The orbitofrontal cortex, drug use and impulsivity: can teenage rebellion be predicted through neural correlates?

Editorial
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Substance misuse is common among adolescents [1]. For instance, nearly 40% of all 13–14-year-old adolescents in the USA report having drunk alcohol and 10% of this age group exhibit regular use. In addition, 10% of 13–14 year olds have experimented with illicit drugs. By 18 years of age, nearly 50% of all adolescents drink alcohol regularly, with more than 40% having tried illicit drugs. It has been demonstrated repeatedly that early substance use is a strong risk factor for adult substance dependence; therefore, identifying predictors of substance use in adolescence would be undeniably advantageous [2]. Exploring intermediate phenotypes (i.e., hidden, pre-existing biomarkers) may be a useful approach for predicting propensity to substance misuse in the teenage years. In this editorial, we propose that orbitofrontal cortex (OFC) activity is a promising intermediate phenotype of substance misuse in adolescence. The OFC is connected with the subcortical reward system, including the nucleus accumbens, and is involved in evaluating reward value, selecting an appropriate response given reward value and response inhibition [3]. In view of the OFC's role in such reward-related behavior, it is not surprising that abnormalities in OFC functioning have often been implicated in impulsivity and addiction pathologies [4].

The teenage years are often associated with 'impulsive' behavior (behavior with diminished regard to potential negative consequences). Developmental neuroscience offers us some clues about the neurobiology of teenage impulsivity, and the important role of the OFC in that behavior. A common 'two systems' model of reward processing posits an interplay between the subcortical reward system and control exerted by the prefrontal cortex. According to this model, teenage impulsivity results from the asynchronous development of these systems [5]. For example, when presented with a choice task involving varying reward values, adolescents' reward-processing (nucleus accumbens) activity was similar to that found in adults, while activity in the OFC was more similar to activity found in children [6].

Although impulsive behavior in teenagers is often believed to be adaptive to some extent, there is widespread agreement that impulsivity is integral in the initiation of substance misuse, and behavioral tests of impulsivity predict future substance misuse. For instance, utilization of a neurobehavioral disinhibition index was able to significantly discriminate high- versus low-risk boys aged 10–12 years [7]. Furthermore, at 16 years of age, by combining this neurobehavioral disinhibition index, substance misuse frequency and determination of risk status, substance use disorders at 19 years old were predicted with 85% accuracy. In another study, response inhibition (the stop-signal task, in which an already-initiated motor response must be stopped) in 12–17 year olds predicted the onset of alcohol and illicit drug use, whereas other tests of executive functioning such as working memory did not [8].

Hypoactivity within the OFC has been observed in abstinent cocaine and alcohol abusers [9]. However, such effects could be due to neuroplastic effects that contribute to continued drug seeking or reflect a predisposition to use drugs. Thus, discovering an intermediate phenotype for substance misuse is complicated

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by the need to disentangle the cause of substance misuse and the subsequent effects of neurotoxic substances on the developing brain. Indeed, there is evidence to suggest that OFC activity is both a cause of substance misuse and is affected by neurotoxic substances. Determining causality in animal models of addiction is relatively straightforward and this type of research shows that drug-induced neuroadaptations in the OFC change how the value of consequences is calculated [10]. However, predicting neural correlates of substance misuse in humans is a challenge, due, in part, to the relatively large sample size needed to ensure an adequate number of participants in both substance use and control groups. Studies of this nature tend to be classified under the rubric of 'population neuroscience', combining epidemiology, genetics and cognitive neuroscience [11]. The utilization of large samples permits the identification of environmental and genetic influences on brain structure and function.

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For example, data from the Saguenay Youth Study [12] have revealed that the OFC is thinner in adolescents who had been exposed to nicotine *in utero* [13]. In an elegant extension of this finding, a more nuanced picture of the neural correlates of adolescent substance misuse has been painted by linking OFC thickness, drug experimentation and epigenetics (environmental effects on gene expression) [14]. In an analysis of 314 adolescents, cortical thickness of the OFC was measured and genotyping was performed. Prenatal exposure to maternal cigarette smoking was associated with an increased likelihood of substance use in adolescence. Among these adolescents with prenatal nicotine exposure, the likelihood of drug experimentation correlated with the degree of reduced OFC thickness. By contrast, in nonexposed-matched controls, the thickness of the OFC increased as a function of the number of drugs tried, which the authors hypothesized resulted from neuroplastic processes. In support of this hypothesis, in the nonexposed group, only carriers of the more efficient *BDNF* Val/Val genotype demonstrated a significant positive correlation between OFC thickness and the number of drugs tried. These findings suggest that, among nonexposed adolescents, OFC thickness was being modified by activity-dependent release of BDNF in response to drug-related behavior.

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In another population neuroscience study, as part of the IMAGEN project, approximately 1900 14 year-old adolescents completed a test of motor inhibition (the stop-signal task) during functional MRI [15]. In addition, other measures, including substance misuse, were also obtained. Brain activity during the motor inhibition task was fractionated into a smaller number of distinct networks using a statistical approach called factor analysis. The resulting networks were then tested for relationships with substance misuse phenotypes. Adolescents who had experimented with substances – either alcohol, cigarettes or illicit substances – showed reduced activity in an OFC network. Notably, this difference remained even for adolescents who had very low levels of alcohol use (one to four lifetime uses). Whelan *et al.* suggested that the decreased OFC activity was more likely to be a cause of substance misuse experimentation because low levels of alcohol drunk were unlikely to have neuroplastic effects [15]. The question of cause-and-effect could be answered more definitely in the future: an ongoing, follow-up analysis of data from the same sample at 16 years old will test if OFC hypoactivation precedes substance misuse by comparing adolescents who were not experimenting at 14 years old to those who subsequently went on to misuse elicit substances.

In this editorial, we provide evidence that it may be possible to index the propensity for substance misuse by measuring OFC activity. Longitudinal population neuroscience studies, though logistically challenging, offer a promising approach to detecting predictors of substance misuse phenotypes. It is also worth considering some key challenges that this field will face in the future.

First, it would seem that analyses of brain activity should focus on structural networks or functional connectomics, rather than isolated regions [16]. Describing brain activity in terms of isolated regions lacks biological plausibility; rather, the brain is a highly complex system of interconnected neurons. Perhaps it is the OFC's relative activity to other brain regions, such as the subcortical reward system, that is more informative than absolute activity levels [6]. One

increasingly popular method of studying brain networks involves recording the intrinsic activity of the brain (often called 'resting-state' activity). A review of intrinsic brain activity in drug-dependent patients reported that 15 out of 18 studies demonstrated involvement of the OFC [17].

Second, future studies should combine information from a number of different modalities, such as diffusion tensor imaging (providing measures of white-matter connectivity) and gray-matter density, with data from functional tasks. That said, combining information from different modalities is not trivial. Advanced methodologies, such as joint and parallel independent component analysis [18], which can both identify networks and integrate information from different modalities, as well as machine learning approaches, may become standard items in the neuroscientist's toolkit [19].

Information derived from brain activity data are critical in understanding why some adolescents experiment with substance use; however, neural activity on its own will not provide a complete explanation for substance misuse vulnerability. For example, one study showed that reward-associated behavior, personality and brain responses all demonstrate a contribution in the explanation of alcohol intake in adolescents [20]. Notably, personality explained a higher proportion of the variance than either behavior or brain responses. In the future, truly comprehensive models that are capable of predicting teenage rebellion will assimilate information from a variety of sources: intermediate phenotypes (structural and functional brain data), personality and environmental variables (including peer relations), genetics and epigenetics.

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