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Neurocognition and Social Cognition in Adolescent Drug Users: Vulnerability and Consequences

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Summary

The onset of substance use coincides with a critical maturation period of the neural substrates that are affected by alcohol and other drugs of abuse. Behaviourally, adolescents exhibit distinct patterns of risk-taking. Moreover, neuroimaging studies have shown that these individuals, when compared to adults, engage different neural systems when processing rewards and punishments. Therefore, a better understanding of the behavioural and neural systems processes during adolescence is very important for the design of effective intervention programming. This review highlights the characteristics of alcohol and other drug use disorders during adolescence and shows examples of behavioural and neural substrate response patterns revealing differential processing of cue-related stimuli and risk-taking behaviour. Recent studies are reviewed, showing that heavy drinking during adolescence is associated with reduced hippocampal volume, disturbed white matter integrity, and abnormal brain response during cognitive tasks, while heavy cannabis use during adolescence is linked to abnormal brain response during cognitive tasks as well as poorer learning and attention performance. We propose that certain individuals may be at a higher risk for substance problems because of a mixture of pre-existing conditions and increased vulnerability to the effects of alcohol or other drugs of abuse. In particular, youth deploying more processing resources to reward-related stimuli and not taking into account risk-related outcomes may be vulnerable to adverse behavioural consequences. Support for this proposition would provide a rational basis for the development of new intervention programmes.

1. Adolescence, drug use and the brain

Individuals often initiate the use of substances during a time when the brain is undergoing a critical maturation period. Moreover, these substances can have profound effects on neural substrates that are important for cognition and emotion. For example, adolescents exhibit distinct patterns of risk-taking behaviour, weighing rewards and potential punishments differently than adults, and neuroimaging studies have shown that these individuals, compared to adults, engage different neural systems when processing rewards and punishments. Therefore, to develop better intervention programmes, we need a thorough understanding of how brains of adolescents process these and other behaviours.

This review highlights the characteristics of alcohol and other drug use disorders during adolescence and shows examples of behavioural and neural substrate response patterns revealing differential processing of cue-related stimuli and risk-taking behaviour. We propose that certain individuals may be at a higher risk for substance problems because of a mixture of pre-existing conditions and increased vulnerability to the effects of alcohol or other drugs of abuse. In particular, young people deploying more processing resources to reward-related stimuli and not taking into account risk-related outcomes may be vulnerable to adverse behavioural consequences. Although the majority of existing studies are cross-sectional by design, support for this proposition can serve as a starting point for the development of new intervention programmes.

2. Prevalence

Alcohol and other drug use are quite common in the UK. Alcohol use is particularly high among youth in the UK, with 91% of 15-16-year-olds reporting past year drinking (Hibell et al., 2004), and more significantly, 68% reported past-year drunkenness in the UK. These rates have held steady since 1995.

Regarding cannabis use, 38% of UK 15-16-year-olds have used it at least once. Other drugs are used by 9% of UK adolescents, with most of the other drugs being inhalants (12%), and ecstasy (5%). A concerning pattern is that 7% report use of alcohol and pills in combination.

3. Normal adolescent brain development

During this period of increasing risk for exposure to intoxicating compounds, the brain remains in an active state of development. Two key processes continue into adolescence which render the brain more efficient: (1) synaptic refinement; and (2) myelination (Yakovlev and Lecours, 1967). Synaptic refinement refers to the elimination of neural connectivity that occurs after the peak number of synaptic connections are attained at around age 9-11 (Shaw et al., 2006). This sculpting of connections between brain cells yields more economical neural activity. Although overall brain size changes little beyond early school-age (Giedd, 2004), grey matter volume begins to decrease around puberty, largely due to synaptic refinement (Huttenlocher, 1990) in subcortical and frontal regions (Sowell et al., 1999), ending with the dorsolateral prefrontal cortex (Gogtay et al., 2004), which is a key brain region for planning, organisation, emotional regulation, response inhibition, and decision-making. Volume increases in the cerebellum, a key brain region for motor coordination and attention (Keller et al., 2003), and hippocampus, a critical structure for encoding new information (Jernigan and Gamst, 2005), and decreases in the thalamus (sensory integration) and nucleus accumbens (reward) continue into young adulthood, concurrent with continuing myelination of the underlying white matter in this region (Jernigan and Gamst, 2005).

Myelination refers to the axons of brain cells becoming coated in a fatty substance called myelin, which results in the electrical signals along the axon shaft transmitting more rapidly. This process causes the size (or volume) of white matter in the brain to increase until at least the second decade of life (Jernigan and Gamst, 2005) due to progressive myelination of neuronal axons (Paus et al., 1999), and white matter integrity improves in subcortical regions between childhood and young adulthood (Snook et al., 2005). Brain activity during mental tasks matures through adolescence, demonstrated by diminishing reliance on frontal regions and the increased use of specialised networks (Luna and Sweeney, 2004). This continuing neuromaturation is also associated with changes in emotional regulation, reward sensitivity (Chambers et al., 2003), working memory (Luna et al., 2004), and other executive functions, which may have important implications for susceptibility to substance use disorders.

Reward is composed of a feeling and an action. Components of reward include the hedonic aspects, i.e. the degree to which a stimulus is associated with pleasure, and the incentive motivational aspects, i.e. the degree to which a stimulus induces an action towards obtaining it. Several studies indicate that adolescents process reward differently than children or adults (Bjork et al., 2007; Galvan et al., 2006; Galvan et al., 2007). In these studies, increased activity in the nucleus accumbens is seen across development, but is exaggerated in adolescents as compared to children and adults (Ernst et al., 2005, Galvan et al., 2006), while ventromedial frontal activation during reward-risk conflict appears underactive in adolescents as compared to adults (Bjork et al., 2007). Children's accumbens response to reward is linked to anticipating negative consequences. In comparison, adults' accumbens response is mainly associated with anticipating positive consequences. Finally, adolescents' nucleus accumbens activity relates to the anticipation of both negative and positive consequences, which is linked to the degree of risk-related behaviour. For example, teenagers who anticipate positive consequences of risk behaviours show greater accumbens activity during reward, and greater involvement with risky behaviours, while adolescents expecting negative outcomes show less reward-related accumbens response and fewer risk behaviours (Galvan et al., 2007).

This shift in the anticipation of outcomes may help explain why some adolescents gravitate toward risky behaviours such as substance use, as immediate positive outcomes (e.g. peer approval) may outweigh potential long-term negative consequences (Galvan et al., 2007). Taken together, people prone to risky behaviour are particularly vulnerable during the adolescent period, when neural systems underlying risky behaviours (e.g. Galvan et al., 2005) incur significant neuromaturation (Galvan et al., 2006).

4. Influence of adolescent alcohol use on the brain

Chronic heavy drinking (that is, drinking four or more drinks on an occasion for females, and five or more drinks on an occasion for males, on a repeated basis for many years) is associated with adverse effects on the brain (Oscar-Berman and Marinkovic, 2003), and recent research suggests that heavy drinking (drinking four or more drinks on an occasion for females, and five or more drinks on an occasion for males on a repeated basis, but not necessarily for many years) may affect brain functioning as soon as early adolescence (Tapert et al., 2004b; Brown et al., 2000). In most countries, alcohol is the most widely used, psychoactive substance among youth, and young people tend to consume alcohol to the point of intoxication. Recent animal and human studies have shown that adolescence may be a period of heightened brain vulnerability for alcohol effects (Spear and Varlinskaya, 2005).

Brain structure. Magnetic resonance imaging (MRI) studies in heavy-drinking adolescents have revealed brain structure abnormalities, including smaller volumes of the hippocampus (Nagel et al., 2005; De Bellis et al., 2000; Medina et al., 2007) and prefrontal cortex (De Bellis et al., 2005) in adolescents with alcohol use disorders (i.e. very heavy drinking characterised by life problems) than age-matched non-drinkers. Diffusion tensor imaging has indicated poorer integrity of the corpus callosum among heavy drinkers (Tapert et al., 2003b). As the hippocampus is expected to increase in volume and white matter integrity to improve during adolescence, these results emphasise the possibility that heavy drinking might alter neurodevelopment.

Brain function. Functional MRI (fMRI) examines brain activity by detecting changes in the amount of oxygen in the blood, indicating neural activity in response to completing a mental task or viewing stimuli (Logothetis et al., 2001). Blood oxygen level dependent fMRI studies suggest abnormal brain response during spatial working memory (Tapert et al., 2004b) in 14- to 17-year-old heavy drinkers as compared to non-drinkers despite intact task performance, suggesting reorganisation and compensation for subtle neuronal injury. Young adult women with adolescent onset of heavy drinking demonstrated impaired performance as well as reduced blood oxygen levels in parietal and frontal brain regions in response to the same working memory task (Tapert et al., 2001).

In combination, these studies indicate that, if heavy drinking continues throughout adolescence, the brain may eventually not be able to compensate due to subtle neuronal damage, and task performance may begin to deteriorate. Some effects are more pronounced in females (Caldwell et al., 2005) and seen in youth consuming as little as five drinks per occasion, six to eight times per month (Tapert et al., 2004b). fMRI has also revealed that adolescent heavy drinkers show greatly enhanced response to alcohol cues in attention and reward-related brain regions (Tapert et al., 2003a).

Cognitive functioning. Neuropsychological test performance can be used to relate brain impairments to day-to-day functioning based on dysfunctions of memory, attention, visuospatial skills, language, and executive functioning (e.g. planning, abstract reasoning, and goal-directed behaviour).

Heavy alcohol use in adolescents appears to be associated with poorer scores on tests of information retrieval (Brown et al., 2000), attention (Tapert and Brown, 1999; Tapert et al., 2002; Tapert and Brown, 2000), and visuospatial functioning (Tapert and Brown, 1999; Tapert et al., 2002). Further, heavy drinking followed by a hangover or withdrawal symptoms is associated with decreases in performance over time (Tapert and Brown, 1999; Tapert et al., 2002). Thus, heavy drinking during adolescence may be associated with decrements in cognitive performance and brain health, perhaps suggesting that the adolescent brain is vulnerable due to ongoing neuromaturation.

However, longitudinal studies are critical to elucidate the extent to which abnormalities pre-date the onset of regular substance use. For adolescents, harmful neurocognitive effects of heavy drinking appear to persist even after extended periods of reduced or halted use (Tapert et al., 2002; Tapert and Brown, 2000; Brown et al., 2000).

Moderating factors. Although heavy drinking during adolescence appears to impair brain functioning, not all young people who drink heavily or become alcohol dependent will experience the same level of impairment. Female adolescents appear more vulnerable to deleterious effects of heavy drinking on brain function than males (Caldwell et al., 2005), and personal alcohol use may interact with family history of alcoholism in predicting neural abnormalities (Tapert and Brown, 2000; Tapert et al., 2003a).

Youth at risk for alcohol use disorders due to a low level of response to alcohol show increased activation to a visual working memory task (Tapert et al., 2004a). Adolescents at risk for alcohol problems due to positive alcohol expectancies have decreased activation to an inhibition task (Anderson et al., 2005), paralleling the inhibition response patterns observed in youths with family histories of alcoholism.

Summary. Heavy drinking during adolescence is associated with subtle yet consequential effects on brain development, functioning, and performance. The abnormalities include reduced hippocampal volume, disturbed white matter integrity, and abnormal brain response during tasks requiring working memory. These aberrancies may represent subtle early harm to neurons and other brain constituents from the neurotoxic effects of alcohol. Longitudinal studies are necessary to confirm these impressions.

Even though the research on alcohol's effects in adolescence and young adulthood is still in its early stages, one message is clear: young people can help maximise their neurocognitive potential by refraining from heavy drinking.

5.Influence of adolescent cannabis use on the brain

Brain structure. Some brain areas developing during adolescence have high densities of cannabinoid receptors (Iversen, 2003), such as frontal and hippocampal regions. Although no studies to date have examined structural brain changes associated with cannabis use in human adolescents (Verdejo Garcia et al., 2004), animal studies suggest that cannabinoid exposure prior to adulthood is associated with lasting abnormalities in behaviour (Stiglick and Kalant, 1985) and hippocampal structure (Landfield et al., 1988). Adults who used cannabis before age 17 show smaller grey matter and larger white matter volumes, suggesting abnormal progression of normal adolescent neuromaturation compared to later-onset users (Wilson et al., 2000).

Brain function. Chronic cannabis-using adults exhibit an altered electrophysiological brain response (Solowij et al., 1995), reduced cerebellar response and frontal blood flow (Lundqvist et al., 2001; Block et al., 2000), and increased brain response during spatial working memory (Kanayama et al., 2004). The degree of abnormality appears related to adolescent cannabis use because early-onset (<17) users show greater brain blood flow (Wilson et al., 2000), attenuated electrophysiological response during selective attention (Kempel et al., 2003), smaller frontal and parietal volumes (Wilson et al., 2000), and increased cerebral blood flow (Wilson et al., 2000) than late-onset (≥17) users. Several recent studies in adolescent cannabis users have suggested abnormal brain response patterns, despite the common perception of this drug as relatively harmless (Johnston et al., 2006). For example, on an inhibition task, adolescent cannabis users with a month of verified abstinence showed more fMRI response than non-users in dorsolateral prefrontal, parietal, and occipital regions, despite equivalent task performance levels, suggesting increased brain processing effort (Tapert et al., 2007).

Adolescent cannabis users often use alcohol or nicotine. Adolescents with both cannabis and alcohol use disorders performed as well as youths with only an alcohol use disorder and non-using controls. However, teenagers with comorbid alcohol and cannabis use disorders had increased dorsolateral prefrontal fMRI response than others, which is consistent with the idea that these individuals need to expend an increased neural or computational effort to show appropriate levels of performance (Schweinsburg et al., 2005). Aberrant activation patterns were observed even after a month of abstinence (Schweinsburg et al., 2008).

Adolescent users of cannabis and nicotine performed less accurately on a working memory task than nicotine-only users and non-using controls, but showed greater fMRI response in the right hippocampus relative to other groups. This suggests that adolescent cannabis users might fail to inhibit hippocampal activity, perhaps due to changes in inhibitory neurotransmission (Jacobsen et al., 2004b). During nicotine withdrawal, cannabis-using adolescents showed poorer verbal recall, increased posterior activation, and disrupted frontoparietal connectivity than non-cannabis users, further suggesting that adolescent cannabis use may disrupt memory-related substrates (Jacobsen et al., 2007). Together, these studies suggest some neural dysfunction among adolescent cannabis users.

Cognitive functioning. Neuropsychological studies of heavy cannabis-using adults have found deficits (Pope and Yurgelun-Todd, 1996; Solowij et al., 2002; Bolla et al., 2002), although most resolve within a month of abstinence (Pope et al., 2001). Few studies have examined cognitive functioning in cannabis-using adolescents. Over an eight-year period, from ages 16 to 24 on average, greater cannabis use predicted poorer follow-up attention functioning (Tapert et al., 2002), and short-term memory decrements show evidence of persisting after six weeks of abstinence (Schwartz et al., 1989).

However, some studies report no correlations between cannabis use and cognition (Teichner et al., 2000), and some abnormalities may predate use (Aytaclar et al., 1999). Among adults, early onset (<17) cannabis users, relative to late onset (≥17) users, performed slower (Ehrenreich et al., 1999) on a visual scanning task on which performance typically matures during adolescence (Kunert et al., 1996), and had lower vocabulary scores, suggesting disadvantaged innate factors or education in early-onset users (Pope et al., 2003).

Summary. Heavy cannabis use during adolescence may adversely affect frontal and hippocampal development. The few studies that have examined cognitive functioning in cannabis-using adolescents report decrements in attention (Tapert et al., 2002), and learning and memory (Millsaps et al., 1994; Schwartz et al., 1989).

6. Influence of other drug use on the adolescent brain

Ecstasy. Methylenedioxymethamphetamine (MDMA, known as 'ecstasy') is a synthetic, psychoactive drug with stimulant and mild hallucinogenic properties. Its influence on the developing adolescent brain has not been clearly assessed, but existing data suggest slowed reaction times during attention tests and abnormal hippocampal functioning (Jacobsen et al., 2004a). In young adults, increased volume of striatal structures (Reneman et al., 2001b), neuroinflammation (Chang et al., 1999), decreased frontal neuronal viability (Reneman et al., 2002b), and abnormal serotonergic function (McCann et al., 2005; Reneman et al., 2001a; Semple et al., 1999) and dopaminergic (Reneman et al., 2002a) markers have been found. Neurobehavioural abnormalities include problems with verbal learning and memory, mental processing speed, impulsivity, depression and anxiety, and aggression (Halpern et al., 2004; McCann et al., 2005; Morgan, 2000; Medina et al., 2005). Some effects, though, may related to other substance use and pre-existing factors (Lyvers and Hasking, 2004).

Stimulants. As with ecstasy, few studies have examined the effects of adolescent methamphetamine and cocaine use on brain functioning. Cocaine (Jacobsen et al., 2001) and methamphetamine (Jernigan et al., 2005) users have shown larger volumes of subcortical structures than non-users, but also smaller cortical and limbic (Bartzokis et al., 2000; Franklin et al., 2002) as well as white matter volumes (Thompson et al., 2004). Methamphetamine users also showed widespread, persistent abnormalities consistent with neurotoxicity and neuroinflammation in basal ganglia and frontal white matter (Ernst et al., 2000). Stimulant-dependent adults consistently show depletion of striatal dopamine transporters (Volkow et al., 2001a; Volkow et al., 2001b; Sekine et al., 2001), which corresponds to the degree of psychomotor and memory impairment and psychiatric symptomatology.

Serotonin transporter binding in abstinent methamphetamine users (Sekine et al., 2006) has revealed widespread reductions throughout the brain, correlated with elevated aggressiveness. Neurocognitive deficits have been reported on tasks of learning, working memory, set shifting, and inhibition (Salo et al., 2002; McKetin and Mattick, 1998; Nordahl et al., 2003), consistent with dopamine depletion (Rogers et al., 1999; Baunez and Robbins, 1999) and serotonergic involvement (Harrison et al., 1997).

Individuals who use stimulants (but who are not dependent) select risky responses more frequently than comparison subjects but also select risky choices less often after punishment. This risk-taking behaviour correlates with measures of sensation-seeking and impulsivity, but not with other personality measures, anxiety, or tendency to use alcohol (Leland and Paulus, 2005). In these individuals, an increase in caudate nucleus activation during a simple decision-making paradigm aimed to determine the influence of outcome uncertainty is correlated with impulsivity (Leland et al., 2006). A longitudinal investigation (Tapert et al., 2002) of substance-dependent youth suggested that more frequent adolescent stimulant use was associated with poorer attention, speeded psychomotor processing, and working memory in young adulthood.

Other substances. Heavy nicotine use in adolescence has been associated with some neural abnormalities (Jacobsen et al., 2005; Jacobsen et al., 2004b) and increased risk-taking propensity (Lejuez et al., 2003), as measured by the Balloon Analogue Risk Task (Lejuez et al., 2002). In evaluations of polysubstance use in young adults, neuropsychological deficits were most strongly related to the heavy use of four or more drugs, particularly when this included excess use of prescription drugs in addition to heavy alcohol use (Grant et al., 1978).

7. Factors conveying vulnerability to adolescent substance problems

Youths with mood problems are at risk for substance use and related problems. In the Munich Epidemiological study (Wittchen et al., 1992), about 22% of subjects who reported substance use also had a mood disorder, with one third of these individuals reporting that their mood disorder occurred prior to substance use. Similarly, of the 20% of substance users found to have an anxiety disorder, 60% had the anxiety disorder prior to substance use. Thus, it is not surprising that the concept of 'negative emotionality' has been invoked as a risk factor for problems with substances, and has found empirical support by some (Kilbey et al., 1992; Sher et al., 2000) but not others (Teichman et al., 1989). Several studies have shown an increased association between drug abuse or dependence and anxiety disorders (Merikangas et al., 1998), and individuals with substance use disorders have significantly elevated anxiety and anger scores (Walfish et al., 1990). Others have observed a significant familial aggregation of anxiety and substance use disorders (Kendler et al., 1997). Conduct disorder more than doubles the risk for early substance use (Sartor et al., 2007), which in turn is linked to increased lifetime risk of substance use disorder (Grant and Dawson, 1997).

While some personality features, such as disinhibition, have been linked to risk of substance use disorder (Sher and Trull, 1994), others have been more elusive. Paulus and colleagues examined whether personality and coping styles of young adults who have used stimulants differ from those who have not. Young adults with lifetime use of cocaine, amphetamine, methamphetamine, non-prescribed methylphenidate, or ecstasy at least once were compared to subjects without such histories. Stimulant users were more disinhibited, neurotic, anxious, and depressed, less resilient, and exhibited a more emotion-oriented coping style. Because levels of drug use were low, differences are not likely a result of stimulant exposure. Therefore, stimulant use may initially occur in the context of mild psychiatric symptoms characterised by increased levels of negative emotionality.

The observation that young substance users show increased neuroticism is consistent with other studies of adolescents (Anderson et al., 2007). Conceptually, the impulsiveness facet of neuroticism relates to under-control of behaviour, consistent with the notion of committing rash or regrettable actions as a result of intense negative affect (d'Acremont and Van der Linden, 2007). Adolescent substance users score high on novelty seeking, yet low on harm avoidance, reward dependence, agreeableness, and conscientiousness traits (Anderson et al., 2007; Wills et al., 1994). Increased substance use has been observed in adolescents with high sensation-seeking scores (Andrucci et al., 1989), and increased behavioural disinhibition has been associated with higher rates of substance abuse or dependence (McGue et al., 1999; Conway et al., 2003). However, the transition from occasional use to abuse or dependence cannot solely be explained by genetic or shared environmental factors. It may arise from the effects of the peer and social context within which the drug is used (Lynskey et al., 2003). For example, individuals growing up in substance-using families scored higher on neuroticism and had a higher rate of suicidality (O'Connor et al., 1995).

8. Implications

Neuroimaging and neuropsychological studies indicate that adolescent substance use is associated with neural disadvantages, particularly in the realms of learning, attention, and executive function. Evidence from human and animal research suggests that adolescence is a period of particular vulnerability to adverse effects of alcohol and other drugs on the brain, likely due to ongoing neuromaturation.

In addition to familial risk, young people with affective disturbance, conduct problems, and neurotic or disinhibited personalities appear at risk for escalating substance use once initiated. These features appear compounded by macro and micro social contexts that are permissive of substance use and minimise negative consequences of risky behaviours. While it is clear that well-developed executive functioning is a protective factor that may be affected by substance use, and peer contexts are highly related to risk-taking activities, very few studies have examined the neural substrates of adolescent social cognition.

Fruitful preventions and intervention programmes for adolescent substance use may need to address the key factors associated with an increased risk for substance problems, such as treating pre-existing anxiety and depressive disorders, and perhaps even subsyndromal presentations of these disorders (Judd et al., 1998). Future studies will need to link these symptom differences to genetic features on the one hand and behavioural or neural substrate differences on the other to better understand what puts youth at risk for substance use.

Further studies are needed to: examine neural, familial, and social factors that predict escalation and de-escalation of substance use and related problems; identify resiliency traits that can be accentuated by interventions; and determine risky populations and contexts at greatest need of interventions and policy change. For example, at-risk youth may require safer settings for meeting peers, thereby deriving the appropriate level of sensation and stimulation, increasing autonomy, and setting personal goals.

9. Conclusions

Ongoing neuromaturational processes during adolescence, such as synaptic refinement and myelination, may heighten the risk for substance-related alterations.

Exposure to alcohol, cannabis, ecstasy, and stimulants during adolescent neurodevelopment has been linked to a variety of structural and functional insults to the brain. Heavy alcohol use has been associated with loss of brain volume, disruption of white matter, disturbances in blood oxygen levels in response to cognitive tasks, and impairment in visuospatial, information retrieval, and attentional tasks. Studies on cannabis use during adolescence found alterations of grey and white matter volumes, abnormal electrophysiological and neural response, and deficits in attention and learning. Abnormalities in serotonin delivery systems, verbal learning/memory, and impulsivity suggest neurotoxic effects associated with ecstasy use. Stimulants, although not yet widely researched in youthful populations, are also associated with a range of abnormalities, such as changes in brain structure, disrupted neurotransmission, and poorer neurocognitive performance.

The characteristics of adolescents using these substances vary tremendously. Consuming alcohol or other drugs to an extent that hangover or withdrawal symptoms are perceived after acute effects suggests a level of intake potentially sufficient to produce a neural insult. Factors that may moderate the amount necessary to experience such changes include gender, family history, or psychiatric status.

The findings and conclusions discussed here are largely derived from cross-sectional research. Longitudinal studies are necessary to better clarify the neural impact of substance use during adolescence.

In the interim, evidence suggests that successful attainment of important neural refinements and cognitive milestones may be derailed by heavy use of psychoactive substances during adolescence. Certain individuals may be at a higher risk for substance problems because of a mixture of pre-existing conditions and increased vulnerability to the effects of alcohol or other drugs of abuse. In particular, those youngsters deploying more processing resources to reward-related stimuli and not taking into account risk-related outcomes may be vulnerable to adverse behavioural consequences.

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References

Anderson, K.G., Schweinsburg, A.D., Paulus, M.P., Brown, S.A. and Tapert, S.F. 2005. Examining personality and alcohol expectancies using fMRI with adolescents. *Journal of Studies on Alcohol,* 66:323-331.

Anderson, K.G., Tapert, S.F., Moadab, I., Crowley, T.J. and Brown, S.A. 2007.) Personality risk profile for conduct disorder and substance use disorders in youth. *Addictive Behaviors,* 32:2377-2382.

Andrucci, G.L., Archer, R.P., Pancoast, D.L. and Gordon, R.A. 1989). The relationship of MMPI and Sensation Seeking Scales to adolescent drug use. *Journal of Personaility Assessment,* 53:253-66.

Aytaclar, S., Tarter, R.E., Kirisci, L. and Lu, S. 1999. Association between hyperactivity and executive cognitive functioning in childhood and substance use in early adolescence. *Journal of the American Academy of Child & Adolescent Psychiatry,* 38:172-178.

Bartzokis, G., Beckson, M., Lu, P.H., Edwards, N., Rapoport, R., Wiseman, E. and Bridge, P. 2000.) Age-related brain volume reductions in amphetamine and cocaine addicts and normal controls: implications for addiction research. *Psychiatry Research,* 98:93-102.

Baunez, C. and Robbins, T.W. 1999. Effects of dopamine depletion of the dorsal striatum and further interaction with subthalamic nucleus lesions in an attentional task in the rat. *Neuroscience,* 92:1343-56.

Bjork, J.M., Smith, A.R., Danube, C.L. and Hommer, D.W W. 2007. Developmental differences in posterior mesofrontal cortex recruitment by risky rewards. *Journal of Neuroscience,* 27:4839-49.

Block, R.I., O'Lleary, D.S., Hichwa, R.D., Augustinack, J.C., Ponto, L.L., Ghoneim, M.M., Arndt, S., Ehrhardt, J.C., Hurtig, R.R., Watkins, G.L., Hall, J. A., Nathan, P.E. and Andreasen, N.C. 2000. Cerebellar hypoactivity in frequent marijuana users. *Neuroreport,* 11:749-53.

Bolla, K.I., Brown, K., Eldreth, D., Tate, K. and Cadet, J.L. 2002. Dose-related neurocognitive effects of marijuana use. *Neurology,* 59:1337-43.

Brown, S. A., Tapert, S.F., Granholm, E. and Delis, D.C. 2000. Neurocognitive functioning of adolescents: Effects of protracted alcohol use. *Alcoholism: Clinical and Experimental Research,* 24:164-71.

Caldwell, L.C., Schweinsburg, A.D., Nagel, B.J., Barlett, V.C., Brown, S. A. and Tapert, S.F. 2005. Gender and adolescent alcohol use disorders on BOLD (blood oxygen level dependent) response to spatial working memory. *Alcohol and Alcoholism,* 40:194-200.

Chambers, R. A., Taylor, J.R. and Potenza, M.N. 2003. Developmental neurocircuitry of motivation in adolescence: a critical period of addiction vulnerability. *American Journal of Psychiatry,* 160:1041-52.

Chang, L., Ernst, T., Grob, C.S. and Poland, R.E. 1999. Cerebral (1)H MRS alterations in recreational 3, 4-methylenedioxymethamphetamine (MDMA, "ecstasy") users. *Journal of Magnetic Resonance Imaging,* 10:521-6.

Conway, K.P., Kane, R.J., Ball, S. A., Poling, J.C. and Rounsaville, B.J. 2003. Personality, substance of choice, and polysubstance involvement among substance dependent patients. *Drug and Alcohol Dependence,* 71:65-75.

d'Acremont, M. and Van Der Linden, M. 2007. How is impulsivity related to depression in adolescence? Evidence from a French validation of the cognitive emotion regulation questionnaire. *Journal of Adolescence,* 30:271-82.

De Bellis, M.D., Clark, D.B., Beers, S.R., Soloff, P.H., Boring, A.M., Hall, J., Kersh, A. and Keshavan, M.S. 2000. Hippocampal volume in adolescent-onset alcohol use disorders. *American Journal of Psychiatry,* 157:737-44.

De Bellis, M.D., Narasimhan, A., Thatcher, D.L., Keshavan, M.S., Soloff, P. and Clark, D.B. 2005. Prefrontal cortex, thalamus and cerebellar volumes in adolescents and young adults with adolescent onset alcohol use disorders and co-morbid mental disorders. *Alcoholism: Clinical and Experimental Research,* 29:1590-1600.

Ehrenreich, H., Rinn, T., Kunert, H.J., Moeller, M.R., Poser, W., Schilling, L., Gigerenzer, G. and Hoehe, M.R. 1999. Specific attentional dysfunction in adults following early start of cannabis use. *Psychopharmacology*, 142:295-301.

Ernst, T., Chang, L., Leonido-Yee, M. and Speck, O. 2000. Evidence for long-term neurotoxicity associated with methamphetamine abuse: A 1H MRS study. *Neurology,* 54:1344-9.

Ernst, M., Nelson, E.E., Jazbec, S., McClure, E.B., Monk, C.S., Leibenluft, E., Blair, J. and Pine, D.S. 2005. Amygdala and nucleus accumbens in responses to receipt and omission of gains in adults and adolescents. *Neuroimage,* 25:1279-91.

Franklin, T.R., Acton, P.D., Maldjian, J.A., Gray, J.D., Croft, J.R., Dackis, C.A., O'Brien, C.P. and Childress, A.R. 2002. Decreased gray matter concentration in the insular, orbitofrontal, cingulate, and temporal cortices of cocaine patients. *Biological Psychiatry,* 51:134-42.

Galvan, A., Hare, T.A., Davidson, M., Spicer, J., Glover, G. and Casey, B.J. 2005. The role of ventral frontostriatal circuitry in reward-based learning in humans. *Journal of Neuroscience,* 25:8650-6.

Galvan, A., Hare, T.A., Parra, C.E., Penn, J., Voss, H., Glover, G. and Casey, B.J. 2006. Earlier development of the accumbens relative to orbitofrontal cortex might underlie risk-taking behavior in adolescents. *Journal of Neuroscience,* 26:6885-92.

Galvan, A., Hare, T., Voss, H., Glover, G. and Casey, B.J. 2007. Risk-taking and the adolescent brain: who is at risk? *Developmental Science,* 10:F8-F14.

Giedd, J.N. 2004. Structural magnetic resonance imaging of the adolescent brain. Adolescent Brain Development: Vulnerabilities and Opportunities *Ann N Y Acad Sci,* 1021:77-85.

Gogtay, N., Giedd, J.N., Lusk, L., Hayashi, K.M., Greenstein, D., Vaituzis, A.C., Nugent, T.F. 3rd, Herman, D.H., Clasen, L.S., Toga, A.W., Rapoport, J.L. and Thompson, P.M. 2004. Dynamic mapping of human cortical development during childhood through early adulthood. *Proceedings of the National Academy of Sciences,* 101:8174-9.

Grant, I., Adams, K.M., Carlin, A.S., Rennick, P.M., Judd, L.L. and Schooff, K. 1978. The collaborative neuropsychological study of polydrug users. *Archives of General Psychiatry,* 35:1063-1074.

Grant, B.F. and Dawson, D.A. 1997. Age at onset of alcohol use and its association with DSM-IV alcohol abuse and dependence: results from the National Longitudinal Alcohol Epidemiologic Survey. *Journal of Substance Abuse,* 9:103-10.

Halpern, J.H., Pope, H.G., Jr., Sherwood, A.R., Barry, S., Hudson, J.I. and Yurgelun-Todd, D. 2004. Residual neuropsychological effects of illicit 3,4 -methylenedioxymethamphetamine (MDMA) in individuals with minimal exposure to other drugs. *Drug and Alcohol Dependence,* 75:135-47.

Harrison, A.A., Everitt, B.J. and Robbins, T.W. 1997. Central 5-HT depletion enhances impulsive responding without affecting the accuracy of attentional performance: interactions with dopaminergic mechanisms. *Psychopharmacology (Berl),* 133:329-42.

Hibell, B., Andersson, B., Bjarnason, T., Ahlström, S., Balakireva, O., Kokkevi, A. and Morgan, M. 2004. The ESPAD Report 2003. *Alcohol and Other Drug Use Among Students in 35 European Countries.* Stockholm: Sweden, The Swedish Council for Information on Alcohol and Other Drugs (CAN) and the Pompidou Group at the Council of Europe.

Huttenlocher, P.R. 1990. Morphometric study of human cerebral cortex development. *Neuropsychologia,* 28:517-527.

Iversen, L. 2003. Cannabis and the brain. *Brain,* 126:1252-70.

Jacobsen, L.K., Giedd, J.N., Gottschalk, C., Kosten, T.R. and Krystal, J.H. 2001. Quantitative morphology of the caudate and putamen in patients with cocaine dependence. *American Journal of Psychiatry,* 158:486-9.

Jacobsen, L.K., Mencl, W.E., Pugh, K.R., Skudlarski, P. and Krystal, J.H. 2004a. Preliminary evidence of hippocampal dysfunction in adolescent MDMA ("ecstasy") users: possible relationship to neurotoxic effects. *Psychopharmacology (Berl),* 173:383-90.

Jacobsen, L.K., Mencl, W.E., Westerveld, M. and Pugh, K.R. 2004b. Impact of cannabis use on brain function in adolescents. *Annals of the New York Academy of Sciences,* 1021:384-90.

Jacobsen, L.K., Krystal, J.H., Mencl, W.E., Westerveld, M., Frost, S.J. and Pugh, K.R. 2005. Effects of smoking and smoking abstinence on cognition in adolescent tobacco smokers. *Biological Psychiatry,* 57:56-66.

Jacobsen, L.K., Pugh, K..R., Constable, R. T., Westerveld, M. and Mencl, W.E. 2007. Functional Correlates of Verbal Memory Deficits Emerging During Nicotine Withdrawal in Abstinent Adolescent Cannabis Users. *Biological Psychiatry,* 61:31-40.

Jernigan, T. and Gamst, A. 2005. Changes in volume with age: Consistency and interpretation of observed effects. *Neurobiology of Aging,* 26:1271-4.

Jernigan, T.L., Gamst, A.C., Archibald, S.L., Fennema Notestine, C., Mindt, M.R., Marcotte, T.L., Heaton, R.K., Ellis, R.J. and Grant, I. 2005. Effects of Methamphetamine Dependence and HIV Infection on Cerebral Morphology. *American Journal of Psychiatry,* 162:1461-72.

Johnston, L.D., O'Malley, P.M., Bachman, J.G. and Schulenberg, J.E. 2006. *Monitoring the Future national results on adolescent drug use,* 1975-2005: Volume 1, Secondary school students. Bethesda, MD: National Institute on Drug Abuse.

Judd, L.L., Akiskal, H.S., Maser, J.D., Zeller, P.J., Endicott, J., Coryell, W., Paulus, M.P., Kunovac, J.L., Leon, A.C., Mueller, T.I., Rice, J.A A. and Keller, M.B. 1998. A prospective 12-year study of subsyndromal and syndromal depressive symptoms in unipolar major depressive disorders. *Archives of General Psychiatry,* 55:694-700.

Kanayama, G., Rogowska, J., Pope, H.G., Gruber, S. A. and Yurgelun-Todd, D. A. 2004. Spatial working memory in heavy cannabis users: a functional magnetic resonance imaging study. *Psychopharmacology,* 16:16.

Keller, A., Castellanos, F.X., Vaituzis, A.C., Jeffries, N.O., Giedd, J.N. and Rapoport, J.L. 2003. Progressive loss of cerebellar volume in childhood onset schizophrenia. *American Journal of Psychiatry,* 160:128-33.

Kempel, P., Lampe, K., Parnefjord, R., Hennig, J. and Kunert, H.J. 2003. Auditory-evoked potentials and selective attention: different ways of information processing in cannabis users and controls. *Neuropsychobiology,* 48:95-101.

Kendler, K., Davis, C. and Kessler, R. 1997. The familial aggregation of common psychiatric and substance use disorders in the National Comorbidity Survey: a family history study. *British Journal of Psychiatry,* 170:541-548.

Kilbey, M.M., Breslau, N. and Andreski, P. 1992. Cocaine use and dependence in young adults: associated psychiatric disorders and personality traits. *Drug Alcohol Dependence,* 29:283-90.

Kunert, H.J., Derichs, G. and Irle, E. 1996. Entwicklung von Aufmerksamkeitsfunktionen im Kindesalter: Ergebnisse einer vorlaufigen Normierung der computergestutzten Testbatterie zur Aufmerksamkeitsprufund TAP) an 9- bis 12 jahrigen Kindern. *Zeitschrift Neuropsychologie,* 7.

Landfield, P.W., Cadwallader, L.B. and Vinsant, S. 1988. Quantitative changes in hippocampal structure following long-term exposure to delta 9-tetrahydrocannabinol: possible mediation by glucocorticoid systems. *Brain Research,* 443:47-62.

Lejuez, C.W., Read, J.P., Kahler, C.W., Richards, J.B., Ramsey, S.E., Stuart, G.L., Strong, D.R. and Brown, R.A. 2002. Evaluation of a behavioral measure of risk taking: the Balloon Analogue Risk Task (BART). *Journal of Experimental Psychology: AppliedJ Exp Psychol Appl,* 8:75-84.

Lejuez, C.W., Aklin, W.M., Jones, H.A., Richards, J.B., Strong, D.R., Kahler, C.W. and Read, J.P. 2003. The Balloon Analogue Risk Task (BART) differentiates smokers and nonsmokers. *Experimental and Clinical Psychopharmacology*, 11:26-33.

Leland, D.S. and Paulus, M.P. 2005. Increased risk taking decision making but not altered response to punishment in stimulant using young adults. *Drug and Alcohol Dependence,* 78:83-90.

Leland, D.S., Arce, E., Feinstein, J.S. and Paulus, M.P. 2006. Young adult stimulant users' increased striatal activation during uncertainty is related to impulsivity. *Neuroimage,* 33:725-31.

Logothetis, N.K., Pauls, J., Augath, M., Trinath, T. and Oeltermann, A. 2001. Neurophysiological investigation of the basis of the fMRI signal. *Nature,* 412:150-7.

Luna, B., Garver, K., Urban, T., Lazar, N. and Sweeney, J. 2004. Maturation of cognitive processes from late childhood to adulthood. *Child Development,* 75:1357-72.

Luna, B. and Sweeney, J. 2004. The Emergence of Collaborative Brain Function: fMRI Studies of the Development of Response Inhibition. *Annals of the New York Academy of Sciences,* 1021: 296-309.

Lundqvist, T., Jonsson, S. and Warkentin, S. 2001. Frontal lobe dysfunction in long-term cannabis users. *Neurotoxicology and Teratology,* 23:437-43.

Lynskey, M.T., Heath, A.C., Bucholz, K.K., Slutske, W.S., Madden, P.A., Nelson, E.C., Statham, D.J. and Martin, N.G. 2003. Escalation of drug use in early-onset cannabis users vs co-twin controls. *Journal of the American Medical Association*, 289:427-33.

Lyvers, M. and Hasking, P. 2004. Have Halpern et al. (2004) detected 'residual neuropsychological effects' of MDMA? Not likely. *Drug and Alcohol Dependence,* 75:149-52; discussion 153.

McCann, U., Szabo, Z., Seckin, E., Rosenblatt, P., Mathews, W., Ravert, H., Dannals, R. and Ricaurte, G. 2005. Quantitative PET studies of the serotonin transporter in MDMA users and. *Neuropsychopharmacology,* 30:1741-50.

McGue, M., Slutske, W. and Iacono, W.G. 1999. Personality and substance use disorders: II. Alcoholism versus drug use disorders. *Journal of Consulting and Clinical Psychology,* 67:394-404.

McKetin, R. and Mattick, R.P. 1998. Attention and memory in illicit amphetamine users: comparison with non-drug-using controls. *Drug and Alcohol Dependence,* 50:181-4.

Medina, K.L., Shear, P.K. and Corcoran, K. 2005. Ecstasy (MDMA) exposure and neuropsychological functioning: A polydrug perspective. *Journal of the International Neuropsychological Society,* 11:753-65.

Medina, K.L., Schweinsburg, A.D., Cohen-Zion, M., Nagel, B.J. and Tapert, S.F. 2007. Effects of alcohol and combined marijuana and alcohol use during adolescence on hippocampal volume and asymmetry. *Neurotoxicology and Teratology,* 29:141-52.

Merikangas, K.R., Mehta, R.L., Molnar, B.E., Walters, E.E., Swendsen, J.D D., Aguilar-Gaziola, S., Bijl, R., Borges, G., Caraveo-Anduaga, J.J., Dewit, D.J., Kolody, B., Vega, W.A., Wittchen, H.U. and Kessler, R.C. 1998. Comorbidity of substance use disorders with mood and anxiety disorders: results of the International Consortium in Psychiatric Epidemiology. *Addict Behaviors,* 23:893-907.

Millsaps, C.L., Azrin, R.L. and Mittenberg, W. 1994. Neuropsychological effects of chronic cannabis use on the memory and intelligence of adolescents. *Journal of Child and Adolescent Substance Abuse,* 3:47-55.

Morgan, M.J. 2000. Ecstasy (MDMA): a review of its possible persistent psychological effects. *Psychopharmacology* Berl), 152:230-48.

Nagel, B.J., Schweinsburg, A.D., Phan, V. and Tapert, S.F. 2005. Reduced hippocampal volume among adolescents with alcohol use disorders without psychiatric comorbidity. *Psychiatry Research,* 139, 181-90.

Nordahl, T.E., Salo, R. and Leamon, M. 2003. Neuropsychological effects of chronic methamphetamine use on neurotransmitters and cognition: a review. *The Journal of Neuropsychiatry and Clinical Neurosciences*, 15:317-25.

O'Connor, L.E., Berry, J.W., Morrison, A. and Brown, S. 1995. The drug-of-choice phenomenon psychological differences among drug users who preferred different drugs. *International Journal of the Addictions,* 30:541-55.

Oscar-Berman, M. and Marinkovic, K. 2003. Alcoholism and the brain: an overview. *Alcohol Research and Health,* 27:125-33.

Paus, T., Zijdenbos, A., Worsley, K., Collins, D.L., Blumenthal, J., Giedd, J.N., Rapoport, J.L. and Evans, A.C. 1999. Structural maturation of neural pathways in children and adolescents: in vivo study. *Science,* 283:1908-11.

Pope, H.G.Jr. and Yurgelun-Todd, D. 1996. The residual cognitive effects of heavy marijuana use in college students. *Journal of the American Medical Association,* 275:521-7.

Pope, H.G.Jr., Gruber, A.J., Hudson, J.I., Huestis, M.A. and Yurgelun-Todd, D. 2001. Neuropsychological performance in long-term cannabis users. *Archives of General Psychiatry,* 58:909-15.

Pope, H.G.Jr., Gruber, A.J., Hudson, J.I., Cohane, G., Huestis, M.A. and Yurgelun Todd, D. 2003. Early onset cannabis use and cognitive deficits: what is the nature of the association? *Drug and Alcohol Dependence,* 69:303-10.

Reneman, L., Booij, J., De Bruin, K., Reitsma, J.B., De Wolff, F.A., Gunning, W.B., Den Heeten, G.J. and Van Den Brink, W. 2001a. Effects of dose, sex, and long-term abstention from use on toxic effects of MDMA (ecstasy) on brain serotonin neurons. *Lancet,* 358:1864-9.

Reneman, L., Majoie, C.B., Habraken, J.B. and Den Heeten, G.J. 2001b. Effects of ecstasy (MDMA) on the brain in abstinent users: initial observations with diffusion and perfusion MR imaging. *Radiology,* 220:611-7.

Reneman, L., Booij, J., Lavalaye, J., De Bruin, K., Reitsma, J. B., Gunning, B., Den Heeten, G.J. and Van Den Brink, W. 2002a. Use of amphetamine by recreational users of ecstasy (MDMA) is associated with reduced striatal dopamine transporter densities: a [123I]beta-CIT SPECT study – preliminary report. *Psychopharmacology (Berl),* 159:335-40.

Reneman, L., Majoie, C.B., Flick, H. and Den Heeten, G.J. 2002b. Reduced N-acetylaspartate levels in the frontal cortex of 3,4-methylenedioxymethamphetamine (Ecstasy) users: preliminary results. *American Journal of Neuroradiology,* 23:231-7.

Rogers, R.D., Everitt, B.J., Baldacchino, A., Blackshaw, A.J., Swainson, R., Wynne, K., Baker, N.B., Hunter, J., Carthy, T., Booker, E., London, M., Deakin, J.F., Sahakian, B.J. and Robbins, T.W. 1999. Dissociable deficits in the decision-making cognition of chronic amphetamine abusers, opiate abusers, patients with focal damage to prefrontal cortex, and tryptophan-depleted normal volunteers: evidence for monoaminergic mechanisms. *Neuropsychopharmacology,* 20:322-39.

Salo, R., Nordahl, T.E., Possin, K., Leamon, M., Gibson, D.R., Galloway, G.P., Flynn, N.M., Henik, A., Pfefferbaum, A. and Sullivan, E.V. 2002. Preliminary evidence of reduced cognitive inhibition in methamphetamine-dependent individuals. *Psychiatry Research,* 111:65-74.

Sartor, C.E., Lynskey, M.T., Heath, A.C., Jacob, T. and True, W. 2007. The role of childhood risk factors in initiation of alcohol use and progression to alcohol dependence. *Addiction,* 102,: 216-25.

Schwartz, R.H., Gruenewald, P.J., Klitzner, M. and Fedio, P. 1989. Short-term memory impairment in cannabis-dependent adolescents. *American Journal of Diseases in Children,* 143:1214-9.

Schweinsburg, A., Nagel, B., Schweinsburg, B., Park, A., Theilmann, R. and Tapert, S. 2008. Abstinent adolescent marijuana users show altered fMRI response during spatial working memory. *Psychiatry Research: Neuroimaging,* 30:40-51.

Schweinsburg, A.D., Schweinsburg, B.C., Cheung, E.H., Brown, G.G., Brown, S.A. and Tapert, S.F. 2005. fMRI response to spatial working memory in adolescents with comorbid marijuana and alcohol use disorders. *Drug and Alcohol Dependence,* 79:201-10.

Sekine, Y., Iyo, M., Ouchi, Y., Matsunaga, T., Tsukada, H., Okada, H., Yoshikawa, E., Futatsubashi, M., Takei, N. and Mori, N. 2001. Methamphetamine-related psychiatric symptoms and reduced brain dopamine transporters studied with PET. *American Journal of Psychiatry,* 158:1206-14.

Sekine, Y., Ouchi, Y., Takei, N., Yoshikawa, E., Nakamura, K., Futatsubashi, M., Okada, H., Minabe, Y., Suzuki, K., Iwata, Y., Tsuchiya, K.J., Tsukada, H., Iyo, M. and Mori, N. 2006. Brain Serotonin Transporter Density and Aggression in Abstinent Methamphetamine Abusers. *Archives of General Psychiatry,* 63:90-100.

Semple, D.M., Ebmeier, K.P., Glabus, M.F., O'Carroll, R.E. and Johnstone, E.C. 1999. Reduced in vivo binding to the serotonin transporter in the cerebral cortex of MDMA ('ecstasy') users. *British Journal of Psychiatry,* 175:63-9.

Shaw, P., Greenstein, D., Lerch, J., Clasen, L., Lenroot, R., Gogtay, N., Evans, A., Rapoport, J. and Giedd, J. 2006. Intellectual ability and cortical development in children and adolescents. *Nature,* 440:676-9.

Sher, K. and Trull, T. 1994. Personality and disinhibitory psychopathology: Alcoholism and antisocial personality disorder. *Journal of Abnormal Psychology,* 103:92-102.

Sher, K.J., Bartholow, B.D. and Wood, M.D. 2000. Personality and substance use disorders: A prospective study. *Journal of Consulting and Clinical Psychology,* 68:818-829.

Snook, L., Paulson, L.A., Roy, D., Phillips, L. and Beaulieu, C. 2005. Diffusion tensor imaging of neurodevelopment in children and young adults. *Neuroimage,* 26:1164-73.

Solowij, N., Michie, P.T. and Fox, A.M. 1995. Differential impairments of selective attention due to frequency and duration of cannabis use. *Biological Psychiatry,* 37:731-9.

Solowij, N., Stephens, R.S., Roffman, R.A., Babor, T., Kadden, R., Miller, M., Christiansen, K., McRee, B. and Vendetti, J. 2002. Cognitive functioning of long-term heavy cannabis users seeking treatment. *Journal of the American Medical Association,* 287:1123-31.

Sowell, E.R., Thompson, P.M., Holmes, C.J., Jernigan, T.L. and Toga, A.W. 1999. In vivo evidence for post adolescent brain maturation in frontal and striatal regions. *Nature Neuroscience,* 2:859-61.

Spear, L.P. and Varlinskaya, E.I. 2005. Adolescence. Alcohol sensitivity, tolerance, and intake. *Recent Developments in Alcoholism*, 17:143-59.

Stiglick, A. and Kalant, H. 1985. Residual effects of chronic cannabis treatment on behavior in mature rats. *Psychopharmacology,* 85:436-9.

Tapert, S.F. and Brown, S.A. 1999. Neuropsychological correlates of adolescent substance abuse: Four year outcomes. *Journal of the International Neuropsychological Society,* 5:481-93.

Tapert, S.F. and Brown, S.A. 2000. Substance dependence, family history of alcohol dependence and neuropsychological functioning in adolescence. *Addiction,* 95:1043-53.

Tapert, S.F., Brown, G.G., Kindermann, S., Cheung, E.H., Frank, L.R. and Brown, S.A. 2001. fMRI measurement of brain dysfunction in alcohol-dependent young women. *Alcoholism: Clinical and Experimental Research,* 25:236-245.

Tapert, S.F., Granholm, E., Leedy, N.G. and Brown, S.A. 2002. Substance use and withdrawal: Neuropsychological functioning over 8 years in youth. *Journal of the International Neuropsychological Society*, 8:873-83.

Tapert, S.F., Cheung, E.H., Brown, G.G., Frank, L.R., Paulus, M.P., Schweinsburg, A.D., Meloy, M.J. and Brown, S. A. 2003a. Neural response to alcohol stimuli in adolescents with alcohol use disorder. *Archives of General Psychiatry,* 60:727-35.

Tapert, S.F., Theilmann, R.J., Schweinsburg, A.D., Yafai, S. and Frank, L.R. 2003b. Reduced fractional anisotropy in the splenium of adolescents with alcohol use disorder. *Proceedings International. Society of Magnetic Resonance Medicine,* 11:8217.

Tapert, S.F., Pulido, C., Paulus, M.P., Schuckit, M.A. and Burke, C. 2004a. Level of response to alcohol and brain response during visual working memory. *Journal of Studies on Alcohol and Drugs,* 65:692-700.

Tapert, S.F., Schweinsburg, A.D., Barlett, V.C., Brown, S.A., Frank, L.R., Brown, G.G. and Meloy, M.J. 2004b. Blood oxygen level dependent response and spatial working memory in adolescents with alcohol use disorders. Alcoholism: *Clinical and Experimental Research*, 28:1577-86.

Tapert, S., Schweinsburg, A., Drummond, S., Paulus, M., Brown, S., Yang, T. and Frank, L. 2007. Functional MRI of inhibitory processing in abstinent adolescent marijuana users. *Psychopharmacology,* 194:173-183.

Teichman, M., Barnea, Z. and Rahav, G. 1989. Sensation seeking, state and trait anxiety, and depressive mood in adolescent substance users. *International Journal of Addictions,* 24:87-99.

Teichner, G., Donohue, B., Crum, T. A., Azrin, N.H. and Golden, C.J. 2000. The relationship of neuropsychological functioning to measures of substance use in an adolescent drug abusing sample. *International Journal of Neuroscience,* 104:113-24.

Thompson, P.M., Hayashi, K.M., Simon, S.L., Geaga, J. A., Hong, M.S S., Sui, Y., Lee, J. Y., Toga, A.W., Ling, W. and London, E.D. 2004. Structural abnormalities in the brains of human subjects who use methamphetamine. *Journal of Neuroscience,* 24:6028-36.

Verdejo Garcia, A., Lopez Torrecillas, F., Gimenez, C.O. and Perez Garcia, M. 2004. Clinical implications and methodological challenges in the study of the neuropsychological correlates of cannabis, stimulant, and opioid abuse. *Neuropsychology Review,* 14:1-41.

Volkow, N.D., Chang, L., Wang, G.J., Fowler, J.S., Ding, Y.S., Sedler, M., Logan, J., Franceschi, D., Gatley, J., Hitzemann, R., Gifford, A., Wong, C. and Pappas, N. 2001a. Low level of brain dopamine D2 receptors in methamphetamine abusers: association with metabolism in the orbitofrontal cortex. *American Journal of Psychiatry,* 158:2015-21.

Volkow, N.D., Chang, L., Wang, G.J., Fowler, J.S., Leonido-Yee, M., Franceschi, D., Sedler, M.J., Gatley, S.J., Hitzemann, R., Ding, Y.S., Logan, J., Wong, C. and Miller, E.N. 2001b. Association of dopamine transporter reduction with psychomotor impairment in methamphetamine abusers. *American Journal of Psychiatry,* 158:377-82.

Walfish, S., Massey, R. and Krone, A. 1990. Anxiety and anger among abusers of different substances. *Drug and Alcohol Dependence,* 25:253-6.

Wills, T. A., Vaccaro, D. and McNamara, G. 1994. Novelty seeking, risk taking, and related constructs as predictors of adolescent substance use: an application of Cloninger's theory. *The Journal of Substance Abuse Treatment*, 6:1-20.

Wilson, W., Mathew, R., Turkington, T., Hawk, T., Coleman, R.E. and Provenzale, J. 2000. Brain morphological changes and early marijuana use: a magnetic resonance and positron emission tomography study. *Journal of Addictive Disorders*, 19:1-22.

Wittchen, H.U., Essau, C. A., Von Zerssen, D., Krieg, J.C. and Zaudig, M. 1992. Lifetime and six-month prevalence of mental disorders in the Munich Follow-Up Study. *European Archives of Psychiatry and Clinical Neuroscience*, 241:247-58.

Yakovlev, P.I. and Lecours, A.R. 1967. The myelogenetic cycles of regional maturation of the brain. In N Mikowski, A. Mikowski (Eds). *Regional Development of the Brain in Early Life.* Oxford, England: Blackwell Scientific.

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