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The impact of acute and short-term methamphetamine abstinence on brain metabolites: A proton magnetic resonance spectroscopy chemical shift imaging study

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ABSTRACT

Background: Abuse of methamphetamine (MA) is a global health concern. Previous ^{1}H-MRS studies have found that, with methamphetamine abstinence (MAA), there are changes in *n*-acetyl-aspartate (NAA/Cr), *myo*-inositol (mI/Cr), choline (Cho/Cr and Cho/NAA), and glutamate with glutamine (Glx) metabolites. Limited studies have investigated the effect of acute MAA, and acute-to-short-term MAA on brain metabolites.

Methods: Adults with chronic MA dependence (n = 31) and healthy controls (n = 22) were recruited. Two-dimensional chemical shift ^{1}H-MRS imaging (TR2000 ms, TE30 ms) slice was performed and included voxels in bilateral anterior-cingulate (ACC), frontal-white-matter (FWM), and dorsolateral-prefrontal-cortices (DLPFC). Control participants were scanned once. The MA group was scanned twice, with acute (1.5 ± 0.6 weeks, n = 31) and short-term MAA (5.1 ± 0.8 weeks, n = 22). The change in ^{1}H-MRS metabolites over time (n = 19) was also investigated. Standard ^{1}H-MRS metabolites are reported relative to Cr + PCr.

Results: Acute MAA showed lower *n*-acetyl-aspartate (NAA) and *n*-acetyl-aspartate with *n*-acetyl-aspartyl-glutamate (NAA + NAAG) in left DLPFC, and glycerophosphocholine with phosphocholine (GPC + PCh) in left FWM. Short-term MAA showed lower NAA + NAAG and higher *myo*-inositol (mI) in right ACC, lower NAA and NAA + NAAG in the left DLPFC, and lower GPC + PCh in left FWM. Over time, MAA showed decreased NAA and NAA + NAAG and increased mI in right ACC, decreased NAA and NAA + NAAG in right FWM, and decreased in mI in left FWM.

Conclusion: In acute MAA, there was damage to the integrity of neuronal tissue, which was enhanced with short-term MAA. From acute to short-term MAA, activation of neuroinflammatory processes are suggested. This is the first ^{1}H-MRS study to report the development of neuroinflammation with loss of neuronal integrity in MAA.

1. Introduction

Methamphetamine (MA) abuse has increased in prevalence globally, and is a serious public health concern (UNODC, 2012). Within our country, the Medical Research Council, through the South African Community Epidemiology Network on Drug Use (SACENDU), reported an increase of MA as the primary substance of abuse in Cape Town, which has escalated from 19.3% in 2004 (Plüddemann et al., 2013) to 46% in 2014 (Dada et al., 2015). This epidemic stresses the importance of understanding the effects of MA on the brain.

Several non-invasive brain imaging techniques have investigated the effects of methamphetamine abstinence (MAA). Positron emission tomography (PET) studies have reported decreased dopamine transporter (DAT), involved in the regulation of presynaptic concentration of dopamine in nerve terminals within the striatum (Chang et al., 2007; Volkow et al., 2001). Computer axial tomography (CAT) and structural magnetic resonance imaging (MRI) studies have reported subcortical gray matter and frontal white matter deficits in chronic MA abusers (Chung et al., 2010; Lukas, 2014; Thompson et al., 2004). Lastly, proton magnetic resonance spectroscopy (^{1}H-MRS) has shown several changes in in vivo neurometabolite concentrations from an array of different brain areas, summarized in Table 1.

The aims of this study were as follows: first, to address the current gap in ^{1}H MRS investigations of acute MAA (0.9–2.1 weeks). First, to date, only a single study has reported metabolite concentrations in the acute phase of MAA, and this was limited to glutamate with glutamine

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Table 1
Summary of previous methamphetamine abstinence (MAA) ^{1}H MRS studies.

Metabolite	Brain area	Study	Duration of abstinence (days)
Lower *n*-acetyl-aspartate (NAA) concentration (Relative to creatine (Cr))	Frontal gray matter	Nordahl et al. (2002)	65.1 ± 23.1
	Frontal gray matter	Scott et al. (2007)	294.89 ± 359.37
	Frontal gray matter	Howells et al. (2014)	60 ± 53
	Frontal white matter	Sung et al. (2007)	3900 ± 1872
	Frontal gray and white matter	Ernst et al. (2000)	Median 127; Range 14–630
Higher *myo*-inositol (Ins) concentration (Relative to creatine (Cr))	Frontal gray matter	Nordahl et al. (2003)	65.1 ± 23.1
	Frontal gray matter	Scott et al. (2007)	294.89 ± 359.37
	Frontal white matter	Sung et al. (2007)	3900 ± 1872
	Frontal gray matter	Ernst et al. (2000)	Median 127; Range 14–630
Higher choline (Cho) concentration (Relative to *n*-acetyl-aspartate (NAA))	Anterior cingulate cortex, visual cortex	Nordahl et al. (2005)	88.5 ± 11.1; 1125 ± 176.1
	Anterior cingulate cortex, Frontal white matter, basal ganglia	Salo et al. (2011)	85.5 ± 50.7; 1408.2 ± 828
Lower choline (Cho) concentration (Relative to *n*-acetyl-aspartate (NAA)	Dorsolateral prefrontal cortex (right)	Howells et al. (2014)	60 ± 53
Lower glutamate with glutamine (Glu + Gln) (Absolute concentration)	Posterior cingulate, precuneus, right inferior frontal cortex	O'Neill et al. (2015)	Range 4–7
	Frontal gray matter	Ernst and Chang (2008)	63 ± 90

(O'Neill et al., 2015). Second, we aimed to address the current gap in ^{1}H MRS metabolite concentrations from acute MAA (0.9–2.1 weeks) to short-term (4.3–5.9 weeks) MAA, there is currently an absence of longitudinal studies, which we have partially addressed with this study. Third, we sought to include of several brain areas that are reported to be affected during MAA using two-dimensional shift imaging (2D-CSI) ^{1}H MRS, as studies employing single voxel spectroscopy are limited in the number of brain areas they are able to investigate. From previous ^{1}H MRS studies conducted in MAA, in the acute and short-term abstinence period from MA, we expect to find compromised neuronal integrity and function in frontal gray matter – specifically reduced the ACC and DLPFC (Nordahl et al., 2002; Scott et al., 2007; Howells et al., 2014; Ernst et al., 2000), as well as frontal white matter (Sung et al., 2007; Ernst et al., 2000), through lower concentrations of NAA/Cr + PCr – related to neuronal function, protein synthesis, bioenergetics and osmosis (Baslow, 2003; Govindaraju et al., 2000; Moffett et al., 2007; Patel and Clark, 1979; Tsai and Coyle, 1995). We expect to find lower GPC + PCh concentration – a marker of glial density, cell membrane integrity and intracellular communication (Blusztajn and Wurtman, 1983; Blusztajn, 1998; Zeisel and da Costa, 2009) in frontal white matter (Howells et al., 2014). Additionally, we expect to find lower NAA concentrations, accompanied by higher mI concentrations, which indicate an increase in glial cell proliferation in response to neuronal injury (Ernst et al., 2000; Moats et al., 1994) in frontal gray matter – i.e., DLPFC and ACC (Nordahl et al., 2003; Scott et al., 2007; Sung et al., 2007; Ernst et al., 2000).

2. Material and methods

2.1. Participants

Adult male participants with a history of MA dependence who are currently abstinent (MAA; n = 31) and healthy control participants (CON; n = 22) were recruited. MA dependent participants were recruited and scanned while they were housed within a rehabilitation facility, refer to Brooks et al. (2016) for further detail. MAA was verified with blood tests on admission to rehabilitation facility; patients were also regularly examined for drugs on their person. Inclusion/exclusion criteria for the MAA group were: 1) MA was the primary substance of use; 2) no history of alcohol use/dependence, although participants were permitted to have concomitant cannabis/methaqualone use and/or absent or subthreshold criteria for alcohol use, as per DSM-IV SCID diagnostic interview; 3) no current or previous history of psychosis as confirmed by clinical staff at an admission interview and by researcher interview; 4) no prescribed medication during the study. Inclusion/exclusion criteria for the control group were: 1) no history of substance or alcohol use disorder, 2) no history of an Axis I DSM-IV psychiatric diagnosis, 3) no previous neurological condition. All participants (MAA and CON) were scanned using a 3T Allegra Siemens head scanner and underwent ^{1}H MRS 2D-CSI. MA participants were scanned at two time points: i) acute MAA (1.5 ± 0.6 weeks, n = 31) and ii) short-term MAA (5.1 ± 0.8 weeks, n = 22) whilst control participants were independently scanned at a single time point (n = 22). First, the effect of acute MAA on ^{1}H MRS metabolites compared to controls was investigated (MAA = 31; CON = 22). Second, the effect of short-term MAA on ^{1}H MRS metabolites compared to controls was investigated (MAA = 22; CON = 22). Then, the effect of time on ^{1}H MRS metabolites were compared within the MAA group (n = 19).

The Research version of the Structured Clinical Interview for DSM-IV (SCID-DSM-IV) was performed to determine history of methamphetamine dependence and simultaneously screened for comorbidities. MA dependent participants were excluded if they presented with psychotic symptoms or held a prescription for anti-psychotic medication on file. Control participants were excluded if they had a history of psychiatric illness or were taking any prescription drugs. All participants were male and between the ages of 18 and 45 years old. General exclusion criteria for both groups included claustrophobia, left-handedness, metal implants, physical impairments, severe visual impairment, or neurological conditions (e.g., cortical infarcts, stroke).

All participants were required to provide informed consent. All drug use information (age started using MA, length of drug taking, drugs other than MA used) were obtained through self-report from the participants. All information collected during this study was kept confidential and has only been used for research purposes. All documents were available in Afrikaans and English, the two most prominent languages in the Western Cape, South Africa. The research study was approved by the Human Research Ethics Committee, Faculty of Health Sciences of the University of Cape Town – UCT HREC Reference number: 554/2012 and was conducted in accordance with the Declaration of Helsinki (World Health Organisation, 2013).