Psychiatry Research: Neuroimaging ∎ (∎∎∎∎) ∎∎∎–∎∎∎

Contents lists available at ScienceDirect

Psychiatry Research: Neuroimaging

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

Fronto-temporal alterations and affect regulation in methamphetamine dependence with and without a history of psychosis

Anne Uhlmann [a,*], Jean-Paul Fouche [a,c], Nastassja Koen [a], Ernesta M. Meintjes [b], Don Wilson [a], Dan J. Stein [a]

[a] Department of Psychiatry and Mental Health, University of Cape Town, Cape Town, South Africa
[b] MRC/UCT Medical Imaging Research Unit, Department of Human Biology, University of Cape Town, Cape Town, South Africa
[c] Department of Psychiatry, University of Stellenbosch, Cape Town, South Africa

ARTICLE INFO

Article history:
Received 10 December 2014
Received in revised form
26 October 2015
Accepted 3 January 2016

Keywords:
Cortical thickness
Psychostimulant use
Emotion regulation
Brain imaging
MRI

ABSTRACT

Methamphetamine (MA) has been shown to have neurotoxic effects associated with brain structure changes and schizophrenia-like psychotic symptoms. Although these abnormalities may in turn be related to cognitive impairment and increased aggression, their association with affect dysregulation is less well studied. We investigated cortical thickness and subcortical volumes in 21 participants with MA dependence, 19 patients with MA-associated psychosis (MAP), and 19 healthy controls. Participants' affect regulation abilities were assessed through self-report scales on emotion reactivity (ERS) and difficulties in emotion regulation (DERS) and correlated with differences in cortical thickness. MAP patients showed thinner cortices in the fusiform and inferior temporal gyrus (ITG), orbitofrontal (OFC) and inferior frontal gyrus (IFG), and insula, compared to the MA group. MAP also showed significantly lower hippocampal volumes relative to MA and CTRL. Both clinical groups showed impairment in affect regulation, but only in MAP was this dysfunction associated with thinner cortices in ITG, OFC and IFG. Our findings suggest significant differences in cortical thickness in MA dependence with and without psychosis. Lower fronto-temporal cortical thickness and smaller hippocampal volumes in MAP are consistent with neuroimaging findings in other psychotic disorders, supporting the notion of MAP being a useful model of psychosis.

1. Introduction

While the initial effects of methamphetamine (MA) may include increased attention, self-confidence and feelings of euphoria (Meredith et al., 2005; Panenka et al., 2013), continued use of this psychostimulant may be far more noxious. Adverse affective symptoms such as depression, anxiety, and aggressive behavior (Lapworth et al., 2009; Plüddemann et al., 2010) have been reported, as well as psychotic symptoms such as delusions and hallucinations (Zweben et al., 2004; Meredith et al., 2005; Barr et al., 2006; Plüddemann et al., 2013), with considerable similarity to those seen in schizophrenia (Grant et al., 2012). These effects are often severe and debilitating, and may persist long after cessation of drug use (Akiyama et al., 2011).

Moreover, MA dependence is characterised by cognitive-affective impairment (Kim et al., 2011), irritability and emotional reactivity, reduced inhibition, and high rates of impulsivity and aggression (Payer et al., 2011; Plüddemann et al., 2010). Such adverse behavioral and affective features are likely due to the reduced ability to regulate negative, hostile feelings and behaviors (Homer et al., 2008). Furthermore, the inability to regulate emotional responses has been associated not only with substance dependence (Cheetham et al., 2010), but also psychiatric disorders, including schizophrenia (Stegmayer et al., 2014). However, despite the clinical importance of this field, current understandings of the neural mechanisms underlying affective symptomatology in MA dependence and MA-associated psychosis (MAP) remain limited.

Both animal and human studies have emphasized the neurotoxic effects of MA on dopaminergic and serotonergic terminals (Sato, 1992; Davidson et al., 2001; Krasnova and Cadet, 2009; Reiner et al., 2009; Yamamoto et al., 2010). Magnetic resonance imaging (MRI) studies have supported these models by demonstrating heterogeneous gray matter morphology in MA abuse. To date, the most consistent changes have been smaller gray matter

* Corresponding author. Postal address: University of Cape Town, Department of Psychiatry and Mental Health, GSH J2-Block, Anzio Road, Observatory, Cape Town 7925, South Africa.
E-mail address: uhlmann.aa@gmail.com (A. Uhlmann).

http://dx.doi.org/10.1016/j.pscychresns.2016.01.010
0925-4927/

volumes in frontal lobe systems (Kim et al., 2006; Schwartz et al., 2010; Daumann et al., 2011; Nakama et al., 2011). Additional findings include lower volumes of the insula (Schwartz et al., 2010), temporal cortex (Nakama et al., 2011), cingulate cortex and hippocampus (Thompson et al., 2004), and striatum and parietal cortex (Morales et al., 2012), as well as larger volumes in the striatum and parietal cortex (Chang et al., 2005; Jernigan et al., 2005). There is some evidence that such structural deficits may be associated with cognitive impairment (Thompson et al., 2004; Kim et al., 2006; Scott et al., 2007; Berman et al., 2008; London et al., 2015). However, very little research has been done on the neural substrates of affect regulation in these cohorts, despite the fact that several of the identified brain regions with smaller volumes in MA-dependent individuals, including the anterior cingulate cortex, prefrontal cortex, superior temporal gyrus, insula, and hippocampus and amygdala have also been shown to be major role players in emotion processing and regulation (Davidson et al., 2000; Phillips et al., 2003; Kohn et al., 2014).

Individuals with MAP may demonstrate specific cortical and subcortical deficits in structure and function (Sato, 1992). Structural abnormalities have been reported in the amygdala and hippocampus (Orikabe et al., 2011) as well as in the inferior frontal gyrus (IFG), frontopolar cortex, and superior temporal gyrus (STG) (Aoki et al., 2013). Similarly, smaller volumes in the hippocampus and fronto-temporal cortex have been described in a number of MRI studies of schizophrenia and individuals at risk for psychosis (Wright et al., 2000; Fusar-Poli et al., 2011). Although most of these affected structures have also been implicated in emotion regulation (Davidson et al., 2000; Quirk and Beer, 2006; Kohn et al., 2014), relatively few clinical studies have specifically explored the associations of MAP with emotional dysregulation; and only one study to date has compared brain imaging in MAP and MA (Howells et al., 2014).

Previous studies have focused mostly on voxel-based morphometry (VBM), providing a mixture of cortical thickness and surface area or folding measures (Hutton et al., 2009). However, cortical thickness analysis allows for a selective investigation of atrophy, and has shown to be highly sensitive to micro-anatomical changes, providing valid measures at submillimeter resolution (Hutton et al., 2009; Fischl, 2012). In order to explore differences in brain structure and emotion regulation in MA dependence and MAP, we compared three study groups: MA-dependent individuals with a history of psychosis; those without a history of psychosis; and healthy controls. Cortical thickness in fronto-temporal brain areas was evaluated, and seven subcortical structures were selected for volumetric assessment. Included structures were the amygdala, hippocampus, nucleus accumbens, caudate, pallidum, putamen, and thalamus, as these are all either involved in emotion regulation or have been found to be altered in MA users. Scores of self-report questionnaires assessing affect regulation were recorded. It was hypothesized that both MA-dependent groups would display thinner cortices in fronto-temporal regions and volumetric differences in subcortical structures, and would have impaired abilities to regulate affect relative to healthy controls. Further, we predicted that observed effects would be strongest in the MAP group, given prior findings in the schizophrenia literature, and the potential additive effects of MA dependence and psychotic disorder on brain structure and affect regulation abilities. Finally, we hypothesized that brain structure characteristics would be associated with affect dysregulation in both MA-dependent groups.

2. Methods

2.1. Participants

Three groups were studied: 22 MAP patients, 21 participants with MA dependence and no psychosis (MA group), and 21 healthy controls (CTRL group). All participants were right-handed and matched for age and gender. Inhalation was the exclusive route of MA administration. Participants were recruited from drug rehabilitation facilities, hospitals and communities in Cape Town. Clinical assessment was carried out by trained staff of the Department of Psychiatry and Mental Health, University of Cape Town (UCT), using the SCID-I for DSM-IV-TR (First et al., 2002). Positive and negative symptoms within the MAP group were rated using the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987). Participants were excluded from the study if they presented with: 1) additional substance dependencies other than nicotine and methamphetamine for the MA and MAP groups, and any substance dependence other than nicotine in the control group; 2) lifetime and current diagnosis of any psychiatric disorders (other than MA dependence and MAP in the MA and MAP groups); 3) a history of psychosis prior to MA abuse; 4) a medical or neurological illness or head trauma; 5) a seropositive test for HIV; 6) MRI incompatibilities or known claustrophobia. All participants in the MAP group, except for two, were on treatment with neuroleptic medication (haloperidol) at the time of testing. The two unmedicated participants stopped treatment three and five months, respectively, before entering the study. Treatment of longer than twelve weeks' duration at the time of scanning was an additional exclusion criterion for the MAP group to reduce potential confounding effects of antipsychotic medication on brain structure. Commonly, MA-dependent individuals show a high prevalence of polysubstance abuse, including cannabis, methaqualone, and alcohol. Although participants with other drug dependencies (except for nicotine) were excluded from this study, the use of other substances was allowed to facilitate participant recruitment. For all study groups, substance use variables were recorded during the assessment session.

After a detailed description of the study, all participants provided written informed consent. On completion of the study, participants received food vouchers for a local supermarket. The study was approved by UCT's Faculty of Health Sciences Human Research Ethics Committee.

2.2. MRI acquisition and image processing

Imaging was performed at the Cape Universities Brain Imaging Centre (CUBIC) using a Siemens Magnetom Allegra 3T system. A high-resolution, T1-weighted, 3D-MEMPRAGE sequence (scan parameters: TR=2530 ms; graded TE=1.53, 3.21, 4.89, 6.57 ms; flip angle=7°; FOV=256 mm) was used to produce 160 1-mm-thick sagittal images. The MEMPRAGE method is beneficial for automated segmentation of brain structures as it produces structural images with low distortion and high signal-to-noise ratio by acquiring four separate structural scans with graded TEs and averaging them into a final high contrast image (van der Kouwe et al., 2008). For screening purposes, transversal T2-weighted images (TR=9000 ms; TR=96 ms; flip angle=180°; FOV=230 mm; slice thickness=5 mm) as well as fluid-attenuated inversion recovery (FLAIR) transversal images (TR=4200 ms; TR=95 ms; flip angle=150°; FOV=230 mm; slice thickness=5 mm) were obtained. An experienced radiologist, blind to diagnosis, examined each scan for structural abnormalities. This resulted in the exclusion of one participant from the study.

MRI scans were analyzed using the FreeSurfer software package v5.1 (http://surfer.nmr.mgh.harvard.edu/). Regional estimates of

Please cite this article as: Uhlmann, A., et al., Fronto-temporal alterations and affect regulation in methamphetamine dependence with and without a history of psychosis. Psychiatry Research: Neuroimaging (2016), http://dx.doi.org/10.1016/j.pscychresns.2016.01.010