



Full length article

White matter disruptions in male cocaine polysubstance users: Associations with severity of drug use and duration of abstinence



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ARTICLE INFO

Article history:

Received 1 June 2016

Received in revised form

14 September 2016

Accepted 17 September 2016

Available online 6 October 2016

Keywords:

Diffusion tensor imaging

Fractional anisotropy

Polysubstance use

Cocaine

Alcohol

Abstinence

ABSTRACT

Background: Cocaine dependence has been associated with alterations in the brain's white matter integrity, yet relevant questions remain about what alterations are linked to cocaine use and/or polysubstance use, and whether they are amenable to abstinence.

Methods: This study applied a single measurement session of diffusion tensor imaging (DTI) to examine white matter structure in male cocaine polysubstance users ($n = 37$) versus male healthy controls ($n = 38$), along with correlations between DTI measures and patterns of polysubstance use and duration of abstinence. Specifically, we conducted voxel-wise analyses of fractional anisotropy (FA) in the corpus callosum, frontolimbic, striatal and cingulate tracts relevant to drug sequelae.

Results: Cocaine polysubstance users, compared to controls, showed lower FA in the body of the corpus callosum, anterior cingulate, uncinate fasciculus and retrolenticular part of the internal capsule. Duration of cocaine use had a marginal negative association with FA in the corpus callosum, and duration of alcohol use was negatively associated with FA in the internal capsule and the uncinate fasciculus. Duration of cocaine abstinence was positively correlated with FA in the uncinate fasciculus, posterior cingulate and fornix-striatum. In the context of cocaine polysubstance use, chronicity of cocaine use is therefore likely to be associated with lower FA in the corpus callosum, and chronicity of alcohol use with lower FA in the frontal-striatal and frontal-limbic tracts. Longer abstinence was correlated to greater FA in frontal-striatal and frontal-limbic tracts, though the direction of causality remains unclear.

Conclusion: Since the results did not survive multiple comparison-corrected thresholds, more studies are needed to confirm these indications.

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1. Introduction

Cocaine dependence is a significant public health problem, particularly among adult males (Agabio et al., 2016). Biologically based treatments are lacking (Everitt and Robbins, 2016), and existing psychosocial interventions have their lowest efficacy in cocaine polysubstance users (Dutra et al., 2008). Therefore, broad knowledge of the neurobiological alterations associated with polysubstance use, and the brain networks associated with successful

abstinence, can improve understanding of cocaine dependence and its treatment. Diffusion tensor Imaging (DTI) is a useful technique for non-invasively investigating the structure of white matter by measuring fractional anisotropy (FA), axial diffusivity (AD), radial diffusivity (RD) and mean diffusivity (MD). These measures reflect the degree of alignment of cellular structures within fiber tracts, as well as structural integrity (Betz et al., 2012; Cercignani et al., 2001). Previous studies using DTI have already found FA reductions in cocaine dependent individuals within the genu and the rostral body of the corpus callosum, as well as in frontal, frontal-limbic and parietal regions (Bell et al., 2011; Lim et al., 2008; Ma et al., 2009; Moeller et al., 2005; Romero et al., 2010). The present study aimed to replicate and extend these findings in a sample of cocaine

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dependent individuals with varying levels of abstinence enrolled in therapeutic community treatment.

An important issue in the context of the neurobiological correlates of cocaine dependence is whether white matter alterations are more severe in users who consume more than one drug, so called 'polysubstance users', compared to users of a single drug. Studying populations of polysubstance users is usually avoided for methodological reasons. However, polysubstance users are clinically representative due to the high prevalence of this pattern in addiction treatment services (Barrett et al., 2006; Redonnet et al., 2012). High rates of polysubstance use have specifically been documented in cocaine dependent users (Connor et al., 2014). In addition, there is growing scientific interest in the impact that other drugs such as alcohol and tobacco have on the neurobiological abnormalities ascribed to cocaine dependence (Abé et al., 2013; Pennington et al., 2015). In polysubstance users with cocaine as their main drug of choice, structural neuroimaging studies have shown significant reductions of the volume of discrete brain regions such as the prefrontal cortex, striatum and amygdala (Barrós-Loscertales et al., 2011; Moreno-López et al., 2012). It has been also found that a higher number of used substances was related to lower whole brain white matter integrity (Kaag et al., 2016). Prefrontal and Striatal regions have been implicated in reward learning and cognitive control processes that are pivotal to addiction (Kahnt et al., 2009; Koob and Volkow, 2009). However, the function of these regions is ultimately determined by their pattern of white matter input and output (Passingham et al., 2002) and thus white matter studies can lead to a better understanding of the impact of polysubstance use in cocaine dependence.

In addition, recent studies have examined white matter recovery following abstinence. Cocaine dependent individuals who received treatment showed a positive correlation between duration of abstinence (measured with both self-reports and urine tests) and FA values in the corpus callosum, cerebellum, frontal, parietal, temporal, and occipital lobes (Xu et al., 2010). Also, cocaine dependent individuals who were treated with transcranial direct current stimulation (tDCS) during abstinence, had increased DTI parameters in the left ventral-medial prefrontal cortex connection to the nucleus accumbens (Nakamura-Palacios et al., 2016) when compared to cocaine dependent individuals treated with a placebo (sham) tDCS. More directly, Bell and colleagues (2011) looked at 43 cocaine dependent individuals who were abstinent varying from 5 to 102 days and found duration of abstinence to correlate with increased FA in the inferior and superior longitudinal fasciculus, anterior and ventral connections from the thalamus, superior corona radiata, cingulum and the precentral gyrus. Mainly the longitudinal fasciculus and tracts connecting the thalamus and the cingulum are involved in emotional and homeostatic processes (Olson et al., 2007; Pisner et al., 2016).

Given the findings of reduced FA in cocaine dependent individuals compared to healthy controls, and the findings of FA recovery in abstinent cocaine users, this study re-assessed these findings in a relatively larger group of male cocaine polysubstance users undergoing therapeutic community treatment. The main aims were (i) to compare white matter integrity in tracts connecting frontal, callosal, striatal and limbic regions in male cocaine polysubstance users versus male non-drug using controls, and (ii) to determine the extent of the association between white matter integrity, chronicity of substance use and duration of abstinence in the cocaine polysubstance group. We hypothesized that cocaine polysubstance users will show lower white matter integrity compared to non-drug using controls. We also hypothesized negative associations between patterns of use of cocaine and other drugs and white matter integrity, and a positive association between duration of abstinence and white matter integrity.

Table 1

Substance use characteristics in male cocaine polysubstance users (CPU) and male healthy controls (HC).

| | CPU | HC |
|----------------------------------------|------------------|-----------------|
| | n = 37 | n = 38 |
| Age | 29.5 ± 6.6 | 31.1 ± 5.1 |
| Years of education | 9.7 ± 1.62 | 10.38 ± 1.96 |
| Duration of cocaine use in months | 48.6 ± 36.86 | – |
| Current abstinence of cocaine in weeks | 36.76 ± 22.60 | – |
| Cocaine use per month (grams) | 18.19 ± 29.84 | – |
| Units of alcohol per month | 107.58 ± 114.03* | 23.83 ± 25.45* |
| Occasions of marijuana use per month | 88.03 ± 107.01 | 11.01 ± 12.03 |
| Percent smokers | 83.8 | 44.7 |
| Number of cigarettes per month** | 488.48 ± 307.40 | 352.16 ± 340.56 |

Note: Mean ± standard deviation of the mean. CPU = cocaine polysubstance users, HC = healthy controls.

* Mean units of alcohol per month (in bold) was significantly different between groups ($p = 0.003$). Due to multiple comparisons, level of significance was adjusted to $p < 0.01$ using Bonferroni correction.

** Use of non-smokers is included as well in the measure of number of cigarettes per month.

2. Material and methods

2.1. Participants

A total of 37 cocaine polysubstance users with a mean age = 29.6, standard deviation (SD) = 6.5, and 38 non-drug users (controls) with a mean age = 31.1, SD = 5.1 were included in this study. Cocaine polysubstance users were recruited in an inpatient addiction treatment clinic ("Proyecto Hombre"), located in Granada, Spain, and were currently undergoing therapeutic community treatment. Due to the low prevalence of women entering drug treatment during the recruitment period, all the participants were male. All the cocaine dependent participants reported cocaine as their main drug of choice and the drug for which they received treatment. Clinical interviews based on Diagnostic and Statistical Manual version IV (DSM-IV) criteria confirmed cocaine dependence diagnosis; in addition, they reported regular use of tobacco, alcohol, marijuana and 3,4-methylenedioxyamphetamine (MDMA; see Table 1). Cocaine dependent users had to be abstinent for at least 15 days (for any drug but tobacco) to participate in the study, as confirmed by weekly urine tests. In this way, it became possible to rule out acute and residual effects of previously used drugs on brain structure; with the exception of tobacco (83.8% of cocaine-dependent patients and 44.7% of controls were current smokers). Although short-term abstinence was objectively monitored, the total duration of abstinence was substantially longer in most participants, and thus this total length of abstinence was self-reported. This self-report data, which was corroborated by clinicians, was used in correlational analyses concerning the relationship between duration of abstinence and white matter measures (see Results subsection 3.3 below).

The non-drug using controls were recruited through a local employment agency, and were matched to the cocaine participants in terms of being unemployed. Selection criteria for control participants were: (i) the absence of current or past substance use, excluding past or current social drinking (less than ten standard alcohol units per week) and tobacco use; (ii) the absence of documented major psychiatric disorders; (iii) the absence of documented head injury or neurological disorder, and (iv) not using medication with effects on the central nervous system.

Potential participants; both cocaine polysubstance users and healthy controls who had previously been diagnosed with any disorder from DSM-IV Axes I and II (other than substance dependence), or who had neurological or systemic diseases affecting central nervous system (CNS) functioning were excluded. Furthermore, none

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