Response inhibition and fronto-striatal-thalamic circuit dysfunction in cocaine addiction

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Abstract

Background: Many studies have investigated how cognitive control may be compromised in cocaine addiction. Here, we extend this literature by employing spatial Independent Component Analysis (ICA) to describe circuit dysfunction in relation to impairment in response inhibition in cocaine addiction.

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Methods: Fifty-five cocaine-dependent (CD) and 55 age- and sex-matched non-drug-using healthy control individuals (HC) participated in the study. Task-relatedness of 40 independent components (ICs) was assessed using multiple regression analyses of component time courses with the modeled time courses of hemodynamic activity convolved with go success (GS), stop success (SS) and stop error (S). This procedure produced beta-weights that represented the degree to which each IC was temporally associated with, or 'engaged', by each task event.

Results: Behaviorally, CD participants showed prolonged stop signal reaction times (SSRTs) as compared to HC participants (p<0.01). ICA identified two networks that showed differences in engagement related to SS between CD and HC (p<0.05, FDR-corrected). The activity of the fronto-striatal-thalamic network was negatively correlated with SSRTs in HC but not in CD, suggesting a specific role of this network in mediating deficits of response inhibition in CD individuals. In contrast, the engagement of the fronto-parietal-temporal network did not relate to SSRTs, was similarly less engaged for both SS and SE trials, and may reflect attentional dysfunction in cocaine addiction.

Conclusions: This study highlights the utility of ICA in identifying neural circuitry engagement related to SST performance and suggests that specific networks may represent important targets in remedying executive-control impairment in cocaine addiction.

Keywords

1. Introduction

Cocaine addiction is a debilitating and relapsing disorder (McLellan et al., 2000; Yuferov et al., 2005). Previous work has suggested deficits in cognitive control as an etiological process of habitual drug use in cocaine addiction (Ersche et al., 2011; Garavan and Hester, 2007; Goldstein and Volkow, 2011). ortical and subcortical dysfunction has been suggested in brain imaging studies of addictions to cocaine or other stimulants (Aron and Paulus, 2007; Goldstein and Volkow, 2011; Hanlon et al., 2009; Hanlon et al., 2011; Hester and Garavan, 2004; Kaufman et al., 2003; Moeller et al., 2005; Peters et al., 2016; Wesley et al., 2011; Zhang et al., 2018). The medial and lateral frontal cortical regions, in particular, have been repeatedly implicated in deficits of response inhibition in association with cocaine misuse (Connolly et al., 2012; Hester et al., 2013; Hester and Garavan, 2004; Lundqvist, 2010). For example, attenuated responses in executive-cortical regions during Go-NoGo task performance was observed in cocaine users (Kaufman et al., 2003). Striatal activation during performance of the Stroop color-word interference task was correlated with the drug-free rate of urine screen and longer duration of self-reported abstinence (Brewer et al., 2008). Combining Bayesian model of stop-signal-task (SST) performance and functional magnetic resonance imaging (fMRI), we highlighted a distinct role of the frontal-subcortical structures in Bayesian learning for goal-directed control and deficits in learning in cocaine dependent (CD) individuals (Hu et al., 2015a; Ide et al., 2014). Among individuals without and with addictions including to cocaine, impulsivity has been associated with smaller volumes in the hippocampus, amygdala ,and insula (Yip et al., 2018). Deficits in goal-directed action control, particularly in situations that involve uncertain outcomes (Mirabella, 2014),

represent a prominent feature of drug addiction. Together, these studies support structural and functional differences in cortical and subcortical regions in association with deficits in cognitive control and related constructs in cocaine addiction. Along with incentivized salient responses to drug cues (Berridge and O'Doherty, 2014; Berridge and Robinson, 2016; Chow et al., 2016; Hickey and Peelen, 2015; Mirabella et al., 2007), cognitive control dysfunction may perpetuate habitual drug use in cocaine-addicted individuals.

Functional connectivity analyses have identified regional interactions associated with cognitive dysfunction in neuropsychiatric populations. Cocaine dependence was related to altered functional interactions of the insula with the prefrontal cortex, suggesting the influence of interoceptive information on cognitive-control and decision-making processes (Cisler et al., 2013). Compulsive cocaine use was associated with decreased cortico-striatal and increased limbic-striatal resting-state functional connectivity (rsFC) (Hu et al., 2015b). Disrupted connectivity dynamics, as reflected by power spectrum scale invariance (PSSI) of cerebral blood oxygenation-level dependent (BOLD) signal, in fronto-parietal-temporal areas was related to compromised post-signal behavioral adjustment in CD individuals (Ide et al., 2016). Interhemispheric coupling of executive-control networks was weakened during early abstinence of cocaine use (McCarthy et al., 2017). Our recent study of dynamic functional connectivity study described a decrease in temporal flexibility of executive networks in CD as compared to non-drug-using control (HC) participants (Zhang et al., 2018a). These studies suggest the importance of characterizing the functional network organization of cerebral activity in support of cognitive control and how these network activities are disrupted in cocaine addiction.

Independent component analysis (ICA) represents a useful tool to investigate functional network activity. A data-driven method, ICA uncovers hidden factors from a set of measurements such that the sources of the observed data are maximally independent (Calhoun and Adali, 2006; Calhoun et al., 2001a; Calhoun et al., 2002; Lange et al., 1999; McKeown et al., 2003; McKeown et al., 1998). Applied to fMRI data, ICA is capable of identifying functionally integrated brain regions, or functional networks, through a decomposition of the blood oxygenation level-dependent (BOLD) signal into maximally independent systems displaying temporally synchronous activity. In contrast to the general linear modeling of BOLD signals, ICA demonstrates the advantage of uncovering task-related regions with concurrent but opposite changes in response to task events (Xu et al., 2015; Xu et al., 2016). ICA has been widely used to describe the cerebral functional organization. For instance, we recently employed ICA to understand how the thalamus is functionally parcellated according to connectivities with identified components (Zhang and Li, 2017). In previous studies, we applied ICA to fMRI data of the SST and characterized the component networks in response to go success, stop success and stop error trials (Zhang and Li, 2012) and how motor network activities may contribute to individual variation in the stop-signal-reaction time (SSRT) (Zhang et al., 2015b). We have also used ICA to identify networks linked to Stroop performance, cocaine addiction and its treatment (Worhunsky et al., 2013), reward and loss processing in cocaine addiction (Worhunsky et al., 2017), and Go-NoGo performance and drinking behaviors among college students (Worhunsky et al., 2016).

In this study, we used ICA to identify network engagement related to response inhibition during SST performance and aimed to characterize how CD and HC individuals may differ in circuitry recruitment. During SST performance, participants must override a prepotent motor response, monitor errors, and adjust the speed of responding after encountering an error (Duann et al., 2009; Hu et al., 2015a; Ide et al., 2013; Li et al., 2006b; Zhang and Li, 2012). The capacity of response inhibition is quantified by the SSRT, the time it requires for subjects to successfully inhibit a response half of the time, with a longer SSRT reflecting impairment in response inhibition. We examined the temporal profiles of the activity during different trial types and how CD and HC participants differed in engaging these component activities. Following our previous work on regional responses relating to stop-signal inhibition (Duann et al., 2009; Li et al., 2008), we hypothesized that a network involving fronto-parietal-subcortical circuits, including the thalamus and subthalamic nucleus, maybe specifically engaged during stop success (SS) trials. In particular, as compared to HC individuals, CD individuals would display reduced SS-related engagement of this functional network.

2. Methods

2.1 Participants

Fifty-five and 55 HC adults participated (Table 1). CD participants met DSM-IV criteria for cocaine dependence, resided in an inpatient treatment unit and tested positive for cocaine but no other substances in urine toxicology prior to admission. All subjects were required to be physically healthy and without major medical or neurological illnesses. Other exclusion criteria included a past or current diagnosis of psychotic disorder or other substance-use disorders except for nicotine dependence. CD patients were admitted to a locked inpatient research unit, where abstinence is strictly monitored during the entire study period. On average, CD participants were abstinent for 13.5 ± 2.6 (mean $\pm$ SD) days, including the time when they were abstinent before admission, prior to MRI. All participants provided written, informed consent in accordance with a protocol approved by the Yale Human Investigation Committee.

2.2 Behavioral Task

Participants performed a SST (Hu and Li, 2012; Li et al., 2009) in which go and stop trials were randomly intermixed in presentation with an inter-trial interval of 2 s. fixation dot appeared on screen to signal the beginning of each trial. After a fore-period varying from 1 to 5 s (uniform distribution), the dot became a circle – the "go" signal – prompting participants to press a button quickly. The circle disappeared at button press or after 1 s if the participant failed to respond. In approximately one-quarter of trials, the circle was followed by a 'cross' – the stop signal – prompting participants to withhold button press. The trial terminated at button press or after 1 s if the participant successfully inhibited the response. The time between the go and stop signals, the stop signal delay (SSD), started at 200 ms and varied from one stop trial to the next according to a staircase procedure, increasing and decreasing by 67 ms each after a successful and failed stop trial (Levitt, 1971). With the staircase procedure, we anticipated that participants would succeed in withholding the response half of the time. Participants were trained briefly on the task before imaging to

ensure that they understood the task. They were instructed to quickly press the button when they saw the go-signal while keeping in mind that a stop signal might come up in some trials. In the scanner, they completed four 10-minute sessions of the task, with approximately 100-trials in each session. There was a total of approximately 300-go and 100-stop trials.

2.3   Behavioral Data Analysis

A critical SSD was computed for each participant that represented the time delay required for the participant to successfully withhold the response in half of the stop trials, following a maximum likelihood procedure (Wetherill et al., 1966). Briefly, SSDs across trials were grouped into runs, with each run being defined as a monotonically increasing or decreasing series. We derived a mid-run estimate by taking the median SSD of every second run. The critical SSD was computed by taking the mean of all mid-run SSDs. It was reported that, except for experiments with a small number of trials (< 30), the mid-run measure was close to the maximum likelihood estimate of X50 (50% positive response, Wetherill et al., 1966). The SSRT was computed for each participant by subtracting the critical SSD from the median go-trial reaction time (Logan et al., 1984).

2.4   FMRI Procedures and Data Analyses

All imaging data were collected using a 3T Siemens Trio scanner (Siemens AG, Erlangen, Germany) while subjects performed the SST. Tobacco- and caffeine-using subjects were allowed to smoke and drink coffee or other caffeinated beverages until 30 m before the fMRI studies. Functional images were acquired with a single-shot gradient-echo echo-planar imaging (EPI) sequence, with 32 axial slices parallel to the AC-PC line covering the whole brain, using published parameters (Li et al., 2006a; Li et al., 2006c): TR=2000 ms, TE=25 ms, bandwidth=2004 Hz/pixel, flip angle=$85°$, FOV=220×220 mm^2, matrix=64×64, slice thickness=4mm, and no gap. A high-resolution 3D structural image (MPRAGE; 1mm resolution) was also obtained for anatomical co-registration.

Functional MRI data were preprocessed with Statistical Parametric Mapping 12 (SPM12; Wellcome Department of Imaging Neuroscience, University College London, UK) with established routines (Farr et al., 2014; Manza et al., 2016; Wang et al., 2018; Zhang et al., 2012). Images from the first five TRs at the beginning of each trial were discarded to enable the signal to achieve steady-state equilibrium between RF pulsing and relaxation. Images of each individual subject were first corrected for slice timing and realigned (motion-corrected) (Andersson et al., 2001; Hutton et al., 2002). A mean functional image volume was constructed for each subject for each run from the realigned image volumes. The anatomical images (T1-weighted) were co-registered to the mean functional image and normalized to an MNI (Montreal Neurological Institute) template with affine registration followed by nonlinear transformation using a unified segmentation and registration framework (Ashburner and Friston, 2005). The normalization parameters determined for the anatomical volume were then applied to the corresponding functional image volumes for each subject.

2.5 Independent Component Analysis

ICA was performed on the fMRI time series using the Group ICA of fMRI Toolbox (GIFT v4.0b; http://icatb.sourceforge.net) (Calhoun et al., 2001b) to identify spatially independent and temporally coherent networks (Calhoun et al., 2001b; Calhoun et al., 2008). The data from CD and HC individuals were concatenated into a single group and reduced through principal component analysis. An infomax algorithm (Bell and Sejnowski, 1995) was used to separate the dataset into 40 maximally independent components (ICs) in order to identify large-scale functional brain networks (Abou- lseoud et al., 2010). This analysis was repeated 20 times with ICASSO to assess the repeatability of ICs (Himberg et al., 2004). Finally, component time courses and spatial maps were back-reconstructed for each participant (Calhoun et al., 2001b).

Task-relatedness of 40 components was assessed using multiple regression analyses of component time courses with the modeled time courses of canonical hemodynamic activity convolved with the three task events: go success (GS), stop success (SS) and stop error (SE). This procedure produces beta-weights that represent the degree to which each IC is temporally associated with, or 'engaged', by each task event. We compared CD and HC participants with respect to the beta-weights relating to SS with two-sample t-tests, and components of interest were determined to be those exhibiting a significant group difference ($P<0.05$, FDR-corrected). The ICs that demonstrated a significant difference in SS-task-related beta-weights were selected for further analyses, with the subject-level spatial source maps of the component time courses entered into factorial models in SPM12 to determine their regional patterns at a voxel-level $P<0.000001$, corrected for family-wise error (FWE) of multiple comparisons, with an extent threshold of 40 voxels (Zhang and Li, 2012).

2.6 Analysis of Group-By-SSRT Interaction and Linear Regression Against SSRT

In an additional analysis, we evaluated whether the differences between CD and HC in network engagement reflected differences in SSRTs primarily (see Results). For both CD and HC groups, participants were divided by a median split according to the SSRT into two sub-groups: low SSRT and high SSRT. Thus, with low SSRT CD (lCD), high SSRT CD (hCD), low SSRT HC (lHC), and high SSRT HC (hHC), we conducted a 2×2 repeated-measures ANOVA on the beta-weights of networks of interest and reported SSRT and group main effects as well as the interaction effect. This analysis permits distinguishing whether the activity of the components of interest differ between subject groups, SSRT groups, and/or interact in a group-by-subject manner.

We also performed a regression analysis of IC beta-weights against SSRTs. Considering 2-components of interest (see Results) and 3-sets of beta-weights (GS, SS, and SE), we used a corrected value of $0.05/6=0.0083$ to define statistical significance. To examine whether CD and HC differ in the relationship between IC beta-weights and SSRTs, we compared the slopes of linear regressions between the two groups (Zar, 1999) as in earlier studies of alcohol addiction (Hu et al., 2018; Ide et al., 2017).

3   . Results

3.1   Behavioral Findings

Table 2 summarizes the performanceMANUSCRIPTmeasuresfromtheSST.BothCDandHC participants succeeded in stopping approximately half of the time, suggesting the success of SSD staircasing in tracking the performance. CD and HC groups did not differ in SS rates, mean go-trial reaction time (goRT) or SE reaction time (Higley et al.). CD participants showed significantly lower go-response rates (t_{108}=−3.24, p=0.002) and longer SSRTs (t_{108}=2.6, p=0.011) than HC participants. The values of SSRTs were within the range as reported in earlier work (Federico and Mirabella, 2014).

3.2   Functional Brain Networks Identified By ICA

3.2.1   Fronto-Striatal-Thalamic Network.—A fronto-striatal-thalamic network (Fig. 1) included rostral, dorsal anterior, and middle cingulate cortex and supplementary motor area (SMA), bilateral anterolateral frontal cortex including predominantly the superior frontal gyrus, insula, and striatum, as well as thalamic and subthalamic areas. This network was positively engaged during SE, SS and GS trials in HC participants, and positively engaged with SE in CD participants. Moreover, SS-related engagement in CD participants was lower than those in HC participants (t_{108}=−3.47, p=0.015, FDR-corrected).

Compared to HC, CD showed prolonged SSRT, suggesting impaired response inhibition, and decreased engagement of the fronto-striatal-thalamic network. We thus examined whether the differences in behavioral performance and network engagement were related. In a two-way ANOVA of group (CD, HC) and SSRT (low, high SSRT; median split in each group), there was a difference between CD and HC ($F_{1,108}$=10.27, p=0.002), but no SSRT main or group-by-SSRT interaction effect (Table 3). Pearson linear regression showed a negative association between SS-related engagement and SSRTs in HC (r=−0.38, p=0.004) but not in CD (r=−0.08, p=0.558) participants (Fig. 3; Table 4). However, although the Kolmogorov-Smirnov test suggested that the SS beta-weights were normally distributed (p=0.148), the Iglewicz and Hoaglin's test indicated a potential outlier, under the recommended threshold of 3.5. Thus, we also employed a Spearman regression, which is robust to outliers, to examine the correlation of SS beta-weights and SSRT. SS beta-weights correlated inversely with SSRTs in HC participants at a numerically more robust value (rho=−0.22, p=0.109) than in CD participants (rho=−0.10, p=0.47), but neither correlation was significant.

3.2.2   Fronto-parietal-temporal network.—A fronto-parietal-temporal network (Fig. 2) included bilateral inferior parietal lobules, angular and supramarginal gyri, and bilateral but predominantly right middle and inferior frontal cortices, the middle and inferior temporal cortex, Parahippocampal gyrus, and cerebellum. This network was positively engaged during SS and SE trials in HC participants and negatively engaged with GS trials in CD participants. Moreover, the engagement was lower in CD than of HC participants in SS trials (t=−3.08, p=0.035, FDR-corrected). two-way group-by-SSRT ANOVA showed a group main effect ($F_{1,108}$ = 8.08, P = 0.005) but no SSRT main or interaction effect (Table 3). In

linear regressions, no beta-weights were significantly correlated with SSRTs at the corrected threshold (Table 4).

4. Discussion

Using ICA, we examined differences in functionally integrated brain activations (or networks) in association with response inhibition in CD and HC participants. Largely consistent with our hypotheses, fronto-striatal-thalamic, and fronto-parietal-temporal networks were identified and found to be less engaged during responses to SS trials in CD as compared with HC participants. In particular, a shorter SSRT indicated better inhibitory control in HC than in CD and the SS beta-weights relating to fronto-striatal-thalamic network engagement were negatively correlated with SSRTs in HC but not in CD participants, suggesting that this network may be particularly related to the capacity of response inhibition in HC individuals and not operating in such a manner in CD participants. As CD participants showed prolonged SSRTs as compared to HC participants, we tested whether the difference in fronto-striatal-thalamic network engagement between CD and HC participants simply reflected this difference in SSRTs. The results of group-by-SSRT ANOVA suggested otherwise; there was a significant group main effect but not a SSRT main effect or a group-by-SSRT interaction, suggesting that differences between CD and HC participants in fronto-striatal-thalamic network engagement may involve cognitive and affective processes other than response inhibition.

4.1 Fronto-Striatal-Thalamic Network

Fronto-striatal-thalamic regions and circuitry have been implicated in complex cognitive functions including response inhibition (Morein-Zamir and Robbins, 2015), working memory (Clemensson et al., 2017; Darki and Klingberg, 2015), and reward processing (de Leeuw et al., 2015). Dysfunction of fronto-striatal-thalamic circuits has been postulated to be relevant to drug addictions (Limbrick-Oldfield et al., 2013; Nestor et al., 2017; Worhunsky et al., 2013).

Here, engagement of a fronto-striatal-thalamic network was diminished during response inhibition in as compared to HC participants. In particular, both the striatum and subthalamic nucleus were part of a fronto-striatal-thalamic network and have been implicated in response inhibition in earlier studies (Li et al., 2008; Mirabella et al., 2013; Mirabella et al., 2012). However, it is worth noting that brain regions within fronto-striatal-thalamic circuits may show different patterns of changes during other cognitive processes. For instance, cocaine cues increased activation in CD participants in left dorsolateral and orbitofrontal cortex as well as the ventral striatum as compared with HC participants in response to appetitive vs. control cues (Wilcox et al., 2011). Thus, individual brain regions may reconfigure as distinct networks in partaking in different cognitive and affective challenges. Speculatively, this consideration may also explain a lack of significant SSRT main effect and/or group-by-SSRT interaction effect in the ANOVA. He fronto-striatal-thalamic network activities may differ between CD and HC participants in other processes that were not captured by response inhibition in the SST. Overall, the current findings

suggest the utility of ICA in providing new insights into network brain functions and dysfunctions in studies of the neural bases of neuropsychiatric conditions.

The beta-weights relating to engagement of the identified fronto-striatal-thalamic network did not differ between CD and HC participants for SE trials. SE trials are arousing (Critchley, 2002; Zhang et al., 2014; Zhang et al., 2012) and individuals who are more impulsive have demonstrated higher physiological arousal to SE trials during the SST (Zhang et al., 2015a). Along with the earlier discussion that the fronto-striatal-thalamic network may respond to drug cues, it is possible that CD demonstrated higher saliency response to SE than HC, potentially masking group differences (Castelluccio et al., 2014; Connolly et al., 2012; Rose et al., 2014). On the other hand, studies have reported diminished response to prediction errors, which are also salient, in CD as compared to HC (Parvaz et al., 2015), and evidence is mixed in relation to how error-related responses may predict relapse (Luo et al., 2013; Marhe et al., 2013). Examining the engagement of fronto-striatal-thalamic functional networks across multiple behavioral tasks, including those involving response inhibition and cue-elicited craving, should help clarify such considerations.

4.2 Fronto-parietal-temporal network

Previous studies have shown fronto-parietal-temporal regions and circuitry broadly involved in cognitive control across behavioral tasks and participant pools (Barros-Loscertales et al., 2011; Hester et al., 2007; Ide et al., 2016; Wang et al., 2017; Worhunsky et al., 2013; Zhang and Li, 2012). The current results showed significantly weaker engagement during SS trials of the identified fronto-parietal-temporal network in CD as compared with HC participants. On the other hand, fronto-parietal-temporal component engagement did not correlate with SSRTs either in HC or CD participants, suggesting that this network may not be as directly involved in response inhibition in the SST as is the identified fronto-striatal-thalamic network. Previous studies have shown that broader dysfunction of a fronto-parietal circuit in CD may contribute to disrupted connectivity dynamics in association with post-signal behavioral adjustment (Hester et al., 2007; Ide et al., 2016). More recently, we found that dynamic functional connectivity of a fronto-parietal control network was also compromised in CD participants (Zhang et al., 2018). Further studies are needed to understand whether the fronto -parietal-temporal network would be engaged specifically in response to post-signal slowing trials. This would require a larger data set from individual subjects, as the trial numbers tend to be much smaller when post-signal trials are distinguished in terms of their reaction times.

Engagement of the identified fronto-parietal-temporal network was diminished in CD participants for both SS and SE trials, as compared with HC participants. In contrast to the go trials, both SS and SE trials involved the stop signal, which is highly salient. Thus, the finding may suggest a broader attentional dysfunction in CD individuals. The identified fronto-parietal-temporal network includes regions of the attention network, which responds to goal-directed movements to attended stimuli (Kim et al., 2014). The stop signal appeared in only approximately one out of four trials and was highly significant, as it instructed a change in the action plan. Thus, diminished fronto-parietal-temporal network engagement

may reflect dysfunction of attentional circuitry in response to the stop signal in CD individuals. The fronto-parietal-temporal network also involved the temporal and occipital cortices and hippocampal regions, which is critical to memory and sensory encoding and retrieval, although data have also suggested a role of higher order occipital cortical neurons in goal selection (Mirabella et al., 2007). Greater engagement of a spatially similar network has been identified during successful response inhibition using a Go/NoGo task. In young adult drinkers, the greater inhibition-related engagement was associated with slower overall reaction times and reduced commission errors (Worhunsky et al., 2016). A similar fronto-parietal-temporal inhibition-related network was also identified across healthy adults and adolescents (Steven et al., 2007). The authors noted differences in this network in effective connectivity influences to and from traditional fronto-parietal and fronto-striatal-thalamic networks associated with age, reaction time, and hit rates. In the current study, the fronto-parietal-temporal network was not associated with SS, suggesting CD may enlist alternative cognitive or neural mechanisms during the performance of the SST. These relationships should be investigated in future work.

4.3 Limitations

Multiple study limitations should be noted. First, a single behavioral task was employed in the current study. Imaging data collected across multiple behavioral tasks may help identify network activities that participate in psychological constructs of inter-related importance to cocaine addiction. Studies are also needed to understand whether the identified fronto-parietal-temporal network may be engaged specifically in response to post-signal slowing trials or relate to other cognitive strategies in SST performance. Second, data from CD and HC participants were included in a single ICA to identify networks related to inhibitory control. This approach may limit the ability to fully characterize all component networks that may contribute to inhibition in individuals with CD; however, this approach allows direct comparison with HC of engagement patterns across shared functional networks. Third, the data were collected from several different studies. Although the imaging parameters were identical, we did not have the same clinical measures for all participants. Thus, clinically relevant measures (for example, of impulsivity, anxiety, and depression) that may influence findings but were not accounted for should be examined in future studies. Fourth, the SSRT reflects the capacity of reactive control, and more studies are needed to examine how proactive control may be compromised in cocaine addiction (Hu et al., 2015a; Wang et al., 2018). Finally, inhibitory control represents one dimension of possible etiological processes relating to drug addiction. The incentive salience hypothesis (Berridge and Robinson, 2016) characterizes robust and mostly unconscious motivations driven by environmental cues as a critical process of habitual drug use. Studies of tasks to address the interaction of inhibitory control and incentive salience may help uncover other neural pathways relevant to cocaine addiction (Hickey and Peelen, 2015; Mirabella et al., 2007).

5. Conclusions

By applying ICA to SST fMRI data, we identified fronto-striatal-thalamic and fronto-parietal-temporal networks showing differences in relation to SS trials between CD and HC participants. The engagement of the fronto-striatal-thalamic network was negatively

correlated with SSRTs in HC but not in CD participants, suggesting a direct role of this independent component in mediating deficits of response inhibition in CD individuals. In contrast, engagement of the fronto-parietal-temporal network did not relate to SSRTs and was similarly diminished for both SS and SE trials. Diminished fronto-parietal-temporal network engagement may reflect attentional dysfunction in the CD. This study adds to the literature by characterizing cortico-subcortical network dysfunction in CD and highlights the utility of ICA in distinguishing neural circuit activities in response to complex cognitive processes. More work is needed to examine how deficits in behavioral control may interact with drug cues and other factors in processes underlying cocaine addiction.

Acknowledgments

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Highlights

- Response inhibition is compromised in cocaine dependent people (CD).

- CD showed prolonged stop signal reaction time (SSRT), compared to controls (HC).

- ICA showed diminished engagement of the fronto-striatal-thalamic network in CD.

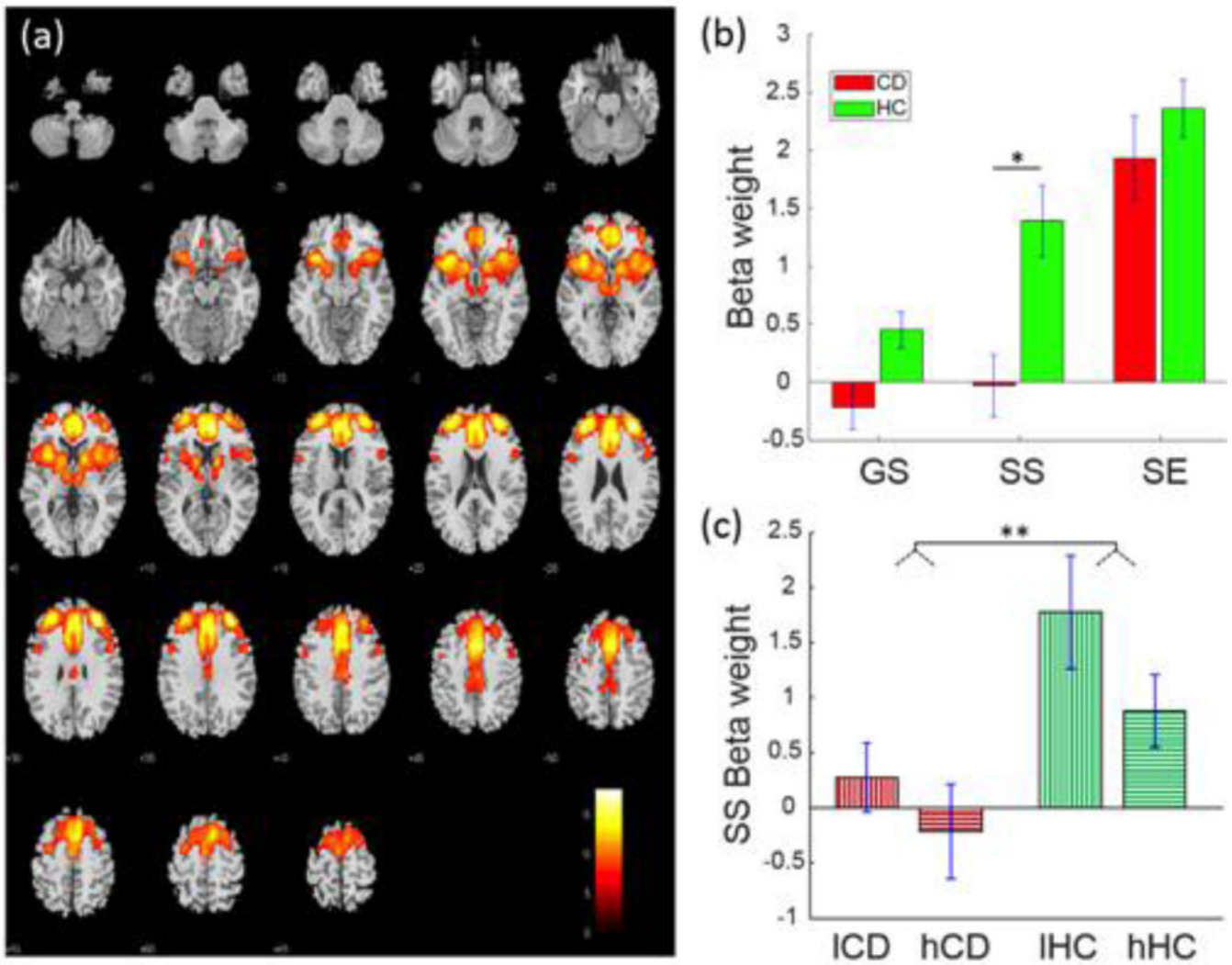- The network engagement is associated with response inhibition in HC but not CD.

Fig. 1.
Fronto-striatal-thalamic network displaying a group difference in SS-related engagement (a)
Spatial map of the brain regions positively integrated into the functional network displayed
at P < 0.000001 (n = 110). (b) Beta-weights of GS, SS and SE trials each in CD and HC
participants for the identified fronto-striatal-thalamic network. (c) Beta-weights relating to
low and high SSRT subgroups each within the CD and HC groups. *p<0.05, **p<0.01, two-
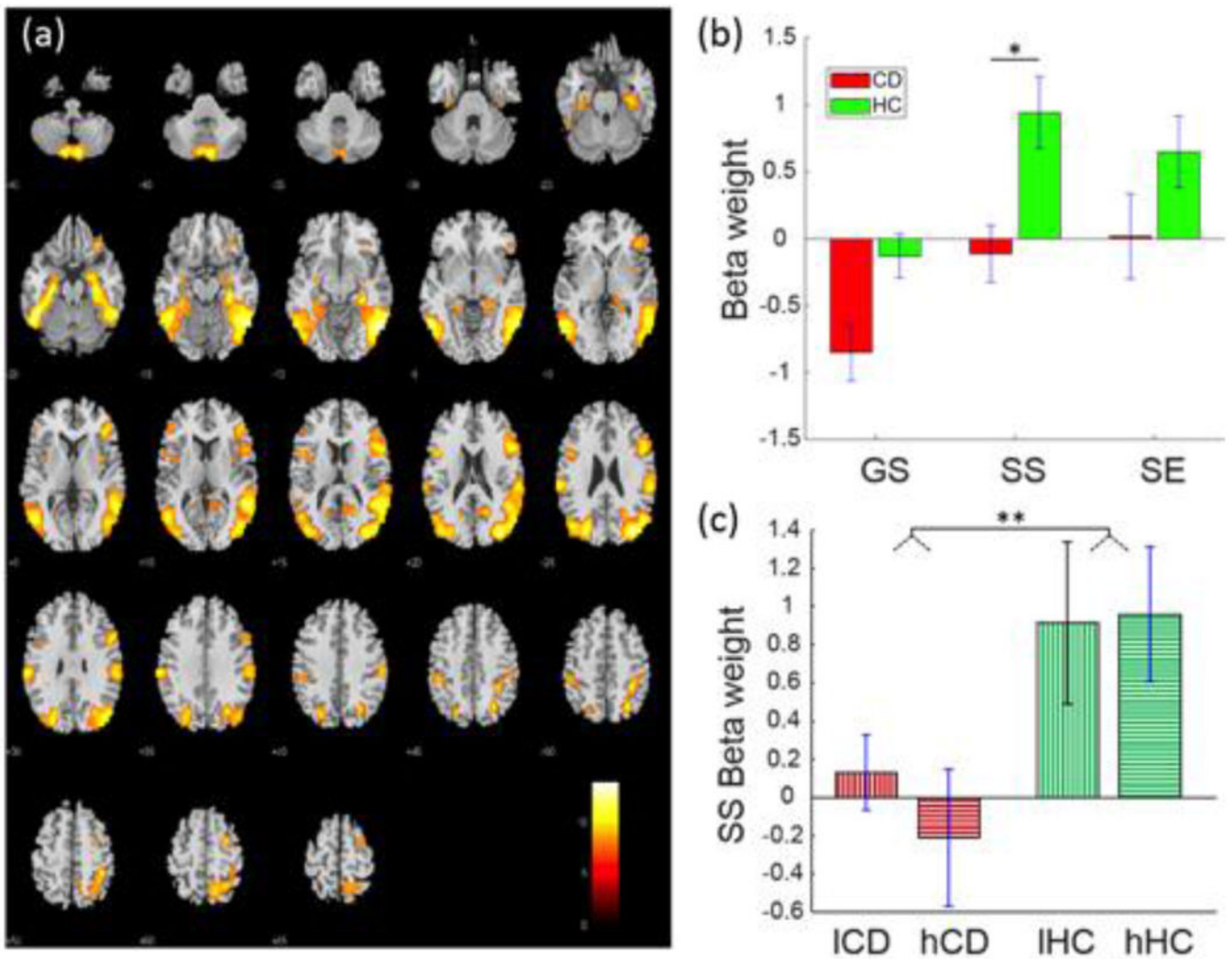sample t test.

Fig. 2.
Fronto-parietal-temporal network displaying a group difference in SS-related engagement.
(a) Spatial map of the brain regions positively integrated into the functional network
displayed at p<0.000001 (n=110). (b) Beta-weights of GS, SS and SE trials each in CD and
HC participants for the identified fronto-parietal-temporal network. (c) Beta-weights in low
and high SSRT subgroups each in the CD and HC groups. *p<0.05, **p<0.01, two-sample t
test. GS = Go Success, SS = Stop Success, SE = Stop Error, lCD = CD participants with low
SSRTs, hCD = CD participants with high SSRTs, lHC = HC participants with low SSRTs,
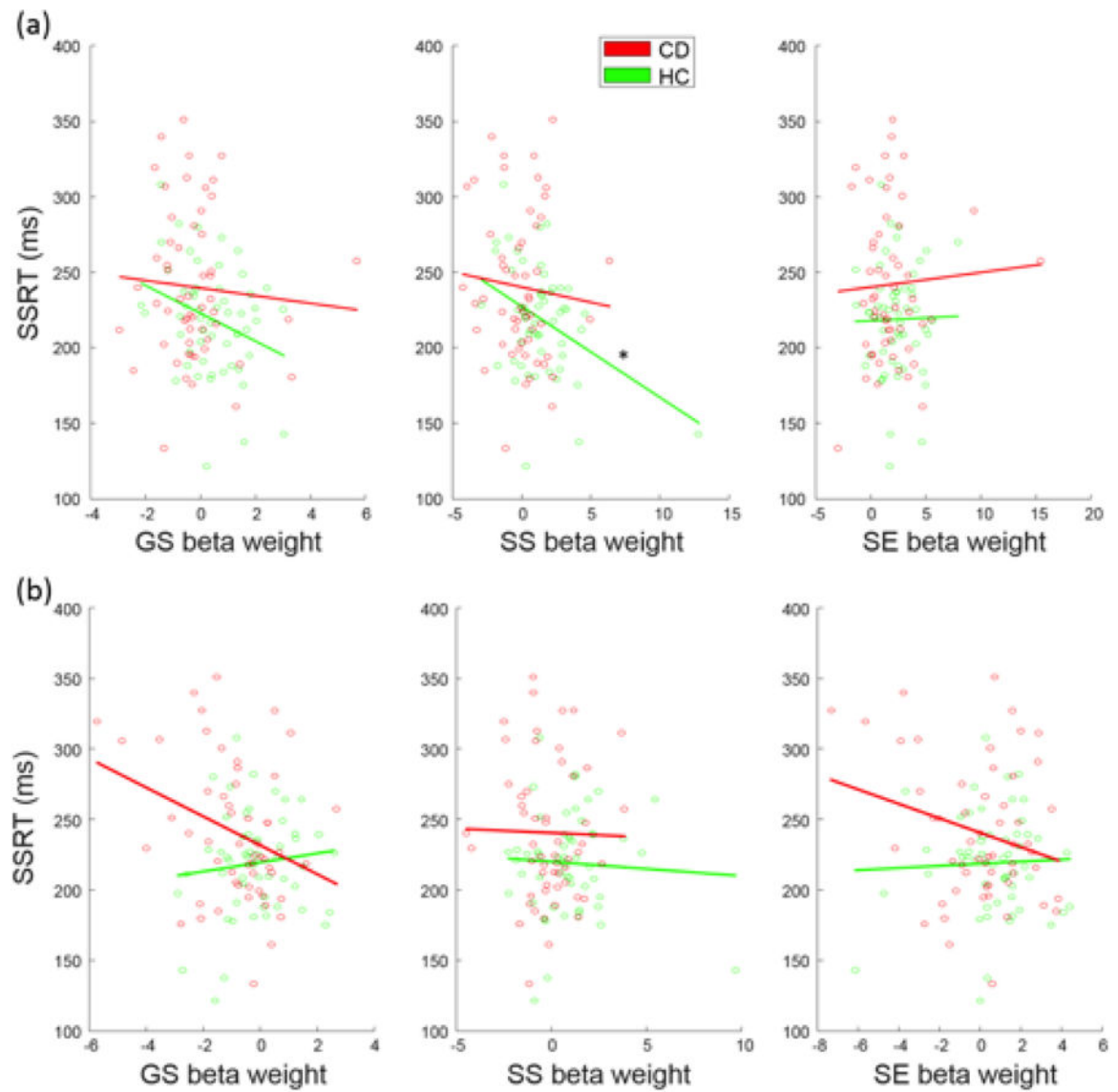hHC = HC participants with high SSRTs.

Fig. 3.
Correlation between SSRT and beta-weights relating to (a) fronto-striatal-thalamic network engagement in CD and HC participants across three task events and (b) fronto- parietal-temporal network engagement in CD and HC participants across three task events. The line indicates the fit according to Pearson regression. *p<0.0083.

Table 1.

Demographics of participants

	CD (n=55)	HC (n=55)	P Value
Age (years)	40.3± 7.3	39.1 ± 10.4	0.460[a]
Gender (M/F)	42/13	35/20	0.145[b]
Amount of average monthly cocaine use (Dambacher et al.) in the prior year	17.7± 29.3	N/A	N/A
Amount per use in grams	1.0 ± 1.2	N/A	N/A
Days of cocaine use in the prior month	13.8± 8.5	N/A	N/A
Years of cocaine use	17.3± 8.4	N/A	N/A

Note: values are mean ± S.D.

[a] two-sample t test.

[b] x^2 test

Table 2.

Stop Signal Task performance.

	CD (n=55)	HC (n=55)	T Value	P Value	Cohen's *d*
GR (%)	95.0 ± 7.3	98.3 ± 2.0	t108 = −3.24	0.002 [*]	0.617
SS (%)	52.0 ± 3.1	51.8 ± 3.3	t108 = 0.27	0.789	0.062
goRT (ms)	643± 125	642± 126	t108 = 0.07	0.942	0.008
SSRT (ms)	240± 49	219± 36	t108 = 2.6	0.011 [*]	0.488
SERT (ms)	534± 100	559±115	t108 = −1.23	0.222	0.232

Note: GR: go response; SS: stop success; goRT: go trial reaction time; SSRT: stop-signal reaction time; SERT: stop-error reaction time; values are mean ± S.D.

[*] p<0.05, two-sample t test. GR instead of GS rate was presented here, as all go trials with a RT were included in the computation of SSRT.

Table 3.

Two-way ANOVA for interaction of SSRT (low, high) by group (CD, HC)

	SSRT			Group			Interaction		
Functional network	F1,108	p	η^2	F1,108	p	η^2	F1,108	p	η^2
Fronto-striatal-thalamic	2.92	0.090	0.052	10.27	0.002[**]	0.168	0.25	0.619	0.005
Fronto-parietal-temporal	0.19	0.667	0.004	8.08	0.005[**]	0.130	0.32	0.575	0.130

Note:

[*]
p<0.05

[**]
p<0.01. η^2: eta squared

Table 4.

Linear regression of beta-weights relating to SSRTs in CD and HC participants

Functional network	Group	GS		SS		SE	
		r	p	r	p	r	p
Fronto-striatal-thalamic	CD	−0.07	0.611	−0.08	0.558	0.05	0.703
	HC	−0.30	0.026	−0.38	0.004 [*]	0.02	0.879
Fronto-parietal-temporal	CD	−0.32	0.018	−0.02	0.887	-0.24	0.073
	HC	0.11	0.416	−0.06	0.690	0.04	0.777

Note:

[*] $p<0.05/(2\times3)=0.0083$, corrected for multiple comparisons. GS = Go Success, SS = Stop Success, SE = Stop Error.