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Substance use and the adolescent brain: A toxic combination?

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Abstract

Early onset substance use has consistently been associated with increased risk for a range of adverse outcomes in late adolescence and early adulthood. However, the mechanisms that underlie this relationship are not fully understood. Recent advances in developmental neuroscience, together with emerging literature on early onset substance use, suggest that the adolescent brain may be more vulnerable to the effects of addictive substances because of the extensive neuromaturational processes that are occurring during this period. Such findings are suggestive of disrupted developmental trajectories in early onset users,

although there is growing evidence that high-risk youths have premonitory neurobiological vulnerabilities. Prospective studies investigating neurobiological correlates and sequelae of early adolescent drug use are urgently required to inform appropriate public health responses.

Keywords

adolescence, drugs, brain development, cannabis, alcohol, inhalants, public health

Adolescent substance use

Over the past several decades in Australia and the European Union, the age of first use of alcohol, tobacco and cannabis have all declined (EMCDDA, 2005; Degenhardt *et al.*, 2000). Early use of any drug predicts an increased risk of regular and problem use in late adolescence and early adulthood, as well as a range of other adverse outcomes (Teesson *et al.*, 2005; Toumbourou and Catalano, 2005). Early drug users also have higher rates of mental health problems – especially anxiety, depression, and conduct disorder – that further increase the likelihood of regular and problematic use (Teesson *et al.*, 2005).

The mechanisms that underlie associations between early drug use, drug dependence and other mental disorders are not fully understood (Macleod *et al.*, 2004). For example, early onset substance use is associated with various aspects of childhood adversity (e.g. material deprivation, early psychological problems, family difficulties, school and behavioural difficulties), which in turn are predictive of later problems – even in children who do not use substances (Macleod *et al.*, 2004). This issue of residual confounding is important to consider and difficult to discount. Nevertheless, the better designed longitudinal studies that have attempted to control for the effects of pre-existing differences between early and late initiators of these drugs (e.g. Fergusson *et al.*, 2006) have generally found that although the relationships are attenuated, they persist.

Complementing these epidemiological findings, recent developmental neuroscience research indicates that adolescence is a key period of neuromaturation (Paus, 2005), with growing evidence that the adolescent brain may be more vulnerable to the effects of addictive substances than the adult brain (Monti *et al.*, 2005; Smith, 2003). Such research raises a number of important empirical questions. What are the specific (and non-specific) effects of alcohol and other drugs on neurodevelopmental processes (and are they similar or distinct for different classes of drugs)? If there are neurobiological sequelae, do these reflect the cumulative effects of longer exposure, or is early adolescence a particularly sensitive period of development in which drug exposure has more pronounced effects on maturing neurobiological systems? Is there evidence for premonitory neurobiological vulnerabilities amongst early onset users, and if so, does substance use have a more severe impact on neuromaturational processes in this high-risk group?

Adolescent brain development

Whilst neurobiological research of human adolescent development is still in its infancy, emerging evidence suggests that there is a substantial increase in cortical grey matter volume during childhood, followed by extensive pruning of cortical synapses

(reductions in cortical grey matter) and increased myelination during adolescence and early adulthood (see Paus, 2005 for review). This remodelling is thought to ensure more efficient communication between cortical and subcortical brain regions, facilitating optimal functioning within cognitive, emotional, motivational and sensorimotor systems. However, it appears that the brain does not mature uniformly across this developmental phase of life. Instead, there is a graded progression of cortical maturation within the medial and lateral frontal areas (regions responsible for higher-cognitive functions) that continues into late adolescence, whereas the more posterior and deep brain structures (regions responsible for more primitive functions) mature much earlier.

Although relatively fewer studies have examined developmental changes in brain function (as opposed to structure), differences in affective, motivational and cognitive capacity during adolescence appear to be consistent with reported maturational neuroanatomical findings (see Steinberg, 2005 for review). For example, early adolescence is characterised by increases in affective reactivity, peer-directed social interactions, risk-taking and sensation-seeking, whilst decision-making and self-regulatory skills (i.e. frontal executive functions) do not fully mature until early adulthood (Steinberg, 2005). Nevertheless, our current understanding of the links between cognitive/affective development and neuroanatomical maturation remains rudimentary, and a more substantive program of research is required to fully characterise the maturational trajectories of these processes as well as their interaction with other biological and environmental factors.

Substance use and adolescent brain development

Growing literature from animal studies suggests that adolescent substance use disrupts neuroendocrine functioning, and can induce greater effects on neural plasticity and cognition than in adults (see Smith, 2003 for review). Substance use during adolescence can also elicit altered sensitivity to later drug exposure, impair adult cognitive functioning, and even induce cortical damage (Monti *et al.*, 2005; Smith, 2003).

Substantially less work has been conducted in adolescent humans, although there is increasing evidence of developmental harms. A number of studies have reported smaller hippocampal volumes amongst adolescents and young adults with alcohol use disorders (AUD) compared to healthy matched controls (De Bellis *et al.*, 2000; Nagel *et al.*, 2005). In one of these studies, hippocampal volumes were positively correlated with age of first use and negatively correlated with duration of use (De Bellis *et al.*, 2000). Adolescents with AUD have also been reported to have smaller prefrontal cortices and white matter volumes, with significant correlations noted between prefrontal cortical volumes and measures of alcohol consumption (De Bellis *et al.*, 2005). Such structural abnormalities are in keeping with reported alcohol-related neurocognitive impairments amongst adolescent drinkers (Brown and Tapert, 2004), as well as recent functional imaging findings (see Brown and Tapert, 2004 and Monti *et al.*, 2005 for a review).

Whilst most research to date has been conducted amongst adolescent drinkers, young drug users have also been found to

demonstrate neurocognitive impairments (e.g. Lubman *et al.*, 2007a; Tapert and Brown, 1999). Young people who begin using cannabis before the age of 17 seem to be more vulnerable to cognitive impairments and show reduced brain grey matter (Pope *et al.*, 2003; Wilson *et al.*, 2000). Chronic inhalant misuse has also been associated with cognitive impairment, sometimes resulting in permanent and irreversible cognitive deficits and structural brain abnormalities (Lubman *et al.*, 2006). Indeed, in one study of 55 chronic users (mean age of 30 years, with the majority commencing use in adolescence), almost 44% had structural brain changes, the extent of which was related to cumulative dose (Rosenberg *et al.*, 2002). There was also a strong correlation between white matter abnormalities and greater cognitive impairment. Bartzokis and colleagues (2002) recently reported that chronic cocaine use substantially interferes with normal white matter maturation, particularly in frontal and temporal brain regions. Enhanced white matter connectivity (especially within these structures) is one of the key maturational processes to occur during adolescence, suggesting that early onset substance use may affect the development of fronto-temporal white matter circuits, potentially resulting in disturbed memory, executive and affective functioning.

Most of the evidence for impaired neurobiology amongst adolescent substance users has been cross-sectional, and hence has limited capacity to distinguish between cause and effect. Studies of high-risk populations (e.g. family history of AUD) suggest impairments in frontal functioning are apparent prior to drug use exposure (e.g. Monti *et al.*, 2005; Schweinsburg *et al.*, 2004) and can predict later substance use (Deckel and Hesselbrock, 1996; Tarter *et al.*, 2003). High-risk young people also fail to demonstrate appropriate age-related decreases in grey matter volume (Hill *et al.*, 2007). Such studies, however, report no differences in hippocampal volume, suggesting that any observed structural findings most likely relate to substance exposure rather than premorbid vulnerability (Hill, 2004).

The limited research on the neurobiological effects of alcohol, tobacco, inhalants and cannabis use during adolescence is at odds with their high rates of use during this important developmental period, and with animal evidence suggesting substantially increased risks. Accordingly, it should be a research priority to conduct prospective studies that examine changes in brain structure and function during early adolescence. These samples could be enriched with adolescents at high and low-risk of substance use who can be identified in existing cohort studies. Indeed, such research is essential if we are to assess the neurobiological impact of substance use during adolescence (including the extent of recovery following abstinence), and identify robust neurobiological markers of risk. Such research is also essential to assess the specificity of exposure to distinct drugs, as well as possible synergistic effects with poly-drug use (see Monti *et al.*, 2005).

Implications for public health

Neurobiological dissection of the associations between adolescent substance use and later psychopathology will also strengthen the already strong case for prevention of early drug use that has consistently been provided by epidemiological studies. The existing

epidemiological evidence provides a strong case for allocating more societal resources to preventing early substance use and mental disorders among young people (Spooner and Hall, 2002). In doing so, we need to do more than fund the favoured political quick fix remedies, such as mass media campaigns and modestly effective, school-based, drug education programs that highlight the harms of drug use (Caulkins *et al.*, 1999).

We need substantial public investment in preschool and early school interventions to reduce the school failure and social disadvantage that are fertile recruiting grounds for early drug use amongst adolescents (Toumbourou and Catalano, 2005). Appropriately targeted early intervention programs will also be required, as well as sophisticated health promotion campaigns that provide credible messages to young people in a persuasive manner that decreases the likelihood of early initiation of all forms of drug use (Lubman *et al.*, 2007b). This must include clearer messages not only about cannabis, tobacco and inhalants, but also about alcohol, a drug that is pervasively used by adolescents and young adults with high rates of acute harm that are often overshadowed by media preoccupation with the effects of newer but less frequently used illicit drugs like MDMA, cocaine and methamphetamine.

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