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Annual Research Review: On the developmental neuropsychology of substance use disorders

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Background: Adolescence represents a period of development during which critical biological, as well as social and cognitive, changes occur that are necessary for the transition into adulthood. A number of researchers have suggested that the pattern of normative brain changes that occurs during this period not only predisposes adolescents to engage in risk behaviours, such as experimentation with drugs, but that they additionally make the adolescent brain more vulnerable to the direct pharmacological impact of substances of abuse. The neural circuits that we examine in this review involve cortico-basal-ganglia/limbic networks implicated in the processing of rewards, emotion regulation, and the control of behaviour, emotion and cognition. **Findings and Conclusions:** We identify certain neurocognitive and personality/comorbidity-based risk factors for the onset of substance misuse during adolescence, and summarise the evidence suggesting that these risk factors may be further impacted by the direct effect of drugs on the underlying neural circuits implicated in substance misuse vulnerability. **Keywords:** Substance use; substance dependence; brain development; adolescence; reward processing; executive control; cognitive control; behavioural inhibition; fMRI; alcohol; marijuana; cigarette use.

Introduction

Adolescence is a period characterised by significant changes in social and cognitive functioning, a shift from parental supervision and behavioural management to independent decision making and self-governed behaviour, and an increase in autonomous peer interactions and exploratory behaviour (Steinberg, 2008). This shift is essential for the progression into adulthood, and in the majority of cases occurs gradually, as adolescents begin to adopt more adult behaviours and responsibilities (Bachman & Schulenberg, 1993). Indeed, a number of youth-directed regulatory policies have been put in place in many societies to ensure that youth are appropriately assisted in safely transitioning into these adult roles and behaviours: Regulations directed at novice drivers is a perfect example (see Conrod et al., 2016, in Anderson et al., 2016).

Other behaviours that increase throughout adolescence are the experimentation with, and the use of, alcohol, nicotine, and illicit drugs (Johnston, O'Malley, Bachman, Schulenberg, & Miech, 2014). However, under most drug and alcohol policies in the Western world, substance use is prohibited and criminalised for youth (Wolfson & Hourigan, 1997). Thus, substance use becomes a risky behaviour for adolescents, not only because of the harsh negative consequences that result from being caught (e.g. school exclusion, incarceration) (Wolfson & Hourigan, 1997), or the potential medical risks associated with the unsupervised use of substances of varied/unknown pharmacological quality (Borawski, Ievers-Landis, Lovegreen, & Trapl, 2003; Cherpitel et al., 2009), but also because there is evidence from prospective epidemiologic and clinical studies that the early onset of substance use and of regular use is associated with future risk for substance use disorder (SUD), and related harm (e.g. Grant & Dawson, 1998).

From a clinical perspective, SUD can be characterised as mild, moderate, or severe, depending on the number of diagnostic criteria displayed by an individual (5th edn; DSM–5; American Psychiatric Association, 2013). These criteria include: spending time on activities necessary to obtain, use, and to recover from the effects of, the substance; reducing or giving up important social, occupational, or recreational activities because of substance use; developing tolerance or needing increased amounts of the substance to achieve a desired effect; experiencing feelings of withdrawal specific to the drug of abuse; and being unable to control the use of the drug. The inability to control drug use manifests as: (a) taking larger amounts of the substance, or over longer periods than was intended, (b) persistent yet unsuccessful efforts to cut down, and (c) continuing substance use despite knowledge of its harmful physical or psychological consequences.

Although psychiatric definitions tend to emphasise personal impairment, tolerance and uncontrollability, other modern definitions of SUD are also worthy of consideration. For example, the public health perspective focuses on the impact of heavy use of a substance over time on the individual and society as a whole, and is less concerned about psychological

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components of SUD, such as the uncontrolled nature of the behaviour (see Anderson et al., 2016; Rehm et al., 2015). From a behavioural neuroscience perspective, "drug addiction" incorporates some of the diagnostic criteria outlined in the DSM, such as the compulsive drug seeking/taking; the inability to control intake and to cut down despite negative social, psychological, and physical consequences of use; and the experience of negative affect and withdrawal symptoms during abstinence (e.g Koob & Volkow, 2010). In addition, however, the neuroscience perspective views addiction as a chronically relapsing brain disorder. In this conceptualisation, drug addiction is the process of transitioning from voluntary and controlled social drug use (which might still cause harm to one's health over time), to habitual, compulsive, and uncontrolled drug seeking and taking (e.g. Everitt et al., 2008; Wise & Koob, 2014).

This process includes three temporal stages: Initiation/experimentation with drug use; transition to regular heavy use; and transition to compulsive/uncontrolled use/relapse to use (Le Moal & Koob, 2007). This temporal distinction is critical, as epidemiological studies have shown that individuals displaying frequent and heavy use over time are at a greater risk of experiencing harm from substances, including the transition into a dependent state and a diagnosis for severe SUD. However, of those who have ever used a particular drug, only a portion will transition into using heavily, and only a portion of those people will become dependent (Substance Abuse and Mental Health Services Administration, 2014), suggesting individual differences in vulnerability to transition through these stages of addiction (Le Moal & Koob, 2007).

Neurobiological theories of addiction

Indeed, heuristic models of drug addiction, based on neuroscientific research in animals and in drug-dependent adults over the past 50 years, collectively suggest that the transition to a chronically relapsing, compulsive, uncontrolled, and problematic drug seeking and taking behavioural state is the result of an interaction between individual differences factors (e.g. genetic vulnerabilities, traumas) and drug-induced pharmacological changes within specific brain circuits (cortico-basal-ganglia-thalamo-cortical, limbic-basal-ganglia, and limbic-cortical). These circuits are also implicated in associative learning and the processing of rewards, goal directed behaviour and behavioural habit formation, the processing of negative (including stress) affect and the control of cognition, behaviour, and emotion (See the following papers for overviews and models: Everitt & Robbins, 2005; Goldstein & Volkow, 2002, 2011; Kalivas & O'Brien, 2008; Koob, 2008; Koob & Volkow, 2010; Robinson & Berridge, 2003). The developmental model of addition is presented in Figure 1.

Computational models of addiction further propose a "reward prediction error signal" to describe dopamine's role in the development of drug-cue sensitivity and compulsive drug taking (Redish, Jensen, & Johnson, 2008; Schultz, 2011). Accordingly, midbrain dopamine neurons construct and distribute information about rewarding events, particularly in anticipation of reward. Drugs of abuse are understood as exaggerating the "value" of the outcome through their impact on the magnitude of dopaminergic signalling in frontal and striatal systems (Redish et al., 2008), which then causes drug cues to become overvalued at the expense of other natural rewards, possibly contributing to compulsion and to a marked narrowing of life goals to obtaining and using drugs (Hyman, Malenka, & Nestler, 2006). An extensive literature shows that drug-dependent individuals exhibit attentional biases to drug-related stimuli (Franken, 2003) which predicts drug craving and relapse (Carter & Tiffany, 1999). This effect has been shown for most drugs of abuse (Ehrman et al., 2002; Field, Eastwood, Bradley, & Mogg, 2006; Hester, Dixon, & Garavan, 2006; Marissen et al., 2006; Mogg, Field, & Bradley, 2005).

It has been suggested that the normative developmental changes that occur in addiction-relevant neural circuits may not only underlie the propensity for adolescents to experiment with substances of abuse, but may also make the adolescent brain more vulnerable to the pharmacological impact of substances of abuse (e.g. Casey & Jones, 2010; Ernst & Luciana, 2015; Ernst, Pine, & Hardin, 2006; Wetherill & Tapert, 2013; Wiers et al., 2007), thus, creating particular vulnerability for addiction among early onset users. As governments are currently revising their drug policies, and considering decriminalising certain substances of abuse, such as cannabis, it is extremely important that we consider all the available neuroscientific findings on individual differences in the vulnerability to SUD, and the effects of drugs of abuse on the adolescent brain, to inform such policies.

Individual differences in vulnerability to addiction

A number of individual difference factors have been identified for addiction, which are generally understood as reflecting three domains on risk: environmental (e.g. access, social norms, and parental, peer or cultural influences), individual (e.g. personality, psychopathology, cognitive ability) and genetic/biological. By impacting on accessibility and acceptability of the behaviour, social influences can impact on age of onset of use, frequency of use, and substance abuse and related harm, and to a lesser extent, transition to dependence (see Strang et al., 2012 and Anderson et al., 2016 for thorough discussion cultural influences and social policies affecting substance use in the general population, including young people). The nature of the relation-

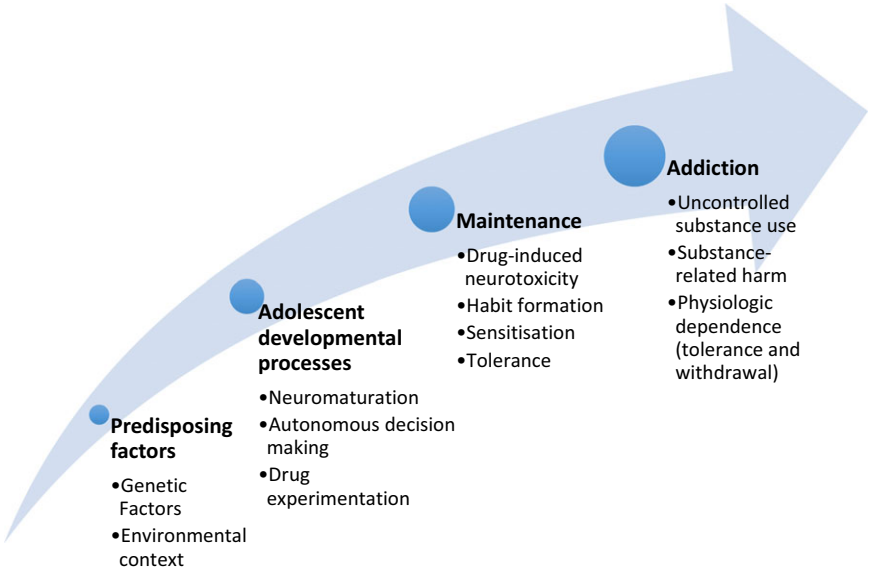

Figure 1 Overview of the developmental process of addiction

ship between substance use and personality or psychopathology is such that no one particular trait or pattern of psychopathology is uniquely linked to risk. Rather a number of personality traits and psychological/psychiatric disorders are associated with risk for SUDs, including externalising disorders, mood disorders, anxiety and psychotic disorders (See Castellanos-Ryan & Conrod, 2012; for review). Finally, another very important individual risk factor for substance misuse is the widely documented heritable nature of SUD. The heritable nature of alcohol dependence was established through twin and adoption studies, with twin studies reporting heritability in the range of 50–60% (Agrawal & Lynskey, 2008; Goodwin, 1979; Heath et al., 1997; Kendler, Heath, Neale, Kessler, & Eaves, 1992; Kendler, Neale, Heath, Kessler, & Eaves, 1994). Substantial genetic components have also been documented for related measures, such as, frequency of alcohol consumption and maximum number of drinks consumed in a 24-hr period (Agrawal et al., 2012; Saccone et al., 2000). The heritable nature of drug use is also well-established, with some studies suggesting genetic influences that are both common and specific to various forms of substance misuse (Kendler et al., 2015).

The present review will provide a summary of recent neuroimaging and neuropsychological studies that attempt to understand the mechanisms underlying these individual differences in vulnerability to addiction during the adolescent period, from a neurocognitive perspective. We will review relevant studies that investigate how individual differences in the functioning of neural networks implicated in addiction are also relevant to substance-related behaviours in the first two stages of this progressive disorder (i.e. the onset of substance use and the escalation into heavier use), and how these processes might be related to long-term risk for transition into addiction or SUD. We will also attempt to differentiate pre-existing vulnerabilities from drug-induced effects on the brain. Given the lack of experimental research directly comparing neurocognitive functioning of adolescent and adult participants with SUD, we will also parallel, where possible, findings in adults, to those in adolescents with various substance use profiles, to further inform our conclusions.

Normal neurodevelopmental processes in adolescence

During normative development, the brain undergoes a number of maturational changes, including synaptic pruning and myelination, that are thought to impact on emotional, motivational and cognitive processes (Luna & Sweeney, 2004), allowing for a more efficient organisation of the cortex, more efficient neural activity, and consequently improved cognitive functioning (Luna, Garver, Urban, Lazar, & Sweeney, 2004).

Neurodevelopmental morphology studies indicate that grey matter volume and cortical thickness change in an inverted U curve trajectory across the life span. Grey matter volume peaks around ages 12–14, followed by a decline in thickness and volume over adolescence (Sowell et al., 2003). These changes occur in stages, with the declines beginning in the striatum and sensorimotor cortices in early adolescence and shifting in later adolescence to the dorsolateral prefrontal cortex (PFC), which is also the last area to myelinate (Paus et al., 1999; Sowell, Trauner, Gamst, & Jernigan, 2002). Prominent grey matter volume decreases have been shown in medial parts of the parietal cortex and posterior parts of the temporal cortex, as well as in middle frontal gyri,

with these regions developing late into adolescence (Giorgio et al., 2010). Grey matter volume group differences were observed in the lateral orbitofrontal cortex (OFC) and in the right nucleus accumbens (NA; a nucleus within the ventral striatum of the basal ganglia) between groups of early adolescents, late adolescents, and adults in their early 20s (Urošević, Collins, Muetzel, Lim, & Luciana, 2012). In addition, cortical thickness declines during adolescence with parietal, as well as medial and superior frontal regions, including the cingulate cortex, showing the most prominent changes (Tamnes et al., 2010). By contrast, white matter volume and density, particularly in fronto-parietal regions, increase across adolescence (Lenroot et al., 2007; Nagel et al., 2006).

Dual-process models of control in adolescence

While further studies are needed to reliably link these morphological brain changes to changes in adolescent behaviour (Bjork & Pardini, 2015), a number of recent neurodevelopmental models of decision making suggest that the differential rates at which certain brain structures and connections develop may underlie stereotypical adolescent behaviours, such as sensation seeking, and impulsive and risky decision making (Casey & Jones, 2010; Ernst, Romeo, & Andersen, 2009; Ernst et al., 2006). Addiction-relevant subcortical circuitry, and their associated projections, implicated in reward-processing, motivation, and emotional reactivity (i.e. basal ganglia/limbic regions, and regions such as the OFC), seem to develop early during adolescence (Bava & Tapert, 2010; Ernst & Luciana, 2015; Galvan, 2010; Spear, 2000). By contrast, frontal cortical circuitry (i.e. dorso-lateral regions of the PFC) implicated in the top-down control of cognition, behaviour, and emotion, are thought to continue to develop into late adolescence (Casey, Getz, & Galvan, 2008; Hare et al., 2008; Spear, 2000; Vink et al., 2014). This early maturity in adolescent fronto-basal-ganglia/limbic circuitry is proposed to result in adolescent behaviour being strongly driven by a heightened sensitivity to rewards and positive affect, and a relative disregard for negative outcomes. Due to the late maturation of prefrontal control circuits, adequate control of these responses is compromised, and thus the propensity to risky decisions is increased (Casey & Jones, 2010; Ernst et al., 2006, 2009).

Dual-process models of cognitive control have also been applied to addiction, whereby increased sensitivity to rewards/positive-affect/motivational-cues (or "bottom-up" driven responses), and immature "top-down" frontal control of "bottom-up" responses, confer risk for the initiation and maintenance of uncontrolled behaviours, such as substance misuse. These models further suggest that the neurodevelopmental imbalance in adolescent fronto-basal-ganglia/limbic circuitry is further prolonged or exaggerated by heavy substance use during this developmental period, resulting in more uncontrolled patterns of substance use, thereby increasing the risk for SUD (Field, Wiers, Christiansen, Fillmore, & Verster, 2010; Gladwin, Figner, Crone, & Wiers, 2011; Wiers et al., 2007).

These theories help to explain why substance use typically has its onset during adolescence, and perhaps why earlier age of onset of substance use so robustly predicts risk for substance abuse and dependence (e.g. Grant & Dawson, 1998). However, to explain the marked individual differences in susceptibility to SUDs, it is necessary to go beyond global dual-process models. Furthermore, these theories focus on cognitive control and reward processing, and fail to explain the role of negative affect, stress, and internalising psychopathology in risk for substance use. In the following sections, we will present cross-sectional, prospective, and where possible longitudinal studies that have examined the extent to which a number of key risk factors for SUD, particularly genetic factors, temperament-based personality factors and neurocognitive factors, might further affect some of the key processes of the dual-process model to further influence individual vulnerability to early-onset substance use and progression to substance misuse. Furthermore, we expand the dual-process model to incorporate other relevant brain circuits, such as those implicated in negative affect, threat processing and psychosis, to consider a broader set of risk factors for early-onset substance use and misuse. Specifically, we examine how risk factors for heavy substance use in adolescence are reflected as individual differences at cognitive and neural levels in the following domains: (a) reward processing, (b) behavioural control, (c) negative affective processing, and (d) psychosis-proneness. Finally, we will also examine whether these indices are further impacted by substance use itself. When considering the evidence for each of these mechanisms we address, where possible, the extent to which the evidence suggests distinct mechanisms that may be unique to SUDs, or common mechanisms associated with a broader externalising spectrum or other dimensions of psychopathology.

Recognising the high rate of comorbidity between SUDs and other externalising disorders, the variability across studies with respect to how comorbidity is addressed is a critical complicating issue when interpreting findings on neurocognitive risk factors for addiction. Evidence indicates that these disorders share some common, as well as distinct, genetic and environmental aetiologies (Hur & Bouchard, 1997; Pedersen, Plomin, McClearn, & Friberg, 1988). A number of empirical studies support the validity of a general externalising spectrum model and indicate that their shared variance may be explained by common genetic and environmental influences, as well as premorbid personality

personality traits and neurocognitive deficits (Castellanos-Ryan, Rubia, & Conrod, 2011; Oosterlaan, Logan, & Sergeant, 1998). Thus, in addressing risk mechanisms for substance use in adolescence it is important to consider the extent to which they represent common mechanisms across externalising disorders or all forms of psychopathology, or ones potentially conferring specific liability to substance use. This review will also attempt to layout a theoretical framework for studying addiction from a developmental perspective which acknowledges and explains the high rate of cooccurrence between substance use behaviours and other forms of psychopathology.

Individual differences in adolescent substance misuse risk: beyond the dual-process model

Reward processing and substance use risk in adolescence

Personality measures. Considering the dominant role of dopamine-reward hypotheses in biological theories of addiction, we first examine how individual differences in reward sensitivity and reward processing are implicated in substance use behaviours in adolescents. A number of personality and neuropsychological studies link cognitive (Castellanos-Ryan et al., 2011; Colder et al., 2013), neural (Castellanos-Ryan et al., 2014) and self-report indices of reward sensitivity (Castellanos-Ryan & Conrod, 2011; Lyvers, Duff, Basch, & Edwards, 2012; Mahu, Doucet, O'Leary-Barrett, & Conrod, 2015) to risk for substance misuse in adolescence, such that the higher the sensitivity, the higher the risk.

Neural measures. Animal and human studies have identified a distributed network of regions within cortico-basal-ganglia-thalamo-cortical loops that respond to natural and monetary rewards (see Haber & Knutson, 2010). This network incorporates dopamine-mediated pathways, including a mesolimbic pathway with dopaminergic (DA) cells in the ventral tegmental area (VTA) projecting into the nucleus accumbens (NA) and the basolateral amygdala; a nigrostriatal pathway with DA projections from the substantia nigra (SN) to dorsal parts of the striatum (dorso-lateral parts of the caudate and the putamen); and a mesocortical pathway with DA cells in the VTA projecting to parts of the PFC, including the OFC, and the anterior cingulate (ACC) [Kalivas & O'Brien, 2008; but see Wise (2009) for alternative findings on the functional and anatomical distinctiveness of nigrostriatal and mesolimbic pathways]. Additional connections include to limbic structures such as the amygdala, the hypothalamus, and the hippocampus, as well as innervation from the ventro-medial PFC (Haber & Knutson, 2010), some of which involve key interactions between dopamine and glutamate or γ-aminobutyric acid (GABA), which explains why drugs of abuse with different chemical properties can all impact on dopamine release in this network.

A recent meta-analysis of human functional neuroimaging (fMRI) data reported that reward-based tasks (irrespective of the reward outcome, or whether participants were in the phase of anticipating, receiving or evaluating an outcome) generally elicited increased Blood-Oxygen-Level-Dependent (BOLD) responses within bilateral NA, caudate, putamen, global pallidus, thalamus, anterior insula, lateral/medial OFC, ACC, supplementary motor area (SMA), dorso-lateral parts of the PFC, as well as the posterior cingulate cortex (PCC) (Liu, Hairston, Schrier, & Fan, 2011), confirming and extending previous findings from animal studies.

However, longitudinal and prospective neuroimaging studies directly investigating reward circuitry in adolescence in relation to risk for substance use are limited; nevertheless, from the data so far, it seems that physiological differences in reward-elicited neural responses in the striatum, are linked prospectively to a specific vulnerability for the onset of substance use, and with heavier/problematic use in adolescence. For example, reduced left NA volume in substance naïve adolescents aged 15, predicted substance use initiation (initiation of regular alcohol use and/or any use of other substances) by age 18 (Urošević et al., 2015). Stice, Yokum, and Burger (2013) showed that increased BOLD responses in caudate and putamen, elicited by the receipt of monetary rewards, relative to a no win condition, at age 15, predicted substance use onset (use of beer/wine/wine coolers, hard liquor, cigarettes, marijuana, stimulants, downers, inhalants, and hallucinogens) over a 1-year follow-up period. Similarly, increased NA activation in anticipation of monetary rewards, in a sample of adolescents at familial risk for alcohol dependence, was associated with future alcohol problems, and interestingly, this effect was influenced by gamma-aminoboutyric acid alpha-2 receptor (GABRA2) genotype via hyperactivation of the NA (Heitzeg et al., 2014).

However, not all studies confirm these findings. Using data from the IMAGEN study, (a functional-structural imaging study with 2200 European adolescents tested every 2 years between ages 14 and 18), and a machine learning prediction model applied to a subset of the IMAGEN sample, Whelan et al. (2014) did not find an association between striatal volume or reward-elicited-striatal-responses, and future binge drinking; rather, future (age 16) binge drinking was predicted by reduced activation during reward anticipation in occipito-temporal and PCC regions, reduced activity in the left temporal pole, and increased activity in bilateral superior frontal gyrus, during reward anticipation at age 14. These findings are corroborated by those of other studies, albeit not all longitudinal in nature, reporting increased activations in frontal regions including

the OFC and ventro-medial PFC (regions implicated in coding the subjective value of rewards; Levy & Glimcher, 2012) to be associated with substance use in adolescence (Chung et al., 2011; De Bellis et al., 2013; Hulvershorn et al., 2015). Therefore, reward-related processing abnormalities in striatal-frontal circuits, and not simply striatal circuits, appear to be observed in youth at risk of early-onset substance use and misuse.

Genetic markers. While animal models of addiction also implicate novelty seeking traits in addiction vulnerability, and confirm a heritable component to this trait, these studies have not yet identified the genetic factors mediating these individual differences (e.g. Meyer & Bardo, 2015). Several candidate gene studies have linked dopamine-related genetic markers to reward-related behaviours and addiction (Baker, Stockwell, Barnes, Haesevoets, & Holroyd, 2015; Dalley et al., 2007); however, meta-analyses (Forero, López-León, Shin, Park, & Kim, 2015) and genome wide association scans (GWAS), which involve an unbiased search across the whole genome to identify or confirm genetic loci associated with a particular trait, have yet to confirm the role of these genetic factors in addiction. One recent genome wide study of alcohol consumption in a very large sample (n = 47,501) of individuals identified the gene RASGRF2 as a top hit mediating alcohol consumption (Schumann et al., 2011). This gene also appears to be involved in ethanol-induced release of dopamine in the striatum in animal models. Using data from the IMAGEN study, these authors also showed a significant association between the RASGRF2 gene and striatal BOLD responses during reward anticipation at 14 years of age and frequency of drinking alcohol at 16 years of age (Stacey et al., 2012). However the role of RASGRF2 in reward-related learning is not clear and requires further investigation.

Behavioural control and substance use risk in adolescence

Personality measures. A weakened ability to control one's behaviour, namely, impulsivity, has also been implicated in the transition from controlled to compulsive drug seeking and taking in both human (e.g. Goldstein & Volkow, 2002) and animal models of addiction (Dalley et al., 2007). Poor behavioural or inhibitory control, whether the deficit is preexisting or is the consequence of substance use, can lead to heavier use and abuse, once substance use has started, through an inability to regulate consumption, or may lead to differential patterns of substance use, as is the case in binge drinking (Field et al., 2010). Using self-report measures of impulsivity and self-control, a large number of well-controlled prospective studies have shown impulsivity scores predict future substance use and misuse, and independent of reward sensitivity, novelty seeking or other measures of risk (Castellanos-Ryan et al., 2011; Krank et al., 2011; Whelan et al., 2014). Studies of child temperament have also shown that two largely uncorrelated temperament profiles of children before the age of 5 (undercontrolled and extraverted/sociable) predict future risk for alcohol problems in adolescence (Dick et al., 2013) and that these longitudinal relationships were respectively mediated through adolescent personality traits of low conscientiousness (impulsivity) and sensation seeking.

Neural measures. Cognitive and neuroimaging studies of top-down, behavioural control have often used the Stop-Signal task (SST; Logan, Cowan, & Davis, 1984), which tests the ability to stop an initiated Go response when a Stop signal appears, and the Go/No-Go task, which tests the ability to withhold a task-induced dominant, prepotent Go response, when less frequent No-Go stimuli are presented. Functional neuroimaging (fMRI) studies in healthy volunteers performing SST and Go/No-Go tasks demonstrate increased inhibition-related BOLD responses in a fronto-basal-ganglia network, encompassing the right IFG (IFG; the pars opercularis moving into the insula), the dorsolateral prefrontal cortex (superior and middle frontal gyri), the dorsomedial prefrontal cortex (supplementary motor area and presupplementary motor area; pre-SMA) and the basal ganglia/thalamus, in response inhibition (Aron, 2007; Aron, Behrens, Smith, Frank, & Poldrack, 2007; Aron & Poldrack, 2006; Aron et al., 2007; Chambers, Garavan, & Bellgrove, 2009; Li, Huang, Constable, & Sinha, 2006). In addition to these areas, the dorsal ACC has also been linked to processes involved in successful behavioural inhibition, including error monitoring (Chevrier, Noseworthy, & Schachar, 2007; Matthews, Simmons, Arce, & Paulus, 2005).

The results of neuroimaging studies using SST and Go/No-Go tasks suggest that dysregulated neural responses linked to inhibition are associated with a future risk for substance use onset and problem use in adolescence; however, the direction of the relationship is not consistent across all studies. Norman et al. (2011) examined BOLD responses to correct stopping in a Go/No-Go task in substance naïve adolescents aged 12–14, and monitored their substance use for 3 years. Those who initiated regular substance use, including alcohol and cannabis, relative to those who remained substance naïve, showed significantly lower activation in response to correct No-Go trials at baseline in IFG, SMA, superior and middle frontal gyri, cingulate cortex, putamen, and the inferior parietal lobule, suggesting that these dysregulated responses confer risk for early-onset substance misuse rather than reflect consequences of such use. Furthermore, Mahmood et al. (2012), examined whether neural responses in a Go/No-Go task would predict an escalation of substance use (use of alcohol, nicotine, marijuana, and other

illicit drugs, as well as using prescription or over-the-counter medication to get high). A group of 16–19 year olds demonstrating either a high or a low frequency of substance use history at baseline were monitored for their substance use for 18 months. Results showed that lower baseline medial PFC (encompassing the ACC) BOLD responses to correct inhibition trials predicted more drug dependence symptoms in the subsequent 18 months above and beyond baseline symptom levels. By contrast, Wetherill, Castro, Squeglia, and Tapert (2013) showed that increased activation during correct No-Go trials in bilateral middle frontal gyrus at ages 12–14, and before the initiation of alcohol use, were predictive of a transition into a pattern of heavy alcohol use that was coupled with alcohol-induced memory blackouts over a 5 year period.

Inconsistent findings with respect to the direction of the predictive neural response are also evident from studies that examined links between neural responses during failed inhibitions and problem substance use in adolescence. Using data from the IMAGEN study, and a machine learning prediction model to predict age 16 binge drinking from age 14 brain data, Whelan et al. (2014) showed that when failing to inhibit a motor response in the SST, future binge drinkers showed greater activity in the right middle, medial and precentral gyri, and in the left postcentral and middle frontal gyri. Future binge drinkers also showed reduced grey matter volume in the right parahippocampal gyrus, and increased grey matter volumes in the left postcentral gyrus. Finally, another study, in a group of 9–12 year olds, found blunted left middle frontal responses to failed inhibitions to be predictive of problem drinking by ages 13–16 (Heitzeg et al., 2014).

Summary of reward processing and cognitive control findings

It appears that findings across studies using self-report, cognitive, neural and to lesser extent, genetic indices of reward processing and cognitive control converge around the conclusion that reward sensitivity, possibly reflected by hypersensitivity of striato-cortical reward circuits (e.g. Heitzeg et al., 2014; Stice et al., 2013), and impulsivity, likely reflected as hypofunction of frontal control circuits (e.g. Mahmood et al., 2012; Norman et al., 2011), are independently associated with adolescent substance use. However, not all studies report consistent directional findings (e.g. Wetherill et al., 2013; Whelan et al., 2014), which might be related to variability across studies in the substance use outcomes that were assessed (e.g. binge drinking vs. substance use onset vs. escalation to "heavy" use vs. heavy use with blackouts), differences in the age groups that were tested, and the extent to which comorbid psychopathology was covaried. Differences across studies in the age groups studied both at baseline and at follow-up periods are important given the proposed neurodevelopmental trajectory of the PFC and related top-down functions (Casey & Jones, 2010; Spear, 2000; Vink et al., 2014). More studies are needed to be able to map these different findings to different developmental stages in adolescence. We address the issue of comorbidity in more detail below.

Substance use and externalising disorders: common and distinct neural mechanisms

Current research in this domain attempts to more closely address the complex issue of determining the extent to which neurocognitive mechanisms associated with reward and behavioural control are unique to substance use risk or are common to the broader externalising spectrum. Although substance use is substantially correlated with other externalising symptoms, when common variance across externalising behaviours is accounted for, variance specific to SUDs can be identified (Krueger, 1999; Krueger & Markon, 2006; Krueger, Markon, Patrick, Benning, & Kramer, 2007; Krueger et al., 2002) Behavioural genetic studies have also shown that the genetic predisposition to substance misuse is shared across a number of externalising problems (e.g. McGue, Iacono, & Krueger, 2006). Studies investigating the cognitive and neural correlates of these latent dimensions of risk suggest that unique variance in substance use appears to be associated with distinct cognitive performance and neural activation patterns during tasks involving reward processing or incentive reward, whereas neural correlates of behaviour control may overlap with conduct problems (CD) and attention deficit/hyperactivity (ADHD) (Castellanos-Ryan et al., 2011). Using data from the IMAGEN study, Castellanos-Ryan et al. (2014) reported a seminal analysis in which they modelled externalising behaviours using a latent substance misuse factor (composed of: age at onset of drinking, number of drugs used, frequency of drunkenness, frequency of bingeing, the interaction of quantity and frequency of drinking, and drinking-related problems), a conduct disorder factor (composed of: scaled likelihood of diagnosis, parent- and self-reported symptoms, self-reported bullying behaviour), and an ADHD factor (composed of: scaled likelihood of diagnosis, parent-, and self-reported symptoms), from age 14 data. Hierarchical structural equation modelling, indicated that the best fitting model was one that included a latent factor reflecting a dimension of psychopathology that is common to all forms of these externalising behaviours, and two subfactors that reflected variance specific to ADHD (with some CD) and substance misuse. Common variance across externalising behaviours was associated with high self-report impulsivity and higher BOLD responses in the pre-SMA and precentral gyrus during successful stopping in a Stop Signal Task,

coupled with low BOLD responses in the SN and subthalamic nucleus (STN). A factor which captured variance specific to ADHD and CD was associated with impulsivity, poor response inhibition (as assessed with a go-nogo behaviuoral task), as well as with low BOLD responses in frontal brain areas bilaterally during failed inhibition on the Stop Signal Task. In contrast, unique variance for early-onset substance misuse was associated with high sensation seeking, as well as with differential BOLD responses elicited by reward anticipation: high BOLD responses in the left OFC but low BOLD responses in the left IFG. Delay discounting (i.e. the tendency to choose smaller, sooner rewards over larger rewards given later in time) was associated with all three dimensions of risk and did not differentiate among them. These authors hypothesised that there are at least three neurocognitive correlates of risk for externalising problems, of which two appear highly relevant to early-onset substance misuse: overactive premotor cortex (i.e. pre-SMA) involvement coupled with underactive SN and STN involvement during correct stopping behaviour, implicated in general behavioural control; and overactive OFC coupled with underactive IFG-related function, during reward anticipation, which might interfere with stopping behaviours in highly incentive-rewarding situations only and which is specifically related to nonimpulsive thrill/sensation seeking (Castellanos-Ryan et al., 2011). Poor response inhibition and reduced frontal activation during failed stopping, according to this study, is more centrally involved in conduct problems and ADHD symptoms. These findings are consistent with other similar studies on the hierarchical structure of psychopathology linking sensation seeking personality to the variance specific to substance misuse in adolescence and impulsivity to variance common to externalising problems (e.g. Castellanos-Ryan & Conrod, 2011; Castellanos-Ryan et al., 2014).

Finally, very few studies have examined how individual differences in these two interacting systems might further influence adolescent substance use behaviour, as would be hypothesised by many dual-process models. One very recent study by the IMAGEN consortium is one of the only studies to examine the interaction between striatal and cortical functioning in the prediction of alcohol misuse in adolescents, and does so within a genetically informed design. Baker, Conrod, and IMAGEN Consortium (2016) recently investigated the role of the dopamine-relevant genetic markers in frontal and striatal response to reward and reported that the functional polymorphism rs686 of the DRD1 gene and Taq1A of the ANKK1 gene influenced medial and lateral OFC activation during reward anticipation, respectively. Using a path model to predict 16 years drinking behaviour from 14-year genetic and brain data, analyses revealed a significant indirect relationship between the functional polymorphism rs686 of the DRD1 gene and early onset of alcohol misuse, which was mediated by the interaction between the medial OFC and the ventral striatum responses to reward. Again, these findings further support many of the hypotheses proposed in the dual-process model of adolescent risk taking behaviour, but provide further qualification of the model by suggesting that genetic factors render individuals particularly susceptible to dysregulation between the two main brain circuits involved in cognitive control and reward-related behaviour.

Externalising traits and sensitivity to the reinforcing properties of substances of abuse

Cross-sectional and pharmacological challenge studies, including positron emission tomography studies of amphetamine-induced dopamine release (e.g. Boileau et al., 2006), have also shown that sensation seeking traits are associated with biological (e.g. cardiac responses) and subjective sensitivity (e.g. self-reported reinforcement) to the incentive rewarding and enhancing effects of drugs of abuse, including nicotine (Perkins et al., 2008) alcohol (Brunelle et al., 2004), cannabis (Comeau, Stewart, & Loba, 2001), amphetamines (Boileau et al., 2006), and prescription opioids (Zacny, 2010). These studies suggest that sensation seeking is not only reflected in behavioural sensitivity to incentive reward cues but also a pharmacological sensitivity to the incentive-rewarding properties of substances of abuse, which might explain the relationship between sensation seeking and variance specific to substance misuse.

Interestingly, a recent literature also links impulsivity with behavioural sensitivity to drugs of abuse, but through different motivational processes. Impulsivity has been specifically linked to a susceptibility to the misuse of stimulant substances (see Conrod, Castellanos-Ryan, & Strang, 2010; Castellanos-Ryan & Conrod, 2012; Woicik et al., 2009). According to animal models of impulsivity, stimulant drugs appear to have paradoxical effects on impulsivity and stopping behaviour depending on baseline levels of impulsivity. For example, nicotine increases impulsivity in nonimpulsive rats, but appears to reduce or normalise impulsivity in animals with higher baseline levels of impulsivity (see Jupp & Dalley, 2014 for review). These effects parallel observations from human studies with children with ADHD treated with psychostimulant medications.

Summary of neurocognitive predictors of substance use risk

In summary, studies investigating the neurocognitive predictors of substance use risk have not been consistent in how comorbid psychopathology is controlled for. Generally, these findings are consistent with suggestions from dual-systems models that

abnormal functioning in frontally mediated control and striato-frontal reward processing are relevant to substance misuse risk. The evidence also suggests that individual differences in the functioning of these systems are respectively linked to personality traits of impulsivity and sensation seeking. Very few studies specifically address the hypothesis that it is the interaction between these systems, specifically poor control and heightened reward processing, that is associated with substance use risk (Geier, 2013). More studies are needed, especially ones investigating how normative interactions between these networks (and personality dimensions) may further predict risk taking and substance misuse in the general population (Geier, 2013). So far, the findings suggest that it is individual differences in how these two cognitive/motivational systems function that predict individual risk for early-onset substance use and misuse, patterns of use, as well as, comorbid psychopathology profiles.

Negative affect/internalising problems, stress, and substance use risk in adolescence

Negative affect/internalising symptoms

In previous publications, we have reviewed the evidence suggesting that internalising problems also appear linked to the risk for substance misuse (Castellanos-Ryan & Conrod, 2011; Newton, O'Leary-Barrett, & Conrod, 2013). Individuals who experience depressed mood and/or anxiety, drink more, and more often (see review by Mackie, Conrod, & Brady, 2012b). The few prospective studies suggest that children with high negative affect, depression, or anxiety symptoms are more likely to initiate alcohol- and nicotine-use early (Deas-Nesmith, Campbell, & Brady, 1998; Wills, Sandy, Shinar, & Yaeger, 1999; Wills, Sandy, & Yaeger, 2002).

Children's temperament manifests early in life, and behavioural differences (e.g. undercontrolled vs. inhibited) as early as 3 years of age have been shown to differentially predict psychopathology in adulthood, as well as to increase the likelihood of having alcohol-related problems (Caspi, Moffitt, Newman, & Silva, 1996). Individuals can thus be situated on developmental pathways that increase or decrease the likelihood of SUDs early in life, and these trajectories can be detected at various developmental stages. Those who show personality deviance at any point, have a greater risk for future substance use and psychopathology. In addition to externalising traits, internalising traits such as neuroticism, hopelessness, and anxiety sensitivity are associated with substance use and alcohol problems, and the tendency to report using substances to regulate a negative affective state, for example, to cope with anxiety and depression (Grant, Stewart, O'Connor, Blackwell, & Conrod, 2007; Woicik, Stewart, Pihl, & Conrod, 2009). Personality traits moderate the association between internalising symptoms and alcohol-use, such that individuals with high levels of hopelessness and depressive symptoms (e.g. Stewart et al., 2011) or high levels of anxiety sensitivity and anxiety, show more rapid increase in alcohol dependence symptoms across adolescence, also known as telescoping (Mackie, Castellanos-Ryan, & Conrod, 2011; Topper, Castellanos-Ryan, Mackie, & Conrod, 2011). Anxiety sensitivity, also shown to be a risk factor for panic-related anxiety disorders (Marshall, Miles, & Stewart, 2010; McLaughlin & Hatzenbuehler, 2009) has been consistently associated with self-medication motivations for substance use and increased substance use in adults (Woicik, et al., 2009; Leventhal & Zvolensky, 2015), particularly misuse of anxiolytic and sedative substances (Conrod, Pihl, Stewart, & Dongier, 2000; Leventhal & Zvolensky, 2015; Woicik et al., 2009). However, this personality trait also appears to be a protective factor against early onset drinking and drug use in early and midadolescence (Castellanos-Ryan, O'Leary-Barrett, Sully, & Conrod, 2013; Whelan et al., 2014), suggesting that this personality characteristic is associated with vulnerability to substance misuse only later in development, following interaction with some specific developmental event.

Stress, trauma, and substance misuse

In addition to, and potentially overlapping with, risk associated with internalising symptoms, is evidence indicating that liability to substance use may be linked to alterations in the HPA axis and associated limbic regions (see Arnsten, 2009; Koob, 2008; Logrip, Zorrilla, & Koob, 2012). Much of this work has been driven by the observation that stressors and traumatic events, including early childhood trauma, loss, neglect, and peer victimisation, appear to confer risk for substance misuse, including early-onset substance use, and telescoping to problematic use (Breslau, 2002; Topper et al., 2011). There is also evidence that internalising symptoms and personality mediate and moderate the relationship between trauma exposure and risk for substance misuse through self-medication motives for substance use (Leventhal & Zvolensky, 2015; Luk et al., 2010; Topper et al., 2011).

However, only a few studies have examined how HPA axis functioning and one's responsiveness to stress, as assessed using cortisol levels, may be related to early substance use in adolescence. Increased evening/night-time cortisol levels in adolescents aged 15, predicted both initiation and persistence of smoking within a 5 year follow-up period (Rao, Hammen, London, & Poland, 2009), as well as onset of alcohol and illicit substance abuse (Rao, Hammen, & Poland, 2009). Adolescents initiating cannabis use at an early age (9–12 years) had lower basal cortisol levels than those who initiated cannabis use at a later age (13–14 years). However, both early-onset and late-onset cannabis using adolescents demonstrated higher

cortisol levels than nonusing adolescents (Huizink, Ferdinand, Ormel, & Verhulst, 2006). After controlling for age, sex, and maternal substance use, Huizink et al. (2009) showed that higher cortisol levels directly after waking were related to current experimentation of smoking in a group of 10–12 year olds. Cortisol levels did not associate with onset of alcohol use in this group. Thus, higher cortisol levels seem to confer risk for the experimentation with cannabis and nicotine, and with persistent nicotine use in adolescence.

By contrast, in response to acute stressors, some studies indicate that it is decreased stress-induced cortisol responses that is associatd with risk for adolescent substance use (but see Chaplin et al., 2012). For example, one study showed that male preadolescent boys of fathers with SUD demonstrated a reduced salivary cortisol response to an anticipated stressor, relative to controls. In addition, lower preadolescent anticipatory cortisol responses were associated with regular monthly cigarette smoking and regular monthly marijuana use during adolescence (Moss, Vanyukov, Yao, & Kirillova, 1999). Van Leeuwen et al. (2011) examined if adolescent cannabis users, tobacco users, and nonusers of both tobacco and cannabis would differ with respect to their HPA axis stress reactivity, as assessed using salivary cortisol, during a social stress task. Adolescents who had ever used cannabis in their lifetime had a significantly lower cortisol response to the acute stress procedure when compared to nonusers and tobacco users that had ever smoked. In addition, repeated cannabis users (defined as having used cannabis on at least five occasions in the past year) exhibited lower cortisol increases when compared to life-time ever users of either tobacco or cannabis. These findings are consistent with reports that high-risk adolescents for later SUD, based on familial history of SUD, demonstrate reduced cortisol levels in anticipation of acute stress, relative to controls (Evans, Greaves-Lord, Euser, Franken, & Huizink, 2013).

However, it is important to note that those studies that investigated self-reported stress reactivity in youth at risk of internalising problems, suggest that *heightened* stress reactivity to stress-induction paradigms confers risk for substance use, particularly among depression-prone and anxious individuals (e.g. Conrod, Pihl, & Vassileva, 1998; MacDonald, Stewart, Hutson, Rhyno, & Loughlin, 2001). A recent stress challenge study with young adults confirms that there might be two different stress-related pathways to substance misuse: one involving ventral medial reactivity to reward cues (reward sensitivity) and reduce amygdala reactivity to stress and the other involving reduced reward sensitivity and heightened amygdala reactivity to stress (Nikolova, Knodt, Radtke, & Hariri, 2015).

Other studies investigating personality risk factors for anxiety and mood disorders suggest that individuals who score high on measures of anxiety sensitivity are particularly sensitive to the fear-reducing effects of alcohol (Conrod et al., 1998; MacDonald et al., 2001; Zack, Poulos, Aramakis, Khamba, & MacLeod, 2007), and other anxiolytic substances, such as benzodiazepines. One process by which substances of abuse, particularly those with sedative/anxiolytic properties, might be particularly attractive for adolescents with internalising psychopathology, anxiety sensitivity, and perceived stress reactivity is by interfering with such individuals' tendencies to selectively process threat cues (Stewart, Westra, Thompson, & Conrad, 2000) and attend to negative self-relevant information (Aramakis, Khamba, MacLeod, Poulos, & Zack, 2012). Substance use might therefore be reinforced through negative reinforcement processes in such individuals, rather than incentive rewarding or poor impulsive control, as suggested for externalising traits.

Psychosis risk and substance use risk in adolescence

Like externalising and internalising psychopathology, psychotic disorders appear to exist along a spectrum with psychotic-like experiences considered as the behavioural expression of an underlying distributed liability for psychosis (Johns & van Os, 2001; van Os, Linscott, Myin-Germeys, Delespaul, & Krabbendam, 2009). This personality/behavioural profile also appears to be particularly susceptible to substance misuse and the psychosis-inducing effects of substances of abuse, particularly cannabis (Arseneault et al., 2002). Using a longitudinal design, Mackie et al. (2011, 2013) twice showed that a subset of young adolescents reporting moderate psychotic-like experiences showed a particular sensitivity to the effects of cannabis use on escalation of psychotic-like experiences. These findings have been replicated in two subsequent studies (Bourque et al., 2016; Wigman et al., 2011). These and other similar cohort studies have also identified childhood negative life events (e.g. early childhood trauma, and peer victimisation; Mackie, Conrod, & Brady, 2012a; Wigman et al., 2011) as factors that further exacerbate psychosis trajectories in those at risk.

Current theories of schizophrenia implicate the attribution of aberrant salience to irrelevant stimuli and a disturbed sense of self (Kapur, 2003; Van der Weiden, Prikken, & van Haren, 2015). Neuroimaging studies indicate that neural pathways underlying these functions include the striatum, hippocampus, and the subcortical dopamine system, and are impaired in adult patients with psychosis and youth at risk for psychosis (Bastos-Leite et al., 2015; Curcic-Blake, van der Meer, Pijnenborg, David, & Aleman, 2015; Debbané et al., 2014; Hall et al., 2008; Potvin et al., 2015; Seifert et al., 2008; Van Buuren, Vink, Rapcencu, & Kahn, 2011). The main cannabinoid receptor (CB1), which has been shown to play a role in brain maturation (Higuera-Matas,

Ucha, & Ambrosio, 2015), is found in high concentrations in these neural pathways (Pertwee, 2012). Recent neuroimaging studies also suggest that acute cannabis intoxication affects neural networks that overlap with those involved in salience attribution and self-reflection (Bossong, Jansma, Bhattacharyya, & Ramsey, 2014; Denier, Walter, Bendfeldt, Lang, & Borgwardt, 2012; Tan, Lauzon, Bishop, Bechard, & Laviolette, 2011).

However, it is also likely that the cannabis-psychosis link is mediated by more global effects on the brain. Using a genetically informed design with data from three large cohort studies, French et al. (2015), showed that genetic risk for psychosis (assessed according to genetic risk scores) was associated with cannabis-induced changes in brain cortical thickness, but in boys only. The findings, which were replicated across the three studied cohorts, suggest that genetic factors implicated in risk for psychosis are also implicated in risk for cannabis-related brain effects which are quite global. Whether these genetic factors are also implicated in the psychotic-like experiences trajectories described above has yet to be confirmed. Nevertheless, the evidence strongly suggests that individuals with psychological and genetic risk for psychosis are particularly sensitive to the harmful effects of cannabis, over and above the effects of other drugs, on brain and psychopathology outcomes.

A personality-based, multidimensional model of substance misuse vulnerability

Figure 2 presents a revision of a figure originally presented by Castellanos-Ryan and Conrod (2012) on personality-based risk pathways for SUDs and addiction. In the current diagram, we add a fifth risk trajectory, the psychosis-proneness trajectory, which appears to be specifically susceptible to cannabis and trauma, and their effects on the acceleration of psychotic-like experiences (e.g. Mackie et al., 2013). In this figure, we attempt to summarise the neurocognitive correlates of each risk trajectory, and the patterns of psychopathology to which they appear most related. Very little research is currently available on how these personality/behavioural dimensions interact, but the evidence strongly suggests that they are independent predictors of risk. In line with a Research Domain Criteria (RDoC) approach to understanding risk for psychopathology, as outlined by (Cuthbert, 2014), behavioural dimensions are considered to exist along a continuum, each with both specific and general environmental and genetic bases to them. Future research must begin to understand how these specific dimensions interact with each other to decrease or further increase risk, as well as how they interact with other environmental events. One very important event from a neuroscientific perspective of addiction is the impact of early onset and repeated use of substances of abuse on the functioning of the neurocognitive processes that appear to underlie these risk trajectories.

Effects of substance misuse on reward processing, behavioural inhibition, and stress in adolescence

Up until this point, we have focused on neurocognitive and affective factors that may confer vulnerability to substance use and misuse. We now move to consider how substance use, in turn, affects, in a potentially reciprocal manner, the functioning of these same systems (as well as impacts on other cognitive functions). Substances of abuse are known to have widespread effects on the brain, and heavy and chronic alcohol and cannabis users have been shown to show abnormalities on a number of global measures of brain structure, function, and connectivity (see meta-analyses by Xiao et al., 2015 and Monnig, Tonigan, Yeo, Thoma, & McCrady, 2013; and review by Newton et al., 2013). However, it is their impact on neural systems that also confer risk for substance use onset and misuse that may be most relevant to an escalation to more severe patterns of substance misuse (Field et al., 2010;Wiers et al., 2007; Xiao et al., 2015). For example, a systematic review of structural brain abnormalities among young adults with alcohol use disorders (under 40 years of age) identified that only PFC brain volumes were consistently reduced in alcohol cases relative to controls (Welch, Carson, & Lawrie, 2013). Because, very few studies are able to address this question longitudinally, we first attempt to review a very extensive literature which examines the gradient of effect with respect to severity of substance use history and brain abnormalities. The following sections will summarise studies that examined differences between adolescents or adults with SUD and matched controls, on neurocognitive indices of reward processing and behavioural control, as well as on cortisol and stress responses.

Effects of adolescent substance use on neural correlates of reward-processing

Cross-sectional neuroimaging studies investigating the effects of adolescent substance use on neural responses elicited by the anticipation and receipt of monetary rewards are few, and the results have been inconsistent based on the type of drug that was investigated. Peters et al. (2011) reported reduced activation in the ventral striatum during reward anticipation in adolescent cigarette smokers compared to controls. This response in smokers was significantly associated with smoking frequency, suggesting an effect of nicotine use, however, blunted ventral striatal reward-related activation was also observed in smokers who had

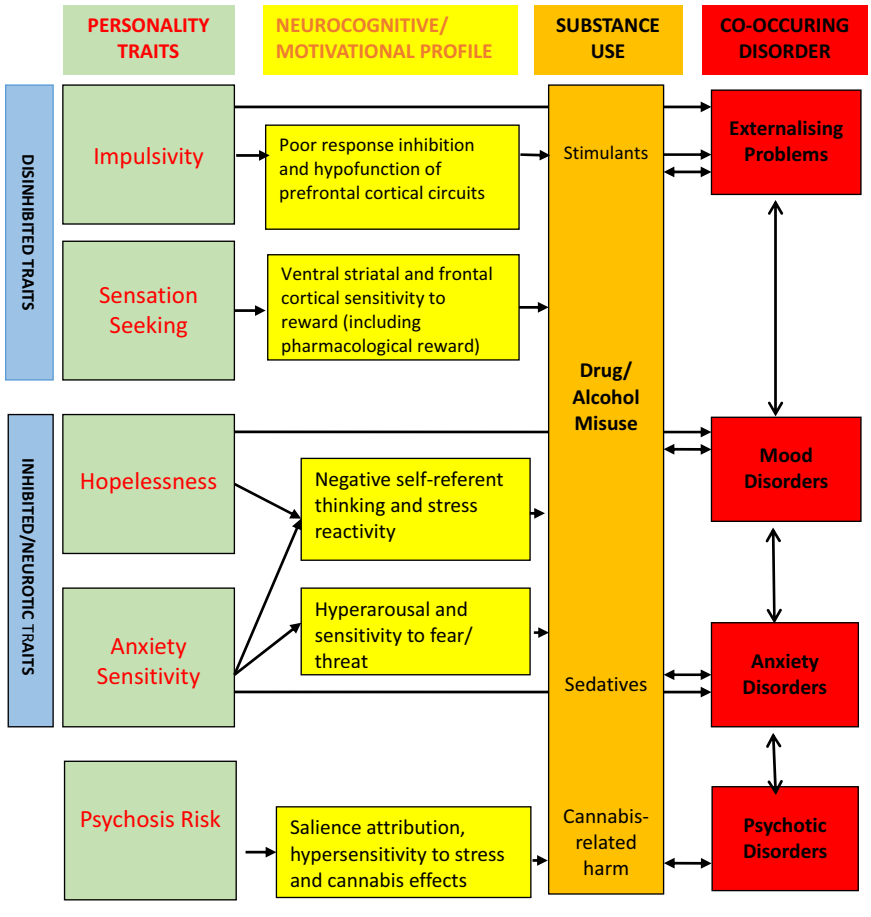

Figure 2 Overview of personality and neurocognitive, adapted from Castellanos-Ryan and Conrod (2012)

smoked on fewer than 10 occasions (Peters et al., 2011). This latter finding seems to converge with those reported by Stice et al. (2013) showing blunted reward-elicited striatal responses occurred as a function of "minimal" substance use. Karoly et al. (2015) also reported significantly lower NA activation to the anticipation of both high and low rewards in adolescent smokers, relative to a group of nonsubstance-using control participants, as well as relative to groups of adolescents using: (a) only alcohol, (b) cannabis and tobacco; and (c) cannabis, tobacco, and alcohol, suggesting reward processing dysregulation specifically as a function of only using nicotine in adolescence. Furthermore, reward-related NA responses observed among groups of cannabis users, alcohol users, cannabis and tobacco users, and poly-drug users, did not differ significantly, nor did they differ from activations found in the control group (Karoly et al., 2015). Jager, Block, Luijten, and Ramsey (2013) also did not find statistically significant differences in striatal activity during reward anticipation between adolescent cannabis users and nonusers. However, in this study, adolescent cannabis users, relative to controls, showed significant hypo-responsiveness of the left caudate and bilateral putamen on nonrewarded anticipation trials, rather than rewarded trials, suggesting abnormalities in a motivational circuit that might not be reward-specific, a possibly consistent with the aberrant salience hypothesis. These findings parallel those reported in adult substance users suggesting hypo-responsiveness to natural rewards in nicotine, cocaine, alcohol, and heroin dependent individuals, with some suggestion that nicotine dependence might further impair reward responding (Balodis & Potenza, 2015).

Thus while hypersensitivity to reward might confer one risk trajectory to substance misuse, early-onset substance misuse, particularly nicotine use, might cause blunted striatal responses to the anticipation of monetary rewards. Evidence from the few studies which have investigated the effects of cannabis use suggests that cannabis either does not cause reward-processing impairments, or causes blunted responses in nonreward conditions.

With reference to computational theories of reward processing and addiction, reduced reward responsiveness to natural rewards should also be coupled with a heightened sensitivity to drug-related cues as drug use becomes more frequent and habitual. Consistent with the adult literature, drug-dependent adolescents demonstrate heightened drug cue-reactivity relative to nondependent adolescents (Gray, LaRowe, & Upadhyaya, 2008; Tapert et al., 2003; Thomas, Drobes, & Deas, 2005; Upadhyaya, Drobes, & Thomas, 2004), including cannabis cue-reactivity (Nickerson et al., 2011).

Effects of substance use on neural correlates of behavioural control

With respect to the effects of adolescent substance misuse on stopping behaviour, Galván, Poldrack, Baker, McGlennen, and London (2011) compared minimally deprived (range between 30 and 1050 min) nicotine dependent adolescents aged 15–21, and matched healthy nonsmoking controls on behavioural performance and neural responses on the SST. There were no performance or activation differences between the two groups, but severity of smoking was negatively correlated with stop-elicited activity in the ACC, SMA, left IFG, left OFC, bilateral middle frontal gyrus, and right superior frontal gyrus, (Galván et al., 2011). Feldstein Ewing, Houck, and Bryan (2015) also reported negative associations between STOP-elicited responses in left IFG, as well as in the right insula, and past month substance use (days of alcohol and cannabis use).

Reduced activation in regions of the PFC, ACC, and SMA during correct inhibitions have also been found in nicotine, cocaine, and heroin using adults relative to matched controls (Fu et al., 2008; Hester & Garavan, 2004; Kaufman, Ross, Stein, & Garavan, 2003; Li et al., 2008; Luijten et al., 2014). These differences also appear to manifest as nondependent adult substance users start to transition to heavy frequent use of a substance. For example, heavy drinkers compared to light drinkers showed reduced activation during correct No-Go trials in the SMA and ACC, right middle frontal gyrus, and the thalamus (Ahmadi et al., 2013).

However, marijuana using college students showed increased stopping-related activation in the SMA relative to nondrug users (Hester, Nestor, & Garavan, 2009). Increases in BOLD responses associated with correct stopping were also found by Roberts and Garavan (2010) in a poly-drug using student population, but who predominantly used ecstasy and marijuana. They did not find performance differences between the groups, however the users, relative to controls, showed increased activation, during successful stopping, in frontal and parietal regions (right middle and inferior frontal gyri; and inferior parietal lobule). Increased activations in frontal and parietal regions (right superior and middle frontal gyri, bilateral medial PFC including SMA, bilateral posterior parietal gyri) were also found in adolescent marijuana users, relative to controls, during correct stop trials on a go/nogo task, relative to rest (Tapert et al., 2007). This study also failed to find behavioural task performance differences between the groups. Finally, the IMAGEN study showed that in a large sample of 1896 adolescents, a right frontal network that included the right IFG, right insula, and the right ACC, showed increased activation in response to correct inhibitions as a function of increased lifetime substance use (including alcohol, nicotine, and illicit drugs) (Whelan et al., 2012). This particular network of brain regions was differentiated from other networks implicated in cognitive control, because it was particularly related to severity of substance use.

Frequency of cannabis use is associated with structural brain abnormalities in the medial temporal lobe, temporal pole, parahippocampus, insula, and orbital frontal PFC (Battistella et al., 2014), areas which are known to contain cannabinoid CB1 receptors, and which are implicated in motivation and affective processing and emotion regulation. Interestingly, these abnormalities have been shown to be associated both with heavy cannabis use, relative to lighter cannabis use (controlling for the same duration of use), and earlier onset of use compared to later onset of use (Battistella et al., 2014). High potency cannabis has also been shown to be associated with greater structural changes on measures of brain connectivity (mean diffusivity) in the corpus collosum, a structure which is central to interhemispheric communication within the brain (Rigucci et al., 2015).

In summary, inconsistent findings are reported from studies examining differences between drug-dependent adults and adolescents, and nonusing controls using the SST and Go/No-Go tasks. Studies examining behavioural task performance are particularly inconsistent, with some studies demonstrating impairments in the ability to withhold a response, while others do not (See Smith, Mattick, Jamadar, & Iredale, 2014 for an extensive meta-analysis on behavioural and neuroimaging findings from several "control" tasks). By contrast, fMRI studies consistently demonstrate inhibition-related activation differences between substance users and controls within brain regions implicated in behavioural inhibition, although not always in the same direction, particularly across drug classes. Structural MR studies also suggest effects of heavy, high potency and early onset use of cannabis on brain structure and connectivity.

Effects of substance misuse on stress and HPA reactivity

Cross-sectional studies in adults also show that heavy alcohol users and those dependent upon alcohol, nicotine, and other drugs, demonstrate increased basal cortisol levels (Beresford et al., 2006; Boschloo et al., 2011; Fox, Tuit, & Sinha, 2013; Gianoulakis, Dai, & Brown, 2003; Steptoe & Ussher, 2006; Thayer, Hall, Sollers, & Fischer, 2006; Wand & Dobs, 1991). These data converge with the findings in adolescents and young adults presented above showing an association between increased basal cortisol levels and experimentation with cannabis and nicotine in adolescence and with findings of structural abnormalities in the areas of the brain involved in affective processing and emotion regulation (e.g. Battistella et al., 2014).

Flatter diurnal cortisol slopes have been associated with greater alcohol consumption in adult drinkers (Badrick et al., 2008). This finding parallels a recent (and the only) longitudinal study in adolescent participants. Ruttle, Maslowsky, Armstrong, Burk, and Essex (2015) examined the association between diurnal cortisol slopes at age 11 with the level of drinking at ages 15–18, as well as the effect of continued alcohol drinking on diurnal cortisol levels by age 18.5. They were unable to control for any drinking at age 11, nevertheless, they found that flatter diurnal cortisol slopes at age 11 significantly predicted heavier alcohol use at ages 15–18, which in turn significantly predicted flatter cortisol slopes at age 18.5, and these findings did not vary by sex. The findings suggest that HPA axis functioning, as assessed using diurnal cortisol levels, may be both a risk factor with respect to the escalation into heavier drinking, and can be influenced by heavy alcohol use both in adolescents and in adults. Studies of adult alcoholics have shown that cortisol levels in response to physical and psychological stressors are reduced even after abstinence (Bernardy, King, Parsons, & Lovallo, 1996; Errico, Parsons, King, & Lovallo, 1993; Lovallo, Dickensheets, Myers, Thomas, & Nixon, 2000), However, it should also be recognised that substance misuse increases the likelihood of victimisation and traumatic injury (Korcha et al., 2014) and few studies attempt to differentiate the effects of trauma exposure from the potential effects of drug exposure on subsequent stress reactivity patterns.

Longitudinal studies attempting to separate causes from consequences of substance misuse in adolescence

The majority of neuropsychological studies investigating the effects of substance use in adolescence have been cross-sectional. Consequently, it has been difficult to conclude whether the observed cognitive abnormalities are causal or consequential to alcohol and substance misuse. To date very few studies have been adequately designed to differentiate neurocognitive correlates of risk for substance use from the developmental changes that occur in cortico-limbic/basal-ganglia systems as a function of starting to use or prolonged substance use in adolescence. Castellanos-Ryan recently reported that heavy cannabis use trajectories from 14 to 16 years of age predicted reduced slope in growth in cognitive functions over time, particularly decision making, and spatial working memory (Castellanos-Ryan et al., 2016). Another similar longitudinal study (Nguyen-Louie et al., 2015), showed that alcohol use behaviours were predictive of neuropsychological functioning over and above baseline performance measures: more alcohol use days predicted worse verbal memory, and visuospatial ability. Postdrinking effects and greater drug use predicted worse psychomotor speed.

Wetherill, Squeglia, Yang, and Tapert (2013) collected fMRI data during performance on a Go/No-Go task from adolescents aged 14, before the onset of heavy drinking, and then again 3 years later. Results showed that youth who transitioned into heavy drinking compared to continuous nondrinkers, showed reduced activations at baseline in bilateral PFC on successful stop trials. This response reversed after the onset of heavy drinking (Wetherill et al., 2013).

More recently, (Squeglia et al., 2015) examined grey and white matter volume trajectories over 3.5 years in 134 adolescents aged 12–24, of whom 75 transitioned to heavy drinking and 59 remained light drinkers or nondrinkers. Heavy-drinking adolescents showed accelerated grey matter volume reduction in lateral frontal and temporal cortices, and reduced white matter growth of the corpus callosum and pons relative to nondrinkers. Importantly, these results were largely unchanged when use of marijuana and other drugs were covaried. However, a secondary analysis of this same dataset showed that youth who reported using cannabis and alcohol through adolescence showed thicker cortical estimates across the brain (23 regions), particularly in frontal and parietal lobes (Jacobus et al., 2015). More cannabis use was associated with increased thickness estimates by the 3-year follow-up.

In summary, of the few studies that have adequately examined the effects of alcohol and cannabis use on adolescent cognitive or neural development, most suggest harmful effects of alcohol on visual-spatial ability and verbal memory, as well as altered function and structural changes in the prefrontal cortex. Results from studies of cannabis users are not as consistent, likely because the cannabis users studied to date were also alcohol users. Nevertheless, designs that examine the relationship between dose of cannabis use and cognitive function suggest that impaired decision making and/or spatial working memory and cognitive control. Most of the evidence suggesting cannabis effects on brain structure and function come from cross-sectional studies, but there is some suggestion that high potency, heavy use, and early onset use are related to greater brain abnormalities, particularly in areas that are involved in affective processing and emotion regulation.

Conclusions and implications for intervention

Figure 3 provides a broad summary of the neural correlates and intermediate phenotypes of risk discussed in the present review and their association with the developmental process of SUD. In this figure, we outline how: (a) Early childhood factors, both of biological and psychosocial nature, can increase a child's risk for early onset and problematic substance use. (b) Adolescence, as a developmental period, is presented as a generic risk factor, when autonomous decision making is promoted,

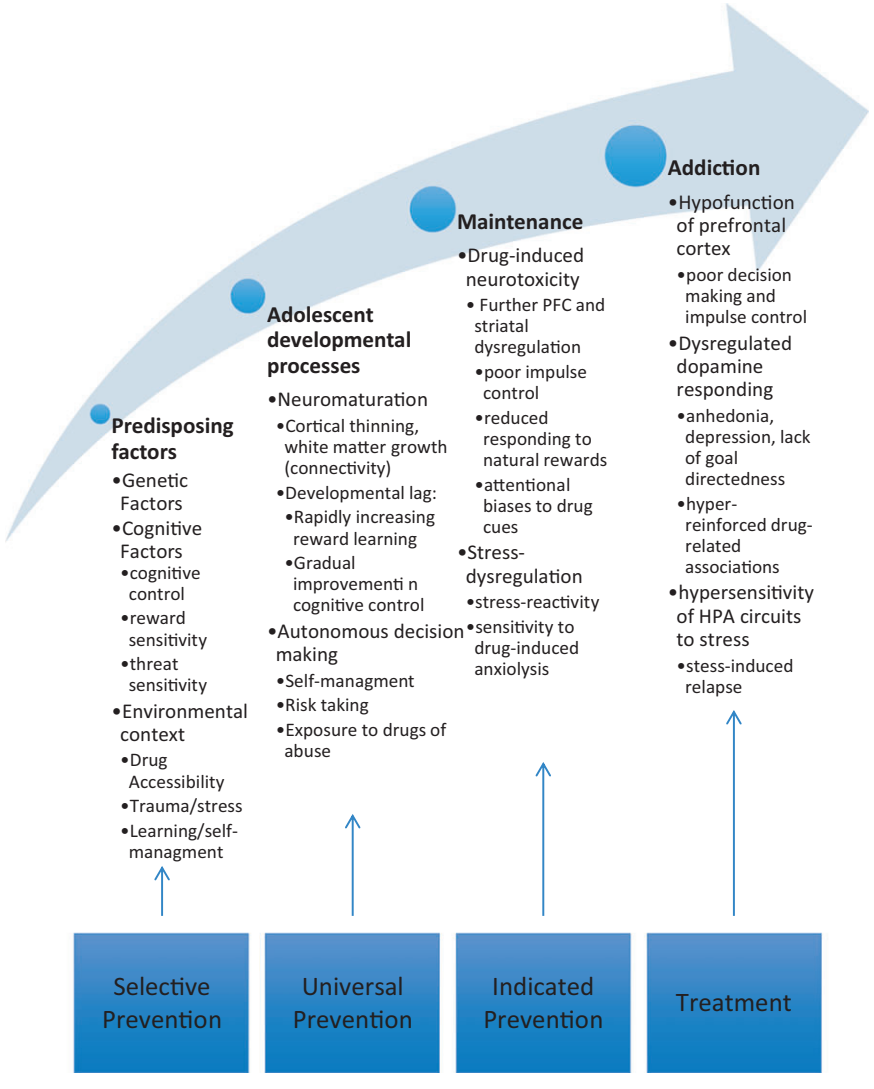

Figure 3 Overview of the neurodevelopmental processes implicated in transition to addiction

and, from a neurodevelopmental perspective, when reward and cognitive systems are temporarily imbalanced. It is also presented as being shaped by early childhood factors, with the assumption that individuals who enter into adolescence with certain risk factors will react more negatively to additional psychological and neurodevelopmental risk factors. (c) The maintenance phase of addiction critically involves an interaction between preexisting vulnerabilities and the effects of substances of abuse on the very brain systems that are involved in reward processing, cognitive control and negative affect reactivity. (d) Although less of a focus of the current review, the addiction phase follows a period of recurrent heavy use in which these brain systems are supraphysiologically stimulated, influencing cue-association and habit formation, to result in a state of frontal–striatal dysregulation that involves uncontrolled and compulsive drug use, despite significant drug-related harm.

While the current model remains heuristic, it accurately represents the state of the literature in many ways. Addiction vulnerability is presented as a progressive or developmental disorder. Multiple biological and psychosocial risk factors are identified and presented, for the moment, as independent. Despite a suggestion that these factors interact, how they interact remains a question for further investigation. Research involving larger samples with longer and multiple follow-up assessments are needed to understand how drugs of abuse interact in this developmental process, and to delineate the specific effects of certain drug classes and specific genetic and environmental moderators of vulnerability and drug effects. Prescription drug use is detrimentally understudied in terms of the effects of substances on brain development, despite being the second most abused class of drugs among individuals aged 12 and older (Center for Behavioral Health Statistics and Quality, 2015) Finally, in addition to the difficulty in differentiating between factors that are causal or consequential to substance abuse, neuroimaging and genetic studies tend to be insufficiently powered to control for psychiatric heterogeneity within and across samples. Most of the studies reviewed above generally are unable to account for the large overlap in clinical symptoms and trajectories between those who misuse a

substance and those who misuse other substances or experience other psychiatric problems that are highly comorbid with SUD. From this perspective, it will be important to understand how multiple brain endophenotypes contribute to a constellation of behavioural outcomes, which all have the potential to have reciprocal effects through development. Figure 2 provides a heuristic model to guide investigators when studying multiple potential risk trajectories in addiction vulnerability.

With respect to clinical implications, in order to be able to offer personalised interventions for those at risk, research designs and heuristic models of addiction must accommodate two important conclusions on the nature of this neurodevelopmental disorder: (a) Multiple interacting and evolving cognitive and neuroendophenotypes appear to be implicated in risk for addiction. (b) Some endophenotypes also appear to be particularly sensitive to the neurotoxic effects of some substances of abuse, possibly at specific periods of neurodevelopment or at certain doses and/or frequencies of use. Interventions that aim to modify endophenotypes prior to onset, delay onset, curb frequency of exposure, or reduce intensity/toxicity of exposure (defined according to brain endophenotypes and not other medical criteria) all appear to of value from this neurodevelopmental perspective of addiction vulnerability. As illustrated in Figure 3, evidence-based targeted prevention programmes that help youth manage impulsivity, reward sensitivity and negative affect (e.g. Conrod et al., 2013; O'Leary-Barrett et al., 2013) have the potential to prevent early uptake of substance misuse in youth with personality and neuropsychological risk profiles. Universal programmes that can reduce social norms and availability of substances in the general population (e.g. Newton, Teesson, Vogl, & Andrews, 2010) will also reduce the likelihood that youth with such risk profiles will be exposed to substances and the neurotoxic effects to which they might be particularly sensitive (e.g. psychosis prone children). Indicated interventions (e.g. brief interventions) targeting those with nonproblematic, but regular heavy use of substances can also help to prevent those at risk from further affecting how cognitive control systems, habit formation and reward centres of the brain respond to natural rewards and drug cues and will ultimately help to prevent the transition to uncontrolled and compulsive drug use.

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Key points

- The evidence implicates prefrontal cortex-mediated cognitive control, striato-cortical reward systems, and brain stress response circuits in substance use behaviours.
- This review provides a synthesis of the evidence suggesting that individual differences in the functioning of these systems are implicated in vulnerability to adolescent substance use and misuse and that through interactions with drug self-administration, these systems become further dysregulated in vulnerable individuals.
- Key clinical implications are that all levels of intervention are necessary to reduce risk in vulnerable individuals, starting with selective interventions that target personality and neurocognitive risk factors for SUDs; followed by universal interventions that will limit access to substances and reduce cultural influences
- Indicated interventions are needed to help protect heavy users from the neurotoxic effects of frequent, high dose/potency and harmful; and treatments must begin to target both the psychosocial and neuropsychological consequences of chronic heavy use on the brain
- To inform the development of more personalised and tailored interventions at each stage of addiction, we must further understand how substances of abuse and neurocognitive risk profiles interact. Larger and long-term follow-up studies are needed in which neurocognitive measures of cognitive control, reward sensitivity, stress, and threat sensitivity are collected on vulnerable individuals before they start using substances and as they begin to use substances of abuse.

- Finally, prevention and intevention studies must begin to incorporate neurocognitive treatment targets and outcomes, in addition to behavioural outcomes, to better understand the processes by which prevention and recovery can be acheived and maintained.

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