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Short communication

Reduced interhemispheric executive control network coupling in men during early cocaine abstinence: A pilot study

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ABSTRACT

Background: Individuals who use cocaine have fewer cognitive resources needed to maintain abstinence. This is evidenced by blunted brain function during cognitive control tasks and reduced communication between brain regions associated with cognitive function. For instance, relapse vulnerability is heightened in individuals with less communication between the right and left frontoparietal executive control network (ECN). Given that recent cocaine use enhances such communication, it is plausible that recency of cocaine use influences interhemispheric ECN communication. However, it is unclear whether ECN communication weakens over the course of early cocaine abstinence, which may then enhance relapse risk.

Methods: In ten men with cocaine use disorder, we conducted a preliminary assessment of the relationship between the number of days since last cocaine use (1–3 days) and interhemispheric ECN coupling using resting state functional magnetic resonance imaging (fMRI).

Results: Reduced interhemispheric ECN coupling was associated with increasing days since last cocaine use; weaker coupling was also associated with lower urine cocaine metabolite concentrations. This association was more prominent in prefrontal than parietal ECN-subregions.

Conclusions: Preliminary results indicate that resting state interhemispheric ECN coupling weakens within the first few days following last cocaine use. Because of the known link between reduced ECN interhemispheric coupling and relapse vulnerability, these results suggest that relapse risk may increase the longer an individual abstains during an early quit attempt. Treatments focused on reversing this coupling deficit may facilitate abstinence.

1. Introduction

Disrupted brain function plays a major role in maintaining chronic cocaine use (Goldstein and Volkow, 2011). For instance, in comparison to non-drug users, individuals with cocaine use disorder (CUD) show reduced engagement of brain regions involved in executive control during cognitive tasks (Bolla et al., 2003; Hester and Garavan, 2004; Kaufman et al., 2003). Additionally, the communication between executive control brain regions is reduced in abstinent individuals with CUD relative to healthy controls (Kelly et al., 2011). This is particularly relevant since *increased* interhemispheric coupling in frontoparietal regions is associated with better executive functioning and attention (He et al., 2007; Kelly et al., 2011; McHugh et al., 2016; Wang et al., 2013). These interhemispheric coupling deficits are associated with drug-related behavior as cocaine relapse vulnerability is heightened in those with reduced interhemispheric coupling of the executive control network (ECN; McHugh et al., 2016), a resting state network comprised of two primary hubs underling cognitive control: dorsolateral prefrontal cortex (dlPFC) and posterior parietal cortex (PPC) (Bressler and Menon, 2010). Due to this networks' anatomy and function, it is sometimes also referred to as the frontoparietal network (Janes et al., 2012; Laird et al., 2011). In contrast, interhemispheric coupling within other resting state networks (default mode and salience networks) was not related to time to relapse (McHugh et al., 2016), indicating that the ECN may play a unique role in abstinence from cocaine.

Though chronic cocaine use is associated with reduced functional connectivity of brain regions involved in executive control, acute cocaine use can temporarily *enhance* such interhemispheric coupling (Reid et al., 2008). In contrast, it is plausible that in the initial days following cocaine use, such interhemispheric communication declines,

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impairing the cognitive resources needed to prevent relapse. Though prior research has shown that reduced interhemispheric coupling after the first few weeks of abstinence is associated with relapse (McHugh et al., 2016), the extent to which interhemispheric coupling strength varies with the days since last cocaine use is unknown. Understanding how recency of use impacts interhemispheric coupling may clarify the neurobiological factors that influence the ability to sustain cocaine abstinence during early withdrawal.

As a preliminary step, we assessed whether the number of days since last cocaine use, during the first three days of abstinence, was associated with weaker connectivity between the right and left lateralized ECN. We focused on the ECN given the prior link between reduced interhemispheric ECN connectivity and relapse (McHugh et al., 2016). We subsequently assessed whether the relationship between ECN coupling and days since last cocaine use was driven by the PFC or PPC ECN-subregions, which are thought to be involved in shared and also distinct cognitive functions (Zhou et al., 2012). The PFC is associated with top-down volitional attentional control, whereas the PPC is thought to have additional involvement with bottom-up attentional processing (Miller and Buschman, 2013). Since these regions have been associated with different patterns of coupling during attentional control tasks (Friese et al., 2016), the extent to which resting state interhemispheric coupling is related to recency of cocaine use may also vary between the PFC and PPC hubs of the ECN. We hypothesized that coupling in the PFC subregion would have the strongest relationship with recency of use, because deficits in the PFC are a key feature of addiction (Goldstein and Volkow, 2011).

2. Material and methods

2.1. Participants

Participants were ten treatment-seeking cocaine-using men who had a history of using cocaine via the smoked and intranasal routes. Eligibility criteria included current cocaine abuse or dependence per the Mini International Neuropsychiatric Interview (MINI; Sheehan et al., 1998) and DSM-IV-TR criteria, having used cocaine at least four times in the past month, and a urine sample positive for benzoylecgonine (BE; > 300 ng/mL; Alere iScreen DX CLIA Waived 12 Panel Instant Drug Test Dip Card) to verify recent cocaine use. Positive urine screens were then quantified for BE metabolite concentration (Quest Diagnostics, Cambridge, MA); one data point was missing due to sample leakage during transit. Exclusion criteria included current DSM-IV-TR psychotic disorder or drug dependence (except cocaine, nicotine, marijuana, and alcohol), magnetic resonance contraindications, head injury with cognitive impairments, and seizure or other neurological disorders. Participants provided informed consent for the study, and procedures were approved by the Partners Human Research Committee.

2.2. Functional magnetic resonance imaging (fMRI) parameters

Brain imaging data were collected on a Siemens 3 T TIM Trio MR imaging system (Erlangen, Germany) with a 32-channel phased-array radio frequency head coil. High-resolution, multiecho multiplanar rapidly acquired gradient-echo (ME-MPRAGE) anatomical scans were collected with a T1-weighted scan with TR = 2.1 s, TE = 3.3 msec, matrix size: 256 × 256 mm, flip angle: 7°, 128 slices, and 1.0 × 1.0 × 1.33 mm voxels. Resting state fMRI scans were collected using multiband echo planar imaging with TR = 0.72 s, TE = 32 msec, matrix size: 85 × 85 mm, flip angle: 66°, 64 slices, and 2.5 mm^3 voxels. Transversal interleaved slices were aligned to the anterior and posterior commissures with phase encoding from posterior to anterior to avoid prefrontal signal loss. During the 6-min fMRI scans, participants were instructed to keep their eyes open, look at a fixation cross on a screen, and remain as still as possible.

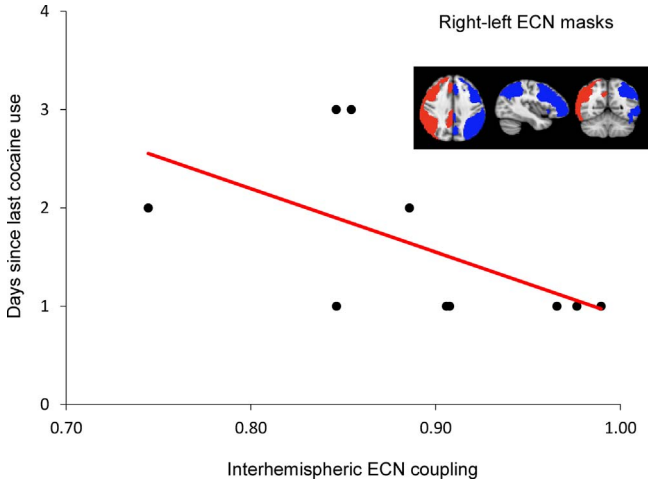

Fig. 1. Correlation between interhemispheric coupling and duration of cocaine abstinence. Weaker interhemispheric coupling in the executive control network (ECN) is associated with more days since last cocaine use ($r = -0.69$, $p = 0.028$). The right and left ECN ROIs are shown in red and blue respectively. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

2.3. fMRI pre-processing and denoising

Data analysis was conducted using the Functional Magnetic Resonance Imaging of the Brain (FMRIB) Software Library (FSL; www.fmrib.ox.ac.uk/fsl). Functional data preprocessing included deleting the first 10 volumes, motion correction (MCFLIRT; Jenkinson et al., 2002), brain extraction (BET; Smith, 2002), slice timing correction, spatial smoothing (Gaussian kernel of 6 mm full-width half-maximum), and Gaussian-weighted least-squares straight line fitting high-pass temporal filter (100 s). Denoising involved identifying and removing motion and other artifactual components from each participant's resting state data using Multivariate Exploratory Linear Decomposition into Independent Components (MELODIC). After all independent components were identified in each participant, components were visually inspected for noise (Janes et al., 2015; Kelly et al., 2010; Putcha et al., 2015), and noise components were regressed out of the resting state data using fsl_regfilt. Individual participant data were affine-registered to standard space at 2 × 2 × 2 mm resolution (MNI152 2 mm^3; Montreal Neurological Institute, Montreal, QC, Canada) using FLIRT (Jenkinson and Smith, 2001; Jenkinson et al., 2002).

2.4. Interhemispheric coupling

The average time courses for each participant were extracted using fslmeants for each bilateral region of interest (ROIs). The right and left ECN were defined using the frontoparietal ROIs in Smith et al. (2009, Fig. 1). The lateralized masks were further divided to separately examine the ECN-subregions: PFC and PPC, which did not include overlap with the opposite hemisphere. For each ROI, the average time course was demeaned, detrended, and Hamming windowed (Oppenheim and Schafer, 1975). The time courses for the right and left ROIs were then time-lagged cross-correlated to establish one maximum correlation value (r) for each participant (Janes et al., 2015), which was exported to SPSS 24 for further analysis.

2.5. Measures and data analyses

Participants completed demographics and substance use history questionnaires, and the Cocaine Craving Questionnaire – Brief (Sussner et al., 2006). Two-tailed Spearman's rank order correlations were conducted to assess the *a priori* relationship between reduced interhemispheric ECN coupling and the number of days since last cocaine