Drug and Alcohol Dependence 134 (2014) 314–321

Contents lists available at ScienceDirect

Drug and Alcohol Dependence

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

Reduced ventral medial prefrontal cortex (vmPFC) volume and impaired vmPFC-default mode network integration in codeine-containing cough syrups users

Ying-wei Qiu[a,*], Xiao-fei Lv[a,b], Gui-hua Jiang[a], Huan-huan Su[a], Tian Yu[a], Jun-zhang Tian[a], Xue-lin Zhang[c], Fu-zhen Zhuo[d]

[a] Department of Medical Imaging, Guangdong No. 2 Provincial People's Hospital, Guangzhou 510317, PR China
[b] Department of Medical Imaging and Interventional Radiology, Cancer Center, Sun Yat-Sen University, Guangzhou 510060, PR China
[c] Medical Imaging Centre, NanFang Hospital, Southern Medial University, Guangzhou 510515, PR China
[d] Addiction Medicine Division, Guangdong No. 2 Provincial People's Hospital, Guangzhou 510317, PR China

ARTICLE INFO

Article history:
Received 14 June 2013
Received in revised form 23 October 2013
Accepted 24 October 2013
Available online 5 November 2013

Keywords:
Codeine-containing cough syrups
Cough medicine
Ventral medial prefrontal cortex (vmPFC)
Voxel-based morphometry (VBM)
Functional connectivity (FC)

ABSTRACT

Objective: To characterize the association between clinical symptoms and anatomical and functional cerebral deficits in codeine-containing cough syrups (CCS) users using voxel-based morphometry and resting state functional connectivity analysis.
Methods: Participants were 30 CCS users and 30 matched controls. Both groups were scanned using a volumetric three-dimensional fast field echo sequence and a gradient-echo echo-planar imaging sequence. Impulsivity traits of both groups were evaluated with the Barratt Impulsiveness Scale 11 (BIS 11). Voxel-based morphometry was used to characterize gray matter (GM) deficits in CCS users. The clinical significance of regional volume reduction was investigated by evaluating its association with impulsivity in CCS users and with alterations in resting state functional connectivity when brain regions with GM volume reduction were used as seed areas.
Results: Significantly decreased GM volume was observed in CCS users in bilateral ventral medial prefrontal cortex (vmPFC) which was related to greater impulsivity in CCS users. Significantly decreased integration was found in CCS users between the vmPFC and the default mode network. Also, significantly enhanced functional connectivity was found between the vmPFC and the right insula, and the right dorsal lateral PFC. Negative correlation was observed between BIS total scores, scores for attentional impulsivity and vmPFC-inferior parietal lobe connectivity in CCS users.
Conclusions: The findings revealed volume loss and aberrant functional organization in vmPFC among CCS users. In addition, the decreased vmPFC GM volume and attenuated functional connectivity of the vmPFC-inferior parietal lobe network were associated with clinical higher impulsivity trait in CCS users.

1. Introduction

Drug addiction is a chronic, relapsing brain disease characterized by compulsive drug seeking and use (Leshner, 1997). Accumulated neuroimaging studies have demonstrated the structural and functional of the brain is impaired in chronic drug dependent individuals, which may underpin the diverse addictive behaviors (Barros-Loscertales et al., 2011; Botelho et al., 2006; Cheetham et al., 2012; King et al., 2011; Ma et al., 2010; Qiu et al., 2011; Tanabe et al., 2009). However, most of previous studies related to drug addiction thus far have been focusing on the illicit psychotropic drugs, such as heroin (Botelho et al., 2006; Ma et al., 2010; Qiu et al., 2011; Tanabe et al., 2009), cocaine (Barros-Loscertales et al., 2011), cannabis (Cheetham et al., 2012; King et al., 2011) and so on, less attention has been directed to the abuse of licit drugs that can be bought over the counter (i.e. OTC drugs), such as codeine-containing cough syrups (CCS), which have become one of the most popular drugs of abuse in young people in the world (Shek and Lam, 2006).

According to the Report of the International Narcotics Control Board for 2012, the abuse of prescription and OTC drugs has continued to spread globally since 2009, and it poses serious health and social challenges in some countries. In the United States, prescription drug abuse is more prevalent than the abuse of any other internationally controlled substance except cannabis. In China, according to the report by Zhou and colleagues, CCS is the most prevalent drug of abuse (50% of all documented substance abuse) in adolescents (Zhou, 2010).

* Corresponding author. Tel.: +86 13602454630; fax: +86 02089168017.
E-mail address: qiuyw1201@gmail.com (Y.-w. Qiu).

0376-8716/$ – see front matter.
http://dx.doi.org/10.1016/j.drugalcdep.2013.10.023

Different from heroin and other illicit drugs, the CCS contains a combination of codeine, a sympathomimetic and an antihistamine, all constituents having a central action, which may cause a special, distinct euphoretic effect (Mattoo et al., 1997). CCS dependent is more prevalent in adolescent. Previous findings showed that friends and curiosity were the main reasons for abuse, and the availability factor, ignorance factor may be the main factors for the adolescent to abuse CCS (Shek and Lam, 2006; Zhou, 2010). Due to the increased incidence of CCS dependency, inquiry into the effects of long-term CCS abuse is highly relevant and timely. Recognition of CCS abuse can help rectify false beliefs of the public and some professionals that CCS is non-addictive and therefore less harmful (Shek and Lam, 2008).

Whether and how can CCS affect the human brain is still unclear. To our best knowledge, only one neuroimaging study pertaining to CCS abuse exists. In this report, single photon emission computed tomography (SPECT) revealed that dopamine transporter (DAT) availability in the striatum as well as volume, weight, and 99mTc-TRODAT-1 uptake ratios of the corpus striatum/whole brain were significantly reduced in CCS users compared with controls (Hou et al., 2011). However, whether these brain functional abnormalities were associated with addictive behavior and the duration of addiction in CCS users are still unclear. Moreover, the radioactivity of the SPECT limits its use in large cohorts of CCS users, which is a drawback to recognizing this new type of drug addiction.

Voxel-based morphometry (VBM) is a spatially-specific and unbiased method of analysis of MR images reflecting the regional GM volume at a voxel scale (Ashburner and Friston, 2000). This technique has already been successfully applied to other illicit and licit substance abuse (Qiu et al., 2013; Moreno-López et al., 2012; Ide et al., 2013), revealing patterns of GM abnormalities that correlate with the duration of substance use (Qiu et al., 2013), and predict the risk of relapse from withdrawal (Ide et al., 2013).

Functional MRI (fMRI) can record spontaneous brain activity fluctuations when subjects lie still in the scanner, at rest. Low-frequency (0.01–0.8 Hz) fluctuations of blood-oxygen-level-dependent (BOLD) signals in the resting state are considered to be physiologically meaningful and related to spontaneous neural activity (Cordes et al., 2001). Recently, numerous resting state functional MRI studies have been performed in substance dependent individuals (Qiu et al., 2011; Jiang et al., 2011; Ma et al., 2010). The regional brain function and functional integrity were reported to be deficient in substance dependent individuals.

However, to our best knowledge, no studies have investigated the brain structural and functional change of CCS users with VBM and resting-state fMRI functional connectivity methods. It is also unclear whether these morphometric and functional alterations are associated with clinical symptom severity.

Impulsivity is a personality trait of healthy individuals, and the substance-dependent individuals have higher impulsivity (Kaufman et al., 2003; Moeller et al., 2001). Previous behavioral studies indicate impulsivity is related to the severity of cocaine abuse and cocaine withdrawal symptom. Furthermore, cocaine-dependent individuals with high impulsivity are likely to drop out of treatment (Kaufman et al., 2003; Moeller et al., 2001). Impulsivity has also bee observed in CCS users in previous clinical and psychological studies (Wang et al., 2011; Yang and Yuan, 2008). Therefore, we used Barratt Impulsiveness Scale 11 (BIS 11) to assess participants' impulsivity after MR imaging.

The purposes of the present study were to (1) identify brain regions with GM volume reduction using VBM, and (2) investigate the clinical significance of GM volume deficits by using the observed structural deficits as seed regions in functional connectivity analysis in order to explore the brain network effect of these anatomic deficits and their association with clinical symptoms in a relatively large sample of chronic CCS users.

2. Materials and methods

2.1. Participants

This prospective study was approved by the local ethics committee. Written informed consent was obtained from all subjects. Sixty subjects, including 30 control subjects and 30 CCS users participated in this study (Table 1). The CCS users were randomly selected from the patients seeking treatment at Addiction Medicine Division of Guangdong No. 2 Provincial People's Hospital. All the CCS users were screened based on the DSM-IV criteria from the medical history, along with a urine test and an interview conducted by a clinical psychologist; all of the patients were treatment naïve, and naive for other types of illicit drug use. They regularly used cigarettes and denied any use of psychotropic agents in the month prior to the resting state functional and structural MRI scan being performed. Inclusion criteria for the control subjects included lack of diagnosis of substance abuse or dependence. Exclusion criteria for all participants included neurological illness, schizophrenia or bipolar disorder, prior significant head trauma, positive HIV status, diabetes, hepatitis C, other major medical illness and left-handedness.

2.2. Impulsivity assessment

BIS 11 is one of the oldest and most widely used self-report measures of impulsive personality traits. This 30-item self-rated scale has three oblique factors: attentional/cognitive, which measures toleration for cognitive complexity and persistence; motor, which measures the tendency to act on the spur of the moment; and nonplanning impulsivity, which measures the lack of sense of the future. Items are rated from 1 (rarely/never) to 4 (almost always/always). To determine overall impulsiveness scores, all items were summed, with higher scores indicating greater impulsivity (Patton et al., 1995). BIS-11 is a valid and reliable instrument for healthy and psychiatric Chinese populations (Yao et al., 2007).

2.3. MRI scanning

MRI data were obtained on a Philips Achieva 1.5 T Nova dual MR scanner using a 16-channel NV coil in the Department of Medical Imaging, Guangdong No. 2 Provincial People's Hospital. None of the subjects were taking any medications at the time of the scans. Tight but comfortable foam padding was used to minimize head motion, and ear plugs were used to reduce scanner noise. Sagittal structural images [160 sagittal slices, repetition time (TR) = 25 ms, echo time (TE) = 4.1 ms, thickness = 1.0 mm, no gap, in-plane resolution = 231 × 232, field of view (FOV) = 230 mm × 230 mm, flip angle = 30°] were acquired using a fast field echo (FFE) three-dimensional T1 weighted sequence. Resting-state fMRI scans were performed with an echo planar imaging (EPI) sequence with scan parameters of TR = 2000 ms, TE = 50 ms, flip angle = 90°, matrix = 64 × 64, FOV = 230 mm × 230 mm, slice thickness = 4.5 mm and slice gap = 0 mm. Each brain volume comprised 22 axial slices and each functional run contained 240 volumes (8 min) (the slices were approximately along the AC-PC line and covered about −30 to 60 in the IS direction), during resting state fMRI scanning, subjects were instructed to close their eyes and keep still as much as possible, and not to think of anything systematically or fall asleep. All the CCS users were scanned after 24–48 h from the last time of CCS use, and none of them experience craving or withdrawal symptoms during the MRI scanning.

After the scan, all the participants were asked the following questions to verify the degree of their cooperation: "what were you thinking during the scan?", "did you get asleep just now?", "were your eyes keeping close during the scan?" and "did you feel uncomfortable when scanning?" And only when the participant answered "nothing", "no, I did not", "yes, I kept my eyes closed", "no, I did not feel any uncomfortable", we would include their data in present study.

2.4. Voxel-based morphometry analysis

Structural image processing was conducted using the voxel-based morphometry toolbox (VBM8; http://dbm.neuro.uni-jena.de/vbm/implemented in Statistical Parametric Mapping-8 [SPM8; Welcome Department of Imaging Neuroscience, London, http://www.fil.ion.ucl.ac.uk/spm]). VBM8 in SPM8 combines tissue segmentation, bias correction, and spatial normalization into a unified model (Lui et al., 2009). Hidden Markov Random Fields were applied to improve accuracy of tissue segmentation (medium HMRF 0.3). Otherwise, default parameters were used. Individual brains were normalized to tissue probability maps provided by the International Consortium for Brain Mapping (ICBM). The optimally processed images were smoothed with an isotropic Gaussian kernel (full-width half maximum = 12 mm). At the second level, whole-brain data were modeled across the groups using analysis of covariance (ANCOVA) with total GM volume and age as covariates. The effects of total GM volume were removed to allow inferences about regional differences in GM volume. An absolute threshold mask of 0.1 was used. The significance of group differences in each region was estimated by distributional approximations from the theory of random Gaussian fields, and significance levels were set at $p < 0.05$ (corrected for multiple comparisons). To identify any association between structural abnormalities and impulsivity traits, the average GM volume values for all voxels in abnormal areas, revealed by VBM, were extracted and