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Commentary

Upregulating brain activity using non-drug reward imagery and real-time fMRI neurofeedback–A new treatment approach for addiction?

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Successful treatments for substance use disorders (SUD), including cocaine use disorder (CUD) remain a persistent problem worldwide. Common treatments for individuals with CUD include behavioral interventions such as contingency management or cognitive behavioral therapy as well as treatment with pharmacotherapy. However, at this time there are no FDA-approved drugs for the treatment of CUD. Furthermore, it is estimated that 40–60% of individuals with SUD remit. Novel approaches are therefore needed to improve clinical outcomes for individuals with SUD, including CUD.

Neurofeedback is a relatively new technique allowing participants to view and learn from their own brain activity in real-time. The most common forms of neurofeedback include electroencephalography (EEG) and functional magnetic resonance imaging (fMRI). Neurofeedback has the advantage of being a safe, non-invasive method of modulating brain activation in humans. As such, it has been widely used to address a range of basic science and clinical questions [1]. In an article published in this issue of *EBioMedicine*, Kirschner and colleagues describe a novel use of fMRI neurofeedback: asking if cocaine users and non-users can upregulate a region involved in addiction and reward processing - the dopaminergic midbrain - using non-drug, reward imagery [2].

Prior work in substance users has employed neurofeedback, but has primarily approached the problem from the point of view of trying to downregulate brain regions involved in craving (for examples, see [3–6]). One theory of addiction suggests that as a person becomes addicted to a drug, reward responses to the drug (e.g., cocaine) and drug-related cues (e.g., pipe) increase while reward responses to non-drug (e.g., favorite food, pasta carbonara) and non-drug cues (e.g., walking past your favorite Italian restaurant) diminish [7]. This reshaping of neural reward responsivity makes it increasingly difficult to disengage from drug-related activity. Rather than asking individuals to decrease reward-related activation and/or craving to drug cues, Kirschner and colleagues took the novel approach of asking individuals to upregulate brain activation to non-drug, rewarding imagery. Both cocaine users and non-users (healthy adults) were recruited to participate in the experiment. All participants were asked to generate non-drug, rewarding imagery (for example, going to the movies with a friend) while trying in increase brain activation in the dopaminergic midbrain. The authors targeted their intervention on the substantia nigra and ventral tegmental area of the midbrain, where the majority of the neurotransmitter dopamine is produced in the brain. Dopamine is critical for a host of adaptive behaviors including learning, memory, action contingency, valuation, agency, response vigor, and effort allocation; importantly, dopamine function is disrupted in SUD [8].

The authors observed that both healthy adults and cocaine users were able to increase activation within the midbrain prior to, during, and following neurofeedback training. Interestingly, there were no group differences in the ability to activate the midbrain: both cocaine users and non-users were equally good at activating the midbrain using non-drug, rewarding thoughts. The authors hypothesized that individuals who use cocaine may show reduced ability to activate the midbrain using non-drug imagery compared to healthy adults, especially prior to neurofeedback training. While the authors did not observe this relationship, there was a significant negative relationship between midbrain activation and the degree of obsessive-compulsive thoughts as well as lifetime cocaine consumption in cocaine users, consistent with their hypotheses. The relationship between obsessive-compulsive thoughts surrounding cocaine use and midbrain activation was particularly strong, suggesting that chronic craving negatively affected one's ability to upregulate the midbrain using non-drug, rewarding imagery. Furthermore, a subset of participants with the highest degree of obsessive-compulsive thoughts regarding cocaine use were significantly worse at activating the midbrain using non-drug reward imagery compared to healthy adults.

A hallmark of learning in neurofeedback studies is referred to as transfer - meaning the ability to volitionally regulate brain activation in the absence of neurofeedback to a greater degree after training than prior to training. Transfer indicates that individuals learned something beyond the training environment - i.e., the ability to regulate brain activation can be applied to a non-training context (for example, a post-training test). Participants in this study did not achieve transfer of training to a post-training test: midbrain activation was not higher in the post-training test run compared to the pre-training test or training runs. However, they were able to successfully increase activation in the midbrain during post-training test, just not to a greater degree than pre-training or training. In addition, clinical outcomes were not examined in this study, leaving it an open question as to whether upregulating midbrain activation impacts future drug seeking behavior in cocaine users.

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Kirschner and colleagues' experiment contributes to the growing field of clinical neurofeedback studies in two main ways: First, individuals who use cocaine (at least low-moderate amounts) can use self-generated, non-drug imagery to upregulate brain activation in the midbrain, corroborating previous demonstrations in healthy adults [9,10]. Second, the ability to upregulate brain activation in cocaine users is related to cocaine use, both in terms of obsessive-compulsive thoughts regarding drug use and lifetime cocaine consumption. Given difficulties in recruiting a large sample of adults with CUD, the authors used a relatively liberal criteria of cocaine use (0.5 g/week compared to typical treatment studies that recruit individuals who use 3 g/week and use on at least 50% of days/month). Therefore, the sample included both recreational users and those with CUD. Nevertheless, there was a negative relationship between metrics of cocaine use and midbrain self-activation.

Several open questions were generated from this study including: 1) Can individuals with a diagnosis of CUD increase midbrain activation using non-drug imagery? 2) If not, can they learn via neurofeedback training to do so? 3) Does this have any clinical impact? And more broadly, 4) Would this approach be successful in other SUD populations (e.g., alcohol use disorder)? Clinicians, patients, and basic scientists alike eagerly await answers to these exciting and important questions.

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