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Enduring changes in brain metabolites and executive functioning in abstinent cocaine users

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ABSTRACT

Background: There is a paucity of data connecting the metabolic and cognitive functioning of abstinent cocaine users. This is a pressing public health concern as approximately 1% of the Canadian population and 0.4% of the global population is estimated to have used cocaine in the past year.
Methods: Our clinical study compared the *in vivo* neurochemical profiles in the prefrontal cortex to cognitive tests associated with the same region in 21 moderate term abstinent cocaine users (average 187 days abstinent, range 15–1432 days), and 30 healthy controls using 3T ^{1}H MRS.
Results: The abstinent cocaine users exhibited a 10% decrease in *N*-acetylaspartate (NAA) relative to healthy control subjects ($p < 0.01$, Cohen's $d = 1.15$). When subdivided by method of administration, a significant decrease in glutamate levels in former crack smokers compared to healthy controls ($p < 0.05$) was observed, this decrease was not present in powder users. Abstinent users were significantly worse than healthy controls on the Trail Making Test B ($p < 0.05$), and performance on this task was inversely related to NAA levels ($p < 0.05$). Abstinent cocaine users showed deficits in the Wisconsin card sorting test with failures to maintain set ($p < 0.01$).
Conclusions: Our work suggests that there are subtle but important changes in the brain that remain even with the moderate term cessation of cocaine use.

1. Introduction

Cocaine addiction is a major public health problem. Cocaine is the second most commonly used drug of abuse in the world at a surveyed use rate of 0.4% of the global population (Crime, 2013). Canada is a location suited to study cocaine addiction as there is an estimated rate of 1.1%, that has been confirmed with municipal wastewater testing (Canada, 2012; Yargeau et al., 2013). While the mechanism of action and neurological consequences of acute cocaine use are well known, the long-term neurological consequences, particularly after a significant period of abstinence, are unclear.

There is evidence that cocaine acts to alter the structure and biochemical operation of the brain with chronic use. While significant research on the dopaminergic system in cocaine use is reported, glutamate is also of particular importance in this discussion. As glutamate is ubiquitous in the brain and the primary excitatory neurotransmitter, it is plausible that the damage done to the brain by chronic cocaine use is as likely to be mediated by the actions of glutamate as well as dopamine (Dong et al., 2009; Shin et al., 2017). Relevant to addictions biology, glutamatergic inputs provide connections between the prefrontal cortex, including the anterior cingulate cortex, to the nucleus accumbens and the basolateral amygdala (Cadet et al., 2014). A driving hypotheses on the mechanism of relapse is the glutamate homeostasis hypothesis, developed from preclinical research, which posits that an imbalance in glutamate homeostasis impairs communication between the nucleus accumbens and the prefrontal cortex (Kalivas, 2009). Pharmacological re-instatement of glutamate homeostasis is the theoretical basis behind using *N*-acetlycysteine clinically to treat cocaine addiction (Schmaal et al., 2012). However, *in vivo* investigations of the glutamatergic system in cocaine use are limited in human clinical models.

One of the methods that can be used to examine *in vivo* brain glutamate levels in human subjects is proton magnetic resonance spectroscopy (^{1}H MRS). Where MRI uses signals from hydrogen protons (^{1}H)

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Table 1
Review of existing literature of Magnetic Resonance Spectroscopy on cocaine addicts.

Authors	N (Subject population)	Quantification method	Paradigm	Brain Region	Results
Chang et al. (1997)	19 abstinent addicts 25 healthy controls	1.5T Absolute values of metabolites and ratio of metabolites to total Cr	Survey of NAA, Glx, Cr, Choline and *myo*-inositol	GM voxel in midoccipital region and WM voxel in subcortical right temporoparietal region (7–15 cc)	Creatine and *myo*-inositol elevated in white matter of abstinent cocaine subjects. NAA/Cr reduced in both WM and GM voxels in abstinent addicts.
Chang et al. (1999)	34 male abstinent 30 female abstinent 29 male controls 29 female controls	1.5T Absolute values and ratio to creatine	NAA, Cr, Cho, MI, Glx	3–5 cc voxels centered on midfrontal grey matter or right frontal white matter.	Reduced NAA and elevated MI in grey matter and elevated Cr and MI in white matter in male addicts. Female abstinent addicts by comparison only had elevated MI in the frontal white matter.
Meyerhoff et al. (1999)	7 abstinent addicts 11 healthy controls	1.5T ratio of metabolites to total Cr	Survey of NAA and choline	Dorsolateral prefrontal cortex voxel (0.9 ml)	NAA/Cr significantly decreased in abstinent cocaine users relative to healthy control subjects.
O'Neill et al. (2001)	8 abstinent addicts 13 healthy controls	1.5T Absolute values of metabolites	NAA, Cr and Choline in gray matter and white matter	Brain regions by Talairach coordinates	Significant increase in Cr in posterior parietal region in abstinent cocaine addicts. However, cocaine dependent group was not age matched to the healthy control group.
Christensen et al. (2000)	30 occasional users who received an acute injection of cocaine	1.5T Area under the curve analysis	NAA, Cho, Cr 15 min before and up to 30 min after injection	8 cm^3 voxel in the left caudate nucleus and putamen.	Both NAA and Cho rose significantly in response to cocaine but not injection of placebo.
Hetherington et al. (2000)	10 cocaine addicts 6 healthy controls	4.1T Absolute values of metabolites	GABA	Occipital lobe	Significant decrease (20%) in GABA in cocaine addicts relative to healthy controls
Hulka et al. (2016)	18 cocaine addicts 18 healthy controls	3T Ratio of metabolites to total Cr	Glu, Gln, GABA, NAA, Cho, mI, and 10 exploratory	Pregenual anterior cingulate cortex and right dorsolateral prefrontal cortex	No changes in Glu or Gln between healthy controls and current users but higher levels of drug usage were associated with lower Glu/Cr in the pgACC. Higher ratios of Cho/Cr were seen in both regions examined in users.
Ke et al. (2003)	24 addicts in treatment 9 healthy controls	1.5T Absolute values of metabolites	Cr and PCr measured before and after 8 weeks of treatment	Left frontal lobe voxel (2.5 × 2.5 × 3 cm^3)	PCr significantly lower in non-responders versus responders at baseline (response defined as 25% decreased in urine cocaine metabolites). After treatment, PCr levels increased significantly for non-responder group. No significant difference between addicts and controls.
Ke et al. (2004)	35 cocaine addicts 20 healthy controls	1.5T Absolute values of metabolites	NAA, GABA and Cho using Cr as an internal reference	18.75 cm^3 voxel in left prefrontal cortex	Significant decrease (30%) in GABA levels in addicts relative to healthy controls.
Li et al. (1999)	21 cocaine addicts 13 healthy controls	1.5T Ratio of metabolites to Cr or Cho	NAA, Cr, Cho	2 × 2 × 1.5 cm voxel in the left basal ganglia and 1.5 × 1.5 × 2 cm voxel in the left thalamus	Reduced NAA/Cr (17%) in the left thalamus but not the left basal ganglia in cocaine users.
Martinez et al. (2014)	15 active addicts	3T Ratio of metabolites to water	Glx, GABA, Cho, Cr, and NAA	3 cm × 1.5 cm × 2 cm voxel placed in left striatum	No differences seen in GLX between healthy controls and active users.
Schmaal et al. (2012)	8 active addicts 14 healthy controls	3T Absolute values of metabolites	Glutamate and NAA with single *N*-acetylcysteine (NAC) dose	Dorsal ACC voxel (1 × 1 × 1 cm^3)	Glutamate levels significantly higher in cocaine-dependent individuals relative to healthy controls, normalized with NAC treatment.
Yang et al. (2009)	14 active addicts 14 healthy control	3T Ratio of metabolites to total Cr	Survey of Glutamate, NAA, total choline, and *myo*-inositol	Anterior cingulate cortex voxel (2 × 2 × 2 cm^3)	Glu/tCr was significantly lower in chronic cocaine addicts relative to healthy controls and correlated to years of use.