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Wavelet-transformed temporal cerebral blood flow signals during attempted inhibition of cue-induced cocaine craving distinguish prognostic phenotypes☆

Shing Chun Benny Lam[a], Ze Wang[a], Yin Li[a], Teresa Franklin[a], Charles O'Brien[a], Jeremy Magland[b], Anna Rose Childress[a,*]

[a] Department of Psychiatry, University of Pennsylvania, Philadelphia, PA 19104, USA
[b] Department of Radiology, University of Pennsylvania, Philadelphia, PA 19104, USA

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ABSTRACT

Background: Cocaine addicted patients with positive cocaine urine status at treatment entry are far less likely to have a successful treatment outcome. This work aims to identify brain substrates that can distinguish this group of patients from their cocaine-negative counterparts in order to better understand this clinical phenotype. Going a step beyond conventional functional connectivity, we used wavelet transform coherence (WTC) to determine in which ways the temporal pattern of fMRI cerebral blood flow (CBF) signals during attempted inhibition of cue-induced cocaine craving may differ between these two groups.
Methods: Using a critical node in motivational circuitry, amygdala, as a seed, whole brain correlations for the entire sample revealed a functional connection with the dorsal cingulate. Next, WTC maps of CBF were constructed for each individual, characterizing the temporal patterns between these two regions during craving inhibition.
Results: As revealed by WTC, during attempted craving inhibition, the cocaine-negative subjects had significantly stronger and longer negative coherence between the amygdala and the dorsal cingulate, as compared to the cocaine-positive subjects. This relationship was neither evident in the resting state nor between two regions unrelated to inhibition processes.
Conclusions: The duration and strength of negative coherence calculated from wavelet-transformed CBF provide an objective and well-defined way to characterize brain responses during attempted inhibition of cue-induced craving, at the level of the individual. The stronger and sustained negative coherence in CBF between motivational (amygdala) and modulatory (dorsal cingulate) regions in cocaine-negative subjects may be a critical brain strength that fosters improved craving inhibition and thus, better clinical outcome.

1. Introduction

There is striking heterogeneity in clinical outcome among cocaine-dependent (CD) patients seeking treatment. Some patients have long periods of abstinence (become "drug free"), whereas others never become abstinent, or do so only briefly and relapse rapidly (McLellan et al., 1996). One of the most robust predictors of clinical outcome is urine status at treatment entry. Patients having cocaine-negative (CocNeg) urine tests usually have less subsequent drug use and less frequent relapse, whereas cocaine-positive (CocPos) urine subjects have more drug use and rapid relapse (Alterman et al., 1997; Ehrman et al., 2001; Sofuoglu et al., 2003). This difference in treatment outcome between these two groups is often attributed to factors such as "readiness for treatment", "motivation for abstinence", and "commitment to recovery". Advances in brain imaging tools allow us to test another possible reason for outcome variability between these groups: CocPos and CocNeg patients may have measureable differences in the functioning of relapse-relevant brain circuits. In the current paper, we compare these two clinically distinct phenotypes on temporal variation in the connectivity of brain circuits critical for resisting craving.

In our view, the brain vulnerabilities associated with drug use and risk of rapid relapse may lie in the poor connection between two brain systems: (1) the limbic motivational ("GO!") circuitry, activated by natural rewards (e.g., food, sex) and rewarding drugs of abuse, and their signals (i.e. cues), and (2) the frontal modulatory ("STOP!") circuitry, which inhibits the downstream motivational systems (Childress, 2006). Several studies have noted brain differences between CD patients and comparison groups in these

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* Corresponding author. Tel.: +1 215 222 3200; fax: +1 215 386 6770.
E-mail address: childress_a@mail.trc.upenn.edu (A.R. Childress).

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brain networks (Childress et al., 1999; Ersche et al., 2012; Franklin et al., 2002; Volkow et al., 2010; Wilson et al., 2004); some of these differences may help explain addicted patients' struggles to inhibit craving, and their high rates of relapse. We and other investigators have begun to examine the functional connections between limbic and frontal networks in substance abuse populations using neuroimaging (Gu et al., 2010; Jiang et al., 2011; Ma et al., 2010), and to link brain differences to clinical prognostic phenotypes/clinical outcome (D'Sa et al., 2011). Specifically, one recent finding indicated that frontal regions maintain significantly stronger amygdala functional connectivity during modulatory attempts in patients who submitted a cocaine-negative urine at treatment entry than those with a cocaine-positive urine (Suh et al., 2009).

Functional magnetic resonance imaging (fMRI) signals from co-activated regions oscillate in patterns across time (Baria et al., 2011; Varela et al., 2001), some of which are negatively correlated ("anticorrelated"): while activity from one region goes up, activity in an anticorrelated region goes down (Fox et al., 2005). Conventional connectivity analysis collapses all time points to yield a correlation coefficient (Biswal et al., 1995) expressing the overall relationship between two regions *for an entire time period*. Unfortunately, this conventional approach cannot reveal dynamic variations (time–frequency changes) *within* a given time period. As time–frequency relationships may carry important, clinically relevant information (Broyd et al., 2009; Salomon et al., 2012), we used a time–frequency analysis technique, wavelet transform coherence (WTC), to investigate the connectivity between the "STOP!" and "GO!" circuitry for the two above-described cocaine subgroups (CocNeg and CocPos) from their fMRI signals. In this study, we hypothesized that the CocNeg group would exhibit a stronger anticorrelation (inverse functional relationship) between frontal and downstream motivational regions than the CocPos group, consistent with inhibition of cocaine craving. Further, we tested whether the temporal characteristics of the signal (e.g., sustained vs. brief anticorrelation) would be associated with urinalysis results.

Here, treatment-seeking CD subjects were asked to inhibit their craving induced by cocaine-related videos while inside a magnetic resonance imaging (MRI) scanner. Cerebral blood flow (CBF) variation was measured throughout the whole session of a craving inhibition task, using arterial spin labeling (ASL) perfusion fMRI (Detre et al., 1992; Wang et al., 2003b). Comparing with blood-oxygen-level-dependent (BOLD) measurement, ASL perfusion fMRI allows functional connectivity analysis based on a single quantitative physiological parameter, CBF, and had shown good within-session reproducibility for the conventional seed-based functional connectivity analysis (Chuang et al., 2008).

Time- and frequency-localized correlations from regional cerebral blood flow (rCBF) signals within specific regions-of-interest (ROIs) in the "STOP!" and "GO!" regions were computed using wavelet transform coherence (Grinsted et al., 2004) for each CocNeg and CocPos subject. Bootstrapping was applied to test the statistical significance of individuals' WTC results, after which the strength and duration of coherence were derived. Self-reported craving in response to drug cues was also recorded.

2. Materials and methods

2.1. Subjects and study design

For this exploratory study with WTC, we made use of a data set (see Section 2.2) from a cohort of cocaine-dependent subjects characterized for the two phenotypes of clinical interest (CocPos, CocNeg) on the basis of objective urine samples at treatment entry. Nineteen male, treatment-seeking cocaine-dependent subjects participated; the project was conducted at the University of Pennsylvania Addiction Treatment Research Center. The University of Pennsylvania Institutional Review Board approved the study, and all subjects signed a written informed consent prior to participation. Sixteen subjects were African American, two were Caucasian and one was Hispanic. Prior to the scanning session, all subjects were admitted to a controlled therapeutic residential setting for 8–10 days to ensure a stable, cocaine-free state. In the week prior to scanning, subjects were introduced to a manualized Coping with Craving Program (Childress et al., 1991), and were given an individualized training session in which they attempted to inhibit cue-induced craving by considering the possible negative consequences of their cocaine use (Childress et al., 2005).

Urine samples were obtained on their first day of admission. Eleven subjects had cocaine-positive urine tests (CocPos group, ≥300 ng/ml of benzoylecognine, the metabolite of cocaine) and eight subjects had cocaine-negative urine tests (CocNeg group) at treatment entry. There was no statistical significant difference (all $p > 0.3$) between the two groups in age, years of education, years of cocaine and alcohol use, number of days since last cocaine use (Table 1). Tetrahydrocannabinol, indicating marijuana usage, was found in the urine from four and three subjects in CocPos and CocNeg group, respectively.

On days 7–10 of the residential stay, subjects were transported to the Hospital of the University of Pennsylvania for the fMRI session, which consisted of several 5-min acquisitions. A 5-min resting state fMRI session was acquired first. The subjects were asked to stay comfortably still inside the MRI scanner with their eyes open. In the attempted craving inhibition condition, the subjects were instructed to try to reduce (inhibit) their cocaine craving by considering the negative consequences of their cocaine use while they were watching a 5-min cocaine-related video. The subjects also rated their cocaine craving (on a scale of 0–9; Childress et al., 2005) before and after the video. Results from WTC analysis of both states were compared.

2.2. MRI acquisition

All scans were conducted on a Siemens 3 Tesla Trio whole-body scanner (Siemens AG, Erlangen, Germany), using a standard 8-channel receive head coil. fMRI CBF time series data were obtained with two custom variants of the ASL fMRI method (Kim, 1995; Wang et al., 2002). ASL MRI is a non-invasive technique measuring CBF with magnetically labeled arterial blood as endogenous tracer (Detre et al., 1992). It has the capability for capturing dynamic brain activity as well (Detre et al., 2009). Although ASL fMRI has lower temporal resolution as compared to BOLD fMRI, it has the potential to provide better localization of functionally connected regions than BOLD (Duong et al., 2001). Of note, our signal analysis techniques are by no means specific to ASL, and could be used with BOLD data as well (Chang and Glover, 2010; Curtis et al., 2005; Sun et al., 2005). We conducted statistical significance tests on both functional connectivity results obtained from conventional correlation (p value from cross-correlation) and WTC (bootstrapping, please see Section 2.6) to ensure the validity of the temporal relationship between the two CBF time series. Calculation of functional connectivity using conventional correlation and WTC from CBF data was performed within each subject after which the resulting connectivity results were compared among the subjects. fMRI parameters of individual subjects are presented in Table S1.[1] High-resolution T1-weighted structural images were acquired using a 3D MPRAGE sequence using the same coil with parameters of resolution = 1 mm^3, TR/TE = 1620/3 ms, matrix size = 192 × 256 × 160, flip angle = 9°.

2.3. ASL CBF signal preprocessing

ASL CBF signal preprocessing including motion correction, filtering, spatial smoothing, CBF quantification, registration to the Montreal Neurological Institute (MNI) standard brain via structural image was performed using a number of SPM-based (Wellcome Department of Imaging Neuroscience, Institute of Neurology, London, UK) batch scripts provided in ASLtbx (Wang et al., 2008). CBF values were calculated with a simplified two-compartment model with sinc-interpolated subtraction method which tends to whiten the low frequency noise typically observed in fMRI experiments and provides relatively flat power spectra in the frequency range below 0.10 Hz (Wang et al., 2003a). No further regression or normalization with any global or physiological signal was done to avoid potential risk of inducing artificial antiphasic relationships.

2.4. Selection of a priori regions-of-interest (ROIs) and control experiments

We chose the amygdala as the anatomical seed region-of-interest (ROI) for the preliminary correlational analyses. The amygdala is a critical node in the limbic motivational ("GO!") circuitry (Everitt and Robbins, 2005): it is triggered by cues for both natural (e.g., food (Morris and Dolan, 2001), sex (Cahill et al., 2004)) and drug (Franklin et al., 2007; See et al., 2003; Wilson et al., 2004) rewards, including appetitive cues occurring completely outside awareness (Childress et al., 2008). Using the amygdala as a seed ROI enabled us to empirically determine which frontal regions were in anticorrelation (inverse relationship) with the amygdala.

For each side of the brain, the region with over 25% probability of being an amygdala defined in Harvard-Oxford subcortical structural atlas was chosen as an ROI. The mean rCBF time series within the amygdala ROI was extracted and used

[1] Supplementary material can be found by accessing the online version of this paper at http://dx.doi.org. Please see Appendix A for more information.