

## Neurocognitive Mechanisms in Cocaine Users

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According to the 2011 National Survey on Drug Use and Health, approximately 36.9 million Americans aged 12 or older had tried cocaine at least once in their lifetimes, representing 14.3% of this population. In spite of extensive and persistent use of cocaine in youth and young adults, the neurocognitive mechanisms that support initiation and continuing use of cocaine in humans are not well understood. It is crucial to understand these mechanisms as they may be important for identifying those at risk for cocaine use and for treatment development in chronic cocaine users.

The leading cognitive and neuroadaptive theories of addiction suggest that the automatic/non-automatic (i.e., implicit/explicit) information processing distinction may guide us in understanding the development of problem drug use behaviors [1]. Yet, literature is restricted in its coverage of examining implicit and explicit memory processes in persistent users of cocaine. In the cocaine literature, only one study has examined implicit and explicit cocaine-related cognitions in cocaine-dependent poly-substance abusers and controls using verbal information [2]. However, none of the previous cocaine studies has examined both implicit and explicit memory processes involving cocaine related visual information within the same cocaine user. This would be important to examine as drug use behaviors in chronic users of cocaine are often activated by observing drug related visual cues in the external world. Examining the combined operation of implicit and explicit memory processes related to drug related visual information within the same individual will lead us in developing individual-specific prevention and intervention techniques.

In the brain imaging literature, the neural correlates of implicit (measured using priming paradigm) and explicit (measured using recognition memory task) memory processes have been well studied in healthy non-substance abusing individuals using neutral stimuli [3]. Extant fMRI and PET literature involving cocaine users has not directly studied neural mechanisms underlying implicit and explicit memory processes for appetitive cues. Nevertheless, separate lines of research have suggested its importance. Usually, in cue reactivity studies, individuals abstain from alcohol/drug use and their brain is scanned while they view addiction-related word or picture cues or related thoughts. Activation in insula, orbitofrontal cortex, amygdala, hippocampus and anterior cingulate brain areas was observed while participants experienced cocaine-cue induced craving [4,5].

Since hippocampus and amygdala were activated during cue exposure, it was suggested that drug and alcohol cue exposure activate memories related to their use [4]. In addition to examining localized brain regions of interest, there has been an increasing focus of neuroscientists on understanding how one brain area influences another, that is, on the 'effective connectivity' or 'functional connectivity' [6] during a cognitive task or at rest in healthy normal and clinical and neurotypical individuals [7]. Functional connectivity provides information about information flows in the brain and influences produced by different areas of the brain on each other during particular cognitive tasks. The modeling of effective connectivity has proved to be a useful tool for understanding brain function in both clinical and neurotypical populations and has been instrumental in developing clinical interventions.

However, this issue of brain interconnectivity is relatively novel in the addiction literature, specifically in the cocaine literature. Only one study has examined the effect of acute cocaine administration on functional connectivity in human primary visual and motor cortex [8], a few studies have examined functional connectivity during the resting state [9,10] and a few studies have examined functional connectivity while participants performed a cognitive task that did not include any memory task [11,12].

I suggest that future studies should examine both implicit and explicit memory processes involving cocaine related visual information in the same cocaine abuser or cocaine dependent individual. The implicit memory processes have not been the focus in the field, although it has been suggested that changing automatic associative effects could be fundamental adjunct to interventions [13]. Also, in addition to examining the localized brain regions of interest, future fMRI research may further examine the connectivity between the craving related and implicit (or explicit) memory related brain areas while participants process cocaine related visual cues during implicit (or explicit) memory task by using multiple advanced state-of-the art causal modeling approaches [6,14]. This would be important to examine as the memory and craving systems have been suggested to play a crucial role in maintenance of drug use behavior [1]. The research findings will elucidate our understanding of how brain functioning may differ in persons who vary in extent and consequences of cocaine exposure, that is, individuals who have limited experience with cocaine versus individuals who are chronic cocaine users. Thus, the proposed research has practical implications in terms of its ability to assess an individual's level of cocaine experience by examining that individual's connectivity map which reveals the individual's strength of connectivity between the memory and craving systems. Furthermore, an examination of the connectivity map between the memory and craving systems during the course of treatment may help clinicians identify individuals who may relapse. The novel medication development strategies for long-term smoked cocaine use (e.g., dopamine receptor agonist (modafinil), dopamine receptor antagonist (ecopipam)) should be examined on cocaine dependent individuals to investigate whether their subjective craving ratings change and whether the connectivity between the memory and craving systems is diminished as a result of medication.

Along with the proposed above research, advances in structural integrity/connectivity obtained by utilizing both Diffusion Tensor Imaging (DTI) and Voxel Based Morphometry (VBM) imaging

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techniques [15] can enhance our understanding of brain dysfunction in cocaine dependent individuals. As these evolving methods mature, a better understanding of structural and functional connectivity and their interplay will further enhance the field. The results from future research will lay the groundwork for more articulated neurocognitive models of craving and impulse control in cocaine users, and potentially suggest ways that implicit memory processes may be harnessed to interrupt craving states. The knowledge gained from this future research will have implications for developing individually-tailored and effective cocaine use prevention and intervention techniques. These techniques could potentially include cognitive restructuring within the implicit memory system, neurofeedback [16], developing therapies to modulate the functions of craving related brain areas, and medication development.

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