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Dynamic network dysfunction in cocaine dependence: Graph theoretical metrics and stop signal reaction time

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ABSTRACT

Graphic theoretical metrics have become increasingly popular in characterizing functional connectivity of neural networks and how network connectivity is compromised in neuropsychiatric illnesses. Here, we add to this literature by describing dynamic network connectivities of 78 cocaine dependent (CD) and 85 non-drug using healthy control (HC) participants who underwent fMRI during performance of a stop signal task (SST). Compared to HC, CD showed prolonged stop signal reaction time (SSRT), consistent with deficits in response inhibition. In graph theoretical analysis of dynamic functional connectivity, we examined temporal flexibility and spatiotemporal diversity of 14 networks covering the whole brain. Temporal flexibility quantifies how frequently a brain region interacts with regions of other communities across time, with high temporal flexibility indicating that a region interacts predominantly with regions outside its own community. Spatiotemporal diversity quantifies how uniformly a brain region interacts with regions in other communities over time, with high spatiotemporal diversity indicating that the interactions are more evenly distributed across communities. Compared to HC, CD exhibited decreased temporal flexibility and increased spatiotemporal diversity in the great majority of neural networks. The graph metric measures of the default mode network negatively correlated with SSRT in CD but not HC. The findings are consistent with diminished temporal flexibility and a compensatory increase in spatiotemporal diversity, in association with impairment of a critical executive function, in cocaine addiction. More broadly, the findings suggest that graph theoretical metrics provide new insights for connectivity analyses to elucidate network dysfunction that may elude conventional measures.

1. Introduction

Neural phenotypes serve as diagnostic or prognostic marker of neuropsychiatric illnesses and numerous studies have shown altered brain activity or connectivity in individuals with cocaine addiction. For instance, dependent cocaine users demonstrated diminished resting state functional connectivity (rsFC) of the salience network, seeded from the insula, as compared to non-drug using controls (Geng et al., 2017). In a treatment cohort, rsFC between right temporal pole and medial prefrontal cortex (MPFC) predicted relapse status at 150 days. Another study demonstrated disrupted interactions between default mode and salience networks in cocaine addiction (Liang et al., 2015). RsFC decreased between the orbitofrontal/dorsal PFC and ventral striatum and increased between dorsal and ventral striatum in abstinent cocaine users, particularly in those who relapsed to drug use (Berlingeri et al., 2017). RsFC among executive and salience networks were higher among individuals who remained abstinent after treatment (McHugh et al., 2017). Spectral dynamic causal modeling showed altered effective connectivity of the mesolimbic circuit involving the ventral tegmental area, nucleus accumbens and MPFC in cocaine users (Ray et al., 2016). In our recent study with multivariable pattern analysis, rsFC of thalamic subregions distinguished cocaine users from non-drug using controls at a higher accuracy, in comparison with brain regions with similar volumes (Zhang et al., 2016).

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Other studies addressed task-related functional connectivity. In a finger tapping task requiring variable speed response, MPFC connectivity with the basal ganglia was decreased in cocaine users, particularly at higher speed, compared to controls (Lench et al., 2017). Compared to non-drug using controls, abstinent cocaine users showed increased left dorsolateral prefrontal cortical (DLPFC) connectivity with the putamen in response to increasing reward magnitude in a counting Stroop task blocked with varying monetary rewards (Rosell-Negre et al., 2016). Current cocaine users demonstrated reduced amygdala connectivity with the anterior cingulate cortex (ACC) in response to angry and fearful facial expressions, compared to controls (Crunelle et al., 2015). In another study cocaine addicted individuals relative to non-drug using pathological gamblers exhibited enhanced connectivity between the ventral caudate and subgenual ACC, in link with steeper delay discounting and relapse to drug use (Contreras-Rodriguez et al., 2015). Dynamic causal modeling showed altered prefrontal striatal connectivity during response inhibition in a go/nogo task in cocaine users (Ma et al., 2015). Combining fMRI of cue-induced craving and a Bayesian search algorithm to identify the causal circuits of craving, investigators reported a positive correlation between the strength of the causal influence of the insula on the DLPFC and craving rating (Ray et al., 2015b).

Together, these and many other studies highlighted changes in functional connectivity during resting or task challenges in cocaine misuse (Adinoff et al., 2015; Albein-Urios et al., 2014; Barros-Loscertales et al., 2011; Caldwell et al., 2015; Cisler et al., 2013; Hu et al., 2015c; Konova et al., 2015; Ma et al., 2014; McHugh et al., 2014; Ray et al., 2015a; Wisner et al., 2013; Zhang et al., 2014). The great majority of these studies focused on specific regions of interest, and none examined the dynamic aspects of functional connectivity (Cohen, 2017).

The bulk of connectivity studies assume that functional connectivity over the data collection period (or chronnectome) is relatively static (Calhoun et al., 2014). This assumption was challenged in studies of time-varying connectivities (Sakoğlu et al., 2010). A rationale is that because of physiological noise, scanner drift, and fluctuation of participants' attention, functional connectivity may not be truly static (Morgan et al., 2015). As also shown in task-based fMRI, brain regions showed a trend toward decreasing activation as participants continued to perform on the same task (Menon and Uddin, 2010). These considerations prompted studies to capitalize on the wealth of information contained within the temporal features of BOLD signals (Hutchison et al., 2013).

More importantly, the coordination of brain activity between neural populations is a dynamic and context-dependent process. Brain dynamics give rise to variations in complex network properties over time, possibly achieving a balance between efficient information processing and metabolic expenditure (Zalesky et al., 2014) and potentially playing a critical role in supporting cognition (Allen et al., 2014; Calhoun et al., 2014; Chang and Glover, 2010; Kang et al., 2011; Thompson et al., 2013). Given sufficient data, a number of metrics could be used to characterize dynamic connectivity (Hutchison et al., 2013). For instance, in a study of network connectivity of the insula using a “sliding window” approach, dynamic states mirrored the cognition-emotion-interoception divisions observed of static networks, with both overlapping and unique connectivity profiles (Nomi et al., 2016). The results highlight how dynamic connectivity better characterizes functional connections of insula subdivisions and suggest more nuanced models of insula function. A study of temporal lobe epilepsy reported that as seizures progress over the years, dynamic connectivity measures showed declining functional independence of the ipsilateral from the midline cingulate network (Morgan et al., 2015). Thus, dynamic connectivity quantifies widespread network alterations and their evolution over the duration of the disease, providing a severity or treatment outcome marker of epilepsy. Together, these and other studies (Damaraju et al., 2014; de Lacy et al., 2017; Kaiser et al., 2016; Sakoğlu et al., 2010; Yaesoubi et al., 2017) highlight the utility of dynamic functional connectivity (DFC) in capturing the neural processes that may be critical to the etiology of neuropsychiatric conditions.

Here we investigated how whole-brain DFC may be altered in cocaine addicted individuals in contrast to non-drug using controls. Specifically, we employed graph theoretical analyses with temporal flexibility and spatiotemporal diversity as two indices to examine how networks of brain regions interact over time (Alnaes et al., 2015; Bassett et al., 2011; Chen et al., 2016; Fornito et al., 2012). Temporal flexibility characterizes how frequently a brain region interacts with regions outside its own community across time. Spatiotemporal diversity reflects how uniformly a brain region interacts with regions in other communities over time.

With a within-subject design, we compared these graph theoretical metrics of imaging data collected during the stop signal task (SST) between cocaine users and controls. On the basis of previous work (Cai et al., 2017; Cai et al., 2016; Cai et al., 2014; Duann et al., 2009; Hu et al., 2016; Zhang and Li, 2010, 2012), we hypothesized that the medial frontal, frontoparietal task control and salience networks as well as the default mode network (DMN) demonstrate altered graph metrics in cocaine dependent individuals, in association with impaired response inhibition, as compared to non-drug using controls.

2. Materials and methods

2.1. Subjects and behavioral task

Eighty-five healthy control (HC) and 78 cocaine dependent (CD) adults participated in this study. CD resided in an inpatient treatment unit and was abstinent between 1 and 2 weeks before fMRI scan was conducted. All participants reported no major medical, neurological, or other psychiatric illnesses (except nicotine use disorder), denied use of other illicit substances and tested negative for cannabis, opioids, amphetamine, methamphetamine, phencyclidine, benzodiazepine, and barbiturate on the day of fMRI. All participants signed a written, informed consent in accordance with a protocol approved by the Yale Human Investigation Committee.

Participants performed a stop signal task or SST, which was described in details in our previous studies (Bednarski et al., 2012; Hu et al., 2014; Winkler et al., 2013; Zhang et al., 2014). Briefly, a “go” signal set up a pre-potent response tendency in go trials (~75%), and an additional, less frequent “stop” signal instructed subjects to withhold their response in stop trials (~25%). Go and stop trials were randomized in presentation, with an inter-trial-interval of 2 s. The time delay between go and stop signal – stop signal delay (SSD) – was staircased, increasing and decreasing by 67 ms each following a stop success and error trial. Participants were instructed to respond as quickly as they could to “go” signal, while watching out for the “stop” signal. In the scanner, participants completed four 10-minute runs of the SST, with approximately 100 trials in each run. With the staircase procedure, participants succeeded in stopping approximately half of time. The stop signal reaction time (SSRT) – the time needed for one to stop the response half of the time, was estimated on the basis of a race model. Briefly, in the race model, go and stop processes independently race toward a finish line and whichever finishes first determines the trial outcome. With the race model, the SSRT can be estimated by subtracting a critical SSD (where subjects would succeed in stopping half of the time) from the mean go trial RT. The SSRT indexes the capacity of response inhibition, with shorter SSRT reflecting better ability of inhibitory control.

2.2. Imaging protocol

Conventional T1-weighted spin-echo sagittal anatomical images were acquired for slice localization using a 3-T scanner (Siemens Trio,