DOI 10.1515/ijamh-2013-0058 — Int J Adolesc Med Health 2013; 25(3): 245–256

Review

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Brain structural and functional changes in adolescents with psychiatric disorders

Abstract: During adolescence, hormonal and neurodevelopmental changes geared to ensuring reproduction and achieving independence are very likely mediated by the growth of neural processes, remodeling of synaptic connections, increased myelination in prefrontal areas and maturation of connecting subcortical areas. These processes, greatly accelerated in adolescence, follow an asynchronous pattern in different brain areas. Neuroimaging research using functional and structural magnetic resonance imaging has produced most of the insights regarding brain structural and functional neuropathology in adolescent psychiatric disorders. In schizophrenia, first episodes during adolescence are linked to greater-than-normal losses in gray matter density and white matter integrity and show a divergence of maturational trajectories from normative neural development in a progression similar to that of adult-onset schizophrenia. Anxiety and mood disorders in adolescence have been linked to abnormally increased activity in the amygdala and ventral prefrontal cortical areas, although some data suggest that neural abnormalities in the amygdala and anxiety maybe particularly more frequent in adolescents than in adults. Alcohol misuse in adolescence results in reduced integrity in the white matter and reduced gray matter density that, given the high intensity of adolescent synaptic and myelin remodeling, may result in persistent and profound changes in circuits supporting memory and emotional and appetitive control. The interaction of persistent changes due to prenatal exposure with the contemporaneous expression of genetic factors and disturbing environmental exposure may be an important factor in the appearance of psychiatric disorders in adolescence. Further progress in understanding adolescent psychopathology will require postmortem research of molecular and cellular determinants in the adolescent brain.

Keywords: development; neuroimaging; psychiatry.

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Introduction

Adolescence is a period in which the need for establishing new social and personal relationships and reaching independence and reproductive success is supported by dramatic hormonal, neural and behavioral changes. Similar to other dynamic developmental processes, changes in brain circuits during adolescence are an integral part of genetically programmed developmental processes. At the same time, those processes allow ample room for plastic changes to adapt to the social and natural environment. The ideal result of those processes is an emotionally balanced young adult. However, the unraveling of the developmental programs and the rapid neuroplastic changes during adolescence (when exposed to negative factors or influenced by inheritable or epigenetic deficits) are susceptible to the formation of faulty brain circuits that manifest themselves as psychiatric or neurological disorders. In fact, the first episodes for many of the main psychiatric disorders diagnosed in adulthood occur during adolescence, or close to the end of adolescence, or may depend on alterations that were primed in adolescence. However, determinig which features of morphology and brain activity in adolescents represent a pathological change when compared to adult brains requires, an understanding of characteristics of the normal, non-psychiatric adolescent brain, as compared to the brain of a psychiatrically maladapted adolescent individual.

Whereas psychological and social aspects of psychiatric disorders have been extensively researched since very early in adolescent psychiatry studies, specific neuropathological, neurological or physiological studies of the brain areas involved in adolescent psychopathology is more recent. In the present review, we present first a summary of cellular, neuroanatomical and neuroimaging characteristics that differentiate a normal adolescent brain from that of an adult as well as those features that signal a transition toward the establishing of adult structure and connectivity. Then we will review studies that report the localization of structural and functional neuropathological changes to specific brain areas in schizophrenia, anxiety, depression and substance abuse disorders

in adolescents, as revealed by neuroimaging techniques. This reporting will be followed by a consideration of the influence of relevant genetic variants on localized neural activity in the brain of adolescents with schizophrenia, anxiety and mood disorders.

During adolescence, changing levels of cognitive abilities, impulse control, language and motor coordination show great plasticity to allow for the transition to mature behavior and cognition. Insofar as the same systems that must display this plasticity are affected by disturbances during prenatal and postnatal life, adolescence could be particularly vulnerable to neuropathological alterations that result in psychopathology. So far, the majority of studies on structural or functional brain changes in adolescents with psychiatric disorders have been based on magnetic resonance imaging (MRI) (1, 2). Brain structural MRI is based on the differential behavior of protons of water molecules in gray and white matter when exposed to a variable magnetic field. The contrast between structures varying in the response to magnetic field alterations allows delineating local groupings of neurons and fibers and determining their size in absolute and relative terms. Computer software specially designed to assess morphometric parameters of MRI-discriminated brain components allows us to measure cortical gray matter thickness, density of gray and white matter, volume of subcortical structures, cortical surface, size and shape of cortical gyri and sulci as well as brain growth.

Diffusion tensor imaging (DTI) is an application of structural MRI to the measurement of the diffusion of water molecules. Within a magnetic field, these molecules tend to align into preferential directions according to their ability to diffuse across or along the arrangement of biological structures that surround them. If diffusion and alignment occur in many directions, a measurement of high fractional anisotropy is made. If, on the contrary, diffusion of water molecules is restricted to specific directions, (e.g., in white matter along myelinated fiber bundles) then fractional anisotropy is reduced, which is interpreted as sign of greater integrity and maturity of the axons involved (3). Functional MRI takes advantage of the differential magnetic properties of oxygenated versus deoxygenated hemoglobin in the brain-blood circulation to determine the blood oxygenation level-dependent contrast signal (BOLD signal) (4). Blood oxygenation changes caused by fluctuations in blood flow and oxygen extraction are considered to closely reflect neural activity because there is a tight coupling between increases in local neuronal activity and increases in blood flow required to support augmented metabolic demand from neurons (5). All the structural and functional variables mentioned above experience significant changes in various brain regions during adolescence, making neuroimaging studies particularly appropriate to defining them.

Earlier studies that revealed developmental changes at the microscopic level in gray and white matter in the adolescent brain were mainly based on histological examination of the postmortem brain (6–8). However, most of what is known on brain development at the cellular and molecular level in adolescents derives from studies in experimental animals, and there is no direct information as yet on the cellular and molecular neuropathology of the human adolescent brain in psychiatric disorders. Consequently, in this review we discuss knowledge of the neuropathological alterations in adolescents with major psychiatric disorders mainly as they have been revealed in structural and functional MRI studies, although evidence from other approaches is introduced when appropriate. The resolution of images in MRI-based neuroimaging research, although improving, is still insufficient for research at the cellular level, however, MRI neuroimaging studies present several distinct advantages: they do not involve the use of potentially deleterious ionizing radiation and thus can be used more than once in living subjects; unlike postmortem neuroanatomical studies, it is practical to include many subjects in a single study, thus increasing statistical power; longitudinal studies are possible to determine developmental trajectories and effects of environmental changes (2). Thus, unless otherwise specified, research results discussed throughout this review will correspond to MRI-based studies.

Neuroanatomical and functional changes in the normal adolescent brain

In the early postnatal years, the brain experiences an exponential increase in the numbers of synapses, dendritic and axonal branches and myelination that result in dramatic increases of brain size (9, 10). Later, in childhood, there is a stabilization of brain size and the number of synapses, although myelination continues to expand into several brain areas, and the white matter connecting the prefrontal cortex to other brain regions appears to increase. In fact, during adolescence, the volume of frontal gray matter as visualized by structural MRI has been described to decrease whereas white matter steadily increases (11). The process of synaptic change, however, retakes vigorously at the beginning of adolescence, and, for most of its duration,

with initial overproduction and later elimination of some synapses, which results in the described synaptic pruning in the prefrontal cortex (7, 12–14), whereas myelination progresses further also in the prefrontal cortex (6) and other regions highly relevant to the development of psychiatric disorders (15). Synaptic changes consist in a reduction of synaptic density that is likely reflected in a concomitant reduction in the volume of gray matter in the prefrontal cortex and the striatum, although volume reductions may not be entirely accounted for by synaptic changes (16), and in some structures, such as the amygdala, the hippocampus and the posterior temporal cortex, there is an increase of gray matter density during adolescence (1, 17, 18). The possibility that neuronal loss also contributes to gray matter size changes or synaptic pruning in specific cortical areas cannot be ruled out because Markham et al. (19) found decreases in neuronal numbers in the ventral prefrontal cortex of adolescent rats. Despite the overall pattern of synaptic pruning, specific axonal pathways connecting the prefrontal cortex and the amygdala experience further grow and branching and result in increased white matter volume during adolescence. As discussed by Sowell et al. (1), some reductions of gray matter density, which are paralleled by increases in white matter volume, and the apparent thinning of the gray matter measured by MRI-based mapping methods, might result from changes in myelination at the border between gray matter and not just be a consequence of synaptic pruning. However, measurement of brain growth at the surface of the cerebral cortex reveals that, despite the reduction of gray matter density, there is growth at the cortical surface of specific brain regions between adolescence and adulthood, particularly in the dorsal aspects of the frontal lobes and the left orbitofrontal cortex (1). In addition, the primary language cortex in the perisylvian region sets itself apart because thickness and density of the gray matter increase during adolescence and into early adulthood (11, 20, 21). Thus, there is a high degree of regional specificity and non-linear occurrence of structural and functional changes in the adolescent gray matter that attest to specific changes geared to adaptations for acquisition of relative independence and the ability to reproduce. Brain imaging techniques support that, in all, the various maturational processes taking place in the adolescent brain result in an increasing regulatory role by the prefrontal cortex (22).

A recent DTI study in children, adolescents and adults showed that measures of radial diffusivity (which diminishes as fiber bundles mature) decrease in particular but broadly distributed pathways connecting cortex and brain stem nuclei in adolescents, indicating an increase in the integrity of axon bundles and myelin maturation. However, other pathways supporting prefrontal-striatal and interhemispheric connections do not fully mature until adulthood (3). It is also important to note that new studies have found that an increase in white matter is largely dependent on hormonal changes, and this hormonal influence very likely also affects the microstructure of fiber bundles in the gray matter (23). The dependence on hormonal changes and the difference in specific hormonal changes between males and females may underpin the distinct microstructural development of white matter tracts in adolescent males and females and clearly deserves further studies.

Brain structural changes in adolescents with psychiatric disorders

Some behavioral features that, on average, appear to be concentrated in the adolescent years may be related to an adolescent pattern of brain activity that is not found during normal childhood or normal adulthood. Thus, absence of this pattern in adolescent subjects might be a sign of psychopathology and be associated to maladaptive behaviors. However, an exacerbation of, rather than a departure from, that pattern in comparison to normal adolescents might result in psychopathology. In other cases, structural and functional alterations in adolescents may be similar to those observed in adults affected by the same disorders. This distinction between adolescent-specific and adult-like changes is important because therapeutic interventions effective in adults may be amenable to the treatment of adolescents in some cases, whereas in others, interventions might be required to be also adolescent-specific. The distinction also applies to psychiatric or personality disorders that, being described in adolescence and childhood, may be either associated with structural alterations that are different in children and adolescents, or respond to the same type of cerebral alterations. For example, although a distinction is made between early-onset and adolescent-onset conduct disorder, regionally specific reductions of gray matter in the amygdala and insular cortex are common to both early- and adolescent-onset conduct disorder (24).

Neuroimaging studies show that the neural activity in various prefrontal regions of normal adolescents is increased or decreased during particular cognitive and emotional tasks as compared to adults and that the relatively altered function is associated with emotional

and cognitive responses reflecting more impulsivity and greater risk-taking by adolescents. As these are normal features of adolescence, there is a legitimate question of whether pathological behavior or emotions in adolescents correspond to only an exacerbation of normal adolescent function or if functional brain changes take on a pattern that differs both from adults and from normal adolescents. A model has been put forward to explain emotional, cognitive and behavioral features of adolescents as they differ from adults in terms of brain functional changes (25). This model proposes the existence of three functional nodes in the brain representing different levels for the processing of stimuli and the establishment of motivations, decisions and plan making: the detection node (some occipital and temporal areas), the affective node (amygdala, hippocampus, ventral striatum and orbitofrontal cortex) and the cognitive-regulatory node (other prefrontal areas). Plasticity and rearrangements in the connectivity within and between these nodes would form the basis for the emotional and behavioral changes observed during adolescence, and provide a substrate for alterations that can lead to the first time appearance of psychiatric disorders (25–27).

The above three-node model stresses the importance of connections between the nodes for the development of social interactions during adolescence. In fact, recent longitudinal studies on the responsiveness of relevant cerebral regions of adolescents to facial affective displays have shown distinctive changes in BOLD fMRI signals in early adolescence as compared to late childhood (28). In adolescents, the activity in the ventromedial prefrontal cortex and the ventral striatum was significantly enhanced in response to affective facial displays, whereas in the amygdala, although the displays caused an increase in BOLD signals, this was not increased as compared to late childhood (28). Most interestingly, a higher response in the ventral striatum has been related to higher positive affect and fewer depressive symptoms in adolescents (29, 30). As the role of other prefrontal regions in emotional regulation appears not to be fully developed until late in adolescence or early adulthood, pathological alterations in the ventral striatum of the ventromedial prefrontal cortex might have to be taken into account when establishing the pathophysiology of affective disorders in adolescents to eventually ascertain the role, if any, of these alterations in adult psychopathology. Prenatal alcohol exposure also results in specific effects on brain structure when examined in young adults (31). Although this study was not done strictly in adolescents, one of the main conclusions is that overall and localized reductions in brain size and IQ scores associated to prenatal alcohol exposure are not directly related to general physical development in the young adult but to head development and gestational factors (31), which could fully show their influence during adolescence and early adulthood. In adolescents, activity in the brain areas involved in the development of cognition and language are also affected by the length of pregnancy (preterm versus fullterm birth), so that preterm birth is associated with higher activity of the medial frontal gyrus when adolescents are confronted with syntactic difficulty in a task of sentence comprehension (32). The significance of these changes is, however, unclear, as formal test scores indicate no differences in scholarly achievement between preterm and fullterm adolescents (32).

As explained by Sturman and Moghadam (25), another triadic node model of brain circuits that would underlie psychiatric alterations in adolescence puts an emphasis on the balance between affective processing and cognitive control, which might explain risk-taking behaviors in adolescence. The nodes in this model include the ventral striatum (reward approach), the amygdala (punishment avoidance) and the prefrontal cortex (modulation node). The balance between the reward approach and punishment avoidance would be controlled by the prefrontal cortex. Underdevelopment of the prefrontal cortex in adolescents as compared to adults would make it difficult to control a predominance of the reward-approach node in detriment of the punishment-avoidance node and thus would generate heightened risk-taking behavior. Recently, it has been observed that in the case of substance abuse, a significant link exists between lower than normal activity and reduced density of gray matter in the ventral striatum and higher risk taking in adolescents with potentially problematic substance problems (33), further supporting the suggestion that adequate levels of activity in the ventral striatum during adolescent is crucial for various aspects of emotional and behavioral control, particularly at a time when prefrontal circuits are still far from having achieved mature development. Disruption of the circuits served by the ventral striatum then could contribute to the appearance of psychiatric problems during adolescence.

Despite the suspected implication of frontal brain plastic changes in the increase of risk-taking behavior during adolescence, there is recent evidence that those types of behaviors might be related to an accelerated maturation of particular circuits. Using DTI, Berns et al (34) found that engagement in dangerous activities in adolescence was positively correlated with fractional anisotropy and negatively correlated with transverse diffusivity in frontal white matter tracts, which was interpreted as increased myelination or an increase in the density of fibers, both considered signs of maturation. Thus,

particular caution must be exercised in interpreting how behavioral, functional and structural maturation interact with behavior during adolescence to eventually achieve a pattern of adult-like behavior. Only the eventual maturation of the prefrontal cortex would result in the fully developed, adult pattern of emotional control and behavior. In both models outlined above, the role of a balanced influence of the brain nodes and the modulating role of the prefrontal cortex are paramount and offer opportunities to formulate hypotheses and test them experimentally.

Structural and functional changes in schizophrenia

In adolescents and children diagnosed with schizophrenia, structural MRI studies have shown a significantly lower volume of total cortical gray matter and superior frontal gyrus gray matter, suggesting that structural and functional pathology might precede the manifestation of schizophrenia in late childhood and adolescence (35). In addition, longitudinal studies in adolescents at very high risk for developing schizophrenia show that abnormal structural changes in gray and white matter during adolescence are critical for the transition to psychosis in adolescents. In subjects at very high risk for schizophrenia, there is a marked reduction of the increase in white matter seen in control adolescent subjects, whereas the shrinkage in the gray matter of the left middle temporal gyrus is significantly greater than in controls or subjects at high risk who do not develop psychosis (36). As maturity of white matter tracts is seen as a sign of increasing control by prefrontal cortical and association areas, it is possible that a reduced maturation of the corresponding connecting pathways during adolescence is a critical anomaly leading to psychosis. Studies on the developmental progression during adolescence of gray and white matter abnormalities in adolescent-onset schizophrenia, as compared to adult-onset schizophrenia, show a greater pathology in the adolescent-onset condition (37). In addition, as compared to gray and white matter development in non-psychiatric subjects, a longitudinal examination revealed that the development of gray and white matter in adolescent schizophrenia is delayed from adolescent controls and progressively diverges from normal control subjects to follow a similar pattern to the abnormal progression of neuropathology in adult-onset schizophrenia (37). The progressive divergence from the normal developmental pattern in adolescent-onset schizophrenia would be in agreement with a study in which examination of the gray and white matter structure in ultrahigh risk adolescent subjects (but not yet diseased) did not reveal significant differences from adolescents not at risk (38), suggesting that the appearance of psychotic symptoms is tightly linked to the development of detectable structural alterations and only upon manifestation of the disorder is there development of brain structural anomalies (36).

In addition to a role for detectable neuropathological alterations in cortical gray matter and the underlying white matter in adolescent schizophrenia, there is a model that stresses the role of pubertal and postpubertal changes in the HPA axis and hippocampus as important contributors to the expression of vulnerability for psychosis in adolescents (39–41). According to this model, a developmental or genetically determined vulnerability to psychosis might find expression during adolescence because there are dramatic hormonal and neural changes in the HPA-hippocampus link that, combined with a heightened chance for stress responses, result in unraveling of the vulnerability. Stress responses result in the release of corticosteroids that, in addition to actions on various cell types across the body, exert an important modulatory role on mineralocorticoid and glucocorticoid receptors (MR and GR). These receptors are very abundant in the hippocampus and modulate responses of hippocampal cells. Sustained increases in corticosteroids, however, can be toxic to hippocampal neurons, and, in fact, in normal subjects or in subjects with pathologically high cortisol levels, there is a significant inverse correlation between cortisol levels and hippocampal volume (42–46). In first-episode, non-medicated subjects with schizophrenia, there is elevated levels of basal cortisol (47), and there is also evidence for smaller hippocampal sizes than non-psychiatric control subjects (48). One study specifically targeted changes in whole brain and hippocampal volumes, showing that whole brain volume was significantly smaller in subjects with schizophrenia but that the difference in hippocampal volume was not statistically significant. However, both duration of illness and severity of psychopathology were negatively correlated with hippocampal volume (49). More recent studies in adolescents with early onset schizophrenia further support marked structural deficits early in the disorder, showing a significant thinning of the gray matter bilaterally in both the gyri and sulci of the superior frontal gyrus and in dorsal, ventral and medial locations within the prefrontal cortex (50). These data together with the first-episode findings suggest that adolescence may be a critical period when the fast progression and manifestation of schizophrenia result in immediate structural changes or these changes, upon appearing, immediately manifest as psychotic symptoms. More recently, DTI,

which examines the integrity of fiber bundles connecting brain areas, has further shown that there is a reduction in connectivity in children and adolescents with schizophrenia, as reflected by a decreased fractional anisotropy and increased average diffusivity (51). These results point to the possibility that a dysfunctional link between the HPA and hippocampus contributes to the first manifestations of schizophrenia.

Higher stress sensitivity during adolescence is proposed to be an important link between environmental influences and the manifestation of psychiatric disorders, particularly psychosis (39). Prolonged exposure to stress would alter the HPA-hippocampus reciprocal modulation to result in alterations increasing the risk for psychosis. Whereas in normative adolescence, there is the expectation of a continued increase in hippocampal volume (52, 53), increased stress sensitivity may, in some predisposed individuals, result in reduced hippocampal volume, as suggested by a smaller hippocampus in animals exposed to prolonged stress after the onset of puberty (54).

Neuroimaging in adolescents with anxiety disorders

While schizophrenia and depression are described in childhood, most first episodes of these disorders occur mainly in late adolescence and early adulthood (39). Moreover, for schizophrenia diagnosed in early adulthood, progressive deterioration of function can be already detected early in adolescence (55). This temporal pattern does not necessarily apply to all psychiatric disorders. For instance, anxiety disorders are highly prevalent in childhood and adolescence (56). Although anxiety is frequent in the course of childhood, it seems to resolve by late adolescence in most cases, but if anxiety persists during adolescence, there is an increased probability for anxiety taking a chronic course in the adult. Thus, chronicity in the adult may result from the inability to resolve during adolescence a disorder that is highly prevalent in adolescence and childhood. The development and refinement of attentional processes during adolescence has been proposed as a substrate for pathological enhancement of anxiety processes in adolescence and into adulthood (56). As circuits and brain responses underlying attention have been relatively well identified and characterized, functional MRI has been used to determine brain centers that may be altered during attentional tasks with emotional components. For instance, when adolescents are presented with angry faces, fMRI studies show increased activity in the ventrolateral PFC of adolescents with generalized anxiety disorder (GAD) as compared to non-anxious adolescents (57). Likewise, adolescents with GAD show greater activation of the amygdala to fearful faces than healthy controls, although a greater response is only evident when the subjects are instructed to focus their attention on their own subjective evaluation of fear, and not when viewing faces without specific instructions (58), consistent with previous studies that found increased activation of the amygdala in adolescents and children with anxiety and depression (59). Other regions of the prefrontal cortex, such as the ventromedial orbitofrontal cortex, have been found to be abnormally low in activity in tests for fear sensitivity, which has lead to a proposal that a misbalance between limbic regions, highly sensitive to the drastic hormonal changes of adolescence, and prefrontal regions, responsible for cognitive control, would greatly contribute to the development of psychopathology during adolescence (60). This proposal also implies that, in the normally developing brain, hormonally driven high activation in reward and limbic systems must be progressively controlled by the more linearly developing cognitive influence of the prefrontal cortex. Prolongation of the period between hormone-related limbic activation and progressive cognitive control would result in increased risk for manifestations of psychopathology in adolescents and young adults (60).

Neuropathology in adolescents with depression

In adolescence, major depressive disorder (MDD) and bipolar disorder (BD) share with anxiety disorders increased activation of the amygdala (61). This greater amygdalar activation appears to extend to healthy children and adolescents at high risk for depression (as compared to non-high-risk children) when presented with fearful faces (62). In addition, some studies describe a decrease in the volume of the amygdala of adolescents with depression, although, intriguingly, the ratio of the amygdala volume to the hippocampal volume is increased in adolescents with depression (63). The hippocampus itself has also been the focus of neuroimaging research. In one study, researchers found a decrease in hippocampal volume in adolescent depression, a finding similar to that in adult recurrent depression (64). However, another study with subjects in early adolescence did not detect a significant difference between subjects with depression

and healthy subjects (61), which suggests that the progression of depression during adolescence might result in hippocampal volume reduction. Unlike studies in adults, fMRI studies in adolescents with bipolar depression did not find altered activation of prefrontal areas (although there was an absence of correlation of activation with age observed in controls), but noted an increase in activation of thalamic and striatal structures when adolescents were subjected to a cognitive color naming Stroop task (known to involve prefrontal circuits) (65). In contrast with decreased gray matter volume in the subgenual prefrontal cortex of adults with MDD and BD, the same region in adolescents with BD is not changed as compared to healthy controls. Nonetheless, the volumes of gray and white matter of the prefrontal cortex of adolescents with MDD are significantly changed as compared to controls, with larger volume in the gray matter and smaller volume in the white matter (66). Application of DTI to the adolescent brain has also shown that integrity of white matter fibers is affected, showing decreased fractional anisotropy in fiber tracts that originate from the subgenual anterior cingulate cortex and involve frontolimbic connecting pathways (67). As during normal adolescence, there is a progressive increase in white matter volume and a reduction in the volume of gray matter, it seems that there is a defect in the maturation of brain pathways in adolescents with depression. Whether this defect is a cause for or an effect of depression remains to be fully elucidated. Functional consequences of suspected altered connections in the adolescent brain with depression have been more recently examined in resting state fMRI. This approach has shown that connectivity between several prefrontal cortical areas, superior temporal gyrus and the insular cortex is significantly reduced (68), whereas connectivity between the amygdala and various prefrontal regions appears to be enhanced (69).

Postmortem neuropathological and molecular studies of the human brain in psychiatric disorders during adolescence are understandably scarce, with the only exception being suicide. Suicide is an important cause of death during the teenage years (70) and, in many cases, is associated with psychiatric disorders. Studies on postmortem brains of suicide adolescents have reported an increase in binding and mRNA for 5-HT2a serotonin receptors, which, in the case of binding, is also observed in adult suicides (71). Also in teenage suicide victims, a postmortem study found the brain-derived neurotrophic factor (BDNF) and its receptor, TrkB, were significantly reduced in the prefrontal cortex and hippocampus (72). CREB (protein and mRNA), a transcription factor that participates in the transcription of BDNF mRNA, was also lower in the prefrontal cortex of adolescent suicides as compared to controls subjects (73). Given the involvement of BDNF in synaptic plasticity and neurite growth, reduced BDNF in critical brain areas may result in reduced plasticity in the brain of suicide victims, which may contribute to psychopathology leading to suicide. Increases in proinflammatory cytokine expression have been described in the postmortem brains of MDD and proposed to contribute to the pathophysiology of depression. Recent studies in brains from teenage suicides have found that there is an increase in the levels of TNF-alpha and IL-beta as compared to controls (74), raising the possibility that neuroimmune alterations are also part of the pathological processes underlying depression in adolescents.

Neuropathology in the adolescent brain and substance of abuse

Due to their great medical and social importance, the neuropathological effects of alcohol intake during adolescence have received increasing attention. Binge and sustained alcohol drinking have been shown to cause effects in adolescents that differ significantly from the effects in adults, although the direction of many of those changes is similar (75). In adolescents, alcohol drinking results in a reduction of the volume of the hippocampus and prefrontal cortex, and the reduction is positively correlated with the duration of alcohol abuse (76–78). Moreover, in binge-drinking adolescents not under medical treatment, there is a significant and widespread decrease in the integrity of the white matter as studied by DTI (79). These structural abnormalities in adolescents are very likely accompanied by physiological and molecular changes in brain regions and processes heavily involved in emotional and cognitive regulation of behaviors related to substance abuse. For instance, alcohol abuse in human adolescents and in animal models causes larger memory impairments than in adults (80–83). Correspondingly, some studies in rats show that binge-drinking causes larger neuronal damage in the frontal cortex of adolescent than adult rats (84, 85), whereas other studies demonstrated greater inhibition of NMDA-based synaptic activity in the adolescent hippocampus and cingulate cortex, and a greater inhibition of long-term potentiation (LTP) (86), which is considered a basic neurophysiologic mechanism involved in learning and memory. Some of the damage and long-term behavioral effects caused by alcohol during adolescence involve significant alterations in dopaminergic and glutamatergic pathways of frontocortical and

striatal brain centers, which could be mediated by epigenetic changes in histone acetylation (87). Knowledge of these changes may open the door to designing treatments of alcohol-related disorders in adolescence based on the inhibition of histone deacetylases (88).

The involvement of addiction or exposure to cocaine in pathological brain changes during adolescence has been also studied with neuroimaging methods. For instance, prenatal exposure to cocaine has been found to result in changes in connectivity as determined by MRI DTI (89), which shows that at least ten different landmarks in several fiber tracts of white matter are different between adolescents exposed to prenatal cocaine and non-exposed controls. It is important to determine these changes because adolescents prenatally exposed to cocaine show deficits in intelligence, executive function and language skills that greatly depend on the systems affected by prenatal cocaine exposure (89). In turn, binge-like cocaine exposure during adolescence in experimental rats results in gene expression changes that involve chromatin remodeling (indicating persistent changes) in the prefrontal cortex in adulthood (90). Thus, in adolescence, there could be expression of pathological alterations as a consequence of prenatal exposure to cocaine or other brain-altering agents while the brain is still susceptible to lasting changes due to adolescent drug abuse, raising the possibility of a compounded or synergistic damaging interaction between acute exposure in adolescence and the consequences of past unwanted exposures. As in the case of adolescent exposure to alcohol, long-term consequences of cocaine abuse during adolescence may involve epigenetic changes as illustrated by reduced methylation of histone 3 in adolescent rats administered cocaine (90).

Gene variants and functional neuroimaging

Recent studies have started to consider the contribution of relevant gene variants to the emergence or presence of anxiety and mood disorders in adolescents and their functional consequences in specific brain areas. Variants of the gene for the serotonin transporter (5-HTT) have been shown to modulate the manifestation of symptoms of anxiety and depression, with subjects (psychiatric and non-psychiatric) carrying the S and L(g) alleles more prone to anxiety and depression symptoms (91) and to higher activation of the amygdala measured by fMRI when looking at fearful faces in a fear-detecting mode than subjects with two L(a) alleles (92). In adolescents, follow-up studies have further shown that in a fear-monitoring situation, fearful faces also cause higher amygdala activation in S and L(g) carriers, but only when the patients are non-psychiatric (93). Surprisingly, adolescent subjects with psychiatric diagnosis had higher amygdala activation when they carried two L(a) alleles, an effect opposite to the one observed in adults. This peculiarity of allelic effects in adolescents may reflect a vulnerability of the asynchronous development pattern of various cortical and subcortical centers in adolescent subjects or a lack of experiences that eventually may result in greater effects of S/L(g) alleles (93), but only in adults.

Allelic variants of BDNF, with probable effects on the activity of BDNF as a trophic factor, might be linked to depression and anxiety in adults (94, 95). To assess whether those gene variants also influenced psychiatric diagnosis in adolescents, Lau et al. (96) studied MRI-detected activity in brain regions that are activated when viewing faces with different emotional loads (fear, happiness, indifference). It was found (96) that adolescents diagnosed with anxiety or depression had higher activation in the amygdala and hippocampus in response to fearful faces than non-psychiatric controls and that this activation was significantly higher in psychiatric adolescent subjects that carried the Met66 allele (as opposed to Val/Val homozygote carriers), suggesting that localized brain functional effects of genetically-based changes in the sequence and the activity of BDNF are already detectable by fMRI in adolescence.

Conclusions

During adolescence, dramatic changes in behavior, bodily growth and in cognitive and emotional control are concomitant with significant morphological and functional changes in brain areas implicated in the pathophysiology of psychiatric disorders. In some individuals, this maturational transition is associated with the first manifestations of major psychiatric disorders during or shortly after the adolescent period. At different times during adolescence, various processes of neural remodeling and growth take place at different locations within the frontal cortex and connecting subcortical structures. Untimely exposure to challenging environmental events or drugs of abuse, in combination with the effects of expression of specific genetic variants may generate dysfunctional circuits, in which changes may have lasting consequences into adulthood psychopathology. So far, the best evidence for the

functional and neuroanatomical changes in the human adolescent brain that may underlie adolescent psychopathology has been obtained using different applications of structural and functional MRI.

Experiments in animals are providing and will continue to provide details about the basic cellular and molecular mechanisms responsible for the appearance of psychiatric disorders. However, the application of knowledge obtained in animals to understanding actual biochemical changes and functional consequences in brain circuits of human adolescents will require a refinement of imaging and molecular and cellular biology tools. Although logistically challenging, postmortem studies of the adolescent brain in psychiatric disorders are key to identifying specific molecular and cellular alterations in the neurobiology of psychiatric disorders in adolescence. These postmortem studies should define neuronal and glial cell types implicated and the molecular pathways in specific brain gray and white matter regions in adolescent pathology, so that the right experimental questions are put to test in animal models, and the right conclusions are drawn about the neuropathological mechanisms underlying neuroimaging findings.

Received August 5, 2012; accepted September 28, 2012; previously published online July 4, 2013

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