Orbitofrontal function and other drugs of abuse

In this review, we focused on the effects of psychostimulants on the orbitofrontal cortex but other drugs of abuse also produce structural and functional changes in this area. Here, we will highlight a few of the similarities and differences among these effects for different classes of drugs of abuse.

At the structural level, the gray matter concentration in the orbitofrontal cortex of cocaine or metamphetamine users is reduced\(^1\)\(^-\)\(^3\). Similar results have been observed in heroin\(^4\), alcohol\(^5\)\(^-\)\(^8\) or polydrug \(^9\)\(^,\)\(^10\) users. Additionally, one recent study\(^11\) reported abnormal connectivity between the nucleus accumbens, orbitofrontal cortex, prefrontal cortex and amygdala, using resting-state fMRI data acquired from heroin users. Functional neuroimaging studies have also shown reduced glucose metabolism in the frontal cortex during acute morphine and alcohol withdrawal\(^12,13\) and during protracted withdrawal in alcoholics\(^14\)\(^-\)\(^18\), heroin\(^19\) and marijuana addicts\(^20\), suggesting some common effects on the orbitofrontal cortex of these drugs of abuse and psychostimulants.

However, other studies have shown opposite effects of opiates and psychostimulants on orbitofrontal neurons. For example, chronic morphine and psychostimulants have different effects on the spine density in orbitofrontal cortex and medial prefrontal cortex after prolonged withdrawal from the drugs\(^21\)\(^-\)\(^23\). We have already highlighted that amphetamine and cocaine exposure increased spine density and dendritic length in medial prefrontal cortex and nucleus accumbens, but decreased spine density in orbitofrontal cortex\(^24\). Chronic morphine exposure causes an opposite pattern: increased spine density in orbitofrontal cortex and decreased spine density medial prefrontal cortex\(^25\). On the other hand, at the molecular level, an accumulation of \(\Delta FosB\) within medial and orbital regions has been demonstrated after chronic exposure of rats to ethanol\(^26\), consistent with the results from cocaine\(^26\)\(^-\)\(^28\). Overall, these data suggest that some but not other drug-induced neuroadaptations in orbitofrontal cortex are likely independent of the drug class.

Evidence showing differential effects of opiates versus psychostimulants on orbital structural plasticity raises the possibility that psychostimulant-induced impairments in orbitofrontal-dependent behaviors may be unique to this drug class and thus may not contribute to addiction to other drugs\(^29\). However, it is also true that a variety of molecular changes may still result, in the end, in qualitatively similar dysfunction. That is, even if different drug classes cause different structural and synaptic changes in orbitofrontal cortex, this may lead to disruptions of the main function of the orbitofrontal cortex and thereby cause the same general psychological consequence--
a shift in the decision making process from an orbital-dependent model-based strategy to an orbital-independent model-free strategy.

However, even with this formulation, when one looks at behavioral data, the picture is mixed. For example, opiate users do not show impairments in the same probabilistic reversal-learning task in which cocaine users show altered performance\(^3\). Additionally, while similar decision making impairments were observed in patients with lesions of the orbitofrontal cortex and chronic amphetamine users, these impairments were not detected in opiate users\(^3\). Likewise, cocaine addicts and cocaine-experienced rats exposed to cocaine appear to be more prone to impulsive behavior than heroin addicts or heroin-experienced rats\(^3\)\(^{30,32-35,36,37,38,39}\).

However, opioid users, as well as alcohol, cannabis and MDMA users\(^4\)\(^ {40-46}\) all show impaired performance on the Iowa Gambling Task, consistent with deficits seen with cocaine users\(^4\)\(^ {41,42}\). These discrepancies may reflect the variable effects of these different classes of drugs on orbitofrontal function. However, they may also reflect the many confounding factors involved in studying human populations or the lack of specificity of the gambling or reversal tasks.

Finally, tasks such as reinforcer devaluation and Pavlovian over-expectation that have been used to link the behavioral effects of chronic psychostimulant exposure to orbitofrontal function have not yet tested with other drug classes. Thus, we do not have the information to highlight possible comparisons. Additionally, more parametric comparisons among different drug classes using the appropriate behaviors are necessary before we can argue that our conceptual framework of drug addiction generalizes beyond psychostimulants.

References


