Published in final edited form as:

Biol Psychiatry. 2012 April 15; 71(8): 664–665. doi:10.1016/j.biopsych.2012.02.022.

Orbitofrontal cortex and neuromaturation: A gateway to risk?

John C. Churchwell^{1,2}, Melissa Lopez-Larson^{1,2}, and Deborah A. Yurgelun-Todd^{1,2,*}

¹The Brain Institute, University of Utah, Salt Lake City, UT, USA

²Department of Psychiatry, University of Utah School of Medicine, Salt Lake City, UT

Adolescence is a period of intense vulnerability to drug use initiation and adolescents may be more susceptible than adults to becoming drug dependent (1). Cannabis use initiation during adolescence has emerged as a significant concern, as early initiation of cannabis use has been associated with increased risk for using a range of other drugs of abuse (2). A central challenge to understanding substance abuse behavior is determining why some individuals initiate drug use and become dependent while others do not (1). Given the potential link between early initiation and dependence, a specific question to ask is what neurobiological markers may be associated with risk for illicit substance use.(3).

A number of investigations have reported that individuals who initiate cannabis use during adolescence may have altered brain morphology. Specifically, it has been found that individuals who began cannabis use before the age of 17 had reduced frontal cortical volume compared to those that initiated after that age (4). More recently, it was shown that adolescent cannabis users have decreased orbitofrontal cortical volume, which correlated with age of first use (5). However, it has been unclear whether changes observed in frontal cortex volume were a consequence of cannabis use or predated initiation. If differences in this region predated the initiation of cannabis use, observed abnormalities may be an indicator of risk for early drug use.

In this issue of *Biological Psychiatry*, Cheetham and colleagues (6) acquired structural magnetic resonance images from a large cohort of 12-year-old primary school students and reassessed them at age 16 while also evaluating whether they began using cannabis during the intervening time period. Based on previous cross-sectional studies examining morphological brain changes in adolescent and adult cannabis users, they hypothesized that several regions would show volumetric differences that predated the initiation of cannabis use. Specifically, they anticipated that increased volume in limbic regions such as the hippocampus/amygdala and decreased anterior cingulate/orbitofrontal cortex volumes at age 12 would be linked to cannabis use at age 16. Of the 121 subjects assessed during follow-up

© 2012 Society of Biological Psychiatry. Published by Elsevier Inc. All rights reserved.

*Correspondence: Dr. Deborah Yurgelun-Todd: The Brain Institute, 383 Colorow Drive, Salt Lake City, UT 84108, USA. Deborah.Yurgelun-Todd@hsc.utah.edu.

All authors report no biomedical financial interests or potential conflicts of interest.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

testing, 28 participants (23%) had initiated cannabis use. After controlling for potential confounding variables including age, gender, IQ, and SES, the results showed that that smaller orbitofrontal cortex volume at age 12 is associated with cannabis initiation prior to age 16. Although their findings were specific to cannabis use, Cheetham and colleagues propose that reduced orbitofrontal volume may be primarily associated with drug initiation vulnerability more broadly, which finds expression in cannabis experimentation at an early age.

The Cheetham et al. study provokes a number of important and interesting questions that may be examined in future research. For example, it is not clear what contribution different orbitofrontal cortex divisions may play in the transition from substance abuse initiation to dependence, or what relationship exists between reward sensitivity, and orbitofrontal cortex morphology in the context of novelty seeking and drug use initiation. Furthermore, improved delineation of the relationship among orbitofrontal cortex, emotional regulation, and drug use initiation is needed to understand the effects of mood disorders as they relate to substance abuse.

Although various approaches to orbitofrontal parcellation have been applied, one notable strategy has been to consider this region being separated based on anatomical relationships (7). Specifically, the medial compartment of orbitofrontal cortex has been associated with connections to visceral limbic structures, whereas the lateral orbitofrontal cortex (orbital as identified by J.L. Price) compartments are associated more strongly with sensory processing systems. It has been suggested that there is a decline in prefrontal functioning which may be related to the progression from initiation of illicit drug use to compulsive drug use and dependence (8). One tempting proposition is that developmental influences on orbitofrontal cortex mediate risk for initiation of illicit drug use, whereas substance abuse itself produces further orbitofrontal abnormalities. Thus, there may be a sequence of observed orbitofrontal change shifting from medial visceral to lateral sensory compartments, reflecting the transition from initiation to dependence (Fig 1.). The Cheetham et al. study assessed both medial and lateral domains of orbitofrontal cortex and the results of the study lay an initial foundation for further refinements regarding the measurement of dynamic morphological changes through neuromaturation and substance abuse coevolution.

Further, interpretation of the observed changes in orbitofrontal morphometry may be more broadly associated with frontostriatal functions. Frontostriatal systems are thought to undergo significant remodeling in the period from adolescence to young adulthood. Specifically, protracted development of prefrontal cortex, in concert with an amplified motivational drive mediated by the striatum, is thought to be critical to increased novelty seeking and suboptimal decision making that leads to risky behavior and experimental drug use. In this light, one possible interpretation of the Cheetham et al. study is that individual differences in neuromaturational rate of the orbitofrontal cortex may contribute to drug use initiation and more specifically to risk for experimentation with cannabis. Assuming that orbitofrontal cortex is critical to making value decisions, individual differences in the development of this region might either increase or decrease sensitivity to reward through suboptimal computation of incentive value based on reward magnitude coded by the striatum. Conversely, reduced orbitofrontal modulation of striatal-mediated motivational

drive could lead to increased novelty seeking and impulsive choice. In either case, significant imbalance in the neurodevelopmental trajectory of this circuit could lead to loss of self-control during a vulnerable period.

An additional area of interest is the relationship between early orbitofrontal development, substance abuse, and the emergence of mood disorders. During adolescence there is a high rate in the occurrence of mood disorders that coincides with risk for substance abuse initiation (9). Depression has been associated with abnormal orbitofrontal function and reductions in orbitofrontal cortex volume have been observed in adults with depression (10). A recent investigation assessed cannabis use, depressive symptoms, and self-control, in a five-wave longitudinal study of adolescents 12–16 years old and found that low self-control predicted both heavy cannabis use and depressive symptoms (11). Given the significant role attributed to orbitofrontal cortex in self-control, the fact that reduced volume in this region predicts initiation of cannabis use, and the presence of reduced orbitofrontal cortex volume in adults with depression, these results suggest that orbitofrontal cortex may be a common factor in the development of both substance abuse behaviors and mood disorders. However, the Cheetham et al. study did not find differences in the prevalence of mood disorders between cannabis using and non-using groups, nor did they find that mood disorders predicted orbitofrontal cortex volume. Their study sample was unique in that it was primarily composed of individuals that engaged in relatively modest cannabis use. In fact, the cannabis use required to be included in the drug group was so low that many adolescents would not be categorized as cannabis abusers and it is unknown whether they would continue to use cannabis on a regular basis. Thus, future studies that are able to examine heavy cannabis use will be critical to understanding whether orbitofrontal cortex is a central neurobiological substrate for drug use risk and the development of mood disorders.

In summary, the Cheetham et al. study provides the first longitudinal evidence that orbitofrontal development may be associated with risk for cannabis use in adolescence.

These findings extend cross-sectional observations that focal brain regions including the insula, putamen, amygdala, as well as the orbitofrontal cortex are associated with increased risk for substance abuse (3–5). Results from this study offer fertile ground for future research and provide a new set of questions that will undoubtedly advance inquiry into the relationship between substance abuse and neurodevelopment.

References

1. Volkow N, Li TK. The neuroscience of addiction. *Nature Neurosci.* 2005; 8:1429–1430. [PubMed: 16251981]
2. Lynskey MT, Vink JM, Boomsma DI. Early onset cannabis use and progression to other drug use in a sample of Dutch twins. *Behav Genet.* 2006; 36:195–200. [PubMed: 16402286]
3. Volkow ND, Baler RD. Neuroscience. To stop or not to stop? *Science.* 2012; 335:546–548. [PubMed: 22301310]
4. Wilson W, Mathew R, Turkington T, Hawk T, Coleman RE, Provenzale J. Brain morphological changes and early marijuana use: a magnetic resonance and positron emission tomography study. *J Addict Dis.* 2000; 19:1–22. [PubMed: 10772599]
5. Churchwell JC, Lopez-Larson M, Yurgelun-Todd DA. Altered frontal cortical volume and decision making in adolescent cannabis users. *Front Psychol.* 2010; 1:225. [PubMed: 21833280]

6. Cheetham A, Allen NB, Whittle S, Simmons J, Yucel M, Lubman DI. Orbitofrontal Volumes in Early Adolescence Predict Initiation of Cannabis Use: A 4-Year Longitudinal and Prospective Study. *Biol Psychiatry*. 2011
7. Price JL. Definition of the orbital cortex in relation to specific connections with limbic and visceral structures and other cortical regions. *Ann N Y Acad Sci*. 2007; 1121:54–71. [PubMed: 17698999]
8. Winstanley CA, Olsson P, Taylor JR, Jentsch JD. Insight into the relationship between impulsivity and substance abuse from studies using animal models. *Alcohol Clin Exp Res*. 2010; 34:1306–1318. [PubMed: 20491734]
9. Davey CG, Yucel M, Allen NB. The emergence of depression in adolescence: development of the prefrontal cortex and the representation of reward. *Neurosci Biobehav Rev*. 2008; 32:1–19. [PubMed: 17570526]
10. Bremner JD, Vythilingam M, Vermetten E, Nazeer A, Adil J, Khan S, et al. Reduced volume of orbitofrontal cortex in major depression. *Biol Psychiatry*. 2002; 51:273–279. [PubMed: 11958777]
11. Otten R, Barker ED, Maughan B, Arseneault L, Engels RC. Self-control and its relation to joint developmental trajectories of cannabis use and depressive mood symptoms. *Drug Alcohol Depend*. 2010; 112:201–208. [PubMed: 20656424]

Figure 1.

3-D reconstruction of sagittal and inferior views of the brain showing the medial compartment of orbitofrontal cortex (blue), which may be linked to risk for initiation, and the lateral compartment of orbitofrontal cortex, which may be linked to dependence (red).