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Resting state connectivity in alcohol dependent patients and the effect of repetitive transcranial magnetic stimulation

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Abstract
Alcohol dependence is thought to result from an overactive neural motivation system and a deficient cognitive control system, and rebalancing these systems may mitigate excessive alcohol use. This study examines the differences in functional connectivity of the fronto-parietal cognitive control network (FPn) and the motivational network (striatum and orbito-frontal cortex) between alcohol dependent patients (ADPs) and healthy controls (HCs), and the effect of repetitive transcranial magnetic stimulation (rTMS) on these networks. This randomized controlled trial included 38 ADPs and 37 HCs, matched on age, gender and education. Participants were randomly assigned to sham or right dorsolateral prefrontal cortex (dlPFC) stimulation with rTMS. A 3T resting state functional Magnetic Resonance Imaging (fMRI) scan was acquired before and after active or sham 10 Hz rTMS. Group differences of within and between network connectivity and the effect of rTMS on network connectivity was assessed using independent component analysis. Results showed higher connectivity within the left FPn ($p=0.012$) and the left fronto-striatal motivational network ($p=0.03$) in ADPs versus HCs, and a further increase in connectivity within the left FPn after active stimulation in ADPs. ADPs also showed higher connectivity between the left and the right FPns ($p=0.025$), and this higher connectivity was related to fewer alcohol related problems ($r=0.30$, $p=0.06$). The results show higher within and between network connectivity in ADPs and a further increase in fronto-

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parietal connectivity after right dlPFC rTMS in ADPs, suggesting that frontal rTMS may have a beneficial influence on cognitive control and may result in lower relapse rates.

1. Introduction

Substance dependence is a relapsing brain disorder characterized by compulsive drug seeking and consumption, despite adverse consequences (American Psychiatric Association, 2000). Neuroimaging studies have identified several brain regions that are related to substance dependence, including regions involved in reward (Volkow et al., 2011), motivation (Volkow et al., 2012) and cognitive control (Goldstein and Volkow, 2011). These studies constitute the basis for the dual-process theory of addiction, which describes two dysfunctional networks; the control network and the reward/motivation network (Kalivas, 2005; Koob and Volkow, 2010). In the course of the development of addiction, motivational and reward processes become hypersensitive to substance related cues as a result of the repeated pleasurable drug effects resulting in increased motivation for drug use (Volkow et al., 2009), whereas the cognitive control mechanisms are weakened, together resulting in loss of control over the frequency and amount of drug use despite adverse consequences (Baler and Volkow, 2006).

These neural networks and their interactions can be detected by resting state fMRI (rsfMRI), which measures spontaneous fluctuations in brain activity at rest and identifies temporally correlated brain regions and brain networks (Laird et al., 2011; Smith et al., 2009; Van Den Heuvel and Hulshoff Pol, 2010). This technique has been used to identify the above mentioned control (Damoiseaux et al., 2006; Janes et al., 2010; Laird et al., 2011; Smith et al., 2009) and motivation networks (Damoiseaux et al., 2006; Janes et al., 2010; Laird et al., 2011; Müller-Oehring et al., 2014; Smith et al., 2009). The control network is also referred to as the fronto-parietal control network (FPn), which can be separated into distinct left and right hemisphere fronto-parietal networks (left FPn and right FPn) (Damoiseaux et al., 2006). These networks consist of the Anterior Cingulate Cortex (ACC), Inferior Frontal Gyrus (IFG), the dorsolateral prefrontal cortex (dlPFC) and the posterior parietal cortex (PPC). The reward/motivation network mainly consists of the ventral striatum and the orbitofrontal cortex (Müller-Oehring et al., 2014).

So far, rsfMRI studies in alcohol dependent patients (ADPs) have produced inconsistent results. Two studies have shown that ADPs show higher connectivity within the control networks and lower connectivity in the reward network when compared to healthy controls (HCs) (Camchong et al., 2013a, 2013b, 2013c). Moreover, within the group of ADPs, higher resting state connectivity in the control network at baseline was associated with longer abstinence rates at follow-up (Camchong et al., 2013a, 2013b, 2013c). However, in a third study, ADPs showed weaker within network connectivity and expanded connectivity outside the executive control network and reward-motivational network compared to HCs (Müller-Oehring et al., 2014). Although the last study seems to contradict the first two studies, differences in seed location may explain the differences in results. These studies do show, however, that resting state connectivity within and between the reward/motivation network and the cognitive control network is compromised in ADPs.

Impaired functioning of these networks may be alleviated by brain stimulation techniques like repetitive transcranial magnetic stimulation (rTMS) (Fox et al., 2014; Fox et al., 2012). The use of rTMS over the dlPFC is an FDA approved treatment for major depressive disorder (Dell'Osso et al., 2011), enhances cognition in psychiatric patients and HCs (Guse et al., 2010), improves emotion regulation in HCs (Jansen et al., 2015b), and may reduce craving in ADPs (Jansen et al., 2013; Jansen et al., 2014). In rTMS, a magnetic field is used to alter brain activity, but the underlying effects on network connectivity remain unclear (George and Aston-Jones, 2010). Previous studies did show that stimulation effects are not restricted to the stimulation site, but spread throughout the brain (Fox et al., 1997; Kobayashi and Pascual-Leone, 2003; Paus et al., 1997). The dlPFC is a central hub in the FP networks, and therefore rTMS may change network dynamics in prefrontal networks as well as networks with anatomic connections to the dlPFC (Fox et al., 2012). A recent study indeed revealed that rTMS normalized elevated functional connectivity in the default mode network in patients with a major depressive disorder (Liston et al., 2014).

To date, there are no combined rsfMRI-rTMS studies in substance dependent populations. The current study first examines possible differences in functional connectivity between ADPs and HCs in prefrontal networks, including: the reward/motivation network, and the left and right FP control networks. Then the effect of high-frequency rTMS over the right dlPFC on these networks is evaluated. In the study, we examine both within and between network connectivity levels. Within network connectivity reflects how strong the spontaneous fluctuations are correlated within one network, whereas between network connectivity reflects the strength of the correlation between two networks. We hypothesize that ADPs show abnormal resting state connectivity within and between the FP control networks and within the reward/motivational network, and that rTMS influences these resting state connectivity abnormalities.

2. Experimental procedures

2.1. Participants

A total of 38 ADPs and 37 HCs matched on age, sex and education were included. ADPs were recruited from