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# Why do many psychiatric disorders emerge during adolescence?

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## Abstract

What do we know about the maturation of the human brain during adolescence? Do structural changes in cerebral cortex reflect synaptic pruning? Are increases in white-matter volume driven by myelination? Is the adolescent brain more or less sensitive to reward? These are but a few questions we ask in this review while attempting to indicate how findings obtained in the healthy brain help in furthering our understanding of mental health during adolescence.

## Introduction

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

In this review we will address the neurobiological changes that occur during adolescence and discuss their possible relationship to the emergence of psychopathology. We will 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 the recent years.

## Typical development: findings and interpretations

The last 15 years have seen an impressive accumulation of knowledge about the development of structure and function of the human brain. Studies carried out with magnetic resonance imaging (MRI) 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, as well age-related changes in brain activity (Box 1)[1-4].

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## Brain structure

Most of the existing literature on age-related changes in brain structure has been reviewed in detail elsewhere [5, 6]. Here we note only the most salient findings.

Volumes of cortical grey-matter appear to increase during childhood, reaching peak levels around the time of the puberty onset, after which they gradually decline; this is the case mostly for the frontal and parietal but not temporal lobes [7]. Local volume of cortical grey-matter declines during childhood and adolescence in most regions, with the slope of the decline varying from flat (e.g. anterior portion of the superior temporal gyrus [STG]) to steep (posterior portion of the STG) and, in some cases, displaying a non-linear relationship with age, for example inverted "U" in post-central gyrus and "U" shaped [between 10 and 20 years] in the mid-dorsolateral frontal cortex [8, 9] (Fig. 1)[8, 10-13].

Volumes of white matter show a rather clear linear increase throughout childhood and adolescence, with the maximum volumes reached often as late as in the third decade of life [14]. It appears that the slope of the age-related increase is steeper in males compared with females [7, 15]. More recently, diffusion tensor imaging (DTI) has been employed to assess age-related changes in the human brain during childhood and adolescence. Overall, DTI studies reveal age-related decreases in magnitude and increases in directionality of water diffusion in a number of white matter regions, many of which are identical to those revealed by the above MRI studies [16-18], such as the arcuate fasciculus. Such changes in DTI-derived measures may indicate ongoing maturation of the axon and/or its myelin sheath.

## Brain activity

The overall picture to be gleaned from the existing descriptive studies of age-related changes in brain activity is less coherent. This is due to the fact that a given functional MRI (fMRI) study focuses on a particular brain function, which is assessed with behavioural paradigms that often differ across laboratories. Interpretation of fMRI is also more challenging than that of structural findings, owing to the indirect nature of the fMRI signal (Box 1) and the large number of potential confounders, such as levels of anxiety/arousal during scanning, varying performance across participants or different cognitive strategies used by different participants in the same task - all of which may interact with the effects of age. We will touch here on two sets of fMRI studies that focused respectively, on cognitive control (or executive functions) and on experiencing gains and losses of various rewards during adolescence.

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[6], many of such "executive" abilities are fully developed by the time a child enters adolescence (Fig. 4 in [6]). On the other hand, certain aspects of executive function, such as planning time[19] and delayed gratification, improve significantly from mid-adolescence (~16 years of age) onward, as indicated by behavioural studies. Using fMRI, Kwon and colleagues[20] found age-related (age 7 to 22 yr) increases in the 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. Similar BOLD increases were observed in these regions during the performance of a variety of tasks involving some form of response inhibition, including the Stroop task[21], anti-saccade task[22], the Stop task[23] and, to a certain extent, during the performance of a go/no-go task[24] and the Eriksen flanker task[25].

Adolescence has been traditionally associated with risk-taking and sensation-seeking behaviour[26]. In this context, several investigators used functional MRI to examine possible differences between children, adolescents and young adults in brain activity during the experience of gains or losses of various rewards. Given its role in reward and motivation[27],

the nucleus accumbens (or ventral striatum) has been the focus of the majority of these studies. If adolescents were "driven" by reward seeking, one would expect heightened engagement of this structure during tasks that involve reward seeking. This appeared to be the case in participants in some[28, 29] but not other[30] studies. For example, Bjork and colleagues[30] 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, when 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 functional maturation of neural circuits involved, for example, in executive functions and reward processing, future studies need to substantially increase sample size and to enhance the behavioural characterization of the performance in the scanner in order to learn more about brain-behaviour relationships during adolescence.

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 adolescence, 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.

## Adolescence = pruning + myelination?

It is the case that MRI-based estimates of the volume of cortical grey-matter and cortical thickness appear to decrease during adolescence. This has been often interpreted as an indication of "synaptic pruning", a process by which "redundant" synapses overproduced in the early years of life are being eliminated (see Purves and colleagues[31] for a critical appraisal of "neural Darwinism").

The initial evidence for accelerated synaptic pruning during development came from *post mortem* studies by Peter Huttenlocher and colleagues who described a decrease in the number of dendritic spines in the human cerebral cortex during childhood and adolescence [10, 32, 33]. It should be noted, however, that these studies were limited by the low number of specimens 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 but a rather gradual decrease in their numbers, beginning (in several cortical regions) in childhood. A more definite evidence of synapse elimination during adolescence was provided by studies carried out by Pasko Rakic and colleagues in non-human primates[34, 35]. Using electron microscopy, they did observe a dramatic decrease in the number of synapses in the visual cortex (and other cortical areas) during puberty (between the age of 2.5 and 5 years), whether expressed as a number of synapses per neuron or per 1 $mm^3$ 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"[35]. 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, may reflect the same cellular events; this is clearly not the case - again especially not during adolescence (Fig. 1).

If the number of synapses per se is unlikely to change the cortical volume/thickness, then what other cellular elements could affect it? About 10% of the (mouse) cortex is occupied by glial cells and about 60% by neuropil, the latter consisting of dendritic and axonal processes [36]. 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 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 [37, 38]. 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[6].

Given the well-documented histology-based increase in the degree of myelination of white-matter pathways during the first two decades of human life[39], 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 been actually measured were volumes of white matter. Is it only a matter of semantics or could other, myelination-independent processes affect 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 those in magnetization transfer ratio (MTR), the latter being an indirect index of the amount of myelin in white matter. Although white-matter volume increased with age during male adolescence, MTR values decreased, thus indicating a decrease in the amount of myelin per unit of volume (Fig. 2)[40]

If myelin does not increase, what could be driving the observed increase in white matter volume during adolescence in males? Our tentative answer is a change in axonal caliber: the larger the calibre, the fewer axons fit in the same unit of the imaged volume, which would result in a relative decrease in the myelination index[40]. Although more work is needed to confirm this initial observation, it serves as a reminder that most of the MRI sequences are not specific enough to interpret MRI-based findings as reflecting a single neurobiological process, such as myelination.

Overall, as tempting as it might be to interpret descriptive findings obtained with 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 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 functional organization of the mammalian brain: specialization and integration. Clearly, structural and functional maturation of neural pathways connecting a set of specialized brain regions is therefore a condition *sine qua non* for the successful development of cognitive, motor and sensory functions from infancy, through childhood and adolescence, and into adulthood. There are many different "connectivities". Anatomic connectivity allows one to determine, using injection of radioactive tracers into the brain of experimental animals, efferent and afferent projections of small populations of neurons. This is not the same as anatomic "connectivity" assessed with DTI-based tractography, which does not allow one to identify point-to-point (or cell-to-cell) connections between distinct neural populations. Functional connectivity captures the correlational relationship across a set of brain regions "engaged" during a particular task or measured at rest. However, such correlations do

not provide information regarding the causality and/or directionality of inter-regional interactions. Finally, effective connectivity attempts to address the latter either by manipulation of brain activity in one region and evaluating the effect of such manipulation elsewhere, or by employing mathematic models [41].

In an example of studies investigating functional connectivity during childhood and adolescence, one study researched memory encoding in subjects between 11 and 19 years of age [42]. The study revealed an age-related *decrease* in the fMRI signal in the left medial temporal-lobe while subjects viewed a series of novel photographs of natural outdoor scenes, as compared with viewing the same scene over and over (control condition). The authors used voxel-wise regression analysis to identify the brain regions in which the fMRI signal correlated with the fMRI signal measured in two subregions of the left medial temporal-lobe, namely the hippocampus and the entorhinal cortex, structures known to participate in the encoding of novel information. This analysis revealed an age-related *increase* in the correlation between the left entorhinal cortex and 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 (entorhinal cortex), the hypothesized interaction between this structure and other brain regions (prefrontal cortex) actually increased with age.

A second study investigated functional connectivity in the context of possible neural substrates of resistance to peer influences (RPI) in early adolescence (10-year old children)[43]. This study aimed to determine whether the probability with which an adolescent follows the goals set by peers or those set by himself/herself might depend on the interplay between the following three neural systems. First, the *action-observation network*, which is considered by many to represent the neural substrate of imitation; it consists of frontal and parietal regions involved in the preparation and execution of actions. So-called 'mirror neurons' within the inferior premotor cortex and/or inferior frontal gyrus, as well as in 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. Second, the *biological-motion processing network*, which plays an important role in extracting socially relevant cues, such as those imparted by the movements of eyes or hands. Neurons within the superior temporal sulcus (STS) respond selectively to the presentation of dynamic bodies, body parts or faces. Third, the *executive network*, which supports a number of cognitive processes underlying decision making, working memory and the suppression of alternative programs interfering with planned actions; it consists of a set of regions in the lateral and medial prefrontal-cortex (PFC). In the scanner, we asked the subjects to watch brief video clips containing face or hand/arm actions that were executed in neutral or angry ways, and measured changes in fMRI signals. Outside the scanner, we administered an RPI questionnaire[44]. We found that the children with high RPI scores showed stronger inter-regional correlations in brain activity across the three networks while watching angry hand-actions, as compared with children who had low RPI scores (Fig. 3). The pattern of inter-regional correlations identified by this method included both regions involved in action observation (the fronto-parietal as well as 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 the individual brain regions but the degree of functional connectivity[43].

## Neurochemistry

The efficacy of communication across neuronal networks depends critically on the state of the various neurotransmitter systems (Box 2)[45-49]..

In adults, positron emission tomography (PET) is one of the *in vivo* techniques used to assess the state of neurotransmitter systems, such as the activity of enzymes involved in the synthesis

or metabolism of a given neurotransmitter or the number of the receptors. Owing to radiation concerns, however, PET cannot be used in healthy children and adolescents. Therefore, we derive most of the knowledge of developmental changes in neurotransmitters 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[50]. 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 the highest during infancy (5-7 months) in the entorhinal cortex [51] and during puberty (2-3 years) in the prefrontal cortex [52].

In humans, two recent *post mortem* studies evaluated age-related changes in TH, 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), adolescents (14-18 yr) and young adults (20-24 yr) [53]; COMT activity increased only in adulthood (31 to 43 yr). A different study showed that TH levels in the human prefrontal cortex were the highest in neonates and, by adolescence, declined to the levels observed in adults[54]. The same was true, in the same region, for expression of the dopamine D2 receptor (DR*D2*) gene. By contrast, expression of *DRD1* was the highest in adolescents (14 to 18 years) and young adults (20 to 24 years) in all layers of the prefrontal cortex. Levels of *DRD4* in the PFC did not change with age. These findings illustrate that, contrary to prior assumptions, developmental changes in the different elements of dopaminergic transmission during adolescence are complex, with very if any peaking during adolescence. As such, these age-related variations - in particular in the prefrontal cortex - are not very likely to account for differences between adolescents and adults in motivation-related modulation of cortical activity.

## Relationship to psychopathology in adolescence

Results of the National Comorbidity Survey Replication study, which entailed in-person household assessments of over 9,000 people representative of the United States population (conducted from February 2001 to April of 2003), have indicated that the peak age of onset for having any mental health disorder is 14 years [55]. Anxiety disorders, bipolar disorder, depression, eating disorder, psychosis including schizophrenia, and substance abuse all most commonly emerge during adolescence [55, 56] (Fig. 4). The emergence of certain psychopathology is likely related to anomalies or exaggerations of typical adolescent maturation processes acting in concert with psychosocial (e.g. school, relationships) and/or biological environmental factors (e.g. pubertal hormonal changes, drugs of abuse), as will be discussed later. In this paper, 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 serve to highlight aberrations in the key developmental domains of cognition, affect and motivational behavior[56, 57]

### Schizophrenia

Schizophrenia is a common disorder with a life-time prevalence of about 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 - that is “negative” symptoms, and cognitive impairments, notably in executive functions. Earlier onset of schizophrenia during adolescence or even before is associated with more severe impairments[58].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 Irwin Feinberg to propose a relationship between late- adolescent onset schizophrenia and changes that occur during adolescent brain development [59]. For example, the amount of "delta" sleep and duration normally decreases during healthy adolescence [59]. In adolescents and young adults with schizophrenia, this reduction in delta sleep is even more pronounced. Delta sleep represents the summed synchronous electrical activities of large assemblies of cortical neurons. Based on these observations, Feinberg speculated that schizophrenia might be a consequence of an exaggeration of the typical synaptic elimination that takes place during adolescence.

Subsequently, several lines of evidence have lent support to this hypothesis that an "exaggeration of typical adolescent changes" has occurred in patients with schizophrenia [60]. In addition to the exaggerated reductions in delta sleep in adolescent patients with schizophrenia [61], patients with schizophrenia have also prominent reductions in the level of membrane phospholipid precursors in the prefrontal cortex [62], prefrontal metabolism [63] and volumes of gray matter in frontal cortex [64]; all these are consistent with an exaggeration of the changes that occur in typical development. In a rare condition of childhood-onset schizophrenia (onset prior age of 12 years), which is phenomenologically similar to the adolescent or adult-onset schizophrenia, the typical decrease in frontal gray-matter that is seen in healthy subjects during adolescence was exaggerated 4-fold [64]. Recent data suggest similar gray-matter losses occurring *before* illness onset, in persons deemed to be at clinical risk for schizophrenia, i.e. in the prodromal phase before the onset of the characteristic psychotic symptoms of this illness [65]

Direct evidence of a decrease in the number of synapses and other neural elements in schizophrenia comes from *post mortem* studies that have indicated a decreased density of synaptic spines [66], reduction in neuropil [67], and decreased expression of the synaptic marker synaptophysin [68] in the brain of schizophrenia patients. Although the above evidence supports a neurodevelopmental pathophysiology of schizophrenia, it does not provide indications regarding its aetiology. The cause of schizophrenia likely lies in the interplay between genetic and the environmental factors, perhaps involving pre- and peri-natal adverse events, suboptimal post-natal 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 teenage years; they may be preceded by behavioral disturbances and poor adjustment in childhood as shown by recent results from the National Child Development Study [69]. Earlier onset of drug use predicts a greater severity of the addiction problem[70] and may serve as a "gateway" to the use of multiple substances later in life [71].

An important risk factor for substance use includes personality traits, including high novelty seeking and low harm avoidance [72, 73]. Across a wide array of mammalian species, adolescents exhibit increased risk taking, novelty seeking, and a greater valuation of social factors [74, 75]. While these characteristics foster independence from the natal family, they also increase the risk for harmful behaviors including substance use and abuse. Some investigators have speculated that risk-taking and reward-seeking behaviors in adolescents might be related to a heightened sensitivity for reward [28]. As reviewed 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 [29]. However, other studies found the opposite pattern, namely lower accumbens activity in response to monetary gains in adolescents as compared with young adults [30]. On the other hand, activity of 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. However, this developmental difference is reduced when potential penalties in the task are severe[76].

Compounding these social and behavioral risks is the possibility that adolescents may 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[77, 78]. Under the influence of alcohol, for instance, adolescent rats are less sensitive to developing motor impairment[79], getting a "hangover"[80], or becoming sedated. These developmental differences might be related to immaturity of the developing GABA-a receptor systems[81].

By contrast to their possibly more rewarding and less aversive responses, adolescents may be more prone to the deleterious effects of substance abuse. Thus, 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[82]. The mechanism for this effect, which occurs at alcohol concentrations as low as 5 mM, equivalent to a single drink, appears to be largely mediated via alcohol's effect on NMDA receptors, occurs at the single-cell level and is not confined to the hippocampus [83].

Clearly, some neural alterations that take place during adolescence predispose to risk whereas others, such as memory impairments, may be actually the result of the abuse. Morphometric studies of humans are in support of this notion. For instance, in youths with a family history of alcohol abuse the right amygdala is smaller even prior to the onset of problem drinking, whereas hippocampal volumes are reduced only after a history of alcohol use [84, 85].

Exposure to substances of abuse in adolescence may also increase the likelihood of addictive disorders emerging later in life. Thus, 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 [86].

## 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 disabling forms of these illnesses[87, 88]. Anxiety symptoms frequently precede depression in adolescence[89] and during childhood [90].

Structural MRI studies of adolescents with anxiety and affective disorders have reported structural anomalies in the superior temporal gyrus, ventral prefrontal cortex and amygdala[91-93]. An fMRI study of depressed and anxious adolescents reported anomalous amygdala response to social stimuli[94]. In another fMRI study, adults but not adolescents were able to engage the orbitofrontal cortex when asked to switch from an emotional assessment of a face (i.e. How afraid does it make you feel?) to a non-emotional one (i.e. How wide is the nose?)[95]. The abnormal engagement of brain regions to emotional facial expressions in adolescents may underlie realistic 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[96]. The

finding that pubertal status predicts the sex difference in prevalence better than chronologic age[97, 98] suggests that sex hormones play a part in the pathophysiology of these disorders.

A recent mouse study examining tetra-hydro-progesterone (THP), a steroid derived from progesterone, provides a possible mechanism for this phenomenon[99]. This hormone is released during stress and has an anxiolytic effect that is mediated by activation of GABA-A receptors, which are also activated by alcohol and benzodiazepines. However, when it binds to a particular subtype of the GABA-A receptor, namely the alpha4-beta2-delta receptor subtype THP has the opposite effect to that of alcohol and benzodiazepines: it increases anxiety. The expression of the alpha4-beta2-delta receptor in the CA1 region of the hippocampus surges after puberty and is accompanied by increased anxiety as measured on an elevated maze paradigm. Moreover, blocking the formation of THP alleviated the increase in anxiety in adolescent mice[99]. Whether stress-related hormone effects on the brain explain differences in rates of anxiety and depressive disorders in prepubescents versus adult 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 may 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 may 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-vs-reward appraisal and motivation. Not surprisingly, when not adequately surmounted, it is precisely these challenges that 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, though a lot remains to be learned.

An emerging theme from pediatric 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 size[100]. Large individual variability in brain anatomy and function call 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 less so for some psychiatric illnesses. 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 versus non-genetic factors. This is best addressed through comparisons of monozygotic and dyzygotic twins. Results from an ongoing pediatric longitudinal neuroimaging project at the Child Psychiatry Branch of the National Institute of Mental Health indicate significant age-by-heritability interactions, with gray-matter heritability generally decreasing with age and white-matter heritability generally increasing with age[101]. Heritability-by-age interactions may be related to the timing of gene expression, which in turn may relate to the timing of the onset of illness. Postmortem 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 (e.g. musical talents 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[102]. Ongoing studies of specific gene effects on brain maturation may help to sharpen our understanding of brain development mechanisms and provide insight into the etiologies of various pathologies. The Saguenay Youth Study, carried out in a geographically isolated population with the known founder effect, will facilitate our search for genes that influence brain and behaviour during adolescence[103]. 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 their pathophysiology. The most obvious outward physical manifestations of puberty are caused by changing levels of hormones[11]. Perhaps this has contributed to the tendency to attribute all of the cognitive and behavioral changes of adolescence to "raging hormones"[104]. But the relationship between hormones, brain and behavior is complex, reciprocal and poorly understood. Steroid hormones affect neuronal activity and morphology throughout development. Most neurons have receptors for adrenal and gonadal hormones that, when these receptors are activated they can affect neurotransmitter function. Short-term effects are mediated by membrane-bound receptors, whereas long-term effects alter gene expression via intraneuronal 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. Behaviorally, 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 likely stem directly from different genes on the X or Y chromosomes or indirectly through the effects of different hormone levels. Studies of subjects with sex-chromosome variations (e.g. XO, XXY, XXYY, XXX, XXXXY) or anomalous hormone levels (e.g. congenital adrenal hyperplasia, androgen insensitivity syndrome, familial male precocious puberty) will be useful to sort 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 skills deficits that are reflected in differences in cortical thickness, consistent with reports in the literature for XY subjects with those disorders[105]. 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[106].

Although neuroimaging is beginning to establish correlations between brain structure/physiology and behavior, the link between typical behavioral changes and psychopathology has not been firmly established. For example, the neural circuitry underlying "moodiness" in an adolescent may not be the same circuitry involved in depression or bipolar disorder. Neuroimaging data can help develop neuroanatomical models of cognitive, affective and social processes based on findings from developmental psychology[107]. 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 at high magnetic field can help to quantify neurotransmitter systems, such as glutamate and GABA, as well as markers of neurogenesis[108]. Combining multiple imaging modalities on the same individuals, such as structural MRI, fMRI, diffusion tensor imaging, magnetization

transfer imaging, EEG or MEG, 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 gaps between genes, brain, and behavior.

Studies of the neural substrates of adolescent behavior and decision-making will need to be integrated better with social and educational science. Laboratory studies of teenagers using hypothetical situations in calm environments without peer influence may have little relevance for understanding real-world decision making that occurs often in the context of intense physical or emotion arousal, conflicting priorities, and in the presence of peers[109].

Many questions about adolescent brain development and its impact on disease can best be investigated in animal models. Modeling the adolescent phase in animals is useful for the investigation of risk for addictive and other early-onset neuropsychiatric disorders[86]. While animal models that represent the full phenotypic spectrum of a psychiatric disorder, such as schizophrenia or depression, are non-existent, 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 unraveling disease mechanisms and that allow testing novel interventions[110].

Another translational approach involves combined *in vivo* (e.g. MRI) and postmortem studies in animals; such studies are essential for clarifying the nature of neurobiological changes driving the MRI findings. Of immediate relevance will be studies that attempt to discern the degree to which changes in cortical gray-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 behavioral change. These changes are usually beneficial and optimize the brain for the challenges ahead, but may also confer a vulnerability to certain types of psychopathology. The technologies to elucidate the relationship between specific neurobiological maturational processes and specific normative or pathologic 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 affecting a substantial number of people.

### Box 1: Neuroimaging

Magnetic resonance imaging has revolutionized the way we can study structure and function of the human brain in living human beings throughout the entire life span[1]. The principles of MRI are relatively straightforward; in most applications, MR signal is based on magnetic properties of the hydrogen atoms, which constitute the most abundant substance in the human body, water. By placing the human body in a strong static magnetic field ($B_0$; 0.5 to 7.0 T) and applying a brief pulse of electromagnetic energy, we can make the little 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 changing slightly 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 3-dimensional (3D) 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 T2-weighted (T2W) images, diffusion-tensor images (DTI) and magnetization-transfer images (MT). The T1W and T2W images are typically used for quantifying the volume of grey and white matter (global and regional), and estimating 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 regional manner. The various features of brain structure that can be extracted from these four types of images are described below. In addition to the above sequences, less common but often even more informative acquisitions include T1 and T2 relaxometry (i.e. measurement of the actual relaxation times [2]) and magnetic resonance spectroscopy [3].

For imaging *brain function*, the most common MR parameter to measure is so-called blood oxygenation-level dependent (BOLD) signal. The BOLD signal reflects the proportion of oxygenated and de-oxygenated 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" [4]. In the majority of functional MRI (fMRI) 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.

### 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 vs. non-myelinated axons and in axons with larger vs. smaller diameter[45-47]. Neurotransmitters are chemicals that either relay action potentials or modulate (e.g. amplify) this process. Neurotransmitters include amino acids (e.g. glutamate and gamma amino-butyric acid [GABA]), monoamines (e.g. dopamine, serotonin, norepinephrine), acetylcholine, and many neuropeptides (e.g. 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, with varied densities[48, 49]. The very complex interaction between different neurotransmitters released at any given time at the synapse is going to determine the number of EPSPs and IPSPs generated on the post-synaptic membrane and, in turn, firing of the neuron.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## Glossary

Diffusion tensor imaging, Diffusion tensor imaging is a MRI-based technique allowing one to characterize structural properties of white matter.; STS network, STS network consists of a set of regions, located along the superior temporal sulcus, that are involved in processing of biological motion related to the movement of different body parts, such as eyes, face, or the entire body.; Delta sleep, Delta sleep is a stage of non-rapid eye movement (non-REM) sleep characterized by slow, or delta waves [0.5-4Hz]; the more delta waves, the deeper the sleep.; Tanner stage III, Tanner stage III is one of the five stages of puberty. Short of a physical exam, pubertal stages can be assessed, for example, using Puberty Development Scale[111], 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:

(1) prepubertal, (2) beginning pubertal, (3) midpubertal, (4) advanced pubertal, (5) postpubertal..

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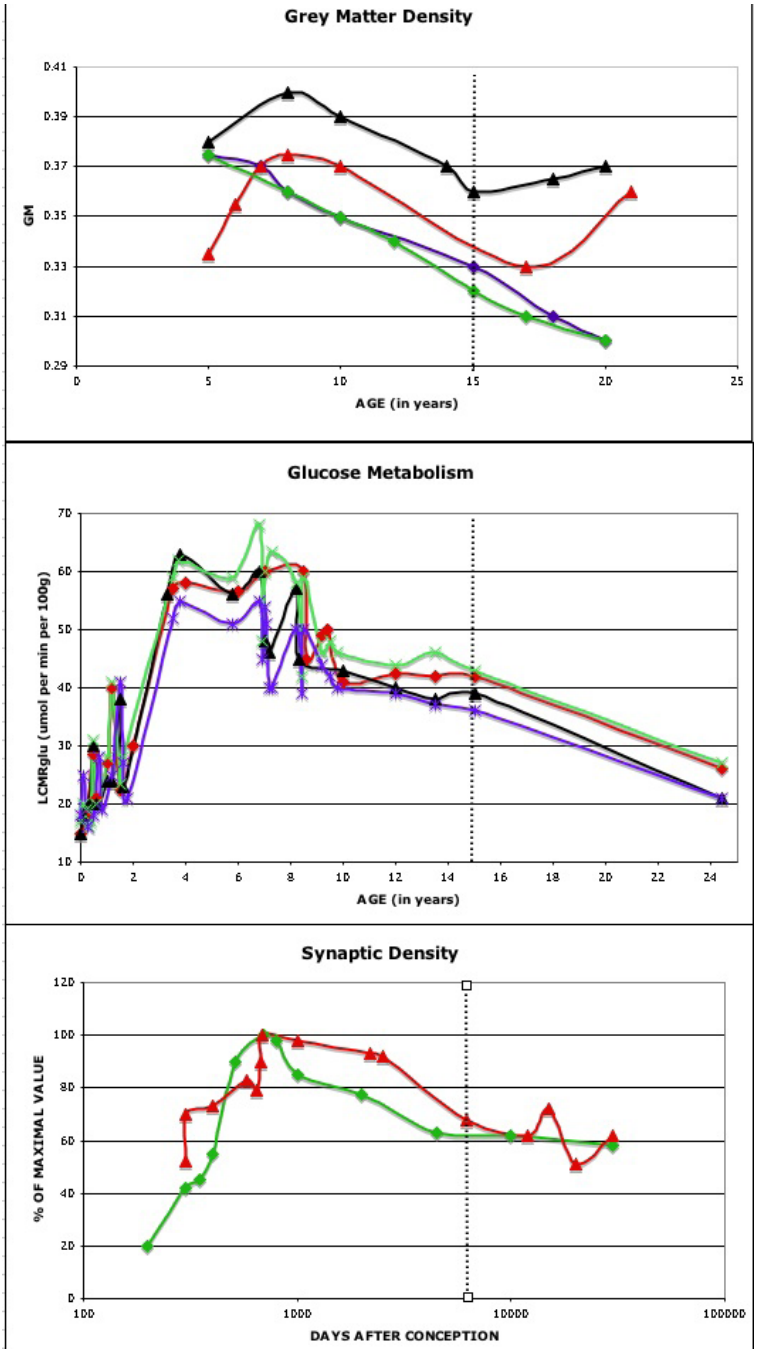


**Figure 1.**

Schematic representations of developmental trajectories in local volume of cortical grey-matter (A), glucose metabolism (B) and synaptic density (C). Plots of grey matter are based on data by Gogtay et al[8] and illustrate local grey-matter volume in the mid-dorsolateral prefrontal cortex in red (plot E in Fig. 1 of the original report), angular gyrus of the parietal cortex in black (plot I), posterior STS of the temporal cortex in purple (plot N), and the occipital pole in green (plot K). Plots of glucose metabolism are based on data by Chugani et al[11] and provide information about the absolute values of local cerebral metabolic rate for glucose (LCMRglc) in the frontal (red), parietal (black), temporal (purple) and occipital (green) cortex. Plots of synaptic density are based on data by Huttenlocher and de Courten[10] and Huttenlocher[12], as

re-plotted on semi-logarithmic scale by Rakic et al[13] (Fig. 4 in their report), and provide information about synaptic density in the prefrontal (red) and the striate (green) cortex. Note the following features of the above trajectories, especially between childhood and adulthood. To facilitate the comparison across the different plots, a vertical line was drawn at the age of 15 years. For cortical grey matter, different trajectories are observed in different cortical regions ((A). For glucose metabolism, the same trajectories are found in the four different lobes (B). This is also the case for the trajectories in synaptic density in the prefrontal and occipital cortex (C). Taken together, it is unlikely that a direct relationship exists between the three sets of measures.

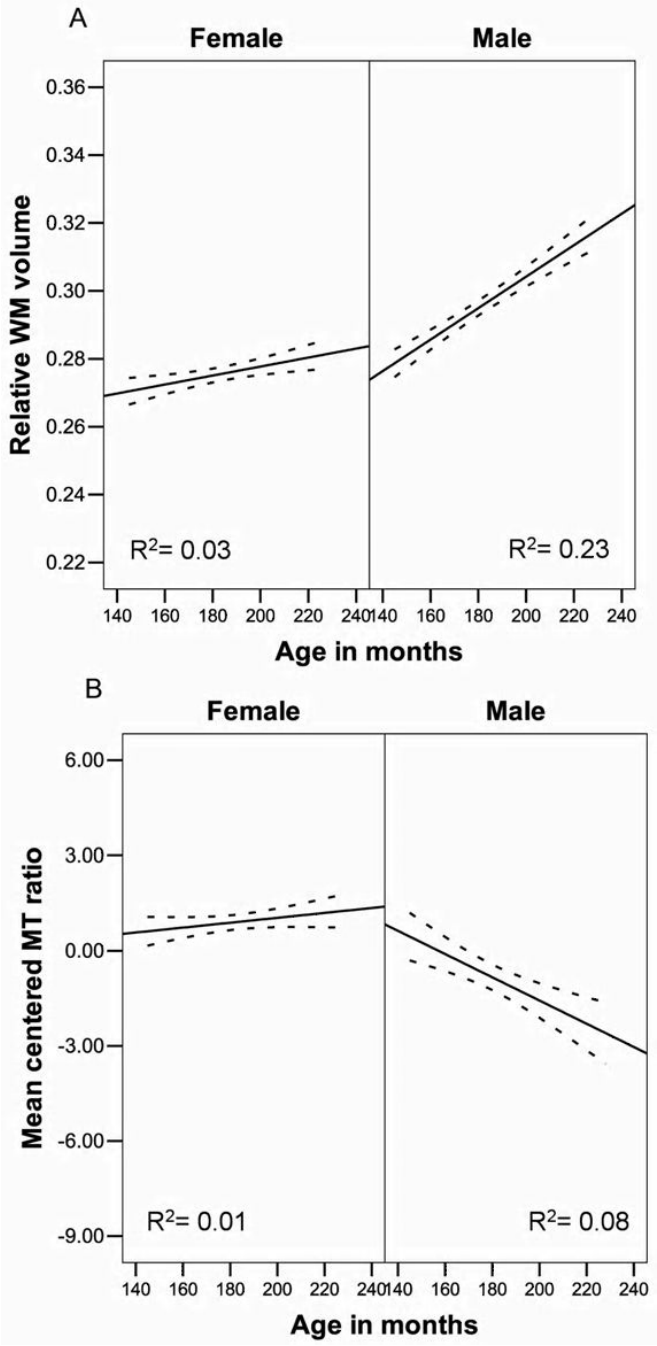


**Figure 2.**

Sexual dimorphism in the maturation of white matter during adolescence. Top panel (A) illustrates age-related changes in the relative (brain-size corrected) volume of white matter summed across the frontal, parietal, temporal and occipital lobes. Bottom panel (B) illustrates age-related changes in mean-centered values of magnetization-transfer ratio (MTR) in the lobar white-matter; MTR provides an indirect index of myelination. The plots are based on data obtained by Perrin et al[40]. Note that the opposite developmental trajectories in the volume and MTR suggest that age-related increases in white matter during male adolescence are not driven by myelination. See the original report for further information about the relationship between

white matter and testosterone in male adolescents with different variants of androgen-receptor gene.

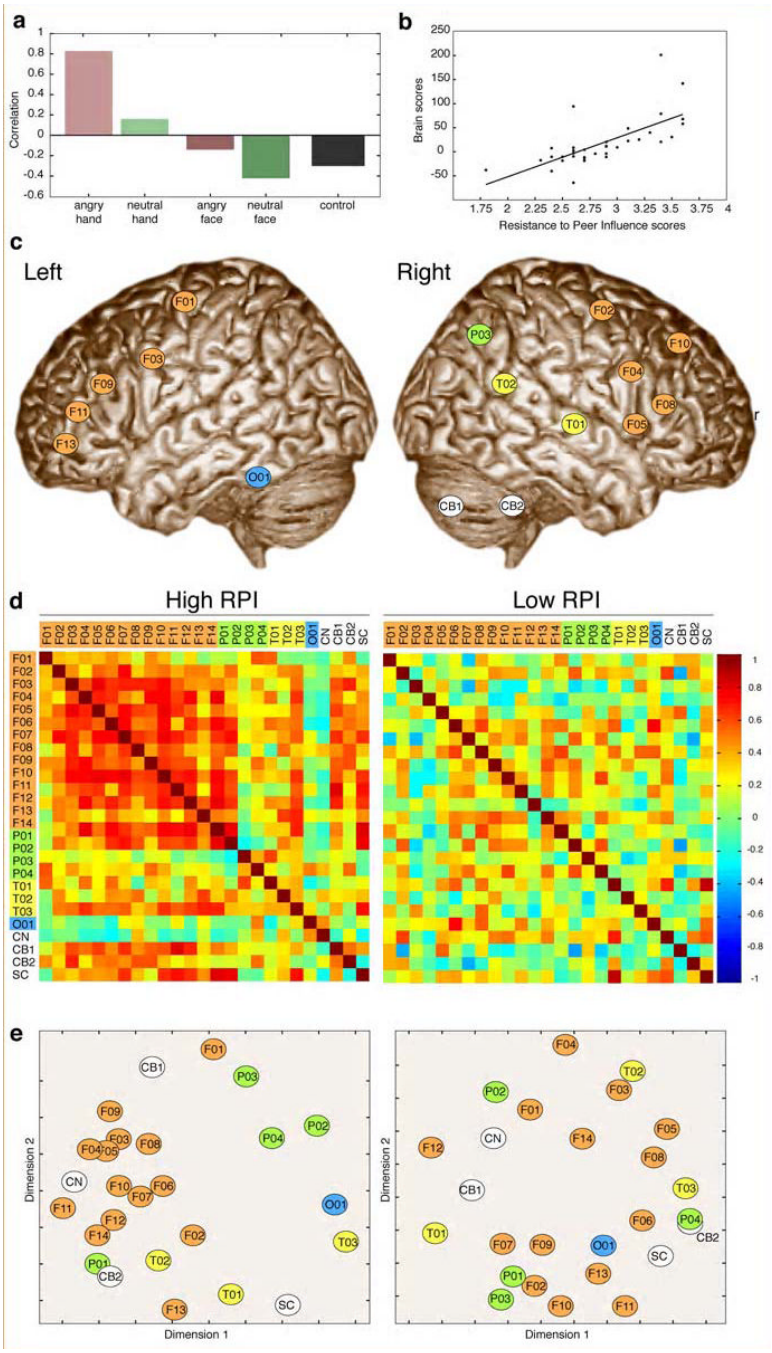


**Figure 3.**

Functional connectivity, indexed by inter-regional correlations in fMRI signal, during the observation of angry hand movements in children differing in their resistance to peer influences.

**a**, Latent Variable 1 (LV1) identified a combination of brain regions that, as a whole, correlated with the Resistance-to-Peer-Influence (RPI) scores. Note that high correlations are observed only for fMRI signal measured during the observation of Angry Hand Movements. **b**, Brains scores (weighted sum of all voxels in an image for each subject, using the weights derived from the brain LV1) derived from the fMRI signal measured during Angry Hand Movements plotted as a function of RPI. **c**, Locations of brain regions identified by LV1; only regions visible on

the lateral surface of the left and right hemispheres are shown. **d**, Correlation matrices depicting inter-regional correlations of fMRI signal measured during the observation of Angry Hand Movements, as revealed by LV1, in subjects with High (left) and Low (right) Resistance to Peer Influence. The High and Low RPI subgroups correspond to the subjects with RPI scores above and below the group median, respectively. **e**, Multidimensional scaling (MDS) representations of the inter-regional correlations of the 26-D matrix depicted above; in the MDS 2-D plots, strongly correlated regions are placed close together. Note, for example, the close grouping of premotor (F03 and F04) and prefrontal (F08 and F09) fronto-cortical regions. **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, ventro-lateral, right; **F09**, Prefrontal cortex, dorso-lateral, left; **F10**, Prefrontal cortex, dorso-lateral, right; **F11**, Prefrontal cortex, ventro-lateral, left; **F12**, Anterior cingulate cortex, right; **F13**, Orbito-frontal cortex, lateral, left; **F14**, Prefrontal cortex, medial; **P01**, Posterior cingulate cortex; **P02**, Precuneus, left; **P03**, Parietal cortex, dorso-lateral, right; **P04**, Parietal cortex, dorso-medial, right; **T01**, Superior Temporal Sulcus, middle, right; **T02**, Superior Temporal Sulcus, posterior, right; **T03**, Hippocampus, right; **O01**, Fusiform gyrus, left; **CN**, Caudate nucleus, right; **CB1**, Cerebellum, right; **CB2**, Cerebellum, right; **SC**, Superior Colliculus, right.
Reprinted with permission from Grosbras et al.[43].

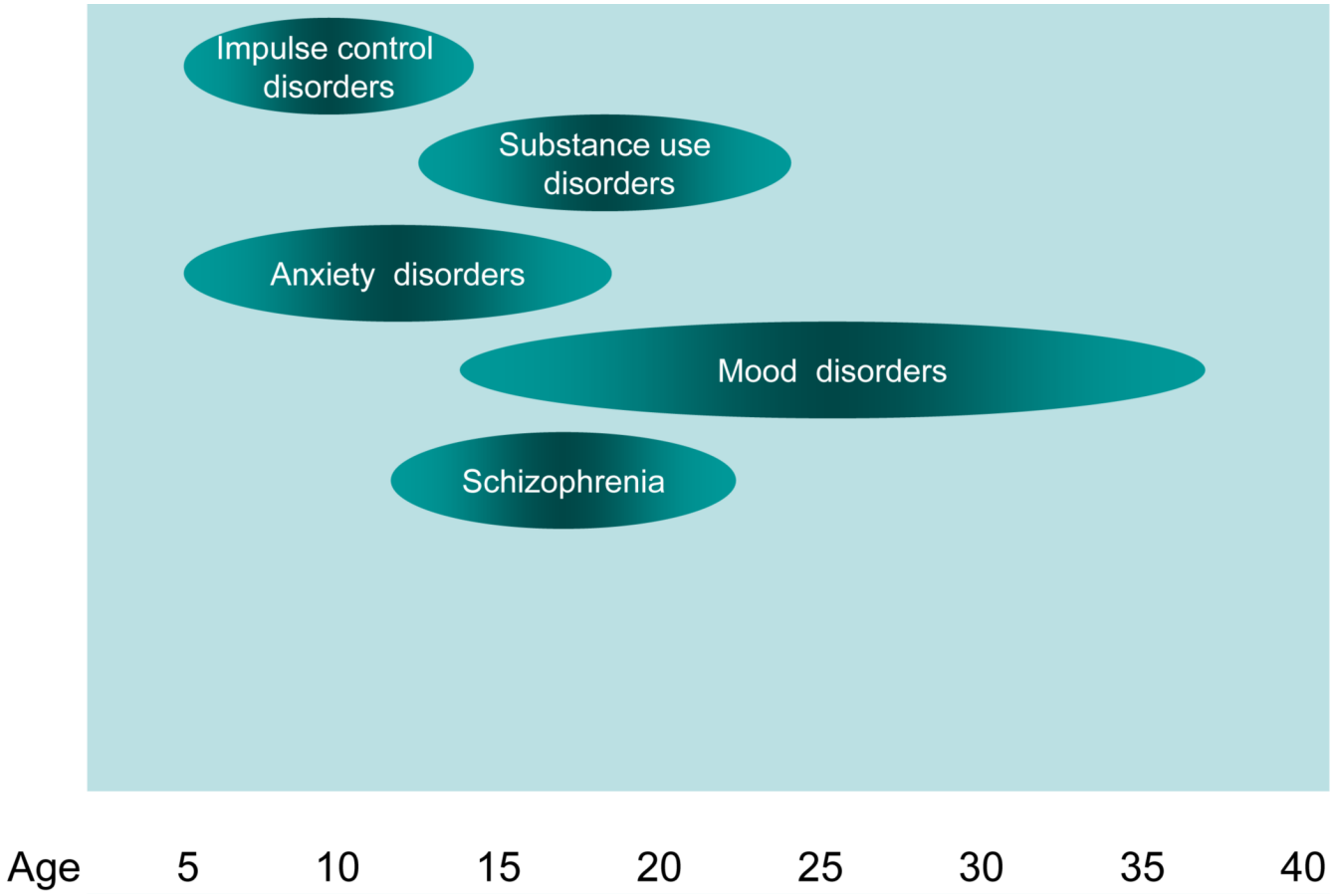


**Figure 4.**

Ranges of onset age for common psychiatric disorders. Recent data from the National Comorbidity Survey Replication study[55, 57], a nationally representative epidemiological survey of mental disorders, suggest that about half of the population fulfill criteria for one or other psychiatric disorders in their lifetimes. The majority of those with a mental disorder have had 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, while other anxiety disorders such as panic, generalized anxiety and post-traumatic stress disorder, substance disorders and mood disorders begin later, with onsets rarely before early teens. Schizophrenia typically begins in late adolescence or the early twenties, with men having a somewhat earlier age of onset compared to women[56]. 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 critical to focus efforts on early identification and intervention.