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ALTERATIONS IN BRAIN CONNECTIVITY IN THREE SUB-REGIONS OF THE ANTERIOR CINGULATE CORTEX IN HEROIN-DEPENDENT INDIVIDUALS: EVIDENCE FROM RESTING STATE fMRI

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Abstract—Previous studies that utilized task-based approaches have demonstrated that the chronic use of heroin is associated with altered activity of the anterior cingulate cortex (ACC). However, few studies have focused on examining the variation in resting-state functional connectivity in heroin-dependent individuals, which might help further understanding the mechanisms underlying heroin addiction. Due to the structural and functional heterogeneity of the ACC, we systematically mapped the resting-state functional connectivity patterns of three sub-regions of the ACC in heroin-dependent individuals, wondered whether the partition of three sub-regions of the ACC is feasible in heroin-dependent individuals, and identified how heroin affected the correlated activities among three sub-regions of the ACC using resting-state functional magnetic resonance imaging (fMRI). In the present study, fMRI data were acquired from 21 heroin-dependent individuals (Her group) and 15 non-addicted controls (CN group). Compared to controls, there were reduced functional connectivities in the dorsal ACC (dACC) and rostral ACC (rACC) networks with different areas of the dorsal striatum (the caudate and the putamen) in the Her group. Meanwhile, there exhibited an inverted alteration of pattern for orbital frontal cortex (OFC) and superior frontal gyrus (SFG) in the functional connectivity network with the dACC and subcallosal ACC (sACC), and a different alteration of the cerebellum and the amygdala in the functional connectivity network with the rACC and the sACC. In addition, we also found reduced connectivities between dACC and rACC, as well as reduced connectivities between sACC and dACC. Our findings of variations of functional connectivities in three sub-regions of ACC in Her group implied that these sub-regions of the ACC together with other key brain areas (such as dorsal striatum, OFC, SFG, cerebellum, amygdale, etc.) might potentially play independent and/or overlapping roles in heroin addiction, which might indicate the potential direction of future research.

Key words: heroin addiction, anterior cingulate cortex, functional connectivity, resting-state magnetic resonance imaging.

INTRODUCTION

Heroin addiction is considered to be a chronic, relapsing brain disease that is characterized by compulsive drug seeking and difficulty controlling impulsive behavior (Koob and Volkow, 2010). Numerous studies have suggested that the chronic use of heroin is related with the lack of inhibition of inappropriate behaviors, which persist even after heroin withdrawal (Ersche and Sahakian, 2007). Many alerting changes in brain regions with vital functions haven been observed in drug-dependent individuals and have been linked to drug abuse, especially in the anterior cingulate cortex (ACC). Some researchers using graph theory analysis (GTA) to probe the topological properties of heroin users' brains found that, compared with healthy controls, heroin-dependent individuals showed more irregular connectivities with the ACC (Liu et al., 2009; Yuan et al., 2010c). Moreover, event-related functional magnetic resonance imaging (fMRI) studies showed that heroin-dependent individuals exhibited poor behavioral control accompanied by hypoactivity of the ACC compared to healthy controls (Lee et al., 2005; Yucel, 2007; Fu et al., 2008), suggesting that lesions in these regions may be responsible for the damaged inhibitory control observed in heroin addiction. Heroin may potentially cause intense euphoria, relaxation, and release from craving, which plays an important part in relapse to drug abuse. A recent study found that in comparison with the heroin-dependent individuals receiving an injection of placebo, the heroin-dependent individuals receiving heroin administration showed low perfusion in the ACC, accompanied by an increasing feeling of

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Abbreviations: ACC, anterior cingulate cortex; AFC, ACC functional connectivity; dACC, dorsal anterior cingulate cortex; dAFC, dorsal AFC; EPI, echo planar image; fMRI, functional magnetic resonance imaging; IFG, inferior frontal gyrus; OFC, orbital frontal cortex; rACC, rostral anterior cingulate cortex; rAFC, rostral AFC; ROI, region of interest; sACC, subcallosal anterior cingulate cortex; sAFC, subcallosal ACC functional connectivity; SFG, superior frontal gyrus; SPGR, spoiled gradient-recalled echo; vACC, ventral anterior cingulate cortex.

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intoxication and relief from withdrawal, suggesting that activity of the ACC is related to the regulation of self-emotion (Denier et al., 2013), which may underlie the subjective affection perceived by heroin-dependent individuals (Blum et al., 2013). It is also reported that the ACC is strongly activated by heroin-related cues, indicating that the ACC plays an important role in craving, incentive salience, and motivated responses (Li et al., 2012). Thus, the ACC is involved in the control of response inhibition and in the modulation of emotional and drug cue-related craving (Lee et al., 2005; Yucel, 2007; Fu et al., 2008; Li and Sinha, 2008; Feil et al., 2010; Li et al., 2012; Denier et al., 2013). In addition, the model of addiction proposed by Volkow et al. (2006) also confirmed the influence of the ACC's dysfunction upon the addicts (Volkow et al., 2003). Volkow et al. pointed out that there were four circuits which have interdependent and overlapping roles in drug abuse: (1) reward, located in the nucleus accumbens and ventral pallidum; (2) memory and learning, located in the amygdala and hippocampus; (3) motivation, drive and salience evaluation, located in the orbital frontal cortex (OFC); and (4) cognitive control, located in the prefrontal cortex and dorsal ACC (dACC) (Volkow et al., 2003; Baler and Volkow, 2006; Ma et al., 2010). Meanwhile, ventral ACC (vACC) together with the amygdala influenced the responses in each loop of addiction model (Bechara, 2005). The hypothetical model suggests that continued drug abuse strengthen drug-related learning and memory systems, enhance the salience evaluation of drugs, so as to establish a motive uncontrolled, while weakening the ability of cognitive control, leading to drug abuse regardless of the consequences (Baler and Volkow, 2006).

Although most studies have failed to determine which part of the ACC is most relevant to addiction, abnormal activities of the dACC have often been noted. Many previous neuroimaging studies observed heroin-dependent individuals tend to be impulsive during the performance of response inhibition tasks, and also have a reduction in dACC activity (Lee et al., 2005; Yucel, 2007; Fu et al., 2008). Another study reported that acute heroin administration during response inhibition exhibited decreased both activity in the dACC and functional connectivity from the dACC to the right inferior frontal gyrus (IFG), indicating the heroin-dependent individuals' trouble in the distribution and regulation of attention (Schmidt et al., 2014). These findings implied that abnormal dACC activity might play a key part in the cognitive control defect in heroin-dependent individuals, leading to poor addicts' inhibitory ability to restrain sustained drug abuse (Yucel, 2007).

Moreover, it has also been observed that during inhibitory control, patients with drug dependence exhibit altered activation of the rostral ACC (rACC) as well (Forman et al., 2004; Li and Sinha, 2008). This sub-region of the ACC is located in an area in which cognitive and affective functions overlap (Li and Sinha, 2008). It has been shown that the rACC plays an important role in the integration of emotion and cognition (Mayberg et al., 2000). Some event-related fMRI studies found that the rACC was activated selectively by the failure of response inhibition (Kiehl et al., 2000; Braver et al., 2001). Therefore, in contrast with the dACC, which is involved in monitoring error, interference, and conflict (Blasi et al., 2006), the rACC instead responds to errors of conflict (Wittfoth et al., 2008) and mediates response inhibition (Li and Sinha, 2008). However, Forman et al. (2004)'s study showed that compared with controls, heroin-dependent individuals performed poorly in the signal detection, and displayed reduction in the rACC's activity associated with errors on the task. These results demonstrated that the error-related activation of the rACC provide an enabling signal to control the behaviors. The heroin-dependent individuals' deficit of the rACC error response may facilitate the impulsive drug-seeking behaviors (Forman et al., 2004). Furthermore, it has been suggested that the rACC may take part in the process of assessing the consequences caused by potentially relevant motivation and emotion (Davidson et al., 2002). Increasing attention is being paid to the role of the rACC in heroin addiction, for example, Yuan et al. (2010a,b,c) have observed abnormal function connectivities between the rACC and some brain areas in heroin-dependent individuals and have suggested that this anomaly is associated with the impairment of response inhibition and decision-making capabilities in heroin-dependent individuals (Yuan et al., 2010a).

Traditionally, the vACCis considered to be an affective region of the ACC that is primarily involved in assessing the salience of emotional information, regulating emotion and craving. Indeed, the so-called vACC is usually defined to consist of the rACC and the subcallosal part of the ACC (sACC) (Bush et al., 2000). For instance, Wang et al. (2010) selected the vACC as the seed region for an overall brain functional connectivity analysis in the resting state, and it should be noted that the vACC comprises part of the rACC and the sACC in this study (Wang et al., 2010). Another study reported decreased functional connectivity between the dACC and the vACC in heroin-dependent individuals (Ma et al., 2010). However, the vACC in this study was defined to include the rACC alone, without the sACC. Actually, the sACC is distinct from the vACC and the rACC functionally and structurally, and is believed to be involved in emotional processing (Aharon et al., 2001). Moreover, recent research on depression tends to consider the sACC and the vACC separately because of the key role of the sACC in depression and in affective modulation (Lozano et al., 2008; Connolly et al., 2013). In addition, recently a study found that compared with natural cues, addicts exhibited higher activation in the sACC and increasing craving for heroin when confronted with heroin-related cues, suggesting that the activation of this region may be related to the high susceptibility of relapse during short-term heroin abstinence (Li et al., 2012). Thus, it can be speculated that the sACC may also play a unique role in heroin addiction. Findings about the vACC that consisted of the rACC and the sACC could therefore lead to confusing and unreliable conclusions. Thus, it is necessary to study the distinctive influence of the sACC on heroin addiction.

In fact, researchers have tended to divide the ACC into three structural and functional sub-regions, the dACC, the rACC, and the sACC, when studying