\gamma$ -aminobutyric acid)), monoamines (for example, dopamine, serotonin and noradrenaline), acetylcholine and many neuropeptides (for example, oxytocin). Glutamate and GABA are the main excitatory and inhibitory neurotransmitters, respectively, and dopamine is one of the most studied neuromodulators. The action of a particular neurotransmitter is mediated by a receptor; a given neurotransmitter can bind to a number of receptor subtypes that are found in different brain regions, or different layers of the cerebral cortex, in different densities<sup>107,108</sup>. The complex interaction between the various neurotransmitters released at any given time at the synapse determines the number of EPSPs and IPSPs generated on the postsynaptic membrane and, in turn, the firing of the neuron.

the receptors for the transmitter. Owing to radiation concerns, however, PET cannot be used in healthy children or adolescents. Therefore, most of our knowledge of developmental changes in neurotransmitters is derived from post-mortem studies in human and non-human primates.

We now consider developmental changes in the dopaminergic system, which has often been conceptualized as underlying adolescent-specific changes in motivational behaviour<sup>45</sup>. The existing data are not entirely consistent with this view, however. In the monkey, levels of the catecholamine-synthesizing enzyme tyrosine hydroxylase (TH) do not change during postnatal development in cortical layers I and VI. In layer III, TH levels are highest during infancy (5–7 months of age) in the entorhinal cortex<sup>46</sup> and during puberty (2–3 years of age) in the prefrontal cortex<sup>47</sup>.

In humans, two recent post-mortem studies evaluated age-related changes in TH, catechol-*O*-methyltransferase (COMT) and a number of dopamine receptors in the human prefrontal cortex; COMT is a dopamine-metabolizing enzyme that is particularly important for dopaminergic transmission in the prefrontal cortex. No differences in COMT activity were found between infants (5–11 months of age), adolescents (14–18 years) and young adults (20–24 years)<sup>48</sup>—COMT activity increased only in adulthood (31–43 years)<sup>48</sup>. The second study showed that TH levels in the human prefrontal cortex were highest in neonates and by adolescence had declined to the levels observed in adults<sup>49</sup>. The same was true, in the same region, for expression of the dopamine D2 receptor gene, *DRD2*. By contrast, expression of *DRD1* was highest in adolescents (14–18 years) and young adults

(20–24 years) in all layers of the prefrontal cortex. Levels of *DRD4* in the prefrontal cortex did not change with age<sup>49</sup>. These findings illustrate that, contrary to prior assumptions, developmental changes in the different elements of dopaminergic transmission during adolescence are complex — very few, if any, of these elements peak during adolescence. As such, these age-related variations — in particular in the prefrontal cortex — are not likely to account for differences between adolescents and adults in motivation-related modulation of cortical activity.

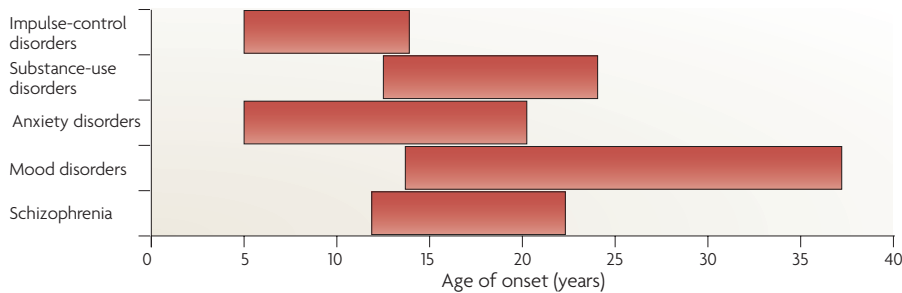
### Psychopathology and adolescence

The results of the National Comorbidity Survey Replication study, which entailed in-person household assessments of over 9,000 people representative of the US population (conducted from February 2001 to April 2003), indicated that the peak age of onset for any mental health disorder is 14 years<sup>50</sup>. Anxiety disorders, bipolar disorder, depression, eating disorder, psychosis (including schizophrenia) and substance abuse all most commonly emerge during adolescence<sup>50,51</sup> (FIG. 4). The emergence of certain psychopathologies is probably related to anomalies or exaggerations of typical adolescent maturation processes acting in concert with psychosocial factors (for example, school and relationships) and/or biological environmental factors (for example, pubertal hormonal changes and drugs of abuse), as will be discussed later. Here we focus on schizophrenia, affective and anxiety disorders and substance-use disorders because they are among the most well-studied, common and disabling disorders that emerge during adolescence, and they serve to highlight aberrations in the key developmental domains of cognition, affect and motivational behaviour.

**Schizophrenia.** Schizophrenia is a common disorder, with a lifetime prevalence of approximately 1%. It typically begins in adolescence or early adulthood and is characterized by unusual beliefs and experiences, namely delusions and hallucinations (collectively termed positive symptoms), social withdrawal and flat affect (negative symptoms), and cognitive impairment, notably in executive functions. An early onset of schizophrenia, during or even before adolescence, is associated with more-severe impairments<sup>52</sup>. The emerging ability to think abstractly during adolescence permits the application of advanced reasoning to social and interpersonal processes. These abilities are critically impaired in patients with schizophrenia, which led Feinberg to propose a relationship between late-adolescence-onset schizophrenia and changes that occur during adolescent brain development<sup>53</sup>. For example, the number and the duration of delta-wave sleep periods normally decrease during healthy adolescence<sup>53</sup>. In adolescents and young adults with schizophrenia, this reduction in delta-wave sleep is even more pronounced<sup>54,55</sup>. Delta-wave sleep represents the summed synchronous electrical activities of large assemblies of cortical neurons. On the basis of these observations, Feinberg speculated that schizophrenia might be a consequence of an exaggeration of the typical synaptic elimination that takes place during adolescence<sup>53</sup>.

Subsequently, several lines of evidence have lent support to this hypothesis (that an “exaggeration of typical adolescent changes” has occurred in patients with schizophrenia)<sup>54</sup>. In addition to the exaggerated reductions in delta-wave sleep in adolescent patients with schizophrenia<sup>55</sup>, patients with schizophrenia have prominent reductions in the level of membrane phospholipid precursors in the prefrontal cortex<sup>56</sup>, in prefrontal metabolism<sup>57</sup> and in volumes of grey matter in the frontal cortex<sup>58</sup>; all of these observations are consistent with an exaggeration of the changes that occur in typical development. In a rare case of childhood-onset schizophrenia (onset before the age of 12 years), which is phenomenologically similar to adolescent- or adult-onset schizophrenia, the typical decrease in frontal grey-matter volume that is seen in healthy subjects during adolescence was exaggerated fourfold<sup>58</sup>.

Direct evidence of a decrease in the number of synapses and other neural elements in schizophrenia comes from post-mortem studies that indicated a decreased density of synaptic spines<sup>59</sup>, a reduction in neuropil<sup>60</sup> and decreased expression of the



**Figure 4 | Ranges of onset age for common psychiatric disorders.** Recent data from the National Comorbidity Survey Replication study<sup>50,112</sup>, a nationally representative epidemiological survey of mental disorders, suggest that approximately half of the population fulfil the criteria for one or other psychiatric disorder in their lifetimes. Most of those with a mental disorder have the beginnings of the illness in childhood or adolescence. Some anxiety disorders (such as phobias and separation anxiety) and impulse-control disorders begin in childhood, whereas other anxiety disorders (such as panic, generalized anxiety and post-traumatic stress disorder), substance disorders and mood disorders begin later, with onsets rarely before the early teens. Schizophrenia typically begins in late adolescence or the early twenties, with men having a somewhat earlier age of onset than women<sup>51</sup>. Psychiatric disorders with childhood or adolescent onsets tend to be more severe, are frequently undetected early in the illness and accrue additional co-morbid disorders, especially if untreated. It is therefore crucial to focus efforts on early identification and intervention.

synaptic marker synaptophysin<sup>61</sup>. Although this evidence supports a neurodevelopmental pathophysiology of schizophrenia, it does not provide indications regarding its aetiology. The cause of schizophrenia probably lies in the interplay between genetic and environmental factors, perhaps involving pre- and perinatal adverse events, a suboptimal postnatal environment during infancy and childhood, and biological stressors during adolescence.

**Substance abuse.** Adolescents are more likely to experiment with drugs. Substance-abuse disorders in adults typically begin during the teenage years; they can be preceded by behavioural disturbances and poor adjustment in childhood, as shown by recent results from the National Child Development Study<sup>62</sup>. An earlier onset of drug use predicts a greater severity of addiction problem<sup>63</sup> and might serve as a 'gateway' to the use of multiple substances later in life<sup>64</sup>.

Certain personality traits are important risk factors for substance use, including high levels of novelty seeking and low levels of harm avoidance<sup>65,66</sup>. Across a wide array of mammalian species, adolescents exhibit increased risk taking and novelty seeking and a greater valuation of social factors<sup>67,68</sup>. Although these characteristics foster independence from the natal family, they also increase the risk for harmful behaviours, including, in humans, substance use and abuse. Some investigators have speculated that risk-taking and reward-seeking behaviours in adolescents might be related to a heightened sensitivity for reward<sup>24</sup>. As

discussed above, this notion has been supported by fMRI studies that found greater feedback-related activity using a monetary-reward task in reward circuitry, namely the nucleus accumbens, in adolescents<sup>25</sup>. But other studies found the opposite pattern, namely lower accumbens activity in response to monetary gains in adolescents than in young adults<sup>26</sup>. On the other hand, the activity of the medial-frontal circuitry, which is implicated in conflict monitoring and decision making, increases from adolescence to adulthood during fMRI tasks in which participants assume some risk of penalty in pursuit of an explicit reward. This developmental difference is less pronounced, however, when potential penalties in the task are severe<sup>69</sup>.

Compounding these social and behavioural risks is the possibility that adolescents have less-aversive biological responses to substances of abuse. In adolescent rats, nicotine, amphetamine and alcohol produce less-pronounced acute effects and milder withdrawal responses<sup>70,71</sup>. Under the influence of alcohol, for instance, adolescent rats are less sensitive to developing motor impairment<sup>72</sup>, getting a 'hangover' (REF. 73) or becoming sedated. These developmental differences might be related to immaturity of the developing GABA<sub>A</sub> receptor ( $\gamma$ -aminobutyric acid type A receptor) systems<sup>74</sup>.

By contrast to their possibly more-rewarding and less-aversive responses, adolescents might be more prone to the deleterious effects of substance abuse. The hippocampus of adolescent rats is unusually susceptible to ethanol-induced inhibition of

long-term potentiation, making the rats more sensitive to the memory-impairing effect of alcohol<sup>75</sup>. This effect (which occurs at alcohol concentrations as low as 5 mM — equivalent to a single drink in humans), seems to be largely mediated through alcohol's effect on NMDA (*N*-methyl-D-aspartate) receptors, occurs at the single-cell level and is not confined to the hippocampus<sup>76</sup>.

Clearly, some neural alterations that take place during adolescence predispose to risk, whereas others, such as memory impairments, might be actually the result of the abuse. Morphometric studies of humans support this notion. For instance, in youths with a family history of alcohol abuse the right amygdala is smaller even before the onset of problem drinking, whereas hippocampal volumes are reduced only after a history of alcohol use<sup>77,78</sup>.

Exposure to substances of abuse in adolescence might also increase the likelihood of addictive disorders emerging later in life. For example, exposure to nicotine during adolescence, but not in the post-adolescent period, increases the reinforcing effects of nicotine in a self-administration paradigm in adult rats<sup>79</sup>.

**Affective and anxiety disorders.** Affective disorders, such as major depression, are common and serious disorders of adolescence; adolescent onset is associated with more-severe and more-disabling forms of these illnesses<sup>80,81</sup>. Anxiety symptoms frequently precede depression in adolescence<sup>82</sup> and during childhood<sup>83</sup>.

Structural MRI studies of adolescents with anxiety and affective disorders have reported structural anomalies in the superior temporal gyrus, the ventral prefrontal cortex and the amygdala<sup>84–86</sup>. An fMRI study of depressed and anxious adolescents reported anomalous amygdala responses to social stimuli<sup>87</sup>. In another fMRI study, adults but not adolescents engaged the orbitofrontal cortex when asked to switch from an emotional assessment of a face (that is, "How afraid does it make you feel?") to a non-emotional one (that is, "How wide is the nose?")<sup>88</sup>. The abnormal engagement of brain regions to emotional facial expressions in adolescents might underlie an unrealistic appraisal of emotions and thereby predispose to anxiety and depression.

Hormonal changes that occur during adolescence are likely to account for at least part of the risk for mood and anxiety disorders. Indeed, an intriguing clue to the biology of depression, anxiety and panic disorders is the change from equal female–male prevalence prepuberty to a 2:1 female–male

prevalence after puberty. Epidemiological evidence indicates that it is only after Tanner stage III that the sex differences in the incidence of depression emerge<sup>89</sup>. The finding that pubertal status predicts the sex difference in prevalence better than age<sup>90,91</sup> suggests that sex hormones play a part in the pathophysiology of these disorders.

A recent mouse study that examined the effect of tetrahydroprogesterone (THP), a steroid derived from progesterone, provides a possible mechanism for this phenomenon<sup>92</sup>. This hormone is released during stress and has an anxiolytic effect that is mediated by the activation of GABA<sub>A</sub>

receptors, which are also activated by alcohol and benzodiazepines. However, when it binds to a particular subtype of GABA<sub>A</sub> receptor, namely the  $\alpha 4\beta 2\delta$  receptor subtype, THP has the opposite effect to that of alcohol and benzodiazepines: it increases anxiety. The expression of the  $\alpha 4\beta 2\delta$  receptor in the CA1 region of the hippocampus surges after puberty and is accompanied by increased anxiety, as measured on an elevated plus maze. Moreover, blocking the formation of THP alleviated the increase in anxiety in adolescent mice<sup>92</sup>. Whether the effects of stress-related hormones on the brain can explain the difference in rates of

anxiety and depressive disorders between prepubescents and adults awaits further investigation.

In summary, robust changes in hormones and hormonal receptors, increasingly powerful emotional responses to social stimuli and rapid alterations in motivation and reward systems might underlie the onset of anxiety and depressive disorders during adolescence.

## Conclusions and future directions

The relationship between typical changes in the adolescent brain and the onset of psychopathology is not a unitary phenomenon, but an underlying theme can be conceptualized as ‘moving parts get broken’. Adolescence is characterized by major changes in the neural systems that subserve higher cognitive functions, reasoning and interpersonal interactions, cognitive control of emotions, risk-versus-reward appraisal and motivation. Not surprisingly, it is precisely these changes that, when suboptimal in timing or magnitude, increase the risk of cognitive, affective and addictive disorders. Understanding the basis of these disorders therefore requires a comprehensive knowledge of how the brain is put together. Many advances are being made, but a lot remains to be learnt.

An emerging theme from paediatric neuroimaging studies is that the journey of brain development is often as important as the destination. For example, IQ is predicted by the developmental trajectory of cortical thickness, not by the adult cortical thickness<sup>93</sup>. The large individual variability in brain anatomy and function calls for longitudinal study designs that capture the nuances of heterochronous developmental curves. The first phases of longitudinal studies have mapped developmental trajectories for typical development, but those of patients with psychiatric illnesses have been mapped to a lesser extent. The next phases should go beyond simply mapping brain growth and begin to discern the adverse as well as protective factors that influence those trajectories.

A common initial approach to assessing causal influences on brain development is to discern the relative effects of genetic and non-genetic factors. This is best addressed through comparisons of monozygotic and dizygotic twins. Results from an ongoing paediatric longitudinal neuroimaging project at the Child Psychiatry Branch of the National Institute of Mental Health indicate significant age-by-heritability interactions, with heritability of grey-matter volume generally decreasing with age and heritability of

## Glossary

### Androgen insensitivity syndrome

(Also known as androgen resistance syndrome or testicular feminization.) An X-linked, recessive condition characterized by a complete or partial failure of virilization that is due to a mutation on the gene that encodes the androgen receptor.

### Anti-saccade task

A task in which subjects are required to suppress the automatic response of making a saccade towards a target and, instead, produce an eye movement in the opposite direction.

### Congenital adrenal hyperplasia

A group of autosomal-recessive disorders caused by mutations in the genes for the enzymes that are involved in steroid synthesis. The result of these mutations is excessive or deficient production of sex steroids.

### Delta-wave sleep

A stage of non-rapid-eye-movement sleep characterized by slow, or delta, waves (0.5–4 Hz); the more delta waves there are, the deeper the sleep.

### Diffusion tensor imaging

(DTI). An MRI-based technique that allows one to characterize the structural properties of white matter.

### Eriksen flanker task

A task in which subjects have to respond to a stimulus that is flanked by other stimuli that may code an alternative response.

### Familial male precocious puberty

An autosomal-dominant disorder that occurs in males and is characterized by the onset of puberty (testicular enlargement) before 4 years of age.

### Founder effect

The loss of genetic variation when a new colony is established by a very small number of individuals from a larger population.

### Fractional anisotropy

(FA). The directionality of the (fast) diffusion of water in the extracellular space around the axons (in most common acquisition protocols). The more unidirectional the water diffusion is in a given fibre tract, the higher the FA value in that location.

### Go/no-go task

A task in which the subject must produce a motor response for one class of stimulus but withhold responding to other classes of stimuli.

### Magnetization transfer ratio

(MTR). A measure used for assessing white-matter properties; it provides information on the macromolecular content and structure of the tissue. Given that the macromolecules of myelin are the dominant source of MT signal in white matter, one can use MTR as an index of myelination. Note, however, that myelin is not likely to be the sole factor influencing the MTR.

### Neural Darwinism

A neurodevelopmental process in which the synapses that are used the most are kept whereas the least-used connections are destroyed (‘pruned’).

### Stop task

A test of response inhibition. On each trial, a stimulus (for example, a leftward- or rightward-pointing arrow) is displayed on a screen, and the subject has to respond as soon as possible by pressing the corresponding (left or right) key, unless a second stimulus (for example, a sound) signals that the response has to be withheld.

### Stroop task

A task in which the subject is asked to name the colour of ink in which a word is displayed. The task is easy when the ink colour is congruent with the printed word (for example, ‘red’ printed in red ink). The task becomes difficult when the ink colour is incongruent with the printed word (for example, ‘red’ printed in green ink).

### STS network

A set of regions, located along the superior temporal sulcus, that are involved in processing biological motion induced by the movement of different body parts, such as the eyes, the face or the entire body.

### Tanner stage III

One of the five stages of puberty. Without resorting to a physical exam, pubertal stages can be assessed using, for example, the Puberty Development Scale, which is an eight-item self-report measure of physical development based on the Tanner stages with separate forms for males and females. For this scale there are five categories of pubertal status: prepubertal, beginning pubertal, midpubertal, advanced pubertal and postpubertal.

### XXY

(Klinefelter’s syndrome). A genetic syndrome that affects males and is caused by the presence of two X chromosomes (resulting in a 47-chromosome karyotype).

white-matter volume generally increasing with age<sup>94</sup>. Heritability-by-age interactions might be related to the timing of gene expression, which in turn might relate to the timing of the onset of illness. Post-mortem human and animal studies indicate that 'developmental' genes have diverse effects at various stages of brain development. But differences in heritability in different age groups may also reflect the cumulative effect of experience on brain structure; depending on certain inherent traits (for example, musical talent or personality), it is only with time that specific experiences start to shape the brain.

Multivariate analyses of twin data indicate that a relatively small number of shared genetic and environmental factors account for a substantial portion of the variance across multiple neuroanatomic structures<sup>95</sup>. Ongoing studies of specific gene effects on brain maturation may help to sharpen our understanding of brain-development mechanisms and provide insight into the aetiologies of various pathologies. The Saguenay Youth Study, carried out in a geographically isolated population with a known founder effect, will facilitate our search for genes that influence brain and behaviour during adolescence<sup>96</sup>. Finally, genetics may also provide biologically relevant subtypes of neuropsychiatric disorders that are obscured in current diagnostic schemes.

The marked sex differences in age of onset, prevalence and symptomatology for nearly every neuropsychiatric disorder may provide important clues as to these disorders' pathophysiology. The most-obvious outward physical manifestations of puberty are caused by changing levels of hormones<sup>97</sup>. Perhaps this has contributed to the tendency to attribute all of the cognitive and behavioural changes of adolescence to 'raging hormones'. But the relationship between hormones, the brain and behaviour is complex, reciprocal and poorly understood. Steroid hormones affect neuronal activity and morphology throughout development. Most neurons have receptors for adrenal and gonadal hormones, and when these receptors are activated they can affect neuronal function. Short-term effects are mediated by membrane-bound receptors, whereas long-term effects alter gene expression through intracellular or nuclear receptors. Conversely, the dramatic hormonal changes of puberty are triggered by alterations in excitatory and inhibitory inputs to gonadotropin-releasing hormone neurons in the pituitary. Hormonal effects drive aggression and sexual interest, but their

impact on impulse control, logical problem solving and other cognitive tasks has not been well established.

Social and cultural factors for boys and girls are profoundly different, and the relationship of these differences to manifest pathology should be explored. In the biological realm, sex differences probably stem directly from different genes on the X and Y chromosomes or indirectly from the effects of different hormone levels. Studies of subjects with sex-chromosome variations (for example, XO, XXY, XXY, XXX or XXXXY) or anomalous hormone levels (for example, owing to congenital adrenal hyperplasia, androgen insensitivity syndrome or familial male precocious puberty) will be useful for sorting out the relative contributions of gene and hormone effects. For instance, males with an extra X chromosome (XXY or Klinefelter's syndrome) have a high incidence of language disorders, ADHD and social-skill deficits that are reflected in differences in cortical thickness, consistent with reports in the literature for XY subjects with such disorders<sup>98</sup>. Girls with congenital adrenal hyperplasia, which is characterized by intrauterine exposure to high levels of testosterone, have an entirely different pattern of structural findings, indicating differential effects of sex chromosomes and hormones on the brain<sup>99</sup>.

Although neuroimaging is beginning to establish correlations between brain structure/physiology and behaviour, the link between typical behavioural changes and psychopathology has not been firmly established. For example, the neural circuitry that underlies 'moodiness' in an adolescent might not be the same as that which is involved in depression or bipolar disorder. Neuroimaging data can help in the development of neuroanatomical models of cognitive, affective and social processes that are based on findings from developmental psychology<sup>100</sup>. Imaging studies of healthy adolescents are also helping to construct age-appropriate structural and functional brain templates.

Newer imaging approaches are being developed. Magnetic resonance spectroscopy studies using strong magnetic fields can help to quantify neurotransmitter systems, such as glutamate and GABA systems, as well as markers of neurogenesis<sup>101</sup>. Combining multiple imaging modalities, such as structural MRI, fMRI, DTI, magnetization transfer imaging, electroencephalography or magnetoencephalography, in the examination of single individuals will enhance our ability to

interpret the signals for each of the modalities. Being able to examine simultaneously inter-individual variation from cellular to macroscopic levels will be instrumental in bridging the gaps between genes, the brain and behaviour.

Studies of the neural substrates of adolescent behaviour and decision making will need to be better integrated with social and educational science. Laboratory studies of teenagers using hypothetical situations in calm environments without peer influence might have little relevance for understanding real-world decision making, which often occurs in the presence of peers and in the context of intense physical or emotional arousal and conflicting priorities<sup>102</sup>.

Many questions about adolescent brain development and its impact on disease can best be investigated in animal models. Modelling the adolescent phase in animals is useful for investigating the risk for addictive and other early-onset neuropsychiatric disorders<sup>79</sup>. Although there are no animal models that represent the full phenotypic spectrum of a psychiatric disorder, such as schizophrenia or depression, individual phenotypic components of disorders — such as developmental alterations that might be associated with the illness — can be used to construct animal models that are aimed at unravelling disease mechanisms and that allow novel interventions to be tested<sup>103</sup>.

Another translational approach involves combined *in vivo* (for example, MRI) and post-mortem studies in animals; such studies are essential for clarifying the nature of the neurobiological changes that drive the MRI findings. Of immediate relevance will be studies that attempt to discern the degree to which changes in cortical grey matter, as detected by MRI, are related to dendritic arborization, intracortical myelination or the encroachment of white matter on the inner cortical border.

Adolescence is a time of substantial neurobiological and behavioural change. These changes are usually beneficial and optimize the brain for the challenges ahead, but they can also confer a vulnerability to certain types of psychopathology. The technologies to elucidate the relationship between specific neurobiological maturational processes and specific normative or pathological changes are already in place. Applying these tools to understand when and how deviations from typical development occur may enhance our ability to prevent or treat disorders that affect a substantial number of people.

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#### DATABASES

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#### FURTHER INFORMATION

Tomáš Paus's homepage:

<http://brainbody.nottingham.ac.uk/people/paus.php>

Matcheri Keshavan's homepage:

<http://brain.wayne.edu/kesh/kesh.htm>

Jay Giedd's homepage:

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## SCIENCE AND SOCIETY

# Beyond polemics: science and ethics of ADHD

Illina Singh

**Abstract** | What is attention-deficit hyperactivity disorder (ADHD)? Why are so many children being diagnosed with ADHD and prescribed medication? Are stimulant drugs an effective and safe treatment strategy? This article explores the current state of scientific research into ADHD and the key social and ethical concerns that are emerging from the sharp rise in the number of diagnoses and the use of stimulant drug treatments in children. Collaborations among scientists, social scientists and ethicists are likely to be the most promising route to understanding what ADHD is and what stimulant drugs do.

Attention-deficit hyperactivity disorder (ADHD) is one of the most common childhood psychiatric disorders in the world<sup>1</sup>. Its core symptoms are inattention, hyperactivity and impulsiveness. Most children are first diagnosed with ADHD when they reach school age<sup>2</sup> and approximately 75% of those diagnosed are male<sup>3</sup>. The most common forms of treatment for ADHD are the stimulants methylphenidate and amphetamine<sup>4</sup>.

Rising rates of ADHD diagnosis and stimulant drug use in children have led to a public debate over the validity of the diagnosis, the root causes of ADHD

and the ethics of treating children with psychotropic drugs. There are three partially overlapping positions in the debate. First, that ADHD is primarily caused by a combination of biological factors. From this perspective, diagnosis is valid and drug treatment is justified because it corrects an underlying neurochemical imbalance that affects cognitive and motor functions. Second, that ADHD is caused by a combination of biological and social factors; the diagnosis does not yet adequately capture the heterogeneity and complexity of the disorder. This perspective accepts the utility of stimulant drug medication, but some