Review

Resting state functional connectivity in addiction: Lessons learned and a road ahead

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ABSTRACT

Despite intensive scientific investigation and public health imperatives, drug addiction treatment outcomes have not significantly improved in more than 50 years. Non-invasive brain imaging has, over the past several decades, contributed important new insights into the neuroplastic adaptations that result from chronic drug intake, but additional experimental approaches and neurobiological hypotheses are needed to better capture the totality of the motivational, affective, cognitive, genetic and pharmacological complexities of the disease. Recent advances in assessing network dynamics through resting-state functional connectivity (rsFC) may allow for such systems-level assessments. In this review, we first summarize the nascent addiction-related rsFC literature and suggest that in using this tool, circuit connectivity may inform specific neurobiological substrates underlying psychological dysfunctions associated with reward, affective and cognitive processing often observed in drug addicts. Using nicotine addiction as an exemplar, we subsequently provide a heuristic framework to guide future research by linking recent findings from intrinsic network connectivity studies with those interrogating nicotine’s neuropharmacological actions. Emerging evidence supports a critical role for the insula in nicotine addiction. Likewise, the anterior insula, potentially together with the anterior cingulate cortex, appears to pivotally influence the dynamics between large-scale brain networks subserving internal (default-mode network) and external (executive control network) information processing. We suggest that a better understanding of how the insula modulates the interaction between these networks is critical for elucidating both the cognitive impairments often associated with withdrawal and the performance-enhancing effects of nicotine administration. Such an understanding may be usefully applied in the design and development of novel smoking cessation treatments.

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Introduction

Drug addiction is a multifaceted neuropsychiatric disorder characterized by the compulsive seeking and taking of a drug, despite the high likelihood of negative consequences. Addiction is notable for the complex, and still only partially understood, interactions between neurobiological, environmental, pharmacological, and genetic...
components. Multiple theories regarding the underlying mechanisms of addiction have been proposed (e.g., Everitt and Robbins, 2005; Goldstein and Volkow, 2002; Koob and Le Moal, 2008; Koob and Volkow, 2010; Redish, 2004; Wise, 2008), and although originally generated mostly from rodent studies, many, but not all, of these neurobiological mechanisms appear well conserved in non-human primates and, where studied, in humans. However, despite tremendous advances over the past several decades, translating preclinical findings of the molecular and cellular neuroadaptations following chronic drug intake has not as yet significantly improved clinical outcomes. As drug abuse is a uniquely human disease, it would seem that a better understanding of the profound disruption of motivational, affective and cognitive processes following, and/or predisposing individuals to drug use is critical to expedite treatment development.

While neuroimaging cognitive-subtraction task paradigms have been essential for delineating the acute effects of addictive drugs and the long-term consequences of use within circumscribed brain areas (e.g., Bickel et al., 2007; Breiter et al., 1997; Diekhof et al., 2008; Kumari et al., 2003; Stein et al., 1998), additional, complementary insight will most likely be obtained by considering alterations in circuit-level interactions between brain regions (Koob and Volkow, 2010). The last decade has witnessed an explosion in the study of functional connectivity using fMRI, largely because it allows for the exploration of large-scale networks and their interactions, thus moving towards a systems-level understanding of brain functioning (Bressler and Menon, 2010; van den Heuvel and Hulshoff Pol, 2010). By extension, resting-state functional connectivity (rsFC) may allow for the identification of neural circuitry dysfunction underlying various neuropsychiatric disorders (Fox and Greicius, 2010). Among its advantages as a potential characterization and diagnostic tool are that: 1) identified rsFC circuit-alterations are less likely to be confounded by subtle differences in specific task-based experimental paradigms; 2) networks so identified appear to be consistent across time within and between individuals (Chen et al., 2008); 3) such networks appear to reflect the entirety of the cognitive elements necessary for task processing (Smith et al., 2009); and 4) relative to task-based fMRI methods, data collection is relatively quick and straight-forward — a useful quality when assessing patient populations with variable constraints on attentional, executive, and motor control. There are, however, certain methodological issues associated with rsFC-based techniques, a few of which will be briefly discussed at points throughout the review. Nonetheless, this emerging neuroimaging tool has provided researchers with additional insights and spurred novel theories about the underlying neural substrates of various neuropsychiatric disorders (e.g., Menon, 2011).

Circuits synchronized “at rest” are constrained to known, direct or polysynaptic anatomically interconnected regions (Damoiseaux and Greicius, 2009; Greicius et al., 2009; Honey et al., 2009), thus constituting plausible functional networks. Critically, the strength of these networks “at rest” predicts both behavioral performance and subsequent activation of the same brain areas during task performance (e.g., Hampson et al., 2006; Kelly et al., 2008; Kim et al., 2009; Seeley et al., 2007; Tambini et al., 2010). Further, there is growing evidence that alterations in rsFC strength can potentially be used to assess various neuropsychiatric disease trajectories, and where available treatment outcomes, including: Alzheimer’s disease (Greicius et al., 2004; Lustig et al., 2003; Rombouts et al., 2005; Wang et al., 2006), autism (Kennedy et al., 2006), depression (Anand et al., 2005), multiple sclerosis (Low et al., 2002), and attention deficit/hyperactive disorder (ADHD; Tian et al., 2006). Emerging evidence further suggests a genetic linkage between rsFC networks and various behavioral phenotypes (Glahn et al., 2010; Meyer-Lindenberg, 2009), raising promise that functional connectivity may serve as a systems-level biomarker to identify individual differences in and provide differential disease diagnoses for various neuropsychiatric disorders. Despite such promise, it is only in the last few years that rsFC has begun to be considered as a characterization and potentially diagnostic tool.

To date, rsFC has been applied in only a handful of drug addiction-related studies and the current review begins with an overview of those findings. As expected in an emerging field, many of these studies have been somewhat exploratory in nature, leading to conflicting findings. Applications of this tool in addiction research may therefore benefit from experimental approaches grounded by stronger a priori theoretical models. To this end, throughout the review we relate extant addiction-related rsFC findings to a larger corpus of neuroimaging research from healthy controls and other neuropsychiatric conditions. In the latter half of the review we continue this theme and in greater detail link recent findings from network connectivity and nicotine-related neuroimaging studies to develop a heuristic framework yielding empirically testable hypotheses regarding the effects of both nicotine abstinence and drug administration on brain and behavior.

Addiction-related rsFC studies

The earliest addiction-related rsFC study reported marked reductions in connectivity within the primary visual and motor cortices after cocaine administration to addicted individuals, presumably reflecting changes in coherent neuronal firing patterns (Li et al., 2000). Subsequently, using a functional connectivity analysis on [15O] PET data, Daglish et al. (2003) identified two networks during opiate craving, one including anterior cingulate cortex (ACC) and temporal cortex and a second involving orbitofrontal cortex (OFC), parietal cortex, and insula, suggesting engagement of motivational and attentional circuits. These networks are similar to those seen following cocaine cue provocation (Caravan et al., 2000), again suggesting that circuits identified at rest reflect those engaged during active task performance. More recent rsFC endeavors in drug addiction have interrogated altered connectivity between specific regions of interest (i.e., “seed” regions) and their interconnected brain regions. As a broad organization principle, we have grouped findings from these initial studies according to general psychological constructs often associated with impairment in drug addiction: 1) reward dysregulation, 2) emotional dysregulation, and 3) cognitive dysregulation.

Reward dysregulation

Large and rapid dopamine increases in the mesocorticolimbic (MCL) system are thought to underlie the initial reinforcing effects of abused drugs (Nestler, 2005). As such, preclinical and clinical studies have generally focused on neuroadaptations in midbrain dopaminergic areas (e.g., ventral tegmental area, substantia nigra pars compacta) and the structures to which they project (e.g., the nucleus accumbens [NAc] of the ventral striatum), following an extended history of drug administration (Everitt and Robbins, 2005; Koob and Volkow, 2010). While understanding of the molecular and cellular drug-induced changes within constituent components of the MCL system has advanced (Morón and Green, 2010), much less is known about the circuit-level manifestations of such regional alterations when considering interactions among and between MCL regions and other subcortical and cortical structures. Insofar as drug addiction has historically been viewed as a dopaminergic dysregulation disorder (Di Chiara et al., 2004; Wise, 2008), rsFC investigations have begun to interrogate the MCL system in the service of elucidating circuit-level alterations associated with reward deficits in the human addict.

Alterations in rsFC strength between ventral striatum and various subcortical and cortical regions have been observed when comparing cocaine (Gu et al., 2010; Tomasi et al., 2010; Wilcox et al., 2011), prescription opioid (Upadhyay et al., 2010), and heroin dependent individuals (Ma et al., 2010) with matched, non-drug...
using controls. Although altered MCL circuitry has been consistently observed in drug addicts, synthesis of a cogent narrative surrounding the precise circuits and direction of change is difficult from these initial studies. While, on the one hand, some studies have reported increased rsFC between MCL regions and subcortical and cortical areas (Ma et al., 2010; Wilcox et al., 2011), others have reported decreased connectivity (Gu et al., 2010; Tomasi et al., 2010; Upadhyay et al., 2010; Wang et al., 2010). For example, testing the hypothesis that MCL circuits are altered in heroin addicts, Ma et al. (2010) noted stronger rsFC between NAc and the ventral aspects of medial prefrontal cortex (including rostral ACC and medial OFC). Although using a small (n = 14) and a heterogeneous subject group (i.e., both methadone maintained and abstinent users), these results suggest enhanced connectivity within reward and motivation circuits that may be interpreted in the perspective of altered incentive salience for drugs and drug-associated stimuli (Berridge and Robinson, 1998). Similarly, Wilcox et al. (2011) observed increased rsFC between ventral striatum and ventromedial PFC (vmPFC) regions in abstinent cocaine-users.

In apparent contrast to the above findings suggesting increased striatal-PFC rsFC strength, a widespread reduction in connectivity between NAc and various subcortical (hippocampus and amygdala) and cortical (parietal, cingulate, prefrontal) regions in prescription opioid addicts (n = 10) has been described (Upadhyay et al., 2010). Individuals in that study were current users, thus results may in part reflect effects of recent opiate use. Nonetheless, a similar pattern of MCL circuit reductions was reported by Gu et al. (2010) who conducted rsFC assessments in a relatively large population (n = 39) of active cocaine-users and a matched, non-using control group. They observed a general decrease in rsFC between most regions within the MCL reward pathway and interconnected brain areas (with the notable exception of the NAc, whose connectivity remained unchanged between groups) (Fig. 1A). Such widespread reductions in the connectivity of multiple MCL system components may reflect putative difficulty in appropriately engaging reward, motivational, and emotional circuitry, which is consistent with perspectives suggesting that the transition from drug-use to addiction is driven by reduced functioning of reward systems, with concurrently increased activation of ‘anti-reward’ systems (Koob and Le Moal, 1997, 2005).

Tomasi et al. (2010) arrived at similar conclusions when observing lower connectivity between midbrain dopaminergic regions and medial PFC regions in cocaine abusers (n = 20) relative to healthy controls performing a sustained attention task.

While clearly more work is needed to untangle the nature of rsFC changes in reward-related circuitry, a general pattern of perturbed connectivity across heterogeneous drug-using cohorts is consistent with a reward dysregulation hypothesis of drug addiction. That said, any effort to draw conclusions at this early stage must be tempered by consideration of the various methodological issues inherent to this literature. For example, relatively small samples sizes (Ma et al., 2010; Upadhyay et al., 2010; Wilcox et al., 2011) necessitate caution when interpreting findings. Additionally, the duration since last drug use and collection of imaging data has often not been adequately considered. Factors such as acute withdrawal (Gu et al., 2010; Ma et al., 2010; Tomasi et al., 2010; Wilcox et al., 2011) or acute drug effects (Ma et al., 2010; Upadhyay et al., 2010) likely contribute significantly to variance both within and between rsFC studies, confounding interpretation of results. Finally, generalizing across different abused

Fig. 1. (A) Summary of regions showing reduced rsFC strength with MCL seed regions in cocaine-users relative to matched non-using controls. (B) Difference map illustrating reduced rsFC between an amygdala seed and medial PFC/rostral ACC regions in cocaine-users relative to matched non-using controls. (C) Top displays a difference map showing stronger interhemispheric connectivity between lateral PFC regions among non-using controls relative to cocaine-users. Bottom shows self-reported cognitive failures as a function of reduced lateral PFC interhemispheric connectivity.
Panel A is reproduced from Gu et al. (2010). Panel B is reproduced from Gu et al. (2010). Panel C is reproduced from Kelly et al. (2011).
drugs is complicated by the potential for drug-specific effects on underlying neural circuitry. In sum, careful consideration of the above methodological factors will be necessary for future work to elucidate the precise nature of rsfC alterations in the reward-related neurocircuitry of drug addiction.

**Emotional dysregulation**

Accompanying alterations in reward-related neurocircuitry, drug-induced changes in amygdala-centered ‘anti-reward’ circuits have been associated with increased anxiety, irritability or aversive stress-like states that may mediate negative reinforcement mechanisms perpetuating drug use (Koob and Le Moal, 2005). Amygdala’s interactions with medial prefrontal, cingulate, hippocampal, and insula regions are further implicated in processing emotional stimuli, generating affective states, and/or regulating emotion (Pezawas et al., 2005; Phillips et al., 2003; Stein et al., 2007). Working under the hypothesis that amygdala and its interconnected circuitry are critical neural substrates mediating continued drug use, preliminary rsfC studies suggest that altered functional and structural amygdala-PFC connectivity may underlie aspects of emotional dysregulation often noted in addicted individuals.

Altered amygdala-centered connectivity has been noted in individuals addicted to multiple pharmacological classes of drugs (Gu et al., 2010; Liu et al., 2009; Upadhyay et al., 2010; Wang et al., 2010; Xie et al., 2011). More specifically, Gu et al. (2010) reported decreased rsfC strength between amygdala and a region of medial PFC (encompassing aspects of vmPFC and rostral ACC) in cocaine addicts (Fig. 1B). Similar decreases in amygdala-vmPFC rsfC strength have also been observed in a sample (n = 15) of active heroin abusers (Wang et al., 2010). Widespread reductions in amygdala’s connectivity with multiple regions, including medial, ventrolateral, and dorsolateral PFC regions, have also been documented in prescription-opioid addicts (Upadhyay et al., 2010). Moreover, amygdala-vmPFC (i.e., subgenual ACC) connectivity was inversely related to duration of opioid dependence, such that longer periods of use were associated with greater rsfC reductions (Upadhyay et al., 2010). Additionally, using diffusion tensor imaging, these authors also showed that opioid use was associated with reduced structural integrity of the uncinate fasciculus, the primary white matter tract connecting amygdala and medial PFC. Thus, while the number of studies is still limited, initial observations in drug addicted samples appear to be converging on functional and structural connectivity abnormalities in an amygdala-medial PFC circuit.

Addiction-related alterations between amygdala and medial PFC are particularly intriguing when considered in light of a larger corpus of research relating such circuit-level interactions to emotional regulation, subjective anxiety, and other neuropsychiatric disorders (Foland-Ross et al., 2010; Hahn et al., 2011; Hariri et al., 2003; Kim et al., 2011a, 2011b; Motzkin et al., 2011; Pezawas et al., 2005). The vmPFC has been posited to actively suppress amygdala functioning (Poland-Ross et al., 2010; Hariri et al., 2003; Kim et al., 2011b), which in turn, is thought to alleviate emotional distress (Berkman and Leiberman, 2009; Ochsner et al., 2004). Such a regulation-circuit perspective is bolstered by rsfC studies demonstrating that amygdala-vmPFC rsfC strength is inversely related to self-reported anxiety levels in non-clinical samples, where increased anxiety is associated with reduced connectivity (Kim et al., 2011a; Pezawas et al., 2005). Taken further, reduced amygdala-vmPFC rsfC strength, as well as compromised uncinate fasciculus structural integrity, has been observed in neuropsychiatric conditions characterized by pathological levels of anxiety (Hahn et al., 2011; Phan et al., 2009). Diminished amygdala-vmPFC functional and structural connectivity has similarly been noted in a sample of psychopathic versus non-psychopathic criminals (Motzkin et al., 2011), which may offer a neurobiological account of the aberrant emotional and social behaviors associated with psychopathy (Blair, 2008). Kim et al. (2011a, 2011b) have reviewed extensive evidence regarding this circuitry and tentatively concluded that more efficient amygdala-vmPFC neurobiological coupling likely yields beneficial behavioral outcomes in terms of elevated emotional regulation and reduced anxiety. Initial addiction-related rsfC studies, combined with evidence from healthy samples and other neuropsychiatric disorders, suggest the intriguing possibility that abnormalities in functional and structural connectivity between amygdala and medial PFC may, at least partly, mediate aspects of emotional dysregulation often observed in drug dependent individuals.

**Cognitive dysregulation**

Drug-addicted individuals are known to exhibit deficits in neural systems associated with cognitive control (Goldstein et al., 2004; Hester and Garavan, 2004; Hester et al., 2009). Neurobiological models of cognitive control emphasize a network of regions centered on the ACC, lateral PFC and parietal areas. Substantial evidence and recent theories suggest that ACC subserves a monitoring role for the detection of salient events, particularly erroneous or error-prone actions (Carter and van Veen, 2007; Riddervik et al., 2004). Upon detection of such salient/erroneous events, the ACC is thought to signal the need for the top-down reorientation of attention, implemented by lateral PFC and parietal regions (Kerns et al., 2004; King et al., 2010; Miller and Cohen, 2001). The top-down influence of lateral PFC appears to bias information processing in lower-level sensorimotor cortices towards relevant input (Enger and Hirsch, 2005; King et al., 2010) for the optimization of goal-directed behavior (Frank et al., 2005; Hester et al., 2008; Magno et al., 2006). Performance decrements on measures of cognitive control in drug addicted individuals (Franken et al., 2010; Hester and Garavan, 2004; Hester et al., 2007, 2009) are associated with reduced functional engagement (Hester and Garavan, 2004; Hester et al., 2009; Li and Sinha, 2008) and structural integrity across these regions (Barrós-Loscertales et al., 2011; Nakama et al., 2011; Yuan et al., 2009, 2010).

Recent rsfC studies have also suggested patterns of abnormal connectivity between these primary nodes of a “cognitive control network” in both heroin (Ma et al., 2010; Yuan et al., 2010) and cocaine addicted samples (Kelly et al., 2011). For example, reduced rsfC strength between the ACC and dlPFC has been noted in heroin addicts (Ma et al., 2010). Additionally, in a sample of chronic cocaine-using individuals (n = 25), Kelly et al. (2011) observed significant reductions in rsfC within and between lateral PFC and parietal areas, where reduced interhemispheric connectivity between lateral PFC regions predicted a higher incidence of self-reported cognitive failures (Fig. 1C). Yuan et al. (2010) observed a similar pattern in abstinent heroin users such that reduced rsfC between lateral PFC and parietal regions was accompanied by reductions in gray matter density in those same regions, with years of use predicting greater reductions across both measures. Reduced rsfC between nodes within this putative cognitive control network is consistent with the behavioral and task-based imaging findings referenced above as well as self-reported cognitive deficits in drug-addicted populations (Ersche et al., 2006; Gruber et al., 2007; Hester and Garavan, 2004; Kelly et al., 2011).

Camchong et al. (2011) recently observed increased positive connectivity between the ACC and dlPFC in a sample of active cocaine users (n = 27). While the direction of this connectivity change initially seems counter-intuitive and contradictory to those results discussed above, greater rsfC in this ACC-dlPFC circuit was in fact associated with poorer task performance during reversal learning. Of note, the ACC seed chosen was located rostral to the dorsal ACC region typically associated with situations necessitating elevated cognitive control (Carter and van Veen, 2007; Riddervik et al., 2004). Rostral ACC and adjacent vmPFC regions are considered part of a “task-negative” or default-mode network (DMN) that typically deactivates during task performance (Buckner et al., 2008; Gusnard and
Raichle, 2001) and shows negative connectivity with cognitive control regions during tasks and “at rest” (Fox et al., 2005; Kelly et al., 2008; Prado and Weissman, 2011). Moreover, altered connectivity between default-mode and cognitive control regions has been reported in smokers following nicotine abstinence and linked with withdrawal-related cognitive deficits (Cole et al., 2010). Importantly, Camchong et al. (2011) examined rsFC in current cocaine users, individuals likely to be experiencing at least some degree of acute withdrawal, and the enhanced positive connectivity they observed between default-mode (rostral ACC) and cognitive control (dIPFC) regions may reflect state changes associated with withdrawal. In the latter sections of this review, we describe in greater detail how maladaptive interactions within and between these two large-scale networks following acute abstinence may provide a neurobiologically plausible account of the cognitive deficits often observed in addicted individuals.

Disease severity

While the preceding sections have highlighted the use of functional connectivity assessments as a tool for the characterization of addiction-related circuit alterations, other rsFC studies have just begun to consider the possibility that this approach could be used as a diagnostic tool to assess individual differences in addiction severity and, by extension, provide a biomarker for treatment efficacy. To this end, Hong et al. (2009) sought to identify neural circuits in cigarette smokers that were modulated as a function of: 1) acute nicotine administration, and 2) severity of nicotine addiction. Based on the hypothesis that the cingulate is an integral component of many addiction-related deficits, seven bilateral cingulate sub-regions were defined and used as seeds in separate rsFC analyses. Two distinct groups of networks were identified. The first consisted of seven cingulate-neocortical pathways that demonstrated enhanced connectivity strength in the presence (versus absence) of an acute nicotine patch (Fig. 2A), including ACC, parietal and medial superior frontal regions. These and other identified circuits are consistent with those implicated in nicotine’s performance-enhancing properties (Heishman et al., 2010). However, in a double dissociation fashion, two bilateral dorsal ACC to ventral striatal circuits were identified whose connectivity strengths were inversely proportional to an individual’s level of nicotine addiction as measured by Fagerström scores, but were unaltered following nicotine patch administration (Fig. 2B).

![Figure 2](image_url)
suggesting specific circuits related to addiction severity and which, the authors speculate, may serve as a biomarker for studies of treatment outcome.

Subsequently, Hong et al. (2010) went on to demonstrate that a gene variant of the α5 subunit of nicotinic acetylcholine receptors is associated with a very similar “addiction related circuit”. Specifically, this α5 gene variant, the most replicated genetic marker of smoking (Bierut et al., 2008), now identified a dorsal ACC-ventral striatum/extended amygdala circuit, such that the risk allele was associated with decreased rsFC between these structures. This circuit, representing a “trait-like” biomarker, was impaired in smokers, not altered by acute nicotine administration, and was anatomically consistent with (although not identical to) that previously shown to predict addiction severity using the phenotypic Fagerström index (Hong et al., 2009).

Another independent smoking-related variant in the same gene cluster (α3) (Bierut et al., 2008) was associated with a separate circuit between dorsal ACC and anterior thalamus that was related to recency of smoking but not addiction severity, resembling a “state-like” marker for smoking, perhaps related to craving or withdrawal in these mildly deprived smokers. The results of these initial studies suggest the intriguing possibility that alterations in specific neural circuits may provide systems-level biomarkers of addiction severity that could be leveraged to track cessation treatment trajectories.

In sum, rsFC studies are beginning to shed light on circuit-level alterations associated with drug addiction. While initial findings are limited and have not been totally consistent, potentially due to between-study methodological and participant-characteristic issues, supplementing traditional task-based neuroimaging data with rsFC analyses may provide a deeper level of understanding regarding psychological deficits associated with reward, emotional and cognitive processing often related to an extended drug use history. By relating extant addiction-related rsFC findings with a larger body of literature related to emotional regulation and cognitive control, we have attempted to provide a heuristic framework allowing for a transition from these early exploratory studies to more model-driven hypothesis testing. The section below extends this theme and provides in greater detail an exemplar model-based framework derived from existing connectivity and task-based activation studies, relating system-level neural circuit interactions with the cognitive deficits often observed during smoking abstinence and the performance-enhancing effects of nicotine administration.

Nicotine and large-scale networks

Nicotine’s performance-enhancing properties manifest in multiple cognitive domains, particularly when considering abstinent smokers (Heishman et al., 1994, 2010; Newhouse et al., 2004). Previous neuroimaging studies exploring such nicotinic or cholinergic effects have often done so in the context of cognitive task paradigms, providing information regarding pharmacological actions generally within specific brain regions (for review, see Bentley et al., 2011). rsFC studies may provide additional, complementary insight by considering circuit interactions between regions (Bressler and Menon, 2010), thus allowing for a systems-level mechanistic account of nicotine’s performance-enhancing properties, which has remained elusive. Below, we synthesize a heuristic framework that may serve to guide future research by integrating recent findings from intrinsic network connectivity neuroimaging studies with those from investigations interrogating nicotine’s neuropharmacological actions. Given that a hallmark feature of the tobacco abstinence syndrome is difficulty concentrating (Hughes, 2007; Parrott et al., 1996), a systems-level theoretical account of nicotine’s effects on cognition could inform the development of improved smoking cessation pharmacotherapies (Lerman et al., 2007) and, additionally, may hold therapeutic utility for other disease states involving attentional dysfunction (Levin et al., 2006).

Dissociable large-scale brain networks are thought to subserve both task-relevant and -irrelevant cognitive operations during attention-demanding tasks. One ensemble, termed the “task-positive” network (TPN; Fox et al., 2005), consists of regions routinely showing activity increases during demanding tasks (e.g., lateral prefrontal, lateral parietal, posterior medial PPC, and insula) presumably supporting exogenous attentional orientation (Corbetta and Shulman, 2002). A second ensemble, termed the “task-negative” (or “default-mode”) network consists of regions routinely showing activity increases during passive states and reciprocal activity decreases during task performance (e.g., dorsomedial prefrontal cortex [dmPFC], vmPFC, posterior cingulate cortex [PCC] and parahippocampal regions) presumably subserving task-independent endogenous information processing (Buckner et al., 2008; Gusnard and Raichle, 2001; Raichle et al., 2001). Most efforts to elucidate the psychological functions supported by the DMN have converged on the view that it is associated with internally directed cognitive operations (e.g., self-reflection on past and future events, autobiographical, social or emotional functions; Amodio and Frith, 2006; Buckner et al., 2008; Gusnard et al., 2001; Schacter et al., 2007). In the absence of explicit task demands (i.e., “at rest”), intrinsic activity in the TPN and DMN fluctuate in a temporally anti-correlated fashion (Fox et al., 2005), such that decreased activity in one coincides with increased activity in the other, suggesting they subserve opposing cognitive processes competing for limited processing resources (Fransson, 2008).

Potentially one of the more heuristically useful perspectives to emerge from the nascent functional connectivity literature relates this antagonistic TPN and DMN dynamic to consequences during goal-directed behavior (e.g., Figs. 3A,B). Specifically, intermittent failures to adequately suppress DMN activity during goal-directed behavior have been identified as one source of interference limiting optimal performance (Sonuga-Barke and Castellanos, 2007). Task-induced DMN suppression is parametrically altered as a function of cognitive load (Fransson, 2006; McKiernan et al., 2003), suggesting reallocation of processing resources as dictated by task demands along a continuum rather than an “all-or-none” phenomenon. Fluctuations along this continuum manifest during monotonous task performance, where decreases in DMN suppression and concomitant reductions in regional TPN activity increase the probability of error commission (Fig. 3C; Eichele et al., 2008) and protracted response times (Weissman et al., 2006). Maladaptive interactions between DMN and TPN regions partly underlie suboptimal performance (Prado and Weissman, 2011), such that decreased negative coupling between these networks predicts increased variability in trial-to-trial response times across individuals (Kelly et al., 2008). As such, altered network dynamics and/or a compromised ability to suppress DMN activity have been proposed as a neurobiological explanation for attentional-control maladjustments in conditions such as ADHD (Fassbender et al., 2009; Sonuga-Barke and Castellanos, 2007), autism spectrum disorders (Broyd et al., 2009; Uddin and Menon, 2009),

1 In fact, during tasks designed to interrogate such introspective functions, regions of the DMN show increased activity (e.g., Sestieri et al., 2011). Additionally, while in the current review we generally refer to the DMN as if it were a single unitary entity, it is important to note that this canonical network appears to be comprised of multiple dissociable components subserving specific aspects of internally oriented cognitive processes (e.g., Andrews-Hanna et al., 2010; Uddin et al., 2008).

2 Although not the intent of the current review, a methodological issue requires mention here. It has been argued that anti-correlations between TPN and DMN simply reflect an artifact resulting from a commonly employed preprocessing step in rsFC analyses involving the removal of non-neuronal, physiological noise (e.g., cardiac and respiration cycles) common across the entire brain (i.e., mean global signal regression) (Anderson et al., 2011; Murphy et al., 2009). Arguing against an artifactual explanation, such anti-correlated networks have been observed in the absence of mean global signal regression (e.g., Fox, 2009); appear modulated by pharmacological manipulations (e.g., Cole et al., 2010), and correlate with aspects of behavioral performance (e.g., Kelly et al., 2008; Prado and Weissman, 2011). Nonetheless, the extent to which anti-correlations between large-scale brain networks reflect an intrinsic property of brain organization or merely a signal processing artifact is an ongoing debate.
chronic pain (Baliki et al., 2008; Tagliazucchi et al., 2010), depression (Sheline et al., 2010), schizophrenia (Williamson, 2007), anxiety, and dementia (Menon, 2011). Thus, the waning of concentration during monotonous task performance may arise from persistent, re-emergent, and/or spontaneously occurring DMN activity supporting task-irrelevant, internally oriented information processing.

On the other hand, nicotine-induced performance enhancement is consistently observed during monotonous tasks requiring sustained attention, vigilance, and visuospatial orientation (Hahn et al., 2007; Lawrence et al., 2002; Newhouse et al., 2004). Emerging evidence suggests nicotine augments performance by suppressing DMN processes while also enhancing those associated with the TPN. For example, in minimally-abstinent smokers, nicotine enhances deactivations in regions overlapping those of the DMN during task cue presentation which is also associated with faster responding to subsequently presented targets (Figs. 4A,B; Hahn et al., 2007). Enhanced suppression of DMN regions may be a general mechanism by which nicotine elevates global task-based focus, as similar enhanced deactivations, occurring concurrently with augmented performance, have been observed when probing different cognitive constructs such as stimulus detection, selective/divided attention (Hahn et al., 2009), sustained attention (Beaver et al., 2011), and overt attentional shifting (Ettinger et al., 2009). Nicotine administered to non-smokers decreases DMN activity “at rest” (Fig. 4C; Tanabe et al., 2011), suggesting such effects are not constrained to task-specific contexts nor limited to the amelioration of abstinence-induced effects in smokers. In contrast to nicotine-induced decreases in DMN and consistent with enhancement of sensory-based information processing, nicotine potentiates rsFC in cingulaneocortical circuits of minimally-deprived smokers (Fig. 2A; Hong et al., 2009) and in extrastriate visual circuits of non-smokers (Tanabe et al., 2011). Such nicotine-induced suppression of DMN and reciprocal enhancement of TPN activity at the systems-level, may parallel acetylcholine’s role in toggling circuit dynamics between cortico-cortical feedback states (low acetylcholine levels) and thalamo-cortical feed-forward states (high acetylcholine levels) described at the cellular-level (Bentley et al., 2011; Hasselmo and McGaughy, 2004).

During acute nicotine withdrawal, smokers often report subjectively experienced “difficulty concentrating” and display objectively assessed impairments in task-based performance (Heishman, 1998; Hendricks et al., 2006; Kozink et al., 2010). In keeping with the dynamic network view discussed above, increased DMN functioning, decreased TPN operations, and/or maladaptive interactions between components of these networks may account for abstinence-induced cognitive impairments. Supporting such a proposal, self-reported improved concentration following nicotine administration to abstinent smokers has been associated with increased negative coupling between DMN and TPN regions (Fig. 4D; Cole et al., 2010). Additionally, nicotine decreases intra-individual response time variability (Hahn et al., 2007); variability thought to arise from maladaptive dynamic interactions between DMN and TPN (Kelly et al., 2008). Relative to the drug-sated state, 24-h abstinence leads to reduced activation in TPN regions (e.g. lateral PFC) during performance of a sustained attention task (Ettinger et al., 2009). Nicotinic stimulation with varenicline, a modestly efficacious pharmacotherapy for smoking cessation, increases activity in core TPN nodes (i.e., lateral and posterior-medial PFC) during demanding working memory performance following smoking abstinence (Loughhead et al., 2010). Thus, we suggest acute nicotine withdrawal may be a particularly relevant endogenous stimulus necessitating further processing resources in the service of returning the individual to a euthymic, homeostatic set point, but at the expense of reduced processing efficiency for exogenous stimuli.

In addition to negatively impacting attention to exogenous stimuli, increased DMN activity may give rise to the percept of drug urges, cravings, and/or ruminative thoughts about use. For example, increased cerebral blood flow to multiple regions, including some overlapping the DMN (e.g., vmPFC, hippocampus) predicts the severity of abstinence-induced smoking urges (Wang et al., 2007). Moreover, independent of withdrawal, increased activity in DMN regions such as
vmPFC, PCC and (para)hippocampus is observed as a function of reactivity to drug cues and/or use-urges (Fig. 5; Brenhouse et al., 2008; Franklin et al., 2011; Garavan et al., 2000; Goudriaan et al., 2010; Langleben et al., 2008; Li and Sinha, 2008; Naqvi and Bechara, 2009; Weinstein et al., 2010; Wilcox et al., 2011; Zhang et al., 2011b). Cognitive down-regulation of cue-induced cravings is accompanied by increased activity in TPN regions (e.g., lateral and posterior-medial PFC) and concomitant decreases in reward-related and DMN regions (e.g., ventral striatum, ACC and vmPFC) (Kober et al., 2010). Cognitive down-regulation of cue-induced cravings is accompanied by increased activity in TPN regions (e.g., lateral and posterior-medial PFC) and concomitant decreases in reward-related and DMN regions (e.g., ventral striatum, ACC and vmPFC) (Kober et al., 2010). Given the overlap between symptoms of major depressive disorder and acute nicotine withdrawal, for example, depressed mood, problems concentrating, restlessness and sleeping difficulties (American Psychiatric Association, 1994), it is noteworthy that enhanced rsFC and reduced deactivation in DMN regions has been observed among clinically anxious and depressed populations characterized by a propensity to perseverate on negative self-reflections (Gentili et al., 2009; Hamilton et al., 2011; Lanius et al., 2010; Sheline et al., 2010; Zhou et al., 2010). Increased DMN activity and/or maladaptive interactions with TPN regions may reflect an intermediate endophenotype associated with acute withdrawal, resulting in cognitive impairments as well as increased use-urges.

Based on the above, we hypothesize that nicotine withdrawal can enhance and nicotine administration suppress DMN functioning. Additionally, maladaptive interactions between DMN and TPN may provide a systems-level mechanistic account regarding deficits in sustained attention, performance monitoring and inhibitory control following acute abstinence from addictive drugs (Garavan and Hester, 2007; Garavan and Stout, 2005; Heishman et al., 1994; Verdejo-García et al.,...
Specifically, nicotine may enhance performance via a shift in activity from a network subserving internally oriented, to one or more networks mediating externally oriented information processing. Such enhancing effects likely are more evident in populations experiencing state- (e.g., abstinent drug users, sleep deprived or fatigued participants) or trait-related (e.g., ADHD, chronic pain) dysfunctions in externally oriented information processing (Newhouse et al., 2004). However, the question remains: what are the neural substrates mediating such dynamic activity switching between large-scale brain networks, and is there a role for nicotine in such a process?

**Insula, network switching and interoception**

The brain is inundated with a continuous flow of information arising from exogenous and endogenous sources, necessitating control mechanisms to identify, and in turn act upon, the currently most

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**Fig. 5.** Increased activity in DMN regions in response to cues. (A) BOLD activation in DMN regions (PCC, precuneus) to heroin-related versus neutral cues in opioid-dependent individuals. (B,C). Heroin-related cues increase BOLD activation in DMN regions (vmPFC, hippocampus) and the insula immediately prior to and after a methadone dose in opioid-dependent individuals.

Panel A reproduced from Wang et al. (2010). Panels B and C are reproduced from Langleben et al. (2008).
salient stimuli. A distinct network, composed of insula and ACC nodes, has been suggested to play a critical and causal role in the initiation, maintenance, and adjustment of attentional control (Bresler and Menon, 2010; Dosenbach et al., 2006, 2007, 2008; Menon and Uddin, 2010). Such findings suggest the fractionation of the TPN discussed above into at least two dissociable sub-networks. Indeed, in the absence of explicit task demands, two distinct networks appear to exist, each subserving different psychological processes: one anchored in anterior insula and ACC termed the “salience network” (SN), and a second composed of lateral prefrontal and parietal regions termed the “executive control network” (ECN; Seeley et al., 2007).

The SN has been proposed to influence moment-to-moment information processing by identifying the most subjectively relevant stimuli (Seeley et al., 2007), whether arising from internal or external loci, and “toggling” activity between the DMN and ECN accordingly (Hamilton et al., 2011; Sridharan et al., 2008; Uddin et al., 2011). In cognitive task paradigms, insula and dorsal ACC activity routinely co-occur (Lawrence et al., 2003; Medford and Critchley, 2010), likely in the service of monitoring ongoing goal-directed behavior for salient stimuli (e.g., errors, response conflict) which precipitates a cascade of neural events resulting in attentional and behavioral adjustments to optimize behavior (Botvinick et al., 1999; Eger and Hirsch, 2005; Kerns et al., 2004). By assessing the temporal dynamics and directional interactions between specific nodes of the SN, DMN and ECN, Sridharan et al. (2008) identified the insula as a causal outflow hub mediating dynamic switching between DMN and ECN activity as dictated by task-events and also occurring intrinsically “at rest.” They further postulated that such network switching is facilitated by a set of specialized spindle neurons (Allman et al., 2011), found exclusively, and in high quantities, within the human anterior insula and dorsal ACC underlying fast, adaptive switching of the prevailing dominant network state. More recently, the same research group has shown that insula’s causal influence on DMN and ECN nodes matures over the course of normal development, as does the underlying structural connectivity between such regions (Uddin et al., 2011). Further suggesting insula’s role in “toggling” between DMN and TPN, Hamilton et al. (2011) have reported insular engagement at points of transition between prevailing DMN or TPN activity in patients suffering from major depressive disorder and healthy controls. From a drug abuse perspective, the proposal that the SN orientates attention to the most homeostatically-relevant source of information arising from endogenous or exogenous stimuli (Seeley et al., 2007) may provide one parsimonious neurobiological account of some of the cognitive deficits often noted, not only in abstinent-smokers, but also in other drug using cohorts (Garavan and Stout, 2005; Verdejo-García et al., 2008).

Complementing a network-switching function, insula’s role in interoception (Craig, 2002; Craig, 2009), and, by extension, drug addiction (Naqvi and Bechara, 2009, 2010), has been of substantial recent interest. Interoception refers to the monitoring of internal bodily states to maintain or procure homeostasis, possibly via rousing the organism through affective, motivational, and attentional alterations. The insula appears to be parsed into multiple subregions along a posterior-to-anterior gradient (Craig, 2009), such that more posterior regions have been related to primary interoceptive operations and more anterior regions associated with affective and cognitive processes. Exploration of these insular functional subdivisions using rsFC analyses has generally bolstered such a conceptualization (Cauda et al., 2011; Deen et al., 2011; Taylor et al., 2009). Accordingly, multiple perspectives have emerged relating insula with subjective drug urges (Naqvi and Bechara, 2009; Garavan, 2010), impaired behavioral monitoring (Goldstein et al., 2009), and maladaptive decision-making (Paulus, 2007) in drug addicts. Naqvi and Bechara (2010) have elucidated a rather thorough model of insula’s interoceptive role at multiple stages of the addiction cycle (e.g., drug-taking, -withdrawal, -urges). Of particular note, during acute abstinence, the insula is theorized to track homeostatically relevant withdrawal-induced bodily changes and in turn interact with other regions (e.g., vmPFC, amygdala and striatum), thereby altering affective (e.g., anxiety, irritability) and motivational (e.g., cue reactivity, smoking urges) states (Naqvi and Bechara, 2010). To this list we suggest adding attentional states, hypothesizing that increased withdrawal-related insula engagement during abstinence interferes with normal network switching processes and perhaps underlies the breakdown in negative coupling between the DMN and ECN. That is to say, during periods of abstinence the most homeostatically relevant stimuli are often internal bodily sensations subjectively experienced as withdrawal symptoms, which result in objectively manifest decreased behavioral performance due to a shift in activity toward DMN and away from ECN.

Given the discussion above, it is not surprising that the insula appears to play a pivotal role in nicotine addiction. Critically, damage to the insula can result in a sudden and profound disruption of smoking behavior (Naqvi et al., 2007). Further supporting insula’s involvement, a recent study observed greater gray matter density in the anterior insula of smokers in comparison to non-smokers (Fig. 5A; Zhang et al., 2011a). Additionally, when deprived of nicotine, elevated activity in the insula, along with other brain regions, covaries with increased abstinence-induced smoking urges (Wang et al., 2007). Multiple studies of cigarette-cue reactivity have noted positive associations between insula responses and subjective use-urges (Naqvi and Bechara, 2009). Connecting insula activity with attentional processes, Janes et al. (2010) reported that attentional bias for smoking-related stimuli assessed in a Stroop task variant was positively correlated with greater insula cue-reactivity (Fig. 6B). Conversely, during performance of a sustained attention task not involving drug-related stimuli, nicotine administered to minimally-deprived smokers decreased insula activity while also improving performance (Fig. 6C; Lawrence et al., 2002). Thus, we propose that insula hyperactivity following nicotine-abstinence or in response to smoking-related cues may precipitate decreased cognitive performance. Such a view is consistent with previous proposals relating insula dysfunction with other neuropsychiatric disorders such as anxiety (hyperactivity: Paulus and Stein, 2006) and autism spectrum disorders (hypoactivity: Uddin and Menon, 2009).

A network model of nicotine addiction

Drawing upon the above literature, we propose a model that integrates contemporary understanding of intrinsic network dynamics with evidence of alterations within and between these networks as a function of nicotine abstinence and administration, cue reactivity and/or drug urges. We hypothesize that during acute abstinence, the insula monitors salient interoceptive states, thus marking the presence of endogenous, withdrawal-related somatic, affective, and/or motivational events. The insula in turn interacts with DMN regions in the service of orienting attention to resolve this inner tumult and return the system to homeostasis, thereby shifting network dynamics and biasing processing towards the DMN and away from the ECN. Such a shift may underlie the cognitive impairments observed across various task domains during abstinence. Additionally, preoccupation with endogenous, withdrawal-related stimuli may hinder the capacity of the SN to engage in extrinsic performance monitoring, further

3 A second methodological point warrants discussion. In addition to assessing functional connectivity between brain regions, the directional influence of one region onto another is often of particular interest. One approach for inferring directionality, termed Granger causality analysis, has been increasingly applied in task-based and rsFC studies (e.g., Sridharan et al., 2008; Uddin et al., 2011). It is important to note that such “lag-based” directionality/causality methods may not be appropriate for inferring causality within fMRI datasets given variability in the hemodynamic response function across brain regions (e.g., Smith et al., 2011). Thus, additional studies using alternative analysis strategies are needed to verify the veracity of seminal studies suggesting insula’s association with dynamic switching between large-scale networks (e.g., Hamilton et al., 2011).
contributes to cognitive deficits. Given the functional heterogeneity within insula, it remains for future research to identify those subregions most critically involved in such processes.

This hypothesized shift in network dynamics during abstinence (Fig. 7A) would result in one or more of the following observable changes in rsFC: 1) enhanced rsFC between insula and DMN, which would correlate with the severity of self-reported withdrawal symptoms and impaired task performance; 2) reduced rsFC between insula and the ECN; 3) enhanced rsFC within the DMN; 4) reduced rsFC within the ECN; (e.g., Cole et al., 2010; Kelly et al., 2011); and 5) a breakdown in negative coupling between the DMN and ECN (e.g., Cole et al., 2010). Conversely, acute nicotine administration (Fig. 7B) may bias processing away from the DMN, resulting in enhanced rsFC within the ECN and between the ECN and insula. Such network dynamics may not only underlie the amelioration of withdrawal symptoms, but may also reflect an inherent property of nicotine to suppress DMN activity and enhance processing of extrinsic task-based stimuli. This latter view derives from the cognitive enhancing effects observed in nicotine-naïve populations (Heishman et al., 2010) as well as evidence that nicotine suppresses the DMN activity in non-smokers (Tanabe et al., 2011). Accordingly, a shift away from an insula-DMN biased pattern of rsFC towards an insula-ECN pattern may be observed in both smokers and non-smokers, accompanied by enhanced attentional performance.

In addition to providing a network-based account of abstinence induced cognitive impairment (and conversely, enhancement following acute nicotine administration), this model may provide a framework within which to interpret the co-activation of insula and DMN regions often observed during reactivity to drug cues and/or drug urges (Franklin et al., 2011; Goudriaan et al., 2010; Janes et al., 2010; Wang et al., 2007), and potentially also drug Stroop interference effects associated with this pattern of co-activation (Janes et al., 2010). We would argue that drug cues elicit a salient interoceptive state increasing insula activity, and in turn the DMN, drawing resources away from extrinsic task-positive regions, producing slower response times and increased error rates.

While the above focus lies with nicotine abstinence, this network-based perspective could apply equally well to acute, and perhaps protracted, withdrawal from other drugs of abuse. Such a model would account, at least in part, for the coincidence of cognitive deficits observed across drug addicted populations, typically assessed during acute abstinent states (Forman et al., 2004; Goldstein et al., 2004; Hester and Garavan, 2004; Hester et al., 2007, 2009; Sofuoglu, 2010). Reduced recruitment of dorsal ACC and ECN regions accompanying these deficits (Forman et al., 2004; Goldstein et al., 2004; Hester and Garavan, 2004; Hester et al., 2009) is also in accordance with such an abstinence model. Of course, any differences arising between abstinent drug-using populations and non-using controls may also reflect pre-existing vulnerabilities or drug-induced functional and/or structural changes independent of acute withdrawal processes (e.g. Zhang et al., 2011b). That said, while there exist obvious limitations to studying acute withdrawal processes in drug-addicted individuals, we suggest that following such individuals across the course of treatment may present a means of testing this heuristic framework within different drug addicted cohorts and in turn, screening for relapse risk. Specifically, as acute and protracted withdrawal symptoms subside, altered network dynamics may ‘normalize’. Individuals showing the least change in rsFC dynamics are hypothesized to present the greatest risk for recidivism to drug use. Finally, while we have emphasized a role for the insula in mediating some of the psychological deficits associated with drug use, given the multifaceted nature of

Fig. 6. Insula involvement in nicotine addiction and attentional processes. (A) Greater gray matter density in smokers (n = 48) relative to matched controls in the left insula. (B) Increased insula activity to smoking-related versus neutral cues is positively correlated with attention to smoking-cues in an affective Stroop task. (C) Difference map and bar graph illustrating enhanced BOLD deactivations in the insula under nicotine relative to placebo conditions during a sustained attention task (RVIP) but not a sensorimotor control task in minimally deprived (~3 h) smokers. Panel A is reproduced from Zhang et al. (2011a). Panel B is reproduced from Janes et al. (2010). Panel C is reproduced from Lawrence et al. (2002).
this neuropsychiatric disease, alternative circuit disruptions (such as those described earlier) also represent potential targets for future treatment development.

In sum, rsFC provides a useful tool for studying multifaceted neuropsychiatric diseases like addiction at a systems-level of assessment. To efficiently leverage the capabilities of this tool, stronger, model-driven approaches need to be utilized. To this end, we attempt to formulate a framework of dynamic large-scale network interactions derived from recent advances in intrinsic functional connectivity to explain the consequences of acute nicotine abstinence and attention enhancing effects of nicotine administration. Complementing an interoceptive monitoring role, emerging evidence implicates insula involvement in directing attention towards either internal or external stimuli by mediating dynamic activity between two large-scale brain networks, the default-mode network (DMN) and the executive control network (ECN). These networks associated with endogenously oriented processes and exogenously oriented attention, respectively, competitively interact during task performance, with suppression of DMN activity often associated with optimal behavioral performance. By modulating dynamic network activity, the anterior insula is hypothesized to expedite processing of the most homeostatically relevant stimuli arising from either internal or external events. During nicotine abstinence, the insula may track withdrawal-induced bodily sensations and in turn direct attention towards this homeostatically salient internal state via increased interactions with the DMN at the expense of decreased exogenously directed attention mediated by ECN.

Fig. 7. A proposed model of activity within and between the default mode network (DMN), executive control network (ECN) and salience network (SN) under nicotine abstinence (A) and following acute nicotine administration (B). Arrow thickness between and within networks reflects the hypothesized strength of interactions between networks. The thick arrow between the insula and endogenously relevant interoceptive events in (A) reflects an influx of such events during nicotine abstinence. Similarly, thick arrows between the dACC and ECN and their conceptual outputs in (B) reflects an enhanced capacity to engage in task execution and performance monitoring following nicotine administration.


