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Neural substrates of substance use disorders

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Purpose of review
Substance use disorders account for a tremendous burden to society, yet despite substantial progress in basic studies, our understanding of the brain-basis of these disorders is still emerging. This review summarizes the recent findings of neuroimaging studies with substance use disorder individuals.

Recent findings
Resting-state functional connectivity studies support for some but not all substances of abuse and disruption in executive control. Structural neuroimaging findings point towards reduced subcortical volumes, which may emerge as an interaction between preexisting factors and recent substance use. Longitudinal studies implicate some of the same core brain structures and their functional role that have also been identified via case–control studies. Finally, meta-analyses support the idea of dysregulation of cortical control over subcortical salience processing.

Summary
Although progress has been made and there is both structural and functional imaging evidence of an imbalance between brain structures involved in executive control and salience processing, there is emerging evidence that brain-behaviour relationships, which are core to discovering the neural processes that lead to and maintain substance use, are small and require larger consortia that prospectively examine individuals with substance use disorder.

Keywords
addiction, control, neuroimaging, prefrontal, salience, striatum, substance use disorder

INTRODUCTION

The U.S. Surgeon General reported that in 2015, 27.1 million adolescents and adults used illicit drugs or misused prescription drugs. Recent estimations suggest that the annual cost for an individual with substance or alcohol use disorder can range from $2600 in agriculture to more than $13 000 in the information and communications sectors [1]. Prevalence and frequencies of cocaine or methamphetamine have increased over the past 5 years [2], with overdose deaths involving psychostimulants increasing by as much as 180% [3▪]. Similarly, risk perception and use patterns for cannabis have changed dramatically following a wave of legalization across the U.S. [4]. Yet, despite these rising rates of substance use and the associated consequences, our understanding of the disease processes underlying the development and maintenance of substance use remains elusive. It is clear that the cause of substance use develops over time and across multiple levels of influence, for example biological, such as genetic or neural circuits, individual, for example temperamental factors or behaviour patterns, and social, for example the influence of parental or peer attitudes [5]. There is emerging consensus among neuroimaging studies suggesting that the prefrontal cortex in assigning excessive salience to drug over nondrug-related processes, which leads to lapses in self-control, and deficits in reward-related decision-making and insight into illness [6▪]. This review provides some of the recent developments and insights that focuses on novel case–control findings (for a predictive overview see Fig. 1), the emerging of prediction of different aspects of substance use, associations between substance use and

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KEY POINTS

- Subcortical disease characterized by increased activation to drug-related cues and lack of prefrontal control is the modal finding in the neuroimaging literature.
- The degree to which this disease is related to preexisting characteristics of individuals susceptible to substance use disorder or a consequence of use is still unresolved.
- Prospective longitudinal follow-up studies of large cohort based on multicentre studies will be necessary to delineate robust and reliable neural processing dysfunctions in individuals with substance use disorder.

different constructs, emerging longitudinal results, meta-analyses and review, and new emerging constructs [7].

CASE–CONTROL STUDIES

Case–control studies tend to be dominated by small samples, which helps to understand why – sometimes – there are contradictory findings. In general, there is strong evidence for subcortical disease from both structural and functional neuroimaging studies that seem to occur in individuals with all substance use disorders. The differences in other parts of the brain are more variable and depend on the type of construct that is being examined. Comparing individuals with cannabis user disorder relative to comparison individuals, researchers found lower resting-state functional connectivity within the dorsal attention network, which was associated with more severe cannabis use measures, including increased lifetime cannabis use, shorter length of abstinence and more severe cannabis use disorder symptoms [8]. On the one hand, in participants with heroin use disorder, there appears to be a marked decrease in resting-state functional connectivity between interhemispheric dorsolateral prefrontal cortex [9]. On the other hand, others have been unable to find reliable univariate between-group differences in cortical structure or edgewise resting state functional connectivity in prescription opioid users [10]. Structural neuroimaging approaches have shown that relative to comparison participants, individuals with substance use disorder have smaller left nucleus accumbens, right thalamus, right hippocampus, left caudal anterior cingulate cortex (ACC) volume and larger right caudal ACC volume, and right caudal ACC, right caudal middle frontal gyrus (MFG) and right posterior cingulate cortex (PCC) surface than Healthy Comparison [11]. Some have speculated that these differences are both due to preexisting factors and the influence of recent substance [12]. Taken together, resting-state functional connectivity studies support some but not for all substances of abuse and disruption in executive control. In comparison, structural neuroimaging findings point towards reduced subcortical volumes, which may emerge as an interaction between preexisting factors and recent substance use.

PREDICTION

There is an increasingly sophisticated approach to building prediction models, some of which focus on group membership and others on continued abstinence. These models take a pragmatic approach [13], that is they focus on obtaining robust test parameters without focusing on the process that is being used to generate the prediction. There is evidence from several studies that neuroimaging provides some predictive utility; however, the current approaches are still insufficient to generate robust individual-level predictions with clinical utility. In a recent study, using the physiological response to smoking-related stimuli, investigators build a classification algorithm that was able to identify smokers who were nearly 2.5 times more likely to be abstinent [14▪]. Others have developed a sophisticated connectome-based predictive modelling (CPM) approach to predict abstinence during treatment, which involves measuring the connectivity between cognitive/executive control regions and those brain areas involved in reward responsiveness [15▪▪]. Using a risk model approach, participants who initiated cannabis use by 15 years of age had activation differences characterized by increases in frontoparietal and decreases in visual association regions [16]. A meta-analysis using an activation likelihood estimation approach showed that not only the right putamen and claustrum, but also rostral-ventral anterior cingulate cortex was associated with relapse resilience [17]. Taken together, although there are initial and intriguing results from both individual studies and meta-analyses that neuro-prediction is possible, these findings are still based on relatively small, single-site studies.

ASSOCIATION

Studies examining the association between a particular construct that is relevant for the initiation or maintenance of drug use and substance use find synergistic effects for some of the brain structures that have been associated with substance use disorder. Specifically, subcortical disease in terms of both

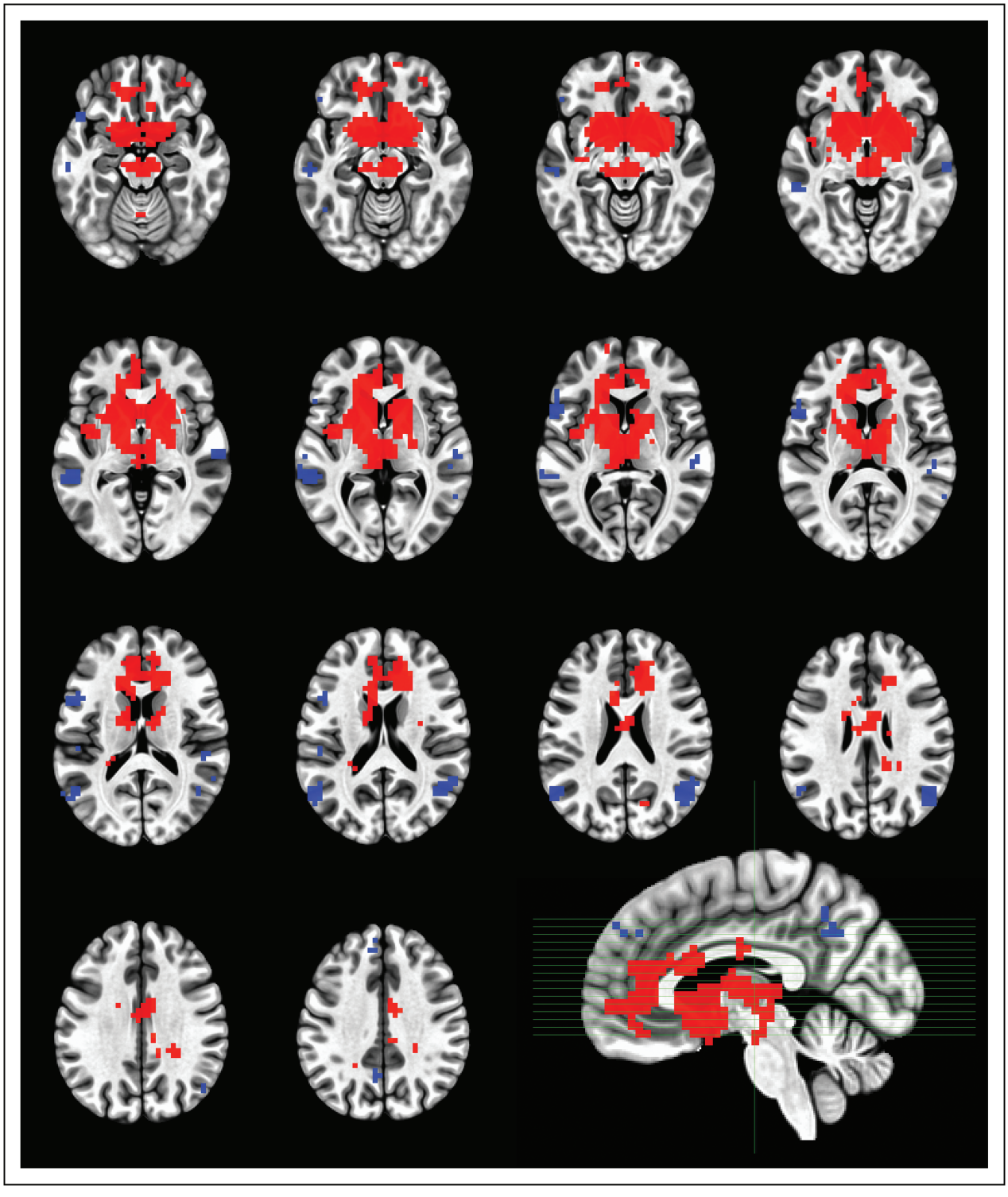

FIGURE 1. Axial slices of prospective meta-analysis using *neuroquery.org* [7], indicating the predicted activations to the keywords 'neuroimaging, substance use, addiction'. The colour codes represent threshold (at 3.0) *z*-values (positive = red, negative = blue).

structure and function is also affected by stress, impulsivity, externalizing disease and paternal substance use. Thus, there appears to be a common neural pathway that involves constructs that often co-occur with substance use and imaging findings observed with substance use disorder individuals. Specifically, individuals with adverse childhood experiences and substance use show decreased gray matter or activation in regions of executive functioning, the hippocampal complex and the

supplementary motor area, as well as altered activation in anterior cingulate cortex, caudate and amygdala during a stress-induction paradigm [18]. Others reported that higher motor impulsivity was positively correlated with right nucleus accumbens volume, but those with greater resting-state functional connectivity between the right nucleus accumbens and bilateral superior frontal gyrus showed lower motor impulsivity [19]. Similarly, substance use individuals with higher nonplanning impulsivity and affect-based impulsivity showed changes in structure and function of the medial orbitofrontal-striatal system and hyperexcitability of dopamine receptors in this network [20]. This connectivity also seems to be modulated by a family history of substance use [21]. Finally, externalizing disorders also show structural and functional changes in the basal ganglia and prefrontal cortex [22]. Taken together, these association studies further support dysregulation of prefrontal-subcortical processing but extend these findings to constructs that are relevant to substance use such as impulsivity and externalizing disease.

LONGITUDINAL

Longitudinal studies of two kinds have emerged. First, studies examine the effect of abstinence on brain structure and functioning and, second, cohort studies investigate the role of brain structure and function as a risk or resilience factor for developing problems with substance use. Interestingly, both types of studies identify a diverse set of neural structures that are not necessarily consistent with those that have been identified in case–control studies. Several cortical brain regions seem to play a role in both increasing the risk and acting as protection from transition to use. The relatively sparse neuroimaging literature based on exposure cohort studies suggests that the neurocognitive deficits in substance-exposed children persist into adulthood [23]. On the contrary, most longitudinal studies following individuals into recovery support the notion that there is a partial neurobiological recovery with abstinence, which includes structures such as frontal cortical regions, the insula, hippocampus and cerebellum [24▪▪]. Several longitudinal cohorts examining cannabis use have found that extended use is associated with smaller hippocampal volume [25▪▪] and cerebellar changes [26]. There is some evidence that frontostriatal, frontolimbic and frontocerebellar systems are altered as a consequence of use [27]. Others have reported increasing risk-related insular cortex activation with prolonged substance use [28▪▪]. Using longitudinal cohorts to predict the emergence of substance use, investigators reported that both decreased anterior cingulate cortex volume [29] and blunted orbitofrontal cortex activation during reward outcome [30▪▪] predicted greater risk for substance and alcohol use initiation. Taken together, the small but developing literature of longitudinal studies implicate some of the same core brain structures as well as their function that have also been identify via case–control studies.

REVIEW OR META-ANALYSES

Over the past years, there have been several important reviews and meta-analysis attempting to synthesize the fast-growing literature on neuroimaging and substance use. These publications have focused on a diverse set of themes. A commonly emerging aspect of these reviews is that despite voluminous literature on the topic, definitive statements are hard to come by. There are several reasons for this. First, most imaging studies are cross-sectional, which makes causal inference impossible. Second, the size of an individual study tends to be small, which results in large errors around the point estimate. Third, there are few multicentre studies, which make it difficult to extrapolate from one finding whether this will hold in other populations. Meta-analyses of individuals with cannabis use disorder point towards reductions in amygdala, accumbens and hippocampus volumes. In addition, these individuals also show lower cortical thickness in the frontal regions, particularly the medial orbitofrontal region [31]. Others have not only reported functional and structural alterations in frontoparietal, fronto-limbic, fronto-striatal and cerebellar regions among adolescent cannabis users [32▪], but also subcortical structures during reward-related processing [33]. Examining studies focusing on the emergence of substance, investigators found that altered neural structure and function of regions in reward processing, cognitive control and impulsivity can predate substance use initiation, escalation and disorder [34]. Individuals with smaller frontoparietal and amygdala volume and larger ventral striatal volume are more likely to engage in prospective substance misuse. Importantly, some of these effects in the striatum, hippocampus, amygdala, insula and corpus collosum might also be sex-specific [35]. Interestingly, similar structures such as anterior cingulate cortex, inferior frontal gyrus, among others, showed consistent brain-behaviour associations with treatment-outcome variables [36]. Several reviews and meta-analyses have been conducted with a focus on delay discounting, that is the degree to which future rewards (or punishments) are appraised as less salient than current rewards (or punishments) of the same magnitude. The ventromedial prefrontal cortex and ventral striatum have been implicated in evaluating reward values, whereas the anterior cingulate

cortex has been linked to cognitive control, and the middle temporal gyrus has been associated with predictions [37]. Attenuated activation in these structures has been associated with differences in delayed discounting [38▪▪]. Among individuals with substance use disorders, there is evidence of greater neural activity in the executive control network during choices for larger-delayed rewards relative to choices for smaller-immediate rewards in cognitive control areas such as the dorsolateral prefrontal cortex [39]. These studies support the emergence of dysregulation of cortical control over subcortical salience processing, but the degree to which this imbalance precedes the emergence of substance use and the degree to which it can heal after cessation of use is still very much unclear.

NEW APPROACHES

Given the limited advance in better understanding the processes and neural substrates that contribute to the development and maintenance of substance use disorder despite the growing number of neuroimaging publications with SUD individuals, it should not be surprising that there have been initiatives to examine novel constructs that might provide further insights into the pathology of this disorder. Computational psychiatry approaches are foremost among them [40]. These approaches use a mathematical model underlying the observed behaviour to extract parameters that can be related to specific processes and can be associated with brain activation. The goal is to improve 'carve nature at its joints'. For example, using a computational approach, investigators have reported that evidence accumulation may provide a process that indicates risk for substance use in youth [41▪]. Deficits in this process are consistent with other findings, suggesting that substance use individuals fail to adequately compute the probability for engaging inhibitor control [42]. Others have suggested that increased variables or decreased consistency in processing as measured by increased inter-trial variability of electrophysiological markers might contribute to these deficits [43▪▪]. Lastly, novel brain areas have emerged as potential targets of dysfunction in substance users. Specifically, the periaqueductal gray has been a core substrate to interact with the ventral tegmental area, extended amygdala, medial prefrontal cortex, pontine nucleus, bed nucleus of the stria terminalis and hypothalamus to integrate responses to the physical discomfort associated with drug withdrawal [44]. These approaches point towards novel directions, which may help to further elucidate the difficult task to delineate the processes that lead to and maintain substance use disorders.

NEUROLOGICAL DISORDERS AND SUBSTANCE USE

There has been an interesting association between Parkinson's disease and substance use disorder. Evidence over the past decade has shown that dopaminergic medication can induce severe addictive behaviours in susceptible Parkinson's disease patients [45]. Imaging studies suggest that medication-induced downregulation of frontostriatal connections and upregulation of striatum might combine to induce impulsive behaviour [46]. Recent reviews of the literature show inconsistent findings for the domains of reward and punishment learning, reflection impulsivity and disadvantageous decision-making. In comparison, there is emerging consensus of dopaminergic agents altering motor or cognitive/attentional control, thereby increasing choice impulsivity [47]. Thus, impulse control problems such as substance use occur in a subset of susceptible patients with Parkinson's disease with dopamine replacement therapy, which may be due to deficits in dopaminergic receptor expression, connectivity patterns in cortico-striatal circuitry and exaggerated neural responses to cue exposure [48]. Those Parkinson disease individuals who report greater levels of depression and show a nontremor phenotype seem to be susceptible to boosting of reward-versus punishment-based choice by medication, which may reflect an underlying dysregulation of the mesolimbic dopamine system [49▪▪]. Taken together, preexisting conditions such as an imbalance between executive control processing and incentive salience processing that involve brain areas such as the prefrontal cortex versus subcortical striatum may put Parkinson's disease patients at risk for substance use when exposed to dopaminergic replacement treatment.

CONCLUSION

There continues to be vigorous progress in neuroimaging research focused on substance use disorders, yet there are several issues that are noteworthy. First, most studies still focus on case–control designs and are unable to draw causal conclusions from the neuroimaging data. However, this is changing with the emergence of large consortium studies such as the Adolescent Brain Cognitive Development study [50]. Nevertheless, as these studies will take years to collect data, results are not yet available. Second, there is clear evidence from several studies that associations between brain and behaviour are weak [51] and that even large-scale studies only show modest correlations between psychopathology and structural or functional brain characteristics [52]. Therefore, it is unlikely that neuroimaging

studies will be able to find substantial associations of behavioural or clinical characteristics. Lastly, there is likely to be significant heterogeneity among substance users in terms of the predisposing factors as well as the substance-related changes that result in a complex mixture of brain phenotypes, which contributes to the difficulty in delineating a core neural substrate underlying substance use disorders.

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Conflicts of interest

The authors report no conflicts of interest.

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