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Abnormal degree centrality in chronic users of codeine-containing cough syrups: A resting-state functional magnetic resonance imaging study

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ABSTRACT

Codeine-containing cough syrups (CCS) have become one of the most popular drugs of abuse in young population worldwide. However, the neurobiological mechanisms underlying CCS-dependence are yet ill-defined. Therefore, understanding the brain abnormalities in chronic users of CCS is crucial for developing effective interventions. The present study depicted the intrinsic dysconnectivity pattern of whole-brain functional networks at the voxel level in chronic users of CCS. In addition, the degree centrality (DC) changes were correlated to the Barratt Impulsiveness Scale (BIS-11) total score, dose, duration of CCS use, and the age at first use of cough syrups. The current study included 38 chronic CCS users and 34 matched control subjects. All patients were evaluated using the BIS-11. Next, resting-state functional magnetic resonance imaging (rs-fMRI) datasets were acquired from these CCS users and controls. Whole-brain connectivity was analyzed using a graph theory approach: degree centrality (DC). CCS-dependent individuals exhibited low DC values in the left inferior parietal lobule and the left middle temporal gyrus, while high DC values were noted in the right pallidum and the right hippocampus ($P < 0.01$, AlphaSim corrected). Also, significant correlations were established between average DC value in the left inferior parietal lobule and attentional impulsivity scores and the age at first CCS use. The rs-fMRI study suggested that the abnormal intrinsic dysconnectivity pattern of whole-brain functional networks may provide an insight into the neural substrates of abnormalities in the cognitive control circuit, the reward circuit, and the learning and memory circuit in CCS-dependent individuals.

1. Introduction

Codeine-containing cough syrup (CCS)-dependent individuals refer to long-term and sustained administration of CCS (in which, codeine and ephedrine are intended for cough and analgesic function, respectively) for pleasure and hallucination (Mattoo et al., 1997; Vree et al., 2000). As CCS is cheap, convenient, and legal to purchase, the abuse of the drug has gained a severe foothold among young individuals worldwide and is considered as an increasing concern in modern society (Shek and Lam, 2006). According to a Report of the International Narcotics Control Board for 2012, the abuse of prescription and over-the-counter (OTC) drugs has continued to spread worldwide since 2009, which poses severe health and social challenges in several countries. In the USA, prescription drug abuse is more prevalent than any other internationally controlled substance except for cannabis (Agnich et al., 2013; Martins et al., 2010). In China, Zhou (2010) demonstrated that CCS is the maximally abused drug (50% of all documented abused substances) in adolescents. Previous studies have confirmed that mental functioning, behavior, and personality were abnormal in CCS-dependent individuals (Mattoo et al., 1997; Yang and Yuan, 2008); these characteristics were similar to those expressed by heroin- and other illicit substances-dependent individuals. However, accumulated evidence has demonstrated that illicit drugs, including heroin, have an effect on brain functional changes as measured by

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functional magnetic resonance imaging (fMRI) (Jiang et al., 2011; Zhang et al., 2011; Zhang et al., 2015) Furthermore, the abnormality of impulsive decision making in illicit drug-dependent individuals may be related to the deficient function of the orbitofrontal cortex and the right inferior parietal lobe. Compared to the illicit drug addiction of the so-called "street drugs," less attention has been directed to the illicit use of drugs such as CCS (Ma et al., 2011; Ma et al., 2010; Qiu et al., 2014).

The rapid development of neuroimaging techniques has provided many new methods for the detection of early changes in the brain in several neuropsychological diseases. Diffusion-tensor imaging (DTI), a non-invasive tool for probing the microanatomical organization of human brain white matter (WM) in vivo, has been used to investigate the properties of WM in CCS-dependent individuals (Qiu et al., 2015). Positron-emission tomography (PET) has also been employed for examining the drug-addicted individuals. Botelho et al. (2006) found that the perfusion of the orbitofrontal region, the occipital, and the temporal lobes was decreased in heroin addicts; these regions were responsible for the control of attention, motor speed, memory, and visual-spatial processing. Volkow et al. (2005) demonstrated that the metabolic responses of the right medial orbital prefrontal cortex significantly increased in cocaine-addicted subjects. Qiu et al. (2013) used the regional homogeneity (ReHo) analysis method and found that ReHo was diminished in the bilateral medial orbitofrontal cortex (mOFC) and the left dorsal striatum in CCS-dependent individuals. These abnormalities were speculated to be related to the dysfunction of learning and memory in CCS-dependent individuals. Using the voxel-based morphometry (VBM) analysis method, Qiu et al. (2014) also found significantly decreased grey matter (GM) volume in CCS users in the bilateral ventral medial prefrontal cortex (vmPFC). The study further explored the changes in spontaneous functional connectivity of the vmPFC-related circuitry and observed reduced integration in CCS users between the bilateral vmPFC and the bilateral hippocampal complex and between the bilateral vmPFC and the bilateral inferior parietal lobule (IPL). Enhanced functional connectivity was observed in CCS users between the bilateral vmPFC and the right insula (extending to the right dorsal striatum) and between the bilateral vmPFC and the right dorsolateral prefrontal cortex (dlPFC). These results implied that the vmPFC plays a major role in chronic CCS abuse that might lead to disordered impulsive control. Using independent component analysis (ICA), Qiu et al. (2017) investigated the intrinsic brain network abnormalities in CCS-dependent males via resting-state fMRI (rs-fMRI). Compared to the healthy control group, the CCS-dependent individuals presented aberrant intrinsic connectivity within the default mode network (DMN), executive control network (ECN), and salience network (SN) ($P < 0.05$, AlphaSim corrected). However, the limitations of the study included the spontaneous functional connectivity of abnormal brain regions in a subnet of individuals. In addition, the spontaneous functional connectivity of abnormal brain regions in the whole-brain network is unknown. Among the graph-based methods, DC is recently gaining attention (Wang et al., 2011). It counts the number of direct connections for a given voxel in a network and reflects the functional connectivity within the brain network. It is one of the more reliable and compelling measures among several nodal network metrics and measures the centrality or importance of individual elements in the brain (for example, brain regions) by capturing their relationships with the entire brain network at the voxel level (Zuo et al., 2012). Furthermore, DC has been used in several studies where the dorsal and ventral precuneus, anterior and posterior cingulate gyrus, ventromedial prefrontal cortex, and inferior parietal lobes showed high DC values in normal individuals, which was found to be in agreement with DMN (Wang et al., 2013; Li et al., 2013; van den Heuvel and Sporns, 2013). Voxel-wise centrality maps provided novel insights into the patterns and complexity of functional connectivity throughout the huge human functional network that has been widely used in brain network studies (Di Martino et al., 2013; Tomasi and Volkow, 2010). In the other studies (Qiu et al., 2013, 2014, 2015, 2017), the DC measure was not calculated in CCS-dependent individuals. However, the analysis level in the present study using DC is based on voxels. Therefore, the present study aimed to depict the intrinsic dysconnectivity pattern of whole-brain functional networks at the voxel level, focusing on network architecture, in CCS-dependent individuals. In addition, we also correlated the DC changes to the BIS-11 total score, dose, duration and the age at first use of CCS. Therefore, we speculated that in CCS-dependent individuals, abnormal activity of some brain regions associated with learning, memory, and executive control might exist. The potential brain changes in impaired cognition provided an in-depth insight of the level of functional integration.

2. Materials and methods

2.1. Participants

This prospective study was approved by the Ethics Committee of Guangdong Second Provincial General Hospital. Written informed consent was obtained from all subjects. A total of 72 right-handed participants, including 34 control subjects and 38 CCS-dependent individuals, were enrolled in this study. The CCS-dependent individuals were recruited from the patients seeking treatment at the Addiction Medicine Division of the Guangdong Second Provincial General Hospital. All the patients were screened based on the DSM-IV criteria from medical history and underwent a urine test and an interview on the same day. All participants regularly smoked cigarettes but did not use any type of psychotropic agents prior to the rs-fMRI scan. The exclusion criteria for all participants included central nervous system diseases, schizophrenia, bipolar disorder, prior significant head trauma, positive human immunodeficiency virus (HIV) status, diabetes, hepatitis C, other major medical illness, and left-handedness. The inclusion criteria for the control subjects was the absence of diagnosis of any type of substance abuse or dependence.

2.2. Impulsivity assessment

BIS-11 was used for assessing the impulsivity. This 30-item self-rated scale has three oblique factors: attentional/cognitive that measures the toleration for cognitive complexity and persistence; motor that estimates the tendency to act on the spur of the moment; and non-planning impulsivity, which evaluates the lack of sense of the future. Items are rated from 1 (rarely/never) to 4 (almost always/always). To determine the overall impulsiveness scores, all items are summed; high scores indicate remarkable impulsivity (Patton et al., 1995). BIS-11 is a valid and reliable instrument for healthy Chinese and psychiatric populations (Yao et al., 2007).

2.3. Data acquisition

All MRI datasets were obtained using a Philips Achieva 1.5 T Nova dual MR scanner at the Department of Medical Imaging, Guangdong Second Provincial General Hospital. These datasets included rs-fMRI dataset and T1-weighted structural images. The rs-fMRI dataset [22 axial slices, repetition time (TR)/echo time (TE) = 2000 ms/50 ms, matrix = 64 × 64, field of view (FOV) = 230 × 230 mm^2, slice thickness = 4.5 mm without gap, flip angle = 90°] was acquired using an echo planar imaging (EPI) sequence. Each functional run contained 240 volumes (8 min) [the slices were approximately along the anterior commissure-posterior commissure (AC-PC) line and covered approximately 230 to 60 in the inferosuperior direction], and the subjects were asked to lie quietly with their eyes closed and avoid eye movement or thinking of anything specific or falling asleep while in the scanner, during the rs-fMRI data acquisition. Sagittal structural images (160 sagittal slices, TR/TE = 25 ms/4.1 ms, thickness = 1.0 mm, no gap, in-plane resolution = 231 × 232, FOV = 230 × 230 mm, flip angle = 30°) were acquired using a fast field echo (FFE) three-