Published in final edited form as:
Prev Sci. 2013 June ; 14(3): 300–309. doi:10.1007/s11121-012-0323-0.

Neuroimaging methods for adolescent substance use disorder prevention science

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Abstract

Magnetic resonance imaging (MRI) methods safely provide in vivo indicators of cerebral macrostructure, microstructure, and activation that can be examined in relation to substance use disorder (SUD) risks and effects. This article will provide an overview of MRI approaches, including volumetric measures, diffusion tensor imaging, functional MRI, that have been applied to studies of adolescent neuromaturation in relationship to risk phenotypes and adolescent SUD. To illustrate these applications, examples of research findings will be presented. MRI indicators have demonstrated that neurobiological maturation continues throughout adolescence. MRI research has suggested that variations in neurobiological maturation may contribute to SUD risk, and that substance use adversely influence adolescent brain development. Directly measured neurobiological variables may be viable preventive intervention targets and outcome indicators. Further research is needed to provide definitive findings on neurodevelopmental immaturity as an SUD risk and to determine the directions such observations suggest for advancing prevention science.

Keywords

Adolescents; Neuroimaging; Substance Use Disorders

Introduction

Neuroimaging methods provide direct measurement and visualization of brain structures and functions. To the extent to that risk characteristics have a neurodevelopmental basis, indices generated by neuroimaging methods may inform substance use disorder (SUD) prevention science. The measurement of neuroimaging endophenotypes may provide causal links from environmental and genetic influences to SUD, revealing opportunities for disrupting the progression to SUD. Neuroimaging indicators may demonstrate neurobiological effects of preventive interventions. The quantification of SUD effects on adolescent neurobiological outcomes would provide cautionary information applicable to preventive interventions. Further advances will be needed, however, for the potential of neuroimaging methods for SUD prevention science to be realized.

This article provides a brief introduction to magnetic resonance imaging (MRI) techniques and applications, including those for measuring cerebral macrostructure (cerebral volumes), white matter microstructure, and cerebral activation. For each method, examples of

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Special Issue: Translation and Integration of Biological Research into Prevention Science, Eds. Fishbein D, Ridenour T (invited article)

neuroimaging findings related to adolescent brain development, risk for SUD, and SUD correlates of adolescent SUD are presented. Other imaging methods (e.g., Positron Emission Tomography, Single Photon Emission Computed Tomography) are not reviewed here, due to their being more hazardous than MRI and therefore of more limited use in research with children and adolescents. The review concludes with a discussion of limitations of existing research, gaps in the knowledge base, and recommendations for future research.

Magnetic Resonance Imaging

MRI techniques can be broadly categorized in structural and functional methods. Structural approaches examine cerebral macrostructure, including regionally segmented volumes, and microstructure, particularly white matter organization. Functional MRI (fMRI) examines brain activity, typically during tasks intended to elicit specific mental functions. Structural and functional approaches may be combined in connectivity studies that integrate microstructural (i.e., white matter tracts) and functional (i.e., resting patterns of temporally correlated gray matter activation) characteristics to identify neural systems (Teipel et al., 2010).

MRI uses the nuclear magnetic resonance properties of hydrogen atoms in biological tissues to construct images. MRI images are created by using a strong magnet to align hydrogen atoms in the direction of the magnetic field. Next, a radio frequency pulse that is specific to hydrogen atoms is applied. The resulting variations in the electromagnetic field result in absorbed and released energy. The signal produced by this released energy may be measured and located over time, and images may be thereby constructed. MRI has very good contrast (i.e., intensity variations) in soft tissue, which makes it especially useful in brain imaging.

Adolescent brain development and psychological regulation

Prefrontal cortex (PFC), limbic regions, white matter, and related circuits undergo active development during adolescence (Lenroot & Giedd, 2006; Spear, 2000). These changes have been demonstrated with MRI. During adolescence, gray matter volume diminishes, and white matter volume and organization increase (Gogtay et al., 2004). These structural changes are believed to underlie advancing integration of PFC with other brain areas (Luna, Garver, Urban, Lazar, & Sweeney, 2004). Immaturity of the cortical networks that control of emotions, cognitions and behaviors may contribute to SUD risk. The quantification of individual variation in neurodevelopment through MRI techniques may be informative for prevention science.

Psychological dysregulation refers to deficiencies in cognitive, behavioral, and affective control (Clark, Thatcher & Tapert, 2008; Clark & Winters, 2002). Deficits in psychological regulation comprise a liability trait that is stable from late childhood through middle adolescence, is heritably transmitted from parent to child, and that predicts SUD (Clark, Cornelius, Kirisci, & Tarter, 2005; Clark, Cornelius, Wood, & Vanyukov, 2004; Tarter et al., 2003; Vanyukov et al., 2009). Adolescents with SUD may have deficits in late developing brain circuits involved in psychological regulation. The measurement of structural or functional neurobiological characteristics through neuroimaging methods may thus identify prevention targets, supplement outcome indicators, or provide scientific insights for advancing prevention science.

Cross-sectional designs and explanatory models for SUD risks and effects

The case-control study is a classic and efficient approach to generating hypotheses that has been extensively used in MRI applications to adolescent SUD research. While study results have been inconsistent, there are arguably MRI findings indicating that adolescents with

SUD compared to controls show delayed neurodevelopment or neurobiological deficits. Two alternative explanatory models need to be considered. The first possibility is that the brain characteristics evident among SUD adolescents predate and contribute to SUD, constituting a neurobiological risk factor (i.e., Neurodevelopmental Immaturity Model: Clark, Chung, Thatcher, Pajtek, & Long, 2012). Applying this model, one would propose that psychological dysregulation is caused by delays or deficits in neurodevelopment that precede and contribute to SUD. A confirmatory study would show that the MRI measured characteristic predicts later SUD. The second possibility is that the brain characteristics evident among SUD adolescents are caused by neurotoxic substance effects (i.e., Substance Effect Model). A confirmatory study would show that high risk individuals have results typical for reference individuals on the MRI measured brain characteristic of interest, with abnormalities evident only after SUD onset. Finally, both models may apply, as has been indicated in some studies with adults (e.g., Ersche et al., 2012). These interpretative issues need to be considered in evaluating available MRI studies.

The challenges presented by MRI methods have necessitated the utilization of designs typical of preliminary research in other SUD prevention science areas. The cost of MRI data collection and processing for a single subject session can easily exceed $1000. MRI research may be inhibited by lack of hardware availability, scheduling difficulties that may result from the demands of mixed research and clinical use at a particular facility, and inadequate local expertise. The MRI literature on SUD prevention science includes few, if any, definitive studies.

Cerebral macrostructure: Volumetric methods and applications

During adolescence, cortical gray matter volume declines while white matter volume increases (Lenroot & Giedd, 2006). Some studies have suggested that individual variations in these regional volumes contribute to SUD risk or are due to SUD effects, and these approaches continue to be utilized in SUD prevention science. However, the extent to which such regional cerebral volumes are informative for SUD prevention science has not been clearly determined.

Principles and methods

Gray matter, white matter, and cerebrospinal fluid, produce different MRI image intensities. Historically, volumetric analyses were conducted by visual inspection and manual tracing to determine the demarcations of cerebral tissue types and regions. This approach is labor intensive, requires extensive training, can produce variable ratings across raters and laboratories, and may be subject to rater bias. Manual tracing methods can be expensive and challenging to apply to large samples. In recent years, automated cortical parcellation methods have become available. For example, the Freesurfer programs (Desikan et al., 2006) automate motion correction, the averaging of multiple images, the identification of non-brain tissue, location of the gray/white/cerebrospinal fluid borders, registration of subjects to a common atlas using individual cortical folding patterns, and cerebral parcellation. Freesurfer measures have been validated against histological and manual measurements and have shown excellent reliability across scanner manufacturers and field strengths. Regions of interest identified by Freesurfer may also be used in DTI and fMRI analyses (e.g., Clark et al., 2012).

Adolescent development

From late childhood to young adulthood, total cerebral volume is relatively unchanged (Lenroot & Giedd, 2006). While historically interpreted as indicating that the brain was fully developed by late childhood, major neurodevelopmental changes occur within this relatively

stable volume. Cortical gray matter shows nonlinear and regionally-specific changes from ages 4 through 20, with a decline in gray matter volume during adolescence thought to be due to synaptic pruning (Blakemore & Choudhury, 2006). White matter volume undergoes a linear increase through adolescence reflecting increased axonal myelination and caliber (Paus, 2010a).

Risks for SUD

Since disruptive behavior disorders reflect psychological dysregulation and predict SUD, related research on regional brain volumes may be relevant. Castellanos and colleagues (2002) compared 152 ADHD youth (ages 5–18) with 139 controls on total cerebral volume as well as regional gray and white matter volumes. Only the cerebellum was significantly smaller in ADHD subjects. Subsequent studies with smaller samples have yielded inconsistent results (e.g., Batty et al., 2010; Huebner et al., 2008; Shaw et al., 2011).

Adolescent SUD

There is some evidence that limbic system structures (e.g., hippocampus, amygdala) are smaller in adolescents with SUD compared to those of controls. In a study comparing 12 adolescents and young adults with adolescent-onset AUD to 24 control subjects (De Bellis et al., 2000), hippocampal volumes were significantly smaller in the AUD subjects. Hippocampal volume correlated negatively with AUD duration and positively with AUD onset age. These findings were interpreted as consistent with the Substance Effect Model. Other investigators have also found smaller hippocampal volumes in AUD adolescents (Nagel, Schweinsburg, Phan, & Tapert, 2005) and alcohol using adolescents (Barros-Loscertales et al., 2006). In adult samples, SUD has been associated with reduced white matter volume (e.g., Carlen, Wortzman, Holgate, Wilkinson, & Rankin, 1978). Smaller white matter volumes have also been reported in samples of adolescents with SUD or substance use in some studies (DeBellis et al., 2005; Medina, Nagel, Park, McQueeny, & Tapert, 2007) and not in others (Clark et al., 2012).

Summary and conclusions

Mixed findings on cerebral volumes related to SUD risk and SUD preclude an unambiguous interpretation. Among children and adolescents at high risk for SUD, the few positive findings are accompanied by inconsistencies across studies. Comparing adolescents with SUD and controls, the regional patterns are also inconsistent. Smaller hippocampal volumes among SUD adolescents has been replicated, but inexplicably noted as occurring on only one side in some studies. These published studies have had significant flaws, and there is likely a bias toward the publication of positive results (Ioannidis, 2011).

Cerebral microstructure: Diffusion Tensor Imaging (DTI)

White matter consists of mylenated axons that transmit neuronal signals. Some white matter regions are comprised primarily of axons of neurons communicating between cortical regions. White matter organizational microstructure may be regionally quantified with DTI. White matter tracts projecting to the PFC increase in organization during adolescence, possibly indicating a neuobiological foundation for advancing psychological regulation. Studies of group differences in white matter organization have suggested that lower organization reflects deficits contributing to SUD risk or due to SUD effects. Compared to white matter volumes, white matter organization may be more sensitive in detecting developmental changes during adolescence, neurobiological characteristics relevant for risk, or SUD effects.

Principles and methods

DTI estimates white matter organization by quantifying water diffusion (Basser & Pierpaoli, 1996). Axonal fibers constrain water movement along primary tract axes. DTI estimates directional water mobility. At each voxel, a three-dimensional ellipsoid or "tensor" indicates diffusion rate and relative direction. The most commonly used diffusion index is fractional anisotropy (FA), a summary indicator calculated using axial diffusivity (AD; diffusion along the axon) and radial diffusivity (RD; diffusion perpendicular to the axon). This information may be used in tractography studies to map the anatomical relationships (de Schotten et al., 2011). FA reflects axonal organization, myelination, and neuronal permeability (Paus, 2010a). Statistical analyses of DTI variables use voxel-based or region of interest (ROI) approaches. Voxel-based analyses examine the entire brain in a model-free manner. By identifying groups of contiguous voxels with similar between-group differences, voxel-based analyses may be used to identify regions where DTI variables differ between groups or correlate with behavioral variables. ROIs may be used to test hypotheses with increased specificity and sensitivity.

Adolescent development

The white matter tracts projecting to PFC areas increase in their organization during adolescence (Ashtari et al., 2007; Spear, 2000). The PFC plays an important role in psychological regulation through its interaction with other brain regions via white matter tracts (Spear, 2000). The organization of white matter in the superior longitudinal fasciculus, for example, increases through adolescence (Bonekamp et al., 2007). Increasing white matter organization during adolescence corresponds with executive function development, and variation in frontal white matter organization may in part explain individual differences in psychological regulation (Lenroot & Giedd, 2006). Some studies suggest that the frontoparietal network may be particularly important in psychological regulation. The frontoparietal network involves the PFC and parietal cortex connected by the superior longitudinal fasciculus (SLF) (Fassbender et al., 2006; Olesen et al., 2003). Since the SLF is a relatively large and directionally organized white matter tract, SLF is particularly amenable to examination with DTI. Immaturity of the cortical white matter generally or, more specifically, the white matter of the frontoparietal network, may contribute to psychological dysregulation and risk for SUD (Clark et al., 2012).

Risk for SUD

Children and adolescents with psychopathology reflecting psychological dysregulation have been found in some studies to have white matter disorganization (Li, Mathews, Wang, Dunn, & Kronenberger, 2005). In two studies comparing ADHD children with controls (age 7–11 years), children with ADHD had decreased FA in several regions (Ashtari et al., 2005; Nagel et al., 2011). At risk adolescents, defined by a family history of AUD, have been shown to have frontoparietal network deficits. Utilizing a combination of DTI and fMRI methods to determine functional connectivity, at risk adolescents compared to controls were found to have less functional PFC-parietal connectivity (Wetherill et al., 2012).

Adolescent SUD

Several studies have examined white matter organization in adolescents with substance involvement. Tapert and colleagues (Bava et al., 2009; McQueeney et al., 2009) compared adolescents with problematic marijuana or alcohol use to controls on white matter organization. The substance using adolescents exhibited lower white matter organization in several brain regions, including the SLF. De Bellis and colleagues (2008) compared SUD adolescents with controls on corpus callosum white matter organization and found that the SUD group did not show significantly lower FA. Clark and colleagues compared SUD

adolescents with controls on FA using voxel-based (Thatcher et al., 2010) and ROI (Clark et al., 2012) approaches. Adolescents with SUD were found to show significantly lower FA in tracts serving the frontoparietal network. In addition, frontoparietal white matter organization was associated with psychological dysregulation (Clark et al., 2012). Among adolescents in SUD treatment, lower PFC white matter organization has been found to predict more alcohol problems after six months indicating poorer treatment outcomes (Chung et al., in press).

Summary and conclusions

Similar to research on cerebral volumes, research on white matter organization and SUD risk versus SUD-related effect remains inconclusive. These studies contain many negative results and, across studies, inconsistent findings for specific regions. In general, published studies suggest lower white matter microstructure organization among those at high risk for or with SUD. While one may accept this interpretation, these cross-sectional studies do not clearly supported either the Neurodevelopmental Immaturity Model or the Substance Effect Model.

In addition to study design issues, technical challenges to interpreting DTI findings have been noted (Thomason & Thompson, 2011). While increased FA is typically interpreted as indicating healthier white matter, lower FA does not necessarily indicate white matter pathology (Hoeft et al., 2007). In areas where tracts cross, for example, healthy white matter shows relatively lower organization by FA. Reduced fiber crossing may, in some instances, explain DTI findings indicating increases in apparent white matter organization associated with pathology, including neurological disease (Hoeft et al., 2007) or adolescent SUD (DeBellis et al., 2008).

Functional MRI (fMRI)

In functional MRI (fMRI), neuronal activation may be estimated and regionally quantified during engagement in tasks presented during neuroimaging. Regional activations and developmental changes in response depend on the presented task. Studies of group differences in task responses and related cerebral activation patterns have suggested developmental delays or deficits in neural systems that may contribute to SUD risk or be adversely altered by SUD.

Principals and methods

These techniques indirectly estimate the location, timing and level of neural activity by measuring the hemodynamic or metabolic consequences of neuronal firing. In most fMRI studies, blood oxygenation dependent (BOLD) contrast is used to measure regional hemodynamic responses. BOLD estimates neuronal activity through measuring changes in the local ratio of oxygenated to deoxygenated hemoglobin (Ogawa, Lee, Kay, & Tank, 1990). The BOLD response peaks roughly 5 seconds after neuronal activation and may persist for as much as 15 seconds. BOLD effects thus have better spatial than temporal resolution.

Cerebral activation by fMRI and SUD risk

Investigating risk and alcohol use, two fMRI studies by Heitzeg and colleagues (2008, 2010) focused on frontolimbic network in groups of adolescents and young adults with parental AUD (pAUD+) having higher (i.e., “vulnerable”) and lower (i.e., “resilient”) alcohol use and control groups with no parental AUD (pAUD−). On a word valence task , the “vulnerable” group had greater PFC activation and lesser activation in the bilateral amygdala and ventral striatum than did the “resilient” and control groups. This result may

reflect an impaired ability to manage negative affect. A second study used the "go/no-go" task, where subjects perform or inhibit pressing a button in response to visual stimuli, with successful responses showing the capacity for behavioral inhibition. On a go/no-go task, the "resilient" and control groups showed decreased orbital and left medial PFC activation during successful inhibition, but the "vulnerable" group did not. Tapert and colleagues (Norman et al., 2011) used the go/no go task with a young adolescent sample, less activation in frontal cortex and other cortical areas in response to the "no-go" behavior inhibition challenge was been found to predict accelerated alcohol use over a four-year follow-up period. Contrasting these findings, whether increased or decreased activation of specific frontal areas facilitates the "no-go" response is unclear.

The anti-saccade task is a behavioral inhibition task that may be presented during fMRI. In this task, subjects inhibit a reflexive eye movement to a novel stimulus and instead look in the opposite direction. Regional activation during cognitive response preparation is thought to indicate neurobiological mechanisms for response inhibition. During adolescence, correct anti-saccade performance improves and related PFC activation increases (Luna et al., 2004).

In a study comparing children (ages 10–12 years) of fathers with SUD and control children (Habeych, Folan, Luna, & Tarter, 2006), high risk children made more anti-saccade task errors than did control children. In addition, high risk children with ADHD, compared to high risk children without ADHD, showed more errors. Using the anti-saccade task with fMRI, McNamee and colleagues (2008) examined high risk and control adolescents (age 12–19 years). During anti-saccade trials, lower PFC activity was correlated with higher psychological dysregulation scores by an independent measure. Delayed development or deficiencies in neural systems serving response inhibition may be the neurobiological foundation for diminished capabilities in voluntary behavioral control and related SUD risk.

To complement behavioral tasks, affective regulation can be examined by presenting affect laden faces during fMRI (Hariri et al., 2000). Adolescents at risk for SUD by parental history, compared to reference adolescents, have been shown to exhibit greater amygdale activation in response to seeing affect-laden faces, indicating frontolimbic network hyper-responsivity to emotional stimuli (Thatcher et al., in press).

Adolescent SUD

Chung and colleagues (2011) used the anti-saccade reward task to examine behavioral inhibition and cerebral activation in adolescents with SUD and controls (ages 15–18). An added reward condition facilitated correct anti-saccade responding among SUD adolescents, while control subjects did not significantly differ on anti-saccade error rates during reward or neutral trials. During anti-saccade reward trials, SUD adolescents, compared to controls, showed greater PFC. These results indicated that, particularly among SUD adolescents, reward anticipation enhanced motivation and related cerebral activity supporting anti-saccade performance.

In a study presenting affect laden faces with fMRI to young adults with cannabis dependence and depression, higher cannabis use was associated with lower amygdale response (Cornelius, et al., 2010). This reduction in neurobiological reactivity to affective stimuli suggested a possible cannabis use motive among those with affective dysregulation.

Summary and conclusions

These fMRI studies emphasize some of the complexities involved in studying cerebral activation in response to a variety of stimuli, and relating individual variation in these changes to risk for SUD or SUD effects. The fMRI measurement directly examines hemodynamic changes and indirectly reflects neural activity. Observed hemodynamic

changes may be similar in a variety of neural activation scenarios, including functionally specific activation or global neuromodulation. Hemodynamic changes may be similar during activation of excitatory or inhibitory neural systems (Logothetis, 2008) Thus, interpreting fMRI signals as functionally specific neural activation may be misleading.

Multi-modal neuroimaging methods

An active area of neuroimaging research involves the integration of complementary MRI, electrophysiological and other neurobiological methods. For example, the combined use of DTI and fMRI to examine correlations between white matter organization and functional cortical activity have been valuable in identifying and understanding neural systems (Olesen, Nagy, Westerberg, & Klingberg, 2003). In addition, to compensate for fMRI's high spatial but relatively poor temporal resolution, some studies utilize concurrent non-invasive measures that have higher temporal resolution, such as electroencephalography (EEG) or magnetoencephalography (MEG) data. Magnetic resonance spectroscopy (MRS) can quantify regional cerebral neurochemical characteristics that may be associated with adolescent SUD risk (Moss, Talagala, & Kirisci, 1997; Yang, Wu, Dung, & Ko, 2010).

Imaging genetics

MRI may be utilized to elucidate the influence of genetic variations on brain functioning, an approach termed "imaging genetics" (Viding, Williamson, & Hariri, 2006). For example, consider the relation between serotonin transporter genotypes and cerebral activation in response to faces depicting affective states (Hariri & Holmes, 2006). The serotonin transporter long promoter region gene (5-HTTLPR) alleles have short (s) and long (l) variants. The s allele variant has been shown to be associated with less serotonin transporter expression, reduced serotonin uptake efficiency, and diminished serotonin 1A receptor binding potential compared to the l variant (David et al, 2005). The s 5-HTTLPR genotype has been found to confer increased risk for negative affect and impulsive behavior in response to traumatic experiences (Caspi et al., 2003; Kaufmann et al., 2004). Those homozygous (l/l) for the long 5-HTTLPR allele have shown greater emotional resilience (Stein, Campbell-Sills, & Gelernter, 2009). The 5-HTTLPR polymorphism has been shown to be associated with substance use characteristics, drug response in laboratory settings, and SUD (Brody, Beach, Philibert, Chen, & Murry, 2009; Covault et al., 2007; Enoch, Gorodetsky, Hodgkinson, Roy, & Goldman, 2010; Feinn, Nellissery, & Kranzler, 2005; Lott, Kim, Cook, & de Wit, 2006). In a family-centered intervention study, Brody and colleagues (2009) found adolescents with the s allele in the control group, compared to other groups, showed an increase in substance use and other high risk behaviors.

The examination of task related cerebral activation in relationship to genotypic variations may provide information on the neurobiological mechanism for the risk associated with the s allele and the reported differential intervention effects. Adults (Hariri et al., 2005) and children (Fortier et al., 2010) with the s allele have shown amygdalar hyperreactivity when shown affect-laden faces. This amygdalar hyperreactivity in individuals with the s allele variants has been found to be maintained over successive stimulus presentations whereas individuals with the l/l variant showed response habituation (Lonsdorf et al., 2011). Lower functional coupling in the frontolimbic circuit has been observed in s 5-HTTLPR variant carriers compared to those with the l/l variant (Pezawas et al., 2005). Findings on relationships among 5-HTTLPR genotype, affect regulation, neural activation patterns, and intervention responses suggest research designs that would advance an understanding of neurobiological factors in SUD prevention.

Challenges and Recommendations for Further Research

The MRI research conducted to date that is relevant for adolescent SUD prevention science has been informative but not conclusive. While promising findings are emerging, the small cross-sectional studies available to date have been inconsistent in their findings and ambiguous with regard to causal relationships. Studies that have examined cerebral structure or function relative to known SUD risks have yet to definitively establish relationships. The effects of adolescent substance use on structural or functional brain characteristics have also not been definitively demonstrated. We therefore must conclude that research on neuroimaging as applied to adolescent SUD prevention science is at an early stage.

The design limitations and inconclusive findings evident in the extant research literature underscore the challenges inherent in applying MRI to adolescent SUD prevention science. MRI hardware availability is a necessary but not sufficient condition for conducting research in this arena. The integration of scholars with specific expertise and experience in neuroimaging into the research team is necessary so that the strengths and weaknesses of particular neuroimaging methods can be taken into consideration in study design. Limitations in MRI facility access, the high cost of scan time, the need for staff expertise in data collection, and the complexities involved in MRI data processing and analyses tend to limit sample sizes. Prevention scientists accustomed to very large samples may find these constraints difficult to accept. A related issue is that statistical approaches applicable to large, longitudinal data sets are often not be applicable to MRI data. Neuroimaging methods also pose challenges for subject recruitment. Subjects with irremovable metal objects, such as dental braces, need to be excluded. The MRI apparatus typically requires the subject to tolerate lying in a small space, which is difficult for some subjects. Subjects with ADHD or restlessness for other reasons may find it difficult to remain still during prolonged scanning sessions, resulting in a high degree of head motion that can reduce the signal-to-noise ratio in imaging analyses (Epstein et al., 2007). Attention to subject activities immediately prior to and during participation may assume enhanced importance for fMRI, since the BOLD response can be influenced by recent substance use and variations in attention during task performance.

A bias toward the publication of positive findings may be a substantial problem in the MRI literature. A recent meta-analysis examining reports of brain volume abnormalities associated with a variety of mental disorders concluded that biases toward publication of positive results were evident (Ioannidis, 2011). Many negative findings go unreported.

Longitudinal MRI studies with larger samples would likely advance SUD prevention science. The largest longitudinally studied sample to date (Shaw et al., 2011) was conducted by the NIMH Intramural program. An on-going large-scale on-going longitudinal study is the IMAGEN study, which aims to recruit 2,000 14-year olds across multiple sites in Europe (Schumann et al., 2010). Functional and structural neuroimaging and genetic analyses will be completed in IMAGEN, with replication planned to in 1,000 youth in the Canadian Saguenay Youth Study (Paus, 2010b). The IMAGEN sample will be followed at age 16 to examine the predictive value of genetics and MRI endophenotypes for development of common psychiatric conditions, including SUD (Schumann et al., 2010). To supplement large scale studies, carefully designed smaller studies may be needed to more flexibly accommodate changes in technology and explore emerging technologies, as well as provide data relevant to specific subgroups, specific aspects of psychological regulation, and environmental conditions (Paus, 2010b).

In imaging studies conducted over many years, creative solutions are needed for research design problems and imaging protocols that become obsolete with rapidly advancing MRI

methods. Substantial resources are needed to conduct such ambitious studies, and replication is critically important in this research area. Replications may need to match risk factors studied, control group characteristics, subject ages, gender composition, task selection and parameters, and variations in participant substance involvement.

Implications for Interventions

Prevention science applications of MRI techniques will likely facilitate insights into the importance of variation in adolescent brain development for SUD risk and identify potential targets for intervention. The Neurodevelopmental Immaturity Model suggests that the examination of cerebral structures and functions that develop during adolescence using neuroimaging techniques may provide a foundation for understanding the neurobiological mechanisms for SUD risks, the interaction of neurodevelopmental vulnerabilities and preventive interventions, and the neurobiological effects of prevention programs.

Neurobiological strengths or weaknesses predictive of adolescent SUD outcomes may suggest tailored preventive interventions. Interventions have been found to improve social and emotional competence in elementary school youth, with prevention effects on behavioral outcomes partially mediated by skills in inhibitory control (Diamond & Lee, 2001; Riggs, Greenberg, Kusche, & Pentz, 2006; Riggs & Greenberg, 2009). The rationale for this approach may be supported by MRI findings. Furthermore, preventive interventions may have differential effects that vary with MRI measured neuromaturational deficits. For example, poorer neurocognitive skills and conduct disorder predicted less improvement in social competency skills in response to a prevention curriculum in young urban males (Fishbein et al., 2006). Future MRI research may indicate deficits or delays in cerebral maturation or functions that supplement phenotypic characteristics to predict responses to preventive interventions. Such findings could lead to the use of MRI methods to identify adolescents who require more intensive or qualitatively distinct preventive approaches.

Studies of the neurobiological effects of preventive interventions can be conducted with available methods. Psychosocial interventions have been demonstrated to change brain function with fMRI (Davidson et al., 2011; Linden, 2006), including cognitive behavior therapy for SUD (DeVito, et al., in press). Furthermore, preventive interventions may be devised to directly target neurobiological characteristics. Intensive training in psychomotor tasks (Bengtsson et al., 2005; Draganski et al., 2004; Scholtz et al, 2009) has been demonstrated to induce regionally specific increases in gray matter volume and white matter organization. Structural brain changes have also been shown to be induced by cognitive training (Draganski et al., 2006; Krafnick et al., 2011). Real-time fMRI neurofeedback has been examined as an intervention intended to train participants to directly control brain activation in areas involved in psychological dysregulation, specifically involving affective regulation and the frontolimbic network (Johnston et al., 2010).

The implications of the Substance Effects Model may also be relevant for SUD prevention science. To the extent that adolescent substance use adversely effects brain development, effective preventive interventions that delay or reduce adolescent substance use become more vital. Definitive studies on substance effects may also provide information that could be useful for prevention messages. The importance of effective SUD treatment would be reinforced by documentation of abstinence leading to recovery of normal brain function or structure. Results with MRI studies (e.g., Chung et al., in press) may suggest neurobiological mechanisms for contingency management interventions to facilitate substance abstinence in adolescents (e.g., Stanger, Budney, Kamon, & Thostensen, 2009). The observation that cannabis use reduces frontolimbic reactivity to emotional stimuli (Cornelius, et al., 2010) suggests that an alternative approach, such as the use of antidepressant medications, may

have specific benefits in individuals with fMRI amydalar hyper-responsivity (Thatcher et al., in press).

Conclusions

The promise of neuroimaging applications for SUD prevention science assumes that individual risk characteristics have a neurodevelopmental basis. While the value of neuroimaging methods for SUD prevention science has yet to be definitively demonstrated, neuroimaging methods are rapidly improving and advances in these methods applied to adolescent SUD prevention science may yield important insights. The integrative study of multimodal neuroimaging endophenotypes, genotypes, and behavioral phenotypes is particularly promising. Neuroimaging findings may soon have direct implications for individually tailoring adolescent SUD preventive interventions. In the forseeable future, the effects of preventive interventions may be substantiated by positive neurodevelopmental outcomes indicated by MRI measured structural and functional cerebral characteristics.

Acknowledgments

This research was supported by NIH [P50 DA05605, R21-AA-016272, K02-AA-00291, K01-DA-018698, R01-AA-13419, K02 AA018195, K01DA032557, R01 AA014357] and the Commonwealth of Pennsylvania [PA-HEAL SPH00010].

References

Ashtari M, Kumra S, Bhaskar SL, Clarke T, Thaden E, Cervellione KL, Ardekani BA. Attention deficit/hyperactivity disorder: A preliminary diffusion tensor imaging study. Biological Psychiatry. 2005; 57:448–455. [PubMed: 15737658]

Barros-Loscertales A, Meseguer V, Sanjuan A, Belloch V, Parcet MA, Torrubia R, Avila C. Behavioral inhibition system activity is associated with increased amygdala and hippocampal gray matter volume: A voxel-based morphometry study. Neuroimage. 2006; 33:1011–1015. [PubMed: 16979909]

Basser PJ, Pierpaoli C. Microstructural and physiological features of tissues elucidated by quantitative-diffusion-tensor MRI. Journal of Magnetic Resonance, Series B. 1996; 111:209–219. [PubMed: 8661285]

Batty MJ, Liddle EB, Pitiot A, Toro R, Groom MJ, Scerif G, Hollis C. Cortical gray matter in attention-deficit/hyperactivity disorder: A structural magnetic resonance imaging study. Journal of the American Academy of Child & Adolescent Psychiatry. 2010; 49:229–238. [PubMed: 20410712]

Bava S, Frank LR, McQueeny T, Schweinsburg BC, Schweinsburg AD, Tapert SF. Altered white matter microstructure in adolescent substance users. Psychiatry Research: Neuroimaging. 2009; 173:228–237.

Bengttson SL, Nagy Z, Skare S, Forsman L, Forssberg H, et al. Extensive piano practice has regionally specific effects on white matter development. Nature Neuroscience. 2005; 8:1148–1150.

Blakemore SJ, Choudhury S. Development of the adolescent brain: Implications for executive function and social cognition. Journal of Child Psychology and Psychiatry. 2006; 47:296–312. [PubMed: 16492261]

Bonekamp D, Nagae LM, Degaonkar M, Matson M, Abdalla W, Barker PB, Mori S, Horska A. Diffusion tensor imaging in children and adolescents: Reproducibility, hemispheric, and age-related differences. NeuroImage. 2007; 34:733–742. [PubMed: 17092743]

Brody GH, Beach SR, Philibert RA, Chen YF, Murry VM. Prevention effects moderate the association of 5-HTTLPR and youth risk behavior initiation: Gene x environment hypothesis tested via a randomized prevention design. Child Development. 2009; 80:645–661. [PubMed: 19489894]

Carlen PL, Wortzman G, Holgate RC, Wilkinson DA, Rankin JC. Reversible cerebral atrophy in recently abstinent chronic alcoholics measured by computed tomography scans. Science. 1978; 200:1076–1078. [PubMed: 653357]

Caspi A, Sugden K, Moffitt TE, Taylor A, Craig IW, Harrington H. Influence of life stress on depression: Moderation by a polymorphism in the 5-HTT gene. Science. 2003; 301:386–389. [PubMed: 12869766]

Castellanos FX, Lee PP, Sharp W, Jeffries NO, Greenstein DK, Clasen LS, Rapoport JL. Developmental trajectories of brain volume abnormalities in children and adolescents with attention-deficit/hyperactivity disorder. Journal of the American Medical Association. 2002; 288:1740–1748. [PubMed: 12365958]

Chung T, Geier C, Luna B, Pajtek S, Terwilliger R, Thatcher D, Clark DB. Enhancing response inhibition by incentive: Comparison of adolescents with and without substance use disorder. Drug and Alcohol Dependence. 2011; 115:43–50. [PubMed: 21115229]

Chung T, Pajtek S, Clark DB. White matter integrity as a link in the association between motivation to abstain and treatment outcome in adolescent substance users. Psychology of Addictive Behaviors. in press.

Clark DB, Chung T, Thatcher D, Pajtek S, Long E. Psychological dysregulation, white matter disorganization and substance use disorders in adolescence. Addiction. 2011; 107:206–214. [PubMed: 21752141]

Clark DB, Cornelius JR, Kirisci L, Tarter RE. Childhood risk categories for adolescent substance involvement: A general liability typology. Drug and Alcohol Dependence. 2005; 77:13–21. [PubMed: 15607837]

Clark DB, Cornelius JR, Wood DS, Vanyukov M. Psychopathology risk transmission in children of parents with substance use disorders. American Journal of Psychiatry. 2004; 161:685–691. [PubMed: 15056515]

Clark DB, Thatcher DL, Tapert SF. Alcohol, psychological dysregulation, and adolescent brain development. Alcoholism: Clinical and Experimental Research. 2008; 32:375–385.

Clark DB, Winters KC. Measuring risks and outcomes in substance use disorders prevention research. Journal of Consulting and Clinical Psychology. 2002; 70:1207–1223. [PubMed: 12472298]

Cornelius JR, Aizenstein HJ, Hariri AR. Amygdala reactivity if inversely related to level of cannabis use in individuals with comorbid cannabis dependence and major depression. Addictive Behaviors. 2010; 35:644–646. [PubMed: 20189314]

Covault J, Tennen H, Armeli S, Conner TS, Herman AI, Cillessen AHN, Kranzler HR. Interactive effects of the serotonin transporter 5-HTTLPR polymorphism and stressful life events on college student drinking and drug use. Biological Psychiatry. 2007; 61:609–616. [PubMed: 16920076]

David SP, Murthy NV, Rabiner EA, Mufano MR, Johnstone RJ, Jacob R, Grasby PM. A functional genetic variation of the serotonin (5-HT) transporter affects 5-HT1A receptor binding in humans. The Journal of Neuroscience. 2005; 25:2586–2590. [PubMed: 15758168]

Davidson RJ, Lutz A. Mental training as a tool in the scientific study of brain and cognitive plasticity. Frontiers in Human Neuroscience. 2011; 5:1–12. [PubMed: 21283556]

DeBellis MD, Clark DB, Beers SR, Soloff P, Boring AM, Hall J, Keshavan MS. Hippocampal volume in adolescent onset alcohol use disorders. The American Journal of Psychiatry. 2000; 157:737–744. [PubMed: 10784466]

DeBellis MD, Narasimhan A, Thatcher DL, Keshavan MS, Soloff P, Clark DB. Prefrontal cortex, thalamus and cerebellar volumes in adolesent onset alcohol use disorders. Alcoholism: Clinical and Experimental Research. 2005; 29:1590–1600.

DeBellis MD, Van Voorhees E, Hooper SR, Gibler N, Nelson L, Hege SG, MacFall J. Diffusion tensor measures of the corpus callosum in adolescents with adolescent onset alcohol use disorders. Alcoholism: Clinical and Experimental Research. 2008; 32:395–413.

De Schotten MT, Ffytche DH, Bizzi A, Dell'Acqua F, Allin M, Walshe M, Catani M. Atlasting location, asymmetry and inter-subject variability of white matter tracts in the human brain with MR diffusion tractography. NeuroImage. 2011; 54:49–59. [PubMed: 20682348]

Desikan RS, Segonne F, Fischl B, Quinn BT, Dickerson BC, Blacker D, Killiany RJ. An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. NeuroImage. 2006; 31:968–980. [PubMed: 16530430]

Devito EE, Worhunsky PD, Carroll KM, Rounsaville BJ, Kober H, Potenza MN. A preliminary study of the neural effects of behavioral therapy for substance use disorders. Drug and Alcohol Dependence. in press.

Diamond A, Lee K. Interventions shown to aid executive function development in children 4 to 12 years old. Science. 2011; 333:959–964. [PubMed: 21852486]

Draganski B, Gaser C, Busch V, Schuierer G, Bogdahn U, May A. Changes in grey matter induced by training. Nature. 2004; 427:311–312. [PubMed: 14737157]

Draganski B, Gaser C, Kempermann G, Kuhn HG, winkler J, Buchel A. Temporal and spatial dynamics of brain structure changes during extensive learning. Journal of Neuroscience. 2006; 26:6314–6317. [PubMed: 16763039]

Enoch MA, Gorodetsky E, Hodgkinson C, Roy A, Goldman D. Functional genetic variants that increase synaptic serotonin and 5-HT3 receptor sensitivity predict alcohol and drug dependence. Molecular Psychiatry. 2010; 16:1139–1146. [PubMed: 20838391]

Epstein JN, Casey BJ, Tonev ST, Davidson M, Reiss AL, Garrett A, Spicer J. Assessment and prevention of head motion during imaging of patients with attention deficit hyperactivity disorder. Psychiatry Research: Neuroimaging. 2007; 155:75–82.

Ersche KD, Jones PS, Williams GB, Turton AJ, Robbins TW, Bullmore ET. Abnormal brain structure implicated in stimulant drug addiction. Science. 2012; 335:601–604. [PubMed: 22301321]

Fassbender C, Simoes-Franklin C, Murphy K, Hester R, Meaney J, Robertson IH, Garavan H. The role of a right fronto-parietal network in cognitive control: Common activations for “cues-to-attend” and response inhibition. Journal of Psychophysiology. 2006; 20:286–296.

Feinn R, Nellissery M, Kranzler HR. Meta-analysis of the association of a functional serotonin transporter promoter polymorphism with alcohol dependence. American Journal of Medical Genetics Part B: Neuropsychiatric Genetics. 2005; 133:79–84.

Fishbein DH, Hyde C, Eldreth D, Paschall MJ, Hubal R, Das A, Yung B. Neurocognitive skills moderate urban male adolescents’ responses to preventive intervention materials. Drug and Alcohol Dependence. 2006; 82:47–60. [PubMed: 16154296]

Fortier E, Noreau A, Lepore F, Boivin M, Perusse D, Rouleau GA, Beauregard M. Early impact of 5-HTTLPR polymorphism on the neural correlates of sadness. Neuroscience Letters. 2010; 485:261–265. [PubMed: 20851164]

Gogtay N, Giedd JN, Lusk L, Hayashi KM, Greenstein D, Vaituzis AC, Thompson PM. Dynamic mapping of human cortical development during childhood through early adulthood. Proceedings of the National Academy of Sciences. 2004; 101:8174–8179.

Habeych ME, Folan MM, Luna B, Tarter RE. Impaired oculomotor response inhibition in children of alcoholics: The role of attention deficit hyperactivity disorder. Drug and Alcohol Dependence. 2006; 82:11–17. [PubMed: 16203110]

Hariri AR, Bookheimer SY, Mazziotta JC. Modulating emotional responses: Effects of a neocortical network on the limbic system. NeuroReport. 2000; 11:43–48. [PubMed: 10683827]

Hariri AR, Drabant EM, Munoz KE, Kolachana BS, Mattay VS, Egan MF, Weinberger MD. A susceptibility gene for affective disorders and the response of the human amygdala. Archives in General Psychiatry. 2005; 62:146–152.

Hariri AR, Holmes A. Genetics of emotional regulation: The role of the serotonin transporter in neural function. Trends in Cognitive Sciences. 2006; 10:182–191. [PubMed: 16530463]

Heitzeg MM, Nigg JT, Yau WY, Zubieta JK, Zucker RA. Affective circuitry and risk for alcoholism in late adolescence: Differences in frontostriatal responses between vulnerable and resilient children of alcoholic parents. Alcoholism: Clinical and Experimental Research. 2008; 32:414–426.

Heitzeg MM, Nigg JT, Yau WY, Zucker RA, Zubieta JK. Striatal dysfunction marks preexisting risk and medial prefrontal dysfunction is related to problem drinking in children of alcoholics. Biological Psychiatry. 2010; 68:287–295. [PubMed: 20416863]

Hoeft F, Barnea-Gorlay N, Haas BW, Golarai G, Ng D, Mills D, Korenberg J, Bellugi U, Galaburda A, Reiss AL. More is not always better: Increased fractional anisotrophy of superior longitudinal fasciculus associated with poor visuospatial abilities in Williams Syndrome. Journal of Neuroscience. 2007; 27:11960–11965. [PubMed: 17978036]

Huebner T, Vloet TD, Marx I, Konrad K, Fink GR, Herpertz SC, Herpertz-Dahlmann B. Morphometric brain abnormalities in boys with conduct disorder. Journal of the American Academy of Child & Adolescent Psychiatry. 2008; 47(5):540–547. [PubMed: 18356764]

Ioannidis JPA. Excess significance bias in the literature on brain volume abnormalities. Archives of General Psychiatry. 2011; 68:773–780. [PubMed: 21464342]

Johnston SJ, Boehm SG, Healy D, Goebel R, Linden DEJ. Neurofeedback: a promising tool for the self-regulation of emotion networks. NeuroImage. 2010; 49:1066–1072. [PubMed: 19646532]

Kaufmann J, Yang B, Douglas-Palumberi H, Houshyar S, Lipschitz D, Krystal JH. Social supports and serotonin transporter gene moderate depression in maltreated children. Proceedings of the National Academy of Sciences. 2004; 101:17316–17321.

Krafnick AJ, Flowers DL, Napoliello EM, Eden GF. Gray matter volume changes following reading intervention in dyslexic children. NeuroImage. 2011; 57:733–741. [PubMed: 21029785]

Lenroot RK, Giedd JN. Brain development in children and adolescents: Insights from anatomical magnetic resonance imaging. Neuroscience and Biobehavioral Reviews. 2006; 30:718–729. [PubMed: 16887188]

Li T, Mathews VP, Wang Y, Dunn D, Kronenberger W. Adolescents with disruptive behavior disorder investigated using an optimized MR diffusion tensor imaging protocol. Annals of the New York Academy of Sciences. 2005; 1064:184–192. [PubMed: 16394156]

Linden DEJ. How psychotherapy changes the brain- the contribution of functional neuroimaging. Molecular Psychiatry. 2006; 11:528–538. [PubMed: 16520823]

Logothetis NK. What we can do and what we cannot do with fMRI. Nature. 2008; 453:869–878. [PubMed: 18548064]

Lonsdorf TB, Golkar A, Lindstom KM, Fransson P, Schalling M, Ohman A, Ingvar M. 5-HTTLPR and COMTval158met genotype gate amygdala reactivity and habituation. Biological Psychology. 2011; 87:106–112. [PubMed: 21356267]

Lott DC, Kim SJ, Cook EH, de Wit H. Serotonin transporter genotype and acute subjective response to amphetamine. American Journal on Addictions. 2006; 15:327–335. [PubMed: 16966188]

Luna B, Garver KE, Urban TA, Lazar NA, Sweeney JA. Maturation of cognitive processes from late childhood to adulthood. Child Development. 2004; 75:1357–1372. [PubMed: 15369519]

McNamee R, Dunfee KL, Luna B, Clark DB, Eddy WF, Tarter RE. Brain activation, response inhibition and increased risk for substance use disorders. Alcoholism: Clinical and Experimental Research. 2008; 32:405–413.

McQueeny T, Schweinsburg BC, Schweinsburg AD, Jacobus J, Bava S, Frank LR, Tapert SF. Altered white matter integrity in adolescent binge drinkers. Alcoholism: Clinical and Experimental Research. 2009; 33:1278–1285.

Medina KL, Nagel BJ, Park A, McQueeny T, Tapert SF. Depressive symptoms in adolescents: Associations with white matter volume and marijuana use. Journal of Child Psychology and Psychiatry. 2007; 48:592–600. [PubMed: 17537075]

Moss HB, Talagala SL, Kirisci L. Phosphorus-31 magnetic resonance brain spectroscopy of children at risk for a subtance use disorder: Preliminary results. Psychiatry Research: Neuroimaging. 1997; 76:101–112.

Nagel BJ, Bathula D, Herting M, Schmitt C, Kroenke CD, Fair D, Nigg JT. Altered white matter microstructure in children with attention-deficit/hyperactivity disorder. Journal of the American Academy of Child & Adolescent Psychiatry. 2011; 50:283–292. [PubMed: 21334568]

Nagel BJ, Schweinsburg AD, Phan V, Tapert SF. Reduced hippocampal volume among adolescents with alcohol use disorders without psychiatric comorbidity. Psychiatry Research. 2005; 139:181–190. [PubMed: 16054344]

Norman AL, Pulido C, Squeglia LM, Spadoni AD, Paulus MP, Tapert SF. Neural activation during inhibition predicts initation of substance use in adolescence. Drug and Alcohol Dependence. 2011; 119:216–223. [PubMed: 21782354]

Ogawa S, Lee TM, Kay AR, Tank DW. Brain magnetic resonance imaging with contrast dependent on blood oxygenation. Proceedings of the National Academy of Sciences. 1990; 87:9868–9872.

Olesen PJ, Nagy Z, Westerberg H, Klingberg T. Combined analysis of DTI and fMRI data reveals a joint maturation of white and grey matter in a fronto-parietal network. Cognitive Brain Research. 2003; 18:48–57. [PubMed: 14659496]

Paus T. Growth of white matter in the adolescent brain: Myelin or axon? Brain and Cognition. 2010a; 72:26–35. [PubMed: 19595493]

Paus T. Population neuroscience: Why and how. Human Brain Mapping. 2010b; 31:891–903. [PubMed: 20496380]

Pezawas L, Meyer-Lindenberg A, Drabant EM, Verchinski BA, Munoz KE, Kolachana BS, Weinberger DR. 5-HTTLPR polymorphism impacts human cingulate-amygdala interactions: A genetic susceptibility mechanism for depression. Nature Neuroscience. 2005; 8:828–834.

Riggs NR, Greenberg MT. Neurocognition as a moderator and mediator in adolescent substance misuse prevention. The American Journal of Drug and Alcohol Abuse. 2009; 35:209–213. [PubMed: 20180672]

Riggs NR, Greenberg MT, Kusche CA, Pentz MA. The mediational role of neuroimaging in the behavioral outcomes of a social-emotional prevention program in elementary school students: Effects of the PATHS curriculum. Prevention Science. 2006; 7:91–102. [PubMed: 16572300]

Scholz J, Klein MC, Behrens TE, Johansen-Berg H. Training induces changes in white matter architecture. Nature Neuroscience. 2009; 12:1370–1371.

Schumann G, Loth E, Banaschewski T, Barbot A, Barker G, Buchel C, Struve M. The IMAGEN Study: Reinforcement-related behavior in normal brain function and psychopathology. Molecular Psychiatry. 2010; 15:1128–1139. [PubMed: 21102431]

Shaw P, Gilliam M, Liverpool M, Weddle C, Malek M, Sharp W, Giedd J. Cortical development in typically developing children with symptoms of hyperactivity and impulsivity: Support for a dimensional view of attention deficit hyperactivity disorder. The American Journal of Psychiatry. 2011; 168:143–151. [PubMed: 21159727]

Spear LP. The adolescent brain and age-related behavioral manifestations. Neuroscience and Biobehavioral Reviews. 2000; 24:417–463. [PubMed: 10817843]

Stanger C, Budney AJ, Kamon JL, Thostensen J. A randomized trial of contingency management for adolescent marijuana abuse and dependence. Drug Alcohol Dependence. 2009; 105:240–247.

Stein MB, Campbell-Sills L, Gelernter J. Genetic variation in 5HTTLPR is associated with emotional resilience. American Journal of Medical Genetics Part B: Neuropsychiatric Genetics. 2009; 150B: 900–906.

Tarter RE, Kirisci L, Mezzich A, Cornelius J, Pajer K, Vanyukov M, Clark DB. Neurobehavioral disinhibition in childhood predicts early age onset substance use disorder. The American Journal of Psychiatry. 2003; 160:1078–1085. [PubMed: 12777265]

Teipel SJ, Bokde A, Meindl T, Amaro E, Soldner J, Reiser MF, Hampel H. White matter microstructure underlying default mode network connectivity in the human brain. Neuroimage. 2010; 49:2021–2032. [PubMed: 19878723]

Thatcher DL, Pajtek S, Chung T, Terwilliger RA, Clark DB. Gender differences in the relationship between white matter organization and adolescent substance use disorders. Drug and Alcohol Dependence. 2010; 110:55–61. [PubMed: 20392574]

Thatcher DL, Pajtek S, Tarter R, Long EC, Clark DB. Amygdala activation and emotional processing in adolescents at risk for substance use disorders. Journal of Child and Adolescent Substance Abuse. in press.

Thomason ME, Thompson PM. Diffusion imaging, white matter, and psychopathology. Annual Review of Clinical Psychology. 2011; 7:63–85.

Vanyukov MM, Kirisci L, Tarter RE, Ridenour TA, Reynolds MD, Maher B, et al. Measurement of the risk for substance use disorders: Phenotypic and genetic analysis of an index of common liability. Behavior Genetics. 2009; 39:233–244. [PubMed: 19377872]

Viding E, Williamson DE, Hariri AR. Developmental imaging genetics: Challenges and promised for translational research. Development and Psychopathology. 2006; 18:877–892. [PubMed: 17152405]

Wetherill RR, Bava S, Thompson WK, Boucquey V, Pulido C, Yang TT, Tapert SF. Frontoparietal connectivity in substance-naïve youth with and without a family history of alcoholism. Brain Research. 2012; 1432:66–73. [PubMed: 22138427]

Yang P, Wu M, Dung S, Ko C. Short-TE proton magnetic resonance spectroscopy investigation in adolescents with attention-deficit hyperactivity disorder. Psychiatry Research: Neuroimaging. 2010; 181:199–203.