Drug and Alcohol Dependence 149 (2015) 122–127

Contents lists available at ScienceDirect

Drug and Alcohol Dependence

journal homepage: www.elsevier.com/locate/drugalcdep

# Investigating the microstructural and neurochemical environment within the basal ganglia of current methamphetamine abusers

Joanne C. Lin[a], Reem K. Jan[a], Rob R. Kydd[b], Bruce R. Russell[a,*]

[a] School of Pharmacy, Faculty of Medical and Health Sciences, University of Auckland, Private Bag 92019, Auckland 1142, New Zealand
[b] Department of Psychological Medicine, Faculty of Medical and Health Sciences, University of Auckland, Private Bag 92019, Auckland 1142, New Zealand

ARTICLE INFO

*Article history:*
Received 7 November 2014
Received in revised form 21 January 2015
Accepted 22 January 2015
Available online 31 January 2015

*Keywords:*
Methamphetamine
Magnetic resonance spectroscopy (MRS)
Diffusion tensor imaging (DTI)
Basal ganglia

ABSTRACT

*Background:* Methamphetamine is a highly addictive psychostimulant and the medical, social, and economic consequences associated with its use have become a major international problem. Current evidence has shown methamphetamine to be particularly neurotoxic to dopamine neurons and striatal structures within the basal ganglia. A previous study from our laboratory demonstrated larger putamen volumes in actively using methamphetamine-dependent participants. The purpose of this current study was to determine whether striatal structures in the same sample of participants also exhibit pathology on the microstructural and molecular level.

*Methods:* Diffusion tensor imaging (DTI) and magnetic resonance spectroscopy (MRS) were carried out in current methamphetamine users ($n = 18$) and healthy controls ($n = 22$) to investigate diffusion indices and neurometabolite levels in the basal ganglia.

*Results:* Contrary to findings from previous DTI and MRS studies, no significant differences in diffusion indices or metabolite levels were observed in the basal ganglia regions of current methamphetamine users.

*Conclusions:* These findings differ from those reported in abstinent users and the absence of diffusion and neurochemical abnormalities may suggest that striatal enlargement in current methamphetamine use may be due to mechanisms other than edema and glial proliferation.



## 1. Introduction

Methamphetamine is a highly addictive psychostimulant and the medical, social, and economic consequences associated with its use have become a major international problem. Addiction is one of the most pervasive, costly, and challenging health problems facing society, and the use and manufacture of amphetamines remain high. The number of amphetamine users worldwide likely exceeds the number of opiate and cocaine users combined (United Nations Office on Drugs and Crime, 2010). Current evidence suggests that long-term exposure to psychostimulants such as methamphetamine is associated with structural, metabolic, and neurochemical changes in both gray and white matter (Bae et al., 2006; London et al., 2004; Thompson et al., 2004). Methamphetamine has also been shown to be particularly neurotoxic to dopamine neurons and striatal structures within the basal ganglia, which are highly innervated by dopamine. Cross-sectional human studies have documented fewer dopamine transporters and dopamine $D_2$ receptors (McCann et al., 1998; Volkow et al., 2001a,c; Wilson et al., 1996), as well as larger caudate and putamen volumes in abstinent methamphetamine users (Chang et al., 2005a; Jernigan et al., 2005).

To date, several DTI and MRS studies have been carried out in abstinent methamphetamine users; findings generally indicate microstructural abnormalities within frontal white matter and corpus callosum regions (Chung et al., 2007; Kim et al., 2009; Salo et al., 2009; Tobias et al., 2010) and neurochemical changes in frontal gray matter (including anterior cingulate regions) and white matter (Nordahl et al., 2005, 2002; Sailasuta et al., 2010; Salo et al., 2011, 2007; Sung et al., 2007). Few studies have applied DTI and MRS to basal ganglia regions in methamphetamine users. A study by Alicata et al. (2009) evaluated the diffusion tensor properties of the subcortical brain regions in a cohort of abstinent methamphetamine-dependent participants. In comparison to control participants, methamphetamine-dependent participants exhibited normal fractional anisotropy (FA) values but higher axial diffusivity in the caudate and putamen, and higher radial diffusivity in the putamen. The authors proposed that this reflects higher

* Corresponding author. Tel.: +64 9 923 6429; fax: +64 9 367 7192.
*E-mail address:* b.russell@auckland.ac.nz (B.R. Russell).

http://dx.doi.org/10.1016/j.drugalcdep.2015.01.026
0376-8716/

water content and diffusion in the basal ganglia, which may also be related to inflammatory processes or myelination abnormalities (Alicata et al., 2009). MRS investigations of the neurochemical environment of the basal ganglia have observed significantly lower concentrations in creatine (Cr) and *N*-acetyl-aspartate (NAA), suggesting lower neuronal density or content (Chang et al., 2005b; Ernst et al., 2000; Sekine et al., 2002), as well as elevated *myo*-inositol (Taylor et al., 2007).

All methamphetamine-dependent participants in the above-mentioned DTI and MRS studies were abstinent, with average periods of abstinence between 4 and 18 months. To our knowledge, the effects of current methamphetamine use on microstructural integrity and neurochemical properties of the basal ganglia of current methamphetamine users have not been determined. A previous study from our laboratory demonstrated larger putamen volumes in actively using methamphetamine-dependent participants (Jan et al., 2012). Although the causative mechanisms of striatal enlargement remain unknown, edema on the microstructural level and gliosis are commonly suggested (Chang et al., 2007; Jernigan et al., 2005). The purpose of this current study was to determine whether striatal structures in the same sample of participants also exhibit pathology on the microstructural and molecular level.

## 2. Materials and methods

### 2.1. Participants

The sample of participants in this study was the same as those from a previously published paper (Jan et al., 2012). Eighteen methamphetamine-dependent participants and 22 healthy control participants volunteered to participate in this trial. The study was granted ethical approval by the Northern X Regional Ethics Committee of New Zealand; written consent was obtained from all participants before this research was undertaken.

Methamphetamine-dependent participants were recruited through Community Alcohol and Drug Services and met DSM-IV criteria for methamphetamine dependence, as determined by a psychiatrist using a structured clinical interview (SCID-I, Clinical Trials Version; First, 2002). For methamphetamine-dependent participants the inclusion criteria were (1) diagnosis of methamphetamine dependence according to DSM-IV criteria and (2) age between 18 and 45 years. Current methamphetamine use was confirmed by qualitative urine drug screens (cut-off 300 μg/l) on the day of testing. The drug screens also tested for opiates, benzodiazepines, cocaine, and tetrahydrocannabinol (THC); participants were excluded if the screen was positive for other drugs except THC. Control participants were recruited from the local community by word of mouth and posters, and were required to meet the same criteria as the dependent group but without a history of methamphetamine use. Control participants were not drug-naïve – some participants had smoked and/or used THC; however, they were not considered 'regular' users and none had ever used methamphetamine. All control participants were required to return a negative urine screen on the day of scanning to ensure no recent drug use.

Both groups of participants were excluded on the basis of (1) other Axis I disorders requiring treatment (including substance-related psychosis, schizophrenia, and mood disorders); (2) primary dependence on any other substances (excluding nicotine) requiring medical treatment; (3) risk of suicide or violent behavior; (4) significant neurological, thyroid, renal, hepatic, gastrointestinal or cardiovascular disease; (5) stroke or head injury leading to loss of consciousness; (6) in females, inadequate pregnancy prevention, current pregnancy or lactation; and (7) metal implantation precluding MRI procedures. Demographic and substance use characteristics of controls and methamphetamine users are outlined in Table 1. Participants were asked whether they regularly drank alcohol (referring to the consumption of the recommended amount of alcohol per week, i.e. 10 standard drinks per week for women, 15 standard drinks for men; one standard drink contains 10 g of alcohol), and used nicotine or THC.

**Table 1**
Demographic characteristics of and control participants and methamphetamine-dependent participants.

| Demographic variable | Control group ($n = 22$) | Methamphetamine group ($n = 18$) |
|---|---|---|
| Age (years ± SD) | 30.73 ± 8.25<br>Range: 18–46 | 35.27 ± 6.48<br>Range: 22–46 |
| Gender: male/female | 15/7 | 13/5 |
| Alcohol use | 10 | 9 |
| Regular nicotine use | 0 | 13 |
| Regular THC use | 0 | 18 |
| **Methamphetamine-related characteristics** | | |
| Route of administration: smoking/intravenous/both | – | 12/4/2 |
| Age at first use (years ± SD) | – | 23.50 ± 6.66<br>Range: 12–34 |
| Duration of use (years ± SD) | – | 10.22 ± 5.64<br>Range: 2–25 |
| Cumulative lifetime dose (g) | – | 1372.55 ± 1842.59<br>Range: 23–5400 |

### 2.2. Image acquisition

Data were acquired on a 1.5 T Siemens Magnetom Avanto System (Siemens Medical Solutions, Erlangen, Germany) with a gradient specification of 45 mT/m peak strength, 200 mT/m/s peak slew rate and running syngo® MR software.

*2.2.1. DTI.* Two high-resolution T1-weighted structural images were acquired using a sagittal Magnetization Prepared Rapid Gradient Echo (MPRAGE) sequence: TR = 2400 ms; TE = 3.61 ms; 1.3 mm isotropic voxel; scan time 7 min 42 s. The two images were averaged in the analysis.

Whole-brain axial diffusion-weighted images were acquired using a single-shot echo planar imaging sequence: TR = 6600 ms; TE = 101 ms, FOV = 230 mm, matrix size = 128 × 128, 45 slices, slice thickness = 3 mm, no gap, NEX = 3. Diffusion gradients were applied along 30 non-collinear directions using *b* value of 0 ($b_0$ image) and 1000 s/mm$^2$.

Images from all participants were reviewed to ensure that there were no structural abnormalities, excess motion, and other artifacts.

*2.2.2. MRS.* A 20 mm × 20 mm × 20 mm voxel of interest was place within the right basal ganglia region parallel to the anterior commissure-posterior commissure orientation to include the same parts of the caudate and putamen. A voxel was also placed in the primary visual cortex as a control region; it was centered on the calcarine fissure and included tissue from the left and right hemispheres (Fig. 1). Localized brain spectra within the basal ganglia were collected using a long TE spin-echo sequence. The following parameters were used for data acquisition: TR = 1500 ms; TE = 135 ms; total number of repetitions 192; water suppression on; scan time, 4 min 54 s. No additional data for determination of T1 and T2 correction factors were acquired, as this would have led to unacceptably long scan times for this clinical population.

### 2.3. Analysis

*2.3.1. DTI analysis.* All data were processed within FSL 5.0.2 (FMRIB Analysis Group, Oxford, UK) (Smith et al., 2004). First, eddy current correction was applied to all images; this step corrects for stretches and shears induced by gradient coils, and simple head motion. After data alignment, the diffusion tensor was calculated using a simple least squares fit of the tensor model to the diffusion data. Diffusion eigenvalues L1, L2, and L3 describe the primary, secondary, and tertiary diffusion directions at each voxel, respectively. Based on these eigenvalues, FA and mean diffusivity were calculated within FMRIB's Diffusion Toolbox (FDT) (Basser et al., 1994; Pierpaoli et al., 1996). Finally, the Brain Extraction Tool (BET) (Smith, 2002) was applied to the $b_0$ image to remove and exclude non-brain tissue from further analysis.

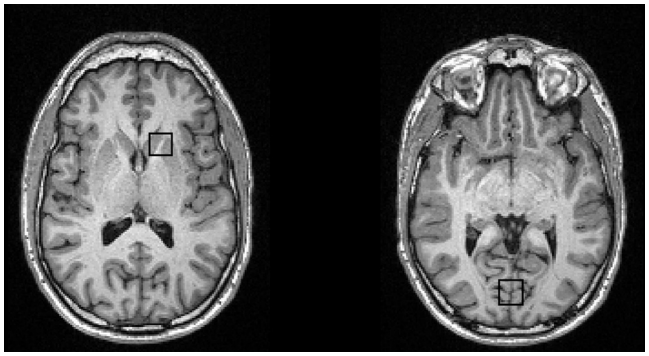

**Fig. 1.** Axial T1-weighted image showing MRS voxel positioning in the basal ganglia (right) and visual cortex (left) in radiological convention.