

Brain Structural and Functional Changes in Cocaine Users during Abstinence

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Editorial

Stimulant abuse, particularly cocaine abuse is an important public health concern, as according to 2013 National Survey on Drug Use and Health (SAMHSA, 2013) [1], there are 1.5 million current cocaine users in the United States and costs to the society for drug abuse including cocaine abuse are calculated to be \$62 billion (NDCS, 1997) [2]. Utilizing brain imaging techniques and neuropsychological tests, earlier studies have shown reduced anterior and posterior cingulate activation, attenuated inferior frontal and dorsolateral prefrontal cortex activation and altered posterior parietal activation, and impaired learning, memory, attention, reaction time and cognitive executive function in chronic cocaine users [3-5]. Long-term stimulant abuse has been associated with brain's structural abnormalities [6,7], as well as functional abnormalities characterized in terms of an enhanced neural reactivity to appetitive drug cues [8-12] enhanced neural response during craving [10], and an impaired neural response in paradigms that measure cognitive control [13-16]. A continuing problem with cocaine dependence is that the majority of cocaine users will frequently resume drug use after a period of abstinence [17]. However, there is relatively little empirical research on how the brain's structural and functional abnormalities change while a stimulant user maintains drug abstinence.

Studies using Diffusion Tensor Imaging (DTI; Beaulieu, 2002) [18] technique have shown that current users of cocaine have reductions in white matter (WM) integrity compared to controls [19,20]. However a fundamental question is whether these white matter differences are present following abstinence from cocaine use. To address this question, a limited number of DTI studies have been conducted that utilized a cross sectional design [21-23]. For example, Bell et al. [21] examined WM integrity in cocaine-abstinent individuals and nonusing controls. Cocaine-abstinent individuals showed lower fractional anisotropy (FA) in the left anterior callosal fibers, left genu of the corpus callosum, right superior longitudinal fasciculus, right callosal fibers and the superior corona radiata bilaterally compared to controls. Differences between the cocaine abstinent sub-groups were observed bilaterally in the inferior longitudinal fasciculus, right anterior thalamic radiation, and right ventral posterolateral nucleus of the thalamus, left superior corona radiata, superior longitudinal fasciculus bilaterally, right cingulum and the WM of the right precentral gyrus. Similarly, Xu et al. [23] found that the long-term abstinence group had significantly higher FA than the short-term abstinence group in corpus callosum, frontal, parietal, temporal, occipital and cerebellar regions. Using structural MRI analyzed with voxel based morphometry (VBM), Hanlon et al. [22] showed that the one-month abstinent cocaine users had significantly higher gray matter density than current cocaine users in neocortical areas including the frontal and temporal cortex. Using a VBM technique, a reduced gray matter volume in the prefrontal

cortex, lateral and medial aspects of the orbitofrontal cortex and right cingulate gyrus in 20-day abstinent cocaine users compared to controls was reported by Matochik et al. [24]. Thus, although a limited number of cross sectional studies have examined structural changes in abstinent cocaine users, no longitudinal data exist on this topic. The cross sectional studies are limited in that they fail to reveal if the structural and functional brain changes in substance users during abstinence are due to dynamic intra-individual changes that characterize successful abstinence, or if they manifest pre-existing differences between substance users.

A more recent focus of neuroimaging studies is understanding not just which individual brain areas are activated by a cognitive task, but how individual brain regions are integrated, i.e., functional connectivity. Functional connectivity has been examined in current cocaine users in the resting state [25-28] as well as while they performed a finger-tapping and an attention task [22,29]. However, earlier studies on functional connectivity in individuals who have abstained from cocaine use are limited with only a handful of imaging studies examining this topic [30-32]. For example, Adinoff et al. [30] assessed alterations in regional cerebral blood flow (rCBF) and related resting state functional connectivity (rsFC) to prospectively predict relapse in cocaine users following treatment for cocaine use disorder. Results showed an enhanced rCBF only in the left posterior hippocampus in the group who relapsed compared with the early remission (Individuals who did not use cocaine within 30 days following discharge) and control groups. Also, the left posterior hippocampus had an increased rsFC strength with the posterior cingulate cortex/precuneus in the relapsed versus early remission subgroups. Differences in measures of intrinsic connectivity during functional magnetic resonance imaging (fMRI) stroop performance were examined by Mitchell et al. [32]. Results demonstrated a relatively greater intrinsic connectivity in the ventral striatum, putamen, inferior frontal gyrus, anterior insula, thalamus and substantia nigra for abstinent cocaine users compared to controls.

To date, only two fMRI effective connectivity studies which reveal the influence that one brain region exerts over another have been conducted with cocaine users. Effective connectivity studies provide enhanced information on the consequences of chronic drug use on the brain compared to functional connectivity studies. My colleagues and I have assessed effective connectivity among brain regions while chronic cocaine users viewed cocaine-related picture cues (Ray et al. [33]). And Ma et al. [34] examined effective connectivity in cocaine users during an immediate and delayed working memory task. I am not aware of any effective connectivity study involving abstinent cocaine users. Thus, although a few studies have examined functional connectivity in cocaine-dependent individuals who are abstinent, no studies implemented a longitudinal design. In order to move the field forward, I propose that a longitudinal fMRI study should be conducted to examine dynamic structural and functional changes in treatment-seeking abstinent cocaine dependent individuals by scanning them at multiple time points during abstinence. Structural and functional brain changes should be examined using structural, functional and effective connectivity analysis approaches. Specifically, the focus should be on the cognitive control network (CCN) [35] which has been associated with impulsive drug seeking behavior. This study may have implications to develop therapies that have potentials to change the neuroplasticity within the CCN which may promote abstinence from cocaine use.

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