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BRAIN STRUCTURAL AND FUNCTIONAL CHANGES IN ADOLESCENTS WITH PSYCHIATRIC DISORDERS

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Abstract

During adolescence hormonal and neurodevelopmental changes geared to ensure reproduction and achieve independence are very likely mediated by growth of neural processes, remodeling of synaptic connections, increased myelination in prefrontal areas, and maturation of connecting subcortical regions. 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, emotional and appetitive control. Interaction of persistent changes due to prenatal exposure with 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

Neuroimaging; development; psychiatry

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 developmental dynamic 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

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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, first episodes for many of the main psychiatric disorders later diagnosed in adults occur during adolescence or close to the end of adolescence or may depend of alterations primed in adolescence. Determining which features of morphology and brain activity in adolescents represent a pathological change when compared to adult brains requires however an understanding of characteristics of the normal, non-psychiatric adolescent brain as compared to the brain of maladapted psychiatrically adolescent individual. While 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 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 the normal adolescent brain from the adults at well as those features that signal a transition towards 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 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, (for example 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 magnetic resonance imaging takes advantage of the differential magnetic properties of oxygenated versus deoxygenated hemoglobin in the brain blood circulation to determine 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 required increases in blood flow 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 on 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 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 while 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 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. (2007) have found decreases in neuronal numbers in the ventral prefrontal cortex of adolescent rats (19). 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. (2007)(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 and white matter and not just be a consequence of synaptic pruning. On the other hand, 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, shows 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 distinct microstructural development of white matter tracts in adolescent in males and females and clearly deserves further studies.

MODELS OF BRAIN FUNCTIONAL CHANGES IN ADOLESCENTS WITH PSYCHIATRIC DISORDERS

Some behavioral features that in average appear to be concentrated in the adolescence 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. On the other hand an exacerbation of, rather than a departure from, that pattern in comparison to normal adolescents might result in psychopathology as well. In other cases, structural and functional alterations in adolescents maybe 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 maybe be amenable to the treatment of adolescents in some cases while, 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, while 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. Since these are normal features of adolescence, there is a legitimate question of whether pathological behavior or emotions in adolescents correspond to just an exacerbation of normal adolescence function or if functional brain changes take onto 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 adolescence as they differ from adults in terms of brain functional changes (25). This model proposes the existence of three brain functional nodes 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, while in the amygdala, although the displays caused an increase in BOLD signal, 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). Since 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 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 brain areas involved in the development of cognition and language are also affected by the length of pregnancy (pre term versus full term birth), so that pre term 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, since formal test scores indicate no differences in scholar achievement between preterm and full term adolescents (32).

As explained by Sturman and Moghadam (2011) (25) another triadic node model of brain circuits that would underlie psychiatric alterations in adolescence puts the 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 exist 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 and 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 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 type of behavior might be related to an accelerated maturation of particular circuits. Using DTI,

Berns et al. 2009 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 increase in the density of fibers (34), 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, while the shrinkage in the gray matter of the left middle temporal gyrus is significantly greater than in controls or subjects with high risk who do not develop psychosis (36). Since 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 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 there is 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 is the HPA-hippocampus link that, combined with heightened chance for stress responses, result in unraveling of the vulnerability. Stress responses result in the release of corticosteroids that, beside 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 in 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 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, diffusion tensor imaging, 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 the 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. While in normative adolescence there is the expectation of 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). Since 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 subjects are presented with angry faces, fMRI studies are showing 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 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 display abnormally low activity in tests for fear sensitivity, which has lead to the proposal that a misbalance between limbic regions highly sensitive to the drastic hormonal changes of adolescence, and prefrontal regions responsible of 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 an increased activation of the amygdala with anxiety disorders (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 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 with anxiety disorders (61), suggesting that 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 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). At a difference with decreased gray matter volume of the subgenual prefrontal 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). Since 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), while connectivity with between the amygdala of 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 of suicide. Suicide is an important cause of death during teenage years (70) and in many cases is

associated with psychiatric disorders. Studies on postmortem brain 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 suicide (71). Also in teenage suicide victims a postmortem study found that 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. Increased proinflammatory cytokine expression has been described in the postmortem brain 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 SUBSTANCES 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), while 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 mechanisms involved in learning and memory. Some of the damage and long-term behavioral effects caused by alcohol during adolescence would 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 of connectivity as determined by MRI diffusion tensor imaging (89), which shows that at least 10 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 which greatly depend in 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 to 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) only in adults.

Allelic variants of brain-derived neurotrophic factor (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. 2010 (77) studied MRI-detected activity in brain regions that are activated when viewing faces with different emotional load (fear, happiness, indifferent). It was found (96) that adolescents diagnosed with anxiety or depression had higher activation in 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 activity of BDNF are already detectable by fMRI in adolescence.

CONCLUSION

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, 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, molecular and cellular biology tools. Although logistically challenging, postmortem studies of the adolescent brain in psychiatric disorders would be key to identify 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.

REFERENCES

1. Sowell, ER.; Thompson, PM.; Toga, AW. Mapping Adolescent Brain Maturation Using StructuralMagnetic Resonance Imaging. In: Romer, D.; Walker, EF., editors. Adolescent psychopathology and the developing brain : integrating brain and prevention science. Oxford University Press; Oxford ; New York: 2007. p. 55-84.
2. Lenroot RK, Giedd JN. Brain development in children and adolescents: insights from anatomical magnetic resonance imaging. Neurosci Biobehav Rev. 2006; 30(6):718–29. Epub 2006/08/05. [PubMed: 16887188]
3. Asato MR, Terwilliger R, Woo J, Luna B. White matter development in adolescence: a DTI study. Cereb Cortex. 2010; 20(9):2122–31. Epub 2010/01/07. [PubMed: 20051363]
4. Raichle ME. A brief history of human brain mapping. Trends Neurosci. 2009; 32(2):118–26. Epub 2008/12/27. [PubMed: 19110322]
5. Heeger DJ, Ress D. What does fMRI tell us about neuronal activity? Nat Rev Neurosci. 2002; 3(2): 142–51. [PubMed: 11836522]
6. Yakovlev, PI.; Lecours, AR. The myelogenetic cycles of regional maturation of the brain. In: Minkowski, A., editor. Regional development of the brain in early life. Blackwell Scientific Publications; Oxford Edinburgh: 1967. p. 3-70.
7. Huttenlocher PR. Synaptic density in human frontal cortex- developmental mental changes and effects of aging. Brain Res. 1979; 163:195–205. [PubMed: 427544]
8. Huttenlocher PR, de Courten C. The development of synapses in striate cortex of man. Human neurobiology. 1987; 6(1):1–9. Epub 1987/01/01. [PubMed: 3583840]
9. Dobbing J, Sands J. Quantitative growth and development of human brain. Arch Dis Child. 1973; 48(10):757–67. Epub 1973/10/01. [PubMed: 4796010]
10. Dobbing J, Sands J. Comparative aspects of the brain growth spurt. Early human development. 1979; 3(1):79–83. Epub 1979/03/01. [PubMed: 118862]
11. Giedd JN. Structural magnetic resonance imaging of the adolescent brain. Ann N Y Acad Sci. 2004; 1021:77–85. Epub 2004/07/15. [PubMed: 15251877]
12. Spear LP. The adolescent brain and age-related behavioral manifestations. Neurosci Biobehav Rev. 2000; 24(4):417–63. Epub 2000/05/19. [PubMed: 10817843]
13. Blakemore SJ, Choudhury S. Development of the adolescent brain: implications for executive function and social cognition. Journal of child psychology and psychiatry, and allied disciplines. 2006; 47(3-4):296–312. Epub 2006/02/24.
14. Bourgeois JP, Goldman-Rakic PS, Rakic P. Synaptogenesis in the prefrontal cortex of thesus monkeys. Cereb Cortex. 1994; 4:78–96. [PubMed: 8180493]
15. Steinberg L. Cognitive and affective development in adolescence. Trends in cognitive sciences. 2005; 9(2):69–74. Epub 2005/01/26. [PubMed: 15668099]
16. Paus T, Keshavan M, Giedd JN. Why do many psychiatric disorders emerge during adolescence? Nat Rev Neurosci. 2008; 9(12):947–57. Epub 2008/11/13. [PubMed: 19002191]

17. Giedd JN, Castellanos FX, Rajapakse JC, Vaituzis AC, Rapoport JL. Sexual dimorphism of the developing human brain. Prog Neuropsychopharmacol Biol Psychiatry. 1997; 21(8):1185–201. Epub 1998/02/14. [PubMed: 9460086]

18. Gogtay N, Thompson PM. Mapping gray matter development: implications for typical development and vulnerability to psychopathology. Brain Cogn. 2010; 72(1):6–15. Epub 2009/10/03. [PubMed: 19796863]

19. Markham JA, Morris JR, Juraska JM. Neuron number decreases in the rat ventral, but not dorsal, medial prefrontal cortex between adolescence and adulthood. Neuroscience. 2007; 144(3):961–8. Epub 2006/12/02. [PubMed: 17137726]

20. Sowell ER, Peterson BS, Thompson PM, Welcome SE, Henkenius AL, Toga AW. Mapping cortical change across the human life span. Nat Neurosci. 2003; 6(3):309–15. Epub 2003/01/28. [PubMed: 12548289]

21. Sowell ER, Thompson PM, Leonard CM, Welcome SE, Kan E, Toga AW. Longitudinal mapping of cortical thickness and brain growth in normal children. J Neurosci. 2004; 24(38):8223–31. Epub 2004/09/24. [PubMed: 15385605]

22. Yurgelun-Todd D. Emotional and cognitive changes during adolescence. Curr Opin Neurobiol. 2007; 17(2):251–7. Epub 2007/03/27. [PubMed: 17383865]

23. Herting MM, Maxwell EC, Irvine C, Nagel BJ. The impact of sex, puberty, and hormones on white matter microstructure in adolescents. Cereb Cortex. 2012; 22(9):1979–92. Epub 2011/10/18. [PubMed: 22002939]

24. Fairchild G, Passamonti L, Hurford G, Hagan CC, von dem Hagen EA, van Goozen SH, et al. Brain structure abnormalities in early-onset and adolescent-onset conduct disorder. Am J Psychiatry. 2011; 168(6):624–33. Epub 2011/04/02. [PubMed: 21454920]

25. Sturman DA, Moghaddam B. The neurobiology of adolescence: changes in brain architecture, functional dynamics, and behavioral tendencies. Neurosci Biobehav Rev. 2011; 35(8):1704–12. Epub 2011/04/30. [PubMed: 21527288]

26. Nelson EE, Leibenluft E, McClure EB, Pine DS. The social re-orientation of adolescence: a neuroscience perspective on the process and its relation to psychopathology. Psychol Med. 2005; 35(2):163–74. Epub 2005/04/22. [PubMed: 15841674]

27. Ernst M, Pine DS, Hardin M. Triadic model of the neurobiology of motivated behavior in adolescence. Psychol Med. 2006; 36(3):299–312. Epub 2006/02/14. [PubMed: 16472412]

28. Pfeifer JH, Masten CL, Moore WE 3rd, Oswald TM, Mazziotta JC, Iacoboni M, et al. Entering adolescence: resistance to peer influence, risky behavior, and neural changes in emotion reactivity. Neuron. 2011; 69(5):1029–36. Epub 2011/03/09. [PubMed: 21382560]

29. Forbes EE, Hariri AR, Martin SL, Silk JS, Moyles DL, Fisher PM, et al. Altered striatal activation predicting real-world positive affect in adolescent major depressive disorder. Am J Psychiatry. 2009; 166(1):64–73. Epub 2008/12/03. [PubMed: 19047324]

30. Forbes EE, Ryan ND, Phillips ML, Manuck SB, Worthman CM, Moyles DL, et al. Healthy adolescents' neural response to reward: associations with puberty, positive affect, and depressive symptoms. J Am Acad Child Adolesc Psychiatry. 2010; 49(2):162–72. e1–5. Epub 2010/03/11. [PubMed: 20215938]

31. Chen X, Coles CD, Lynch ME, Hu X. Understanding specific effects of prenatal alcohol exposure on brain structure in young adults. Human brain mapping. 2012; 33(7):1663–76. Epub 2011/06/22. [PubMed: 21692145]

32. Barde LH, Yeatman JD, Lee ES, Glover G, Feldman HM. Differences in neural activation between preterm and full term born adolescents on a sentence comprehension task: implications for educational accommodations. Developmental cognitive neuroscience. 2012; 2(Suppl 1):S114–28. Epub 2012/06/15. [PubMed: 22682901]

33. Schneider S, Peters J, Bromberg U, Brassen S, Miedl SF, Banaschewski T, et al. Risk taking and the adolescent reward system: a potential common link to substance abuse. Am J Psychiatry. 2012; 169(1):39–46. Epub 2011/10/01. [PubMed: 21955931]

34. Berns GS, Moore S, Capra CM. Adolescent engagement in dangerous behaviors is associated with increased white matter maturity of frontal cortex. PloS one. 2009; 4(8):e6773. Epub 2009/08/27. [PubMed: 19707512]

35. Kumra S, Ashtari M, Wu J, Hongwanishkul D, White T, Cervellione K, et al. Gray matter volume deficits are associated with motor and attentional impairments in adolescents with schizophrenia. Prog Neuropsychopharmacol Biol Psychiatry. 2011; 35(4):939–43. Epub 2011/01/11. [PubMed: 21216271]
36. Ziermans TB, Schothorst PF, Schnack HG, Koolschijn PC, Kahn RS, van Engeland H, et al. Progressive structural brain changes during development of psychosis. Schizophr Bull. 2012; 38(3):519–30. Epub 2010/10/12. [PubMed: 20929968]
37. Douaud G, Mackay C, Andersson J, James S, Quested D, Ray MK, et al. Schizophrenia delays and alters maturation of the brain in adolescence. Brain. 2009; 132(Pt 9):2437–48. Epub 2009/05/30. [PubMed: 19477963]
38. Ziermans TB, Durston S, Sprong M, Nederveen H, van Haren NE, Schnack HG, et al. No evidence for structural brain changes in young adolescents at ultra high risk for psychosis. Schizophr Res. 2009; 112(1-3):1–6. Epub 2009/05/08. [PubMed: 19419840]
39. Walker, EF.; Mcmillan, A.; Mittal, V. Neurohormones, Neurodevelopment, and the Prodrome of Psychosis in Adolescence. In: Romer, D.; Walker, EF., editors. Adolescent psychopathology and the developing brain : integrating brain and prevention science. Oxford University Press; Oxford ; New York: 2007. p. 264-83.
40. Walker EF, Diforio D. Schizophrenia: a neural diathesis-stress model. Psychol Rev. 1997; 104(4): 667–85. Epub 1997/10/24. [PubMed: 9337628]
41. Cunningham MG, Bhattacharyya S, Benes FM. Amygdalo-cortical sprouting continues into early adulthood: implications for the development of normal and abnormal function during adolescence. J Comp Neurol. 2002; 453(2):116–30. Epub 2002/10/10. [PubMed: 12373778]
42. Wolf OT, Convit A, de Leon MJ, Caraos C, Qadri SF. Basal hypothalamo-pituitary-adrenal axis activity and corticotropin feedback in young and older men: relationships to magnetic resonance imaging-derived hippocampus and cingulate gyrus volumes. Neuroendocrinology. 2002; 75(4): 241–9. Epub 2002/04/30. [PubMed: 11979054]
43. Tessner KD, Walker EF, Dhruv SH, Hochman K, Hamann S. The relation of cortisol levels with hippocampus volumes under baseline and challenge conditions. Brain Res. 2007; 1179:70–8. Epub 2007/10/16. [PubMed: 17936736]
44. Starkman MN, Giordani B, Gebarski SS, Berent S, Schork MA, Schteingart DE. Decrease in cortisol reverses human hippocampal atrophy following treatment of Cushing's disease. Biol Psychiatry. 1999; 46(12):1595–602. Epub 2000/01/07. [PubMed: 10624540]
45. Lupien SJ, de Leon M, de Santi S, Convit A, Tarshish C, Nair NP, et al. Cortisol levels during human aging predict hippocampal atrophy and memory deficits. Nat Neurosci. 1998; 1(1):69–73. Epub 1999/04/09. [PubMed: 10195112]
46. Starkman MN, Gebarski SS, Berent S, Schteingart DE. Hippocampal formation volume, memory dysfunction, and cortisol levels in patients with Cushing's syndrome. Biol Psychiatry. 1992; 32(9): 756–65. Epub 1992/11/01. [PubMed: 1450290]
47. Ryan MC, Sharifi N, Condren R, Thakore JH. Evidence of basal pituitary-adrenal overactivity in first episode, drug naive patients with schizophrenia. Psychoneuroendocrinology. 2004; 29(8): 1065–70. Epub 2004/06/29. [PubMed: 15219658]
48. Steen RG, Mull C, McClure R, Hamer RM, Lieberman JA. Brain volume in first-episode schizophrenia: systematic review and meta-analysis of magnetic resonance imaging studies. Br J Psychiatry. 2006; 188:510–8. Epub 2006/06/02. [PubMed: 16738340]
49. Matsumoto H, Simmons A, Williams S, Pipe R, Murray R, Frangou S. Structural magnetic imaging of the hippocampus in early onset schizophrenia. Biol Psychiatry. 2001; 49(10):824–31. Epub 2001/05/10. [PubMed: 11343679]
50. Janssen J, Reig S, Aleman Y, Schnack H, Udias JM, Parellada M, et al. Gyral and sulcal cortical thinning in adolescents with first episode early-onset psychosis. Biol Psychiatry. 2009; 66(11): 1047–54. Epub 2009/09/01. [PubMed: 19717139]
51. White T, Kendi AT, Lehericy S, Kendi M, Karatekin C, Guimaraes A, et al. Disruption of hippocampal connectivity in children and adolescents with schizophrenia--a voxel-based diffusion tensor imaging study. Schizophr Res. 2007; 90(1-3):302–7. Epub 2006/12/05. [PubMed: 17141478]

52. Gogtay N, Giedd JN, Lusk L, Hayashi KM, Greenstein D, Vaituzis AC, et al. Dynamic mapping of human cortical development during childhood through early adulthood. Proc Natl Acad Sci U S A. 2004; 101(21):8174–9. Epub 2004/05/19. [PubMed: 15148381]
53. Suzuki M, Hagino H, Nohara S, Zhou SY, Kawasaki Y, Takahashi T, et al. Male-specific volume expansion of the human hippocampus during adolescence. Cereb Cortex. 2005; 15(2):187–93. Epub 2004/07/09. [PubMed: 15238436]
54. Isgor C, Kabbaj M, Akil H, Watson SJ. Delayed effects of chronic variable stress during peripubertal-juvenile period on hippocampal morphology and on cognitive and stress axis functions in rats. Hippocampus. 2004; 14(5):636–48. Epub 2004/08/11. [PubMed: 15301440]
55. Neumann CS, Grimes K, Walker EF, Baum K. Developmental pathways to schizophrenia: behavioral subtypes. J Abnorm Psychol. 1995; 104(4):558–66. Epub 1995/11/01. [PubMed: 8530757]
56. McClure, EB.; Pine, DS. Social Stress, Affect, and Neural Function in Adolescence. In: Romer, D.; Walker, E., editors. Adolescent psychopathology and the developing brain : integrating brain and prevention science. Oxford University Press; Oxford ; New York: 2007. p. 219-44.
57. Monk CS, Nelson EE, McClure EB, Mogg K, Bradley BP, Leibenluft E, et al. Ventrolateral prefrontal cortex activation and attentional bias in response to angry faces in adolescents with generalized anxiety disorder. Am J Psychiatry. 2006; 163(6):1091–7. Epub 2006/06/03. [PubMed: 16741211]
58. McClure EB, Monk CS, Nelson EE, Parrish JM, Adler A, Blair RJ, et al. Abnormal attention modulation of fear circuit function in pediatric generalized anxiety disorder. Arch Gen Psychiatry. 2007; 64(1):97–106. Epub 2007/01/03. [PubMed: 17199059]
59. Thomas KM, Drevets WC, Dahl RE, Ryan ND, Birmaher B, Eccard CH, et al. Amygdala response to fearful faces in anxious and depressed children. Arch Gen Psychiatry. 2001; 58(11):1057–63. Epub 2001/12/26. [PubMed: 11695953]
60. Casey BJ, Duhoux S, Malter Cohen M. Adolescence: what do transmission, transition, and translation have to do with it? Neuron. 2010; 67(5):749–60. Epub 2010/09/10. [PubMed: 20826307]
61. Rosso IM, Cintron CM, Steingard RJ, Renshaw PF, Young AD, Yurgelun-Todd DA. Amygdala and hippocampus volumes in pediatric major depression. Biol Psychiatry. 2005; 57(1):21–6. Epub 2004/12/21. [PubMed: 15607296]
62. Monk CS, Klein RG, Telzer EH, Schroth EA, Mannuzza S, Moulton JL 3rd, et al. Amygdala and nucleus accumbens activation to emotional facial expressions in children and adolescents at risk for major depression. Am J Psychiatry. 2008; 165(1):90–8. Epub 2007/11/08. [PubMed: 17986682]
63. MacMillan S, Szeszko PR, Moore GJ, Madden R, Lorch E, Ivey J, et al. Increased amygdala: hippocampal volume ratios associated with severity of anxiety in pediatric major depression. J Child Adolesc Psychopharmacol. 2003; 13(1):65–73. Epub 2003/06/14. [PubMed: 12804127]
64. MacMaster FP, Kusumakar V. Hippocampal volume in early onset depression. BMC medicine. 2004; 2:2. Epub 2004/02/19. [PubMed: 14969587]
65. Blumberg HP, Martin A, Kaufman J, Leung HC, Skudlarski P, Lacadie C, et al. Frontostriatal abnormalities in adolescents with bipolar disorder: preliminary observations from functional MRI. Am J Psychiatry. 2003; 160(7):1345–7. Epub 2003/07/02. [PubMed: 12832254]
66. Steingard RJ, Renshaw PF, Hennen J, Lenox M, Cintron CB, Young AD, et al. Smaller frontal lobe white matter volumes in depressed adolescents. Biol Psychiatry. 2002; 52(5):413–7. Epub 2002/09/21. [PubMed: 12242057]
67. Cullen KR, Klimes-Dougan B, Muetzel R, Mueller BA, Camchong J, Houri A, et al. Altered white matter microstructure in adolescents with major depression: a preliminary study. J Am Acad Child Adolesc Psychiatry. 2010; 49(2):173–83. e1. Epub 2010/03/11. [PubMed: 20215939]
68. Cullen KR, Gee DG, Klimes-Dougan B, Gabbay V, Hulvershorn L, Mueller BA, et al. A preliminary study of functional connectivity in comorbid adolescent depression. Neurosci lett. 2009; 460(3):227–31. Epub 2009/05/19. [PubMed: 19446602]

69. Jin C, Gao C, Chen C, Ma S, Netra R, Wang Y, et al. A preliminary study of the dysregulation of the resting networks in first-episode medication-naive adolescent depression. Neurosci lett. 2011; 503(2):105–9. Epub 2011/08/30. [PubMed: 21871534]
70. Pandey, GN.; Dwivedi, Y. Neurobiology of Teenage Suicide. In: Dwivedi, Y., editor. The neurobiological basis of suicide. Taylor & Francis/CRC Press; Boca Raton, FL: 2012. p. 315-32.
71. Pandey GN, Dwivedi Y, Rizavi HS, Ren X, Pandey SC, Pesold C, et al. Higher expression of serotonin 5-HT(2A) receptors in the postmortem brains of teenage suicide victims. Am J Psychiatry. 2002; 159(3):419–29. Epub 2002/03/01. [PubMed: 11870006]
72. Pandey GN, Ren X, Rizavi HS, Conley RR, Roberts RC, Dwivedi Y. Brain-derived neurotrophic factor and tyrosine kinase B receptor signalling in post-mortem brain of teenage suicide victims. Int J Neuropsychopharmacol. 2008; 11(8):1047–61. Epub 2008/07/10. [PubMed: 18611289]
73. Pandey GN, Dwivedi Y, Ren X, Rizavi HS, Roberts RC, Conley RR. Cyclic AMP response element-binding protein in post-mortem brain of teenage suicide victims: specific decrease in the prefrontal cortex but not the hippocampus. Int J Neuropsychopharmacol. 2007; 10(5):621–9. Epub 2006/09/19. [PubMed: 16978443]
74. Pandey GN, Rizavi HS, Ren X, Fareed J, Hoppensteadt DA, Roberts RC, et al. Proinflammatory cytokines in the prefrontal cortex of teenage suicide victims. J Psychiatr Res. 2012; 46(1):57–63. Epub 2011/09/13. [PubMed: 21906753]
75. Guerri C, Pascual M. Mechanisms involved in the neurotoxic, cognitive, and neurobehavioral effects of alcohol consumption during adolescence. Alcohol. 2010; 44(1):15–26. Epub 2010/02/02. [PubMed: 20113871]
76. De Bellis MD, Clark DB, Beers SR, Soloff PH, Boring AM, Hall J, et al. Hippocampal volume in adolescent-onset alcohol use disorders. Am J Psychiatry. 2000; 157(5):737–44. Epub 2000/04/28. [PubMed: 10784466]
77. Nagel BJ, Schweinsburg AD, Phan V, Tapert SF. Reduced hippocampal volume among adolescents with alcohol use disorders without psychiatric comorbidity. Psychiatry Res. 2005; 139(3):181–90. Epub 2005/08/02. [PubMed: 16054344]
78. De Bellis MD, Narasimhan A, Thatcher DL, Keshavan MS, Soloff P, Clark DB. Prefrontal cortex, thalamus, and cerebellar volumes in adolescents and young adults with adolescent-onset alcohol use disorders and comorbid mental disorders. Alcohol Clin Exp Res. 2005; 29(9):1590–600. [PubMed: 16205359]
79. McQueeny T, Schweinsburg BC, Schweinsburg AD, Jacobus J, Bava S, Frank LR, et al. Altered white matter integrity in adolescent binge drinkers. Alcohol Clin Exp Res. 2009; 33(7):1278–85. Epub 2009/04/25. [PubMed: 19389185]
80. Tapert SF, Schweinsburg AD, Barlett VC, Brown SA, Frank LR, Brown GG, et al. Blood oxygen level dependent response and spatial working memory in adolescents with alcohol use disorders. Alcohol Clin Exp Res. 2004; 28(10):1577–86. Epub 2004/12/15. [PubMed: 15597092]
81. Markwiese BJ, Acheson SK, Levin ED, Wilson WA, Swartzwelder HS. Differential effects of ethanol on memory in adolescent and adult rats. Alcohol Clin Exp Res. 1998; 22(2):416–21. [PubMed: 9581648]
82. White AM, Swartzwelder HS. Hippocampal function during adolescence: a unique target of ethanol effects. Ann N Y Acad Sci. 2004; 1021:206–20. Epub 2004/07/15. [PubMed: 15251891]
83. White AM, Swartzwelder HS. Age-related effects of alcohol on memory and memory-related brain function in adolescents and adults. Recent Dev Alcohol. 2005; 17:161–76. Epub 2005/03/26. [PubMed: 15789865]
84. Crews FT, Braun CJ, Hoplight B, Switzer RC 3rd, Knapp DJ. Binge ethanol consumption causes differential brain damage in young adolescent rats compared with adult rats. Alcohol Clin Exp Res. 2000; 24(11):1712–23. Epub 2000/12/05. [PubMed: 11104119]
85. Crews FT, Mdzinarishvili A, Kim D, He J, Nixon K. Neurogenesis in adolescent brain is potently inhibited by ethanol. Neuroscience. 2006; 137(2):437–45. [PubMed: 16289890]
86. Li Q, Wilson WA, Swartzwelder HS. Differential effect of ethanol on NMDA EPSCs in pyramidal cells in the posterior cingulate cortex of juvenile and adult rats. J Neurophysiol. 2002; 87(2):705–11. Epub 2002/02/05. [PubMed: 11826039]

87. Pascual M, Boix J, Felipo V, Guerri C. Repeated alcohol administration during adolescence causes changes in the mesolimbic dopaminergic and glutamatergic systems and promotes alcohol intake in the adult rat. J Neurochem. 2009; 108(4):920–31. Epub 2008/12/17. [PubMed: 19077056]

88. Pandey SC, Ugale R, Zhang H, Tang L, Prakash A. Brain chromatin remodeling: a novel mechanism of alcoholism. J Neurosci. 2008; 28(14):3729–37. Epub 2008/04/04. [PubMed: 18385331]

89. Li K, Zhu D, Guo L, Li Z, Lynch ME, Coles C, et al. Connectomics signatures of prenatal cocaine exposure affected adolescent brains. Human brain mapping. 2012 Epub 2012/03/31.

90. Black YD, Maclaren FR, Naydenov AV, Carlezon WA Jr. Baxter MG, Konradi C. Altered attention and prefrontal cortex gene expression in rats after binge-like exposure to cocaine during adolescence. J Neurosci. 2006; 26(38):9656–65. Epub 2006/09/22. [PubMed: 16988036]

91. Lesch KP, Bengel D, Heils A, Sabol SZ, Greenberg BD, Petri S, et al. Association of anxiety-related traits with a polymorphism in the serotonin transporter gene regulatory region. Science. 1996; 274(5292):1527–31. Epub 1996/11/29. [PubMed: 8929413]

92. Munafo MR, Brown SM, Hariri AR. Serotonin transporter (5-HTTLPR) genotype and amygdala activation: a meta-analysis. Biol Psychiatry. 2008; 63(9):852–7. Epub 2007/10/24. [PubMed: 17949693]

93. Lau JY, Goldman D, Buzas B, Fromm SJ, Guyer AE, Hodgkinson C, et al. Amygdala function and 5-HTT gene variants in adolescent anxiety and major depressive disorder. Biol Psychiatry. 2009; 65(4):349–55. Epub 2008/10/28. [PubMed: 18950748]

94. Bath KG, Lee FS. Variant BDNF (Val66Met) impact on brain structure and function. Cognitive, affective & behavioral neuroscience. 2006; 6(1):79–85. Epub 2006/07/28.

95. Chen ZY, Jing D, Bath KG, Ieraci A, Khan T, Siao CJ, et al. Genetic variant BDNF (Val66Met) polymorphism alters anxiety-related behavior. Science. 2006; 314(5796):140–3. Epub 2006/10/07. [PubMed: 17023662]

96. Lau JY, Goldman D, Buzas B, Hodgkinson C, Leibenluft E, Nelson E, et al. BDNF gene polymorphism (Val66Met) predicts amygdala and anterior hippocampus responses to emotional faces in anxious and depressed adolescents. Neuroimage. 2010; 53(3):952–61. Epub 2009/11/26. [PubMed: 19931400]