Behavioural Brain Research 289 (2015) 78–83

Contents lists available at ScienceDirect

Behavioural Brain Research

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

Research report

Hippocampal volume reduction in female but not male recent abstinent methamphetamine users

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HIGHLIGHTS

- For the first time, we examined the gender difference in hippocampal volume in abstinent MA users.
- We found reduced right hippocampus relative volume in female but not in male abstinent MA users.
- No significant correlations were found between hippocampal volume and cognitive measures in abstinent MA users.

ARTICLE INFO

Article history:
Received 29 January 2015
Received in revised form 13 April 2015
Accepted 19 April 2015
Available online 25 April 2015

Keywords:
Methamphetamine dependence
Gender difference
Hippocampal volume

ABSTRACT

Growing evidence suggests abnormalities in brain morphology including hippocampal structure in patients with methamphetamine (MA) dependence. This study was performed to examine hippocampal volume in abstinent MA users, and to further explore its relationship with cognitive function. 30 abstinent MA users (20 males and 10 females) with average 5.52 months of duration of abstinence and 29 healthy controls (19 males and 10 females) age 18–45 years old were recruited for clinical assessment and imaging scan. FreeSurfer was used to segment the hippocampus bilaterally, and hippocampal volumes were extracted for group and gender comparisons. Cognitive function was measured using the CogState Battery Chinese language version (CSB-C). Analysis of covariance (ANCOVA) controlling for education showed a significant group by gender interaction for the right hippocampal relative volume adjusted for total brain size ($p = 0.020$); there was a significant difference between male controls and female controls ($p < 0.001$), but such a difference did not exist between male patients and female patients ($p = 0.203$). No significant correlations were found between hippocampal volume and cognitive measures. There seems to be a gender difference in how MA affects hippocampal volume in abstinent MA users. Hippocampus might be an important treatment target for cognitive improvement and functional recovery in this patient population, especially in females.

1. Introduction

Amphetamine-type stimulants (ATS) are a group of drugs including amphetamine and methamphetamine (MA). The use of ATS drugs has been spreading rapidly across many countries, and has become a worldwide problem in recent years [1]. In the United States, over 12 million people have used ATS in their lifetimes, and 1.2 million people reported using ATS in the past year [2]. China also faces a serious drug use problem. The number of registered drug users rose from 70,000 in 1990 to 2.14 million in 2013, according to the numbers reported by the Ministry of Public Security of China [3,4]. Heroin and other opiate drugs used to be the primary drugs of choice in China. After the implementation of "Anti-drug campaign" in 2005, the use of heroin and illicit opiate drug has decreased significantly; however, the use of ATS has been increasing rapidly in China over the past decade. The prevalence of ATS users amongst identified drug users has risen from 6.7% in 2005 to 34.4% in 2012 according to the data from China State Food and Drug Administration (SFDA) [4].

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http://dx.doi.org/10.1016/j.bbr.2015.04.033
0166-4328/

MA is the most commonly used ATS [5]. Studies have suggested various negative health consequences related to MA use, such as brain abnormalities and cognitive impairment, cardiovascular disease, and HIV/AIDS [6]. As a psychostimulant, MA has direct effects on the neurotransmitter system, causing the release of dopamine from vesicular storage pools into the cytoplasm and increased cytosolic levels of monoamines by inhibiting the activity of monoamine oxidase [6,7], therefore leading to functional and structural changes in the brain [8].

Hippocampus plays a critical role in memories, learning, and emotions. Growing evidence from both human [9–11] and animal [12–14] studies have found that MA use might be associated with structural and functional abnormalities of hippocampus, therefore contributing to the clinical manifestations in MA users. For example, Thompson et al. reported hippocampal volume reduction in recent abstinent MA users compared to control subjects [8]. Similar findings also have been found in patients with MA induced psychosis [15] or methylenedioxy-methamphetamine (MDMA) users [16].

Cognitive dysfunction in MA users, especially memory impairment, has been reported previously [6,8]. It has been suggested that hippocampus might be involved in MA-related cognitive impairment. For example, one study found that hippocampal metabolic and structural measures were associated with the performance on a vigilance test of sustained attention in MA abusers [11]. Other studies suggested that the damage in hippocampus in MA users may contribute to altered emotional experience and misunderstanding of others, leading to deteriorated interpersonal communication and social interactions in this patient population [9,10]. Animal studies found that extracellular signal-regulated kinase (ERK) and the cAMP response element-binding protein (CREB) signaling pathway in hippocampus might be involved in MA induced impairment in spatial memory [12]. The interruption of hippocampal integrity by even modest doses of MA may cause significant clinical symptoms in MA abusers [13].

We now presented a cross-sectional study to examine hippocampal volume, and the relationship between hippocampal volume and cognitive function in MA users. Because the gender difference in hippocampal volume has been reported previously in both non-clinical and clinical populations [17], our study also examined the gender difference in hippocampal volume in MA users.

2. Methods

2.1. Subjects

In China, according to the "Narcotic Control Law," newly identified drug users will receive mandatory inpatient treatment; after discharge, they will continue to receive mandatory rehabilitation treatment in the community under the supervision of social workers. If they relapse, drug users will be sent to the Compulsory Isolation Center for Drug Rehabilitation, which is under the jurisdiction of the forensic system. Routine physical exam and HIV test will be performed before they are admitted to the center. Those with serious physical illness or tested HIV positive will be referred to other appropriate medical facilities to receive treatment.

Abstinent MA users who met the diagnostic criteria for MA dependence according to the Diagnostic and Statistical Manual of Mental Disorders criteria (DSM-IV) [18] were recruited from Shanghai Compulsory Rehabilitation Treatment Center. Other inclusion criteria included: (1) age 18–45 years old; (2) more than 9 years of education; (3) normal or corrected-to-normal vision and hearing; (4) no current medication treatment except oral contraceptives or vitamins; (5) capacity to provide informed consent. Exclusion criteria included: (1) major medical or neurological disorders, including HIV; (2) comorbid psychiatric disorders including schizophrenia, bipolar disorder; (3) current use of other illicit drugs; (4) contraindications to the MRI scan.

Age-matched healthy controls were recruited from the community through advertising. All of them received a comprehensive physical and psychiatric assessment by the research psychiatrists (J.D. and H.J.). Healthy control subjects fulfilled the same inclusion and exclusion criteria as the patient subjects, but had no current or previous history of drug use (except nicotine).

The study was approved by the Shanghai Mental Health Center Institutional Review Board, prior to the start of the study. Written consent was obtained from all study participants.

2.2. Clinical and cognitive measures

Clinical interview and cognitive assessment were conducted by the research psychiatrists (J.D. and H.J.). Demographic information and drug use history were collected from patient interview and medical records. Questions about drug use history included age of onset (age when using MA for the first time), types of drugs ever used in addition to MA, duration of abstinence (time interval between last time MA use and imaging date), duration of drug use (time interval between first and last time MA use), duration of continuous drug use (the longest time period using MA daily), average number of grams of MA used per occasion in the past one year before abstinence.

The CogState Battery Chinese language version (CSB-C) [19] was used to assess cognitive function. The detailed procedure has been described elsewhere [20], and more information can be found on the website http://www.Cogstate.com. The CSB-C contains eight computerized tasks; among them, we selectively chose 5 that are presumably related to hippocampus function. These 5 tasks included the One Card Learning Task (OCL, visual learning and memory), the Two Back Task (TWOB, working memory), the International shopping List Task (ISLT, verbal learning and memory), the Groton Maze Learning Task (GML, problem solving/error monitoring), and the Continuous Paired Association Learning Task (CPAL, spatial working memory).

2.3. Image acquisition and processing

T1-weighted Spoiled Gradient Echo (SPGR) images were obtained from all subjects on a 3.0 Tesla scanner (Siemens Verio 1) at the Imaging Center of Shanghai Mental Health Center. All scans were clinically reviewed by a neuroradiologist during a continuous scan period. Each subject was asked to stay awake, lie on his/her back with body remaining still and eyes closed. A foam mat was used to limit head motion. The acquisition protocol included the following pulse sequence and parameters: repetition time (TR) = 2530 ms, echo time (TE) = 2.34 ms, flip angle 7°, field of view (FOV) = 224 × 256 mm, matrix size 224 × 256 mm, slice thickness 1 mm, echo spacing 7 ms, voxel dimension 1 × 1 × 1 mm. All data acquisitions were performed in the coronal plane, which was perpendicular to the anterior commissure–posterior commissure (AC–PC) line. Scans were optimized by high contrast in the gray/white and gray/CSF boundaries to obtain the best structure and surface segmentation images.

MRI data were coded and catalogued, and transferred to the Neuroinformatics Lab, Department of Psychiatry at University of Massachusetts Medical School (UMMS) for blinded analysis. The FreeSurfer software (http://surfer.nmr.mgh.harvard.edu/) was used to segment T1-weighted SPGR images into cortical and subcortical gray and white matter regions, as well as total intracranial volume for each subject [21]. FreeSurfer segmentation of hippocampus has been shown to have comparable accuracy as in