Published in final edited form as:
Neuroimage. 2012 October 1; 62(4): 2281–2295. doi:10.1016/j.neuroimage.2012.01.117.

Resting State Functional Connectivity in Addiction: Lessons Learned and a Road Ahead

Matthew T. Sutherland, **Meredith McHugh**, **Vani Pariyadath**, and **Elliot A. Stein***
Neuroimaging Research Branch, National Institute on Drug Abuse, Intramural Research Program, NIH/DHHS, Baltimore, MD

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.

Keywords

fMRI; connectivity; drug abuse; nicotine; insula; default mode; attention

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

*Corresponding Author, Elliot A. Stein, PhD., Chief, Neuroimaging Research Branch, National Institute on Drug Abuse, 251 Bayview Blvd, Suite 200, Baltimore, MD 21224, estein@mail.nih.gov, Tel: 443-740-2650, Fax: 443-740-2734.

The authors declare no conflicts of interest.

between neurobiological, environmental, pharmacological, and genetic components. Multiple theories regarding the underlying mechanisms of addiction have been proposed (e.g., Goldstein and Volkow, 2002; Redish, 2004; Everitt and Robbins, 2005; Wise, 2008; Koob and Le Moal, 2008; Koob and Volkow, 2010), 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., Breiter et al., 1997; Stein et al., 1998; Kumari et al., 2003; Bickel et al., 2007; Diekhof et al., 2008), 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 & 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 (Greicius et al., 2009; Honey et al., 2009; Damoiseaux and Greicius, 2009), thus constituting plausible functional networks. Critically, the strength of these networks “at rest” predicts both behavioral accuracy and subsequent activation of the same brain areas during task performance (e.g., Hampson et al., 2006; Seeley et al., 2007; Kelly et al., 2008; Kim et al., 2009; 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 (Lustig et al., 2003; Greicius et al., 2004; Rombouts et al., 2005; Wang et al., 2006), autism (Kennedy et al., 2006), depression (Anand et al., 2005), multiple sclerosis (Lowe 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 (Meyer-Lindenberg, 2009; Glahn et al., 2010), 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, which have led 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 [^{15}O] 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, and insula, suggesting engagement of motivational and attentional circuits. These networks are similar to those seen following cocaine cue provocation (Garavan 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 (Tomasi et al., 2010; Gu et al., 2010; Wilcox et al., 2011), prescription opioid (Upadhyay et al., 2010), and heroin dependent individuals (Ma, 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 2010; Wilcox 2011), others have reported decreased connectivity (Upadhyay 2010, Gu 2010, Tomasi 2010, Wang 2010). For example, testing the hypothesis that MCL circuits are altered in heroin addicts, Ma and colleagues (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 and colleagues (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 and colleagues (2010) who conducted a 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 and coworkers (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., 2011; 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., 2011) likely contribute significantly to variance both within and between rsFC studies, confounding interpretation of results. Finally, generalizing across different abused 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; Philips 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; Upadhyay et al., 2010; Wang et al., 2010; Liu et al., 2009; Xie et al., 2011). More specifically, Gu and colleagues (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 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 2010). Additionally, using diffusion tensor imaging, these authors also showed that opioid use was associated with reduced structural integrity of the uncinate fasiculus, 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; Hariri et al., 2003; Kim et al., 2011a; Kim et al., 2011b; Pezewas et al., 2005; Hahn et al., 2011; Motzkin et al., 2011). The vmPFC has been posited to actively suppress amygdala functioning (Foland-Ross et al., 2010; Hairiri et al., 2003; Kim et al., 2011b), which in turn, is thought to alleviate emotional distress (Ochsner et al., 2004, Berkman and Lieberman, 2009). 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, Pezewas et al., 2005). Taken further, reduced amygdala-vmPFC rsFC strength, as well as compromised uncinate fasiculus 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 and colleagues (2011) 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 & Garavan, 2004; Hester, Nestor, & Garavan, 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; Ridderinkhof 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 (Egner 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 & Garavan, 2004; Hester et al., 2009; Hester et al., 2007) are associated with reduced functional engagement (Hester & Garavan, 2004; Hester et al., 2009; Li et al., 2008) and structural integrity across these regions (Yuan et al., 2010; Yuan et al., 2009; Nakama et al., 2011; Barrós-Loscertales et al., 2011).

Recent rsFC studies have also suggested patterns of abnormal connectivity between these primary nodes of a “cognitive control network” in both heroin (Yuan et al., 2011; Ma 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 and coworkers (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 and coworkers (2011) 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., 2005; Gruber et al., 2007; Hester & Garavan, 2004; Kelly et al., 2011).

Camchong and coworkers (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; Ridderinkhof 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 (Gusnard and Raichle 2001; Buckner et al., 2008) 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., 2011). Importantly, Camchong and coworkers (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 (dlPFC) 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 and coworkers (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), suggesting specific circuits related to addiction severity and which, the authors speculate, may serve as a biomarker for studies of treatment outcome.

Subsequently, Hong and colleagues (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 nicotine intake, 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 (Parrott et al., 1996, Hughes 2007), 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 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 PFC, 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 (Raichle 2001; Gusnard and Raichle 2001; Buckner et al., 2008). Most efforts to elucidate the psychological functions supported by the DMN have converged on the view that it is associated with internally directed cognitive operations1 (e.g., self-reflection on past and future events, autobiographical, social or emotional functions; Amodio & 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

[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., Uddin et al., 2009; Andrews-Hanna et al., 2010).

activity in the other2, suggesting they subserve opposing cognitive processes competing for limited processing resources (Fransson, 2006).

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., Fig 3AB). Specifically, intermittent failures to adequately suppress DMN activity during goal-directed behavior have been identified as one source of interference limiting optimal performance (Songua-Barke et al., 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 (Sonuga-Barke and Castellanos, 2007, Fassbender et al., 2009), autism spectrum disorders (Uddin and Menon 2009, Broyd et al., 2009), 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 (Lawrence et al., 2002; Newhouse et al., 2004; Hahn et al., 2007). 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 (Fig 4AB; 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

[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) (Murphy et al., 2009; Anderson et al., 2011). Arguing against an artifactual explanation, such anti-correlated networks have been observed in the absence of mean global signal regression (e.g., Fox et al., 2009), appear modulated by pharmacological manipulations (e.g., Cole et al., 2010), and correlate with aspects of behavioral performance (e.g., Prado and Weissman, 2011; Kelly et al., 2008). 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.

cingulate-neocortical 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 (Hasselmo and McGaughy, 2004; Bentley et al., 2011).

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-hr 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 (Loughead et al., 2011). 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; Garavan et al., 2000; Brenhouse et al., 2008; Li and Sinha 2008; Naqvi and Bechara 2009; Weinstein et al., 2010; Goudriaan et al., 2010; Franklin et al., 2011; Wilcox et al., 2011; Langleben et al., 2008; Zhang et al., 2011). 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). Finally, 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; Lanius et al., 2010; Zhou et al., 2010; Sheline et al., 2010, Hamilton et al., 2011). 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 (Heishman et al., 1994; Garavan and Stout, 2005; Garavan and Hester, 2007; Verdejo-García et al., 2008). 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 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 (Bressler and Menon 2010; Menon and Uddin 2010; Dosenbach et al., 2006, 2007, 2008). 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 (Uddin et al., 2011; Hamilton et al., 2011; Sridharan et al., 2008). 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 precipitate a cascade of neural events resulting in attentional and behavioral adjustments to optimize behavior (Botvinick et al., 1999; Kerns et al., 2004; Egner and Hirsch, 2005). By assessing the temporal dynamics and directional interactions between specific nodes of the SN, DMN and ECN, Sridharan and colleagues (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” 3. 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

[3]A second methodological point warrants discussion. In additional 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 alterative 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).

"toggling" between DMN and TPN, Hamilton and coworkers (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 orients 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 et al., 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 contains multiple subregions that have been parsed 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 et al., 2010), impaired behavioral monitoring (Goldstein et al., 2009), and maladaptive decision-making (Paulus et al., 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 towards 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 grey matter density in the anterior insula of smokers in comparison to non-smokers (Fig 6A; Zhang et al., 2011). 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 and colleagues (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 & 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 contributing 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 and 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 (Wang et al., 2007; Janes et al., 2010; Goudriaan et al., 2010; Franklin et al., 2011), 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 & Garavan, 2004; Hester et al., 2007, 2009; Sofuoglu et al., 2010). Reduced recruitment of dorsal ACC and ECN regions

accompanying these deficits (Goldstein et al., 2004; Forman 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., 2010). 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 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.

Highlights

- We review the addiction-related resting state functional connectivity (rsFC) literature.
- We propose a framework to guide future research of rsFC in nicotine addiction.
- Nicotine and withdrawal alterrsFC of executive control, default mode and salience networks.
- Insula/dACC salience network plays a critical role in craving and network switching.
- Shifts in rsFC network dynamics underlie cognitive effects of nicotine and withdrawal.

Acknowledgments

This work was supported by the National Institute on Drug Abuse, Intramural Research Program, NIH/DHHS.

References

Allman JM, Tetreault NA, Hakeem AY, Park S. The von economo neurons in apes and humans. American Journal of Human Biology. 2011; 23:5–21. [PubMed: 21140464]

American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 4th ed.. Washington D.C: 1994.

Amodio DM, Frith CD. Meeting of minds: the medial frontal cortex and social cognition. Nature Reviews Neuroscience. 2006; 7:268–277.

Anand A, Li Y, Wang Y, Wu J, Gao S, Bukhari L, Mathews VP, Kalnin A, Lowe MJ. Activity and connectivity of brain mood regulating circuit in depression: a functional magnetic resonance study. Biological Psychiatry. 2005; 57:1079–1088. [PubMed: 15866546]

Anderson JS, Druzgal TJ, Lopez-Larson M, Jeong E-K, Desai K, Yurgelun-Todd D. Network anticorrelations, global regression, and phase-shifted soft tissue correction. Human Brain Mapping. 2011; 32:919–934. [PubMed: 20533557]

Andrews-Hanna JR, Reidler JS, Sepulcre J, Poulin R, Buckner RL. Functional-Anatomic Fractionation of the Brain's Default Network. Neuron. 2010; (65):550–562. [PubMed: 20188659]

Baliki MN, Geha PY, Apkarian AV, Chialvo DR. Beyond feeling: chronic pain hurts the brain, disrupting the default-mode network dynamics. Journal of Neuroscience. 2008; 28:1398–1403. [PubMed: 18256259]

Barrós-Loscertales A, Garavan H, Bustamante JC, Ventura-Campos N, Llopis JJ, Belloch V, Parcet MA, et al. Reduced striatal volume in cocaine-dependent patients. NeuroImage. 2011; 56(3):1021–1026. [PubMed: 21338692]

Beaver JD, Long CJ, Cole DM, Durcan MJ, Bannon LC, Mishra RG, Matthews PM. The Effects of nicotine replacement on cognitive brain activity during smoking withdrawal studied with simultaneous fMRI/EEG. Neuropsychopharmacology. 2011; 36(9):1792–1800. [PubMed: 21544072]

Berridge KC, Robinson TE. What is the role of dopamine in reward: hedonic impact, reward learning, or incentive salience? Brain Research Reviews. 1998; 28:309–369. [PubMed: 9858756]

Bentley P, Driver J, Dolan RJ. Cholinergic modulation of cognition: Insights from human pharmacological functional neuroimaging. Progress in Neurobiology. 2011; 94:360–388. [PubMed: 21708219]

Berkman ET, Liberman MD. Using neuroscience to broaden emotion regulation: Theoretical and methodological considerations. Social and Personality Psychology Compass. 2009; 3:1–19.

Bickel WK, Miller ML, Yi R, Kowal BP, Lindquist DM, Pitcock JA. Behavioral and neuroeconomics of drug addiction: competing neural systems and temporal discounting processes. Drug and Alcohol Dependence. 2007; 90(Suppl 1):S85–S91. [PubMed: 17101239]

Bierut LJ, Stitzel JA, Wang JC, Hinrichs AL, Grucza RA, Xuei X, Saccone NL, Saccone SF, Bertelsen S, Fox L, Horton WJ, Breslau N, Budde J, Cloninger CR, Dick DM, Foroud T, Hatsukami D, Hesselbrock V, Johnson EO, Kramer J, Kuperman S, Madden PA, Mayo K, Nurnberger J Jr, Pomerleau O, Porjesz B, Reyes O, Schuckit M, Swan G, Tischfield JA, Edenberg HJ, Rice JP, Goate AM. Variants in nicotinic receptors and risk for nicotine dependence. American Journal of Psychiatry. 2008; 165:1163–1171. [PubMed: 18519524]

Blair RJ. The amygdala and ventromedial prefrontal cortex: functional contributions and dysfunction in psychopathy. Philosophical Transactions of Royal Society of London B Biological Sciences. 2008; 363:2557–2565.

Botvinick M, Nystrom LE, Fissell K, Carter CS, Cohen JD. Conflict monitoring versus selection-for-action in anterior cingulate cortex. Nature. 1999; 402:179–181. [PubMed: 10647008]

Breiter HC, Gollub RL, Weisskoff RM, Kennedy DN, Makris N, Berke JD, Goodman JM, Kantor HL, Gastfriend DR, Riorden JP, Mathew RT, Rosen BR, Hyman SE. Acute effects of cocaine on human brain activity and emotion. Neuron. 1997; 19:591–611. [PubMed: 9331351]

Brenhouse HC, Sonntag KC, Andersen. Transient D1 dopamine receptor expression on prefrontal cortex projection neurons: relationship to enhanced motivational salience of drug cues in adolescence. Journal of Neuroscience. 2008; 28:2375–2382. [PubMed: 18322084]

Bressler SL, Menon V. Large-scale brain networks in cognition: emerging methods and principles. Trends in Cognitive Sciences. 2010; 14:277–290. [PubMed: 20493761]

Broyd SJ, Demanuele C, Debener S, Helps SK, James CJ, Sonuga-Barke EJS. Default-mode brain dysfunction in mental disorders: a systematic review. Neuroscience and Biobehavioral Reviews. 2009; 33:279–296. [PubMed: 18824195]

Buckner RL, Andrews-Hanna JR, Schacter DL. The brain's default network: anatomy, function, and relevance to disease. Annals of the New York Academy of Sciences. 2008; 1124:1–38. [PubMed: 18400922]

Bullmore E, Sporns O. Complex brain networks: graph theoretical analysis of structural and functional systems. Nature Reviews Neuroscience. 2009; 10:186–198.

Camchong J, MacDonald AW, Nelson B, Bell C, Mueller BA, Specker S, Lim KO. Frontal hyperconnectivity related to discounting and reversal learning in cocaine subjects. Biological Psychiatry. 2011; 69:1117–1123. [PubMed: 21371689]

Cauda F, D'Agata F, Sacco K, Duca S, Geminiani G, Vercelli A. Functional connectivity of the insula in the resting brain. NeuroImage. 2011; (55):8–23. [PubMed: 21111053]

Chen S, Ross TJ, Zhan W, Myers CS, Chuang K-S, Heishman SJ, Stein EA, Yang Y. Group independent component analysis reveals consistent resting-state networks across multiple sessions. Brain Research. 2008; 1239:141–151. [PubMed: 18789314]

Chiara, GDi; Bassareo, V.; Fenu, S.; Luca, MA De; Spina, L.; Cadoni, C.; Acquas, E.; Carboni, E.; Valentini, V.; Lecca, D. Dopamine and drug addiction: the nucleus accumbens shell connection. Neuropharmacology. 2004; 47(Suppl 1):227–241. [PubMed: 15464140]

Cole DM, Beckmann CF, Long CJ, Matthews PM, Durcan MJ, Beaver JD. Nicotine replacement in abstinent smokers improves cognitive withdrawal symptoms with modulation of resting brain network dynamics. NeuroImage. 2010; 52:590–599. [PubMed: 20441798]

Corbetta M, Shulman GL. Control of goal-directed and stimulus-driven attention in the brain. Nature Reviews Neuroscience. 2002; 3:201–215.

Craig AD. How do you feel? Interoception: the sense of the physiological condition of the body. Nature Reviews Neuroscience. 2002; 10(1):59–70.

Craig AD. How do you feel--now? The anterior insula and human awareness. Nature Reviews Neuroscience. 2009; 10:59–70.

Craig AD, Chen K, Bandy D, Reiman EM. Thermosensory activation of insular cortex. Nature Neuroscience. 2000; 3:184–190.

Daglish MRC, Weinstein A, Malizia AL, Wilson S, Melichar JK, Lingford-Hughes A, Myles JS, Grasby P, Nutt DJ. Functional connectivity analysis of the neural circuits of opiate craving: "more" rather than "different"? NeuroImage. 2003; 20(4):1964–1970. [PubMed: 14683702]

Damoiseaux JS, Greicius MD. Greater than the sum of its parts: a review of studies combining structural connectivity and resting-state functional connectivity. Brain Structure & Function. 2009; 213:525–533. [PubMed: 19565262]

Deen B, Pitskel NB, Pelphrey KA. Three systems of insular functional connectivity identified with cluster analysis. Cerebral Cortex. 2011; 21(7):1498–1506. [PubMed: 21097516]

Diekhof EK, Falkai P, Gruber O. Functional neuroimaging of reward processing and decision-making: a review of aberrant motivational and affective processing in addiction and mood disorders. Brain Research Reviews. 2008; 59:164–184. [PubMed: 18675846]

Dosenbach NUF, Fair DA, Cohen AL, Schlaggar BL, Petersen SE. A dual-networks architecture of top-down control. Trends in Cognitive Sciences. 2008; 12:99–105. [PubMed: 18262825]

Dosenbach NUF, Fair DA, Miezin FM, Cohen AL, Wenger KK, Dosenbach RAT, Fox MD, Snyder AZ, Vincent JL, Raichle ME, Schlaggar BL, Petersen SE. Distinct brain networks for adaptive and stable task control in humans. Proceedings of the National Academy of Sciences USA. 2007; 104:11073–11078.

Dosenbach NUF, Visscher KM, Palmer ED, Miezin FM, Wenger KK, Kang HC, Burgund ED, Grimes AL, Schlaggar BL, Petersen SE. A core system for the implementation of task sets. Neuron. 2006; 50:799–812. [PubMed: 16731517]

Egner T, Hirsch J. Cognitive control mechanisms resolve conflict through cortical amplification of task-relevant information. Nature Neuroscience. 2005; 8:1784–1790.

Eichele T, Debener S, Calhoun VD, Specht K, Engel AK, Hugdahl K, Cramon DY von, Ullsperger M. Prediction of human errors by maladaptive changes in event-related brain networks. Proceedings of the National Academy of Sciences USA. 2008; 105:6173–6178.

Ersche KD, Clark L, London M, Robbins TW, Sahakian BJ. Profile of executive and memory function associated with amphetamine and opiate dependence. Neuropsychopharmacology. 2006; 31(5): 1036–1047. [PubMed: 16160707]

Ettinger U, Williams SCR, Patel D, Michel TM, Nwaigwe A, Caceres A, Mehta MA, Anilkumar AP, Kumari V. Effects of acute nicotine on brain function in healthy smokers and non-smokers: estimation of inter-individual response heterogeneity. NeuroImage. 2009; 45:549–561. [PubMed: 19159693]

Everitt BJ, Robbins TW. Neural systems of reinforcement for drug addiction: from actions to habits to compulsion. Nature Neuroscience. 2005; 8:1481–1489.

Fassbender C, Zhang H, Buzy WM, Cortes CR, Mizuiri D, Beckett L, Schweitzer JB. A lack of default network suppression is linked to increased distractibility in ADHD. Brain Research. 2009; 1273:114–128. [PubMed: 19281801]

Foland-Ross LC, Altshuler LL, Bookheimer SY, Lieberman MD, Townsend J, Penfold C, Moody T, Ahlf K, Shen JK, Madsen SK, Rasser PE, Toga AW, Thompson PM. Amygdala reactivity in healthy adults is correlated with prefrontal cortical thickness. Journal of Neuroscience. 2010; 30:16673–16678. [PubMed: 21148006]

Fox MD, Snyder AZ, Vincent JL, Corbetta M, Essen DC Van, Raichle ME. The human brain is intrinsically organized into dynamic, anticorrelated functional networks. Proceedings of the National Academy of Sciences USA. 2005; 102:9673–9678.

Fox MD, Zhang DY, Snyder AZ, Raichle ME. The global signal and observed anticorrelated resting state brain networks. Journal of Neurophysiology. 2009; 101:3270–3283. [PubMed: 19339462]

Franklin T, Wang Z, Suh JJ, Hazan R, Cruz J, Li Y, Goldman M, Detre J a, O'Brien CP, Childress A-R. Effects of varenicline on smoking cue-triggered neural and craving responses. Archives of General Psychiatry. 2011; 68:516–526. [PubMed: 21199958]

Fransson P. How default is the default mode of brain function? Further evidence from intrinsic BOLD signal fluctuations. Neuropsychologia. 2006; 44:2836–2845. [PubMed: 16879844]

Garavan H. Insula and drug cravings. Brain Structure & Function. 2010; 214:593–601. [PubMed: 20512373]

Garavan H, Hester R. The role of cognitive control in cocaine dependence. Neuropsychology Review. 2007; 17:337–345. [PubMed: 17680368]

Garavan H, Pankiewicz J, Bloom a, Cho JK, Sperry L, Ross TJ, Salmeron BJ, Risinger R, Kelley D, Stein E a. Cue-induced cocaine craving: neuroanatomical specificity for drug users and drug stimuli. American Journal of Psychiatry. 2000; 157:1789–1798. [PubMed: 11058476]

Garavan H, Stout JC. Neurocognitive insights into substance abuse. Trends in Cognitive Sciences. 2005; 9:195–201. [PubMed: 15808502]

Gentili C, Ricciardi E, Gobbini MI, Santarelli MF, Haxby JV, Pietrini P, Guazzelli M. Beyond amygdala: Default Mode Network activity differs between patients with social phobia and healthy controls. Brain Research Bulletin. 2009; 79:409–413. [PubMed: 19559343]

Glahn DC, Winkler AM, Kochunov P, Almasy L, Duggirala R, Carless MA, Curran JC, Olvera RL, Laird AR, Smith SM, Beckmann CF, Fox PT, Blangero J. Genetic control over the resting brain. Proceedings of the National Academy of Sciences USA. 2010; 107:1223–1228.

Goldstein RZ, Alia-Klein N, Tomasi D, Carrillo JH, Maloney T, Woicik P a, Wang R, Telang F, Volkow ND. Anterior cingulate cortex hypoactivations to an emotionally salient task in cocaine addiction. Proceedings of the National Academy of Sciences USA. 2009; 106:9453–9458.

Goldstein RZ, Leskovjan AC, Hoff AL, Hitzemann R, Bashan F, Khalsa SS, Wang G-J, et al. Severity of neuropsychological impairment in cocaine and alcohol addiction: association with metabolism in the prefrontal cortex. Neuropsychologia. 2004; 42(11):1447–1458. [PubMed: 15246283]

Goldstein RZ, Volkow ND. Drug addiction and its underlying neurobiological basis: neuroimaging evidence for the involvement of the frontal cortex. American Journal of Psychiatry. 2002; 159:1642–1652. [PubMed: 12359667]

Goudriaan AE, Ruiter MB De, Den Brink W Van, Oosterlaan J, Veltman DJ. Brain activation patterns associated with cue reactivity and craving in abstinent problem gamblers, heavy smokers and healthy controls: an fMRI study. Addiction Biology. 2010; 15:491–503. [PubMed: 20840335]

Greicius MD, Srivastava G, Reiss AL, Menon V. Default-mode network activity distinguishes Alzheimer's disease from healthy aging: evidence from functional MRI. Proceedings of the National Academy of Sciences USA. 2004; 101:4637–4642.

Greicius MD, Supekar K, Menon V, Dougherty RF. Resting-state functional connectivity reflects structural connectivity in the default mode network. Cerebral Cortex. 2009; 19:72–78. [PubMed: 18403396]

Gruber SA, Silveri MM, Yurgelun-Todd DA. Neuropsychological consequences of opiate use. Neuropsychology Review. 2007; 17(3):299–315. [PubMed: 17690984]

Gu H, Salmeron BJ, Ross TJ, Geng X, Zhan W, Stein EA, Yang Y. Mesocorticolimbic circuits are impaired in chronic cocaine users as demonstrated by resting-state functional connectivity. NeuroImage. 2010; 53:593–601. [PubMed: 20603217]

Gusnard DA, Akbudak E, Shulman GL, Raichle ME. Medial prefrontal cortex and selfreferential mental activity: relation to a default mode of brain function. Proceedings of the National Academy of Sciences USA. 2001; 98:4259–4264.

Gusnard DA, Raichle ME. Searching for a baseline: functional imaging and the resting human brain. Nature Reviews Neuroscience. 2001; 2:685–694.

Hahn B, Ross TJ, Wolkenberg FA, Shakleya DM, Huestis MA, Stein EA. Performance effects of nicotine during selective attention, divided attention, and simple stimulus detection: an fMRI study. Cerebral Cortex. 2009; 19:1990–2000. [PubMed: 19073624]

Hahn B, Ross TJ, Yang Y, Kim I, Huestis M a, Stein E a. Nicotine enhances visuospatial attention by deactivating areas of the resting brain default network. Journal of Neuroscience. 2007; 27:3477–3489. [PubMed: 17392464]

Hahn A, Stein P, Windischberger C, Weissenbacher A, Spindeleggera C, Moser E, Kaspera S, Lanzenberger R. Reduced resting-state functional connectivity between amygdala and orbitofrontal cortex in social anxiety disorder. NeuroImage. 2011; 56(3):881–889. [PubMed: 21356318]

Hamilton JP, Furman DJ, Chang C, Thomason ME, Dennis E, Gotlib IH. Default-Mode and Task-Positive Network Activity in Major Depressive Disorder: Implications for Adaptive and Maladaptive Rumination. Biological Psychiatry. 2011; 70(4):327–333. [PubMed: 21459364]

Hampson M, Driesen NR, Skudlarski P, Gore JC, Constable RT. Brain connectivity related to working memory performance. Journal of Neuroscience. 2006; 26:13338–13343. [PubMed: 17182784]

Hariri AR, Mattay VS, Tessitore A, Fera F, Weinberger DR. Neocortical modulation of the amygdala response to fearful stimuli. Biological Psychiatry. 2003; 53:494–501. [PubMed: 12644354]

Hasselmo ME, McGaughy J. High acetylcholine levels set circuit dynamics for attention and encoding and low acetylcholine levels set dynamics for consolidation. Progress in Brain Research. 2004; 145:207–231. [PubMed: 14650918]

Heishman SJ. What aspects of human performance are truly enhanced by nicotine? Addiction. 1998; 93:317–320. [PubMed: 10328040]

Heishman SJ, Kleykamp BA, Singleton EG. Meta-analysis of the acute effects of nicotine and smoking on human performance. Psychopharmacology. 2010; 210:453–469. [PubMed: 20414766]

Heishman SJ, Taylor RC, Henningfield JE. Nicotine and smoking: a review of effects on human performance. Experimental and Clinical Psychopharmacology. 1994; 2(4):345–395.

Hendricks PS, Ditre JW, Drobes DJ, Brandon TH. The early time course of smoking withdrawal effects. Psychopharmacology. 2006; 187:385–396. [PubMed: 16752139]

Hester R, Garavan H. Executive dysfunction in cocaine addiction: evidence for discordant frontal, cingulate, and cerebellar activity. The Journal of Neuroscience. 2004; 24(49):11017–11022. [PubMed: 15590917]

Hester R, Nestor L, Garavan H. Impaired error awareness and anterior cingulate cortex hypoactivity in chronic cannabis users. Neuropsychopharmacology. 2009; 34(11):2450–2458. [PubMed: 19553917]

Heuvel, MP van den; Hulshoff Pol, HE. Exploring the brain network: a review on resting-state fMRI functional connectivity. European Neuropsychopharmacology. 2010; 20:519–534. [PubMed: 20471808]

Honey CJ, Sporns O, Cammoun L, Gigandet X, Thiran JP, Meuli R, Hagmann P. Predicting human resting-state functional connectivity from structural connectivity. Proceedings of the National Academy of Sciences USA. 2009; 106:2035–2040.

Hong LE, Gu H, Yang Y, Ross TJ, Salmeron BJ, Buchholz B, Thaker GK, Stein EA. Association of nicotine addiction and nicotine's actions with separate cingulate cortex functional circuits. Archives of General Psychiatry. 2009; 66:431–441. [PubMed: 19349313]

Hong LE, Hodgkinson CA, Yang Y, Sampath H, Ross TJ, Buchholz B, Salmeron BJ, Srivastava V, Thaker GK, Goldman D, Stein EA. A genetically modulated, intrinsic cingulate circuit supports human nicotine addiction. Proceedings of the National Academy of Sciences USA. 2010; 107:13509–13514.

Hughes JR. Effects of abstinence from tobacco: valid symptoms and time course. Nicotine & Tobacco Research. 2007; 9:315–327. [PubMed: 17365764]

Janes AC, Pizzagalli DA, Richardt S, Frederick Bde B, Holmes AJ, Sousa J, Fava M, Evins AE, Kaufman MJ. Neural substrates of attentional bias for smoking-related cues: an FMRI study. Neuropsychopharmacology. 2010; 35(12):2339–2345. [PubMed: 20703221]

Kelly AMC, Uddin LQ, Biswal BB, Castellanos FX, Milham MP. Competition between functional brain networks mediates behavioral variability. NeuroImage. 2008; 39:527–537. [PubMed: 17919929]

Kelly C, Zuo X-N, Gotimer K, Cox CL, Lynch L, Brock D, Imperati D, Garavan H, Rotrosen J, Castellanos FX, Milham MP. Reduced interhemispheric resting state functional connectivity in cocaine addiction. Biological Psychiatry. 2011; 69:684–692. [PubMed: 21251646]

Kennedy DP, Redcay E, Courchesne E. Failing to deactivate: resting functional abnormalities in autism. Proceedings of the National Academy of Sciences USA. 2006; 103:8275–8280.

Kerns JG, Cohen JD, MacDonald AW, Cho RY, Stenger VA, Carter CS. Anterior cingulate conflict monitoring and adjustments in control. Science. 2004; 303:1023–1026. [PubMed: 14963333]

Kim E, Ku J, Namkoong K, Lee W, Lee KS, Park J-Y, Lee SY, Kim J-J, Kim SI, Jung Y-C. Mammillothalamic functional connectivity and memory function in Wernicke's encephalopathy. Brain. 2009; 132:369–376. [PubMed: 19036763]

Kim MJ, Gee DG, Loucks RA, Davis FC, Whalen PJ. Anxiety dissociates dorsal and ventral medial prefrontal cortex functional connectivity with the amygdala at rest. Cerebral Cortex. 2011a; 21:1667–1673. [PubMed: 21127016]

Kim MJ, Loucks RA, Palmer AL, Brown AC, Solomon KM, Marchante AN, Whalen PJ. The structural and functional connectivity of the amygdala: from normal emotion to pathological anxiety. Behavioural Brain Research. 2011b; 223:403–410. [PubMed: 21536077]

Kober H, Mende-Siedlecki P, Kross EF, Weber J, Mischel W, Hart CL, Ochsner KN. Prefrontal-striatal pathway underlies cognitive regulation of craving. Proceedings of the National Academy of Sciences USA. 2010; 107:14811–14816.

Koob GF, Moal M Le. Drug abuse: hedonic homeostatic dysregulation. Science. 1997; 278:52–58. [PubMed: 9311926]

Koob GF, Moal M Le. Plasticity of reward neurocircuitry and the "dark side" of drug addiction. Nature Neuroscience. 2005; 8:1442–1444.

Koob GF, Moal M Le. Neurobiological mechanisms for opponent motivational processes in addiction. Philosophical transactions of the Royal Society of London. 2008; 363:3113–3123. Review. [PubMed: 18653439]

Koob GF, Volkow ND. Neurocircuitry of addiction. Neuropsychopharmacology. 2010; 35:217–238. [PubMed: 19710631]

Kozink RV, Lutz AM, Rose JE, Froeliger B, McClernon FJ. Smoking withdrawal shifts the spatiotemporal dynamics of neurocognition. Addiction Biology. 2010; 15:480–490. [PubMed: 21040240]

Kumari V, Gray JA, ffytche DH, Mitterschiffthaler MT, Das M, Zachariah E, Vythelingum GN, Williams SCR, Simmons A, Sharma T. Cognitive effects of nicotine in humans: an fMRI study. NeuroImage. 2003; 19:1002–1013. [PubMed: 12880828]

Langleben DD, Ruparel K, Elman I, Busch-Winokur S, Pratiwadi R, Loughead J, O'Brien CP, Childress AR. Acute effect of methadone maintenance dose on brain FMRI response to heroin-related cues. American Journal of Psychiatry.

Lanius RA, Bluhm RI, Coupland NJ, Hegadoren KM, Rowe B. Default mode network connectivity as a predictor of post-traumatic stress disorder symptom severity in acutely traumatized subjects. Journal of Psychiatry & Neuroscience (JPN). 2010:33–40.

Lawrence NS, Ross TJ, Hoffmann R, Garavan H, Stein EA. Multiple neuronal networks mediate sustained attention. Journal of Cognitive Neuroscience. 2003; 15:1028–1038. [PubMed: 14614813]

Lawrence NS, Ross TJ, Stein EA. Cognitive mechanisms of nicotine on visual attention. Neuron. 2002; 36:539–548. [PubMed: 12408855]

Lerman C, LeSage MG, Perkins KA, O'Malley SS, Siegel SJ, Benowitz NL, Corrigall WA. Translational research in medication development for nicotine dependence. Nature Reviews Drug Discovery. 2007; 6:746–762.

Levin ED, McClernon FJ, Rezvani AH. Nicotinic effects on cognitive function: behavioral characterization, pharmacological specification, and anatomic localization. Psychopharmacology. 2006; 184:523–539. [PubMed: 16220335]

Li, C-shan R.; Sinha, R. Inhibitory control and emotional stress regulation: neuroimaging evidence for frontal-limbic dysfunction in psycho-stimulant addiction. Neuroscience and Biobehavioral Reviews. 2008; 32:581–597. [PubMed: 18164058]

Li SJ, Biswal B, Li Z, Risinger R, Rainey C, Cho JK, Salmeron BJ, Stein EA. Cocaine administration decreases functional connectivity in human primary visual and motor cortex as detected by functional MRI. Magnetic Resonance in Medicine. 2000; 43:45–51. [PubMed: 10642730]

Liu J, Liang J, Qin W, Tian J, Yuan K, Bai L, Zhang Y, Wang W, Wang Y, Li Q, Zhao L, Lu L, Deneen KM von, Liu Y, Gold MS. Dysfunctional connectivity patterns in chronic heroin users: an fMRI study. Neuroscience Letters. 2009; 460:72–77. [PubMed: 19450664]

Lowe MJ, Phillips MD, Lurito JT, Mattson D, Dzemidzic M, Mathews VP. Multiple sclerosis: low-frequency temporal blood oxygen level-dependent fluctuations indicate reduced functional connectivity initial results. Radiology. 2002; 224:184–192. [PubMed: 12091681]

Lustig C, Snyder AZ, Bhakta M, O'Brien KC, McAvoy M, Raichle ME, Morris JC, Buckner RL. Functional deactivations: change with age and dementia of the Alzheimer type. Proceedings of the National Academy of Sciences USA. 2003; 100:14504–14509.

Ma N, Liu Y, Li N, Wang C-X, Zhang H, Jiang X-F, Xu H-S, Fu X-M, Hu X, Zhang D-R. Addiction related alteration in resting-state brain connectivity. NeuroImage. 2010; 49:738–744. [PubMed: 19703568]

McKiernan KA, Kaufman JN, Kucera-Thompson J, Binder JR. A parametric manipulation of factors affecting task-induced deactivation in functional neuroimaging. Journal of Cognitive Neuroscience. 2003; 15:394–408. [PubMed: 12729491]

Medford N, Critchley HD. Conjoint activity of anterior insular and anterior cingulate cortex: awareness and response. Brain Structure & Function. 2010; 214:535–549. [PubMed: 20512367]

Menon V. Large-scale brain networks and psychopathology: a unifying triple network model. Trends in Cognitive Sciences. 2011; 15(10):483–506. [PubMed: 21908230]

Menon V, Uddin LQ. Saliency, switching, attention and control: a network model of insula function. Brain Structure & Function. 2010; 214:655–667. [PubMed: 20512370]

Meyer-Lindenberg A. Neural connectivity as an intermediate phenotype: brain networks under genetic control. Human Brain Mapping. 2009; 30:1938–1946. [PubMed: 19294651]

Morón JA, Green TA. Exploring the molecular basis of addiction: drug-induced neuroadaptations. Neuropsychopharmacology. 2010; 35:337–338.

Motzkin JC, Newman JP, Kiehl KA, Koenigs M. Reduced Prefrontal Connectivity in Psychopathy. The Journal of Neuroscience. 2011; 31(48) 17348-1735.

Murphy K, Birn RM, Handwerker DA, Jones TB, Bandettini PA. The impact of global signal regression on resting state correlations: Are anti-correlated networks introduced? NeuroImage. 2009; 44(3):893–905. [PubMed: 18976716]

Nakama H, Chang L, Fein G, Shimotsu R, Jiang CS, Ernst T. Methamphetamine users show greater than normal age-related cortical gray matter loss. Addiction. 2011; 106(8):1474–1483. [PubMed: 21438934]

Naqvi NH, Bechara A. The hidden island of addiction: the insula. Trends in Neurosciences. 2009; 32:56–67. [PubMed: 18986715]

Naqvi NH, Bechara A. The insula and drug addiction: an interoceptive view of pleasure, urges, and decision-making. Brain Structure & Function. 2010; 214:435–450. [PubMed: 20512364]

Naqvi NH, Rudrauf D, Damasio H, Bechara A. Damage to the insula disrupts addiction to cigarette smoking. Science. 2007; 315:531–534. [PubMed: 17255515]

Nestler EJ. Is there a common molecular pathway for addiction? Nature Neuroscience. 2005; 8:1445–1449.

Newhouse PA, Potter A, Singh A. Effects of nicotinic stimulation on cognitive performance. Current Opinion in Pharmacology. 2004; 4:36–46. [PubMed: 15018837]

Ochsner KN, Ray RD, Cooper JC, Robertson ER, Chopra S, Gabrieli JDE, Gross JJ. For better or for worse: neural systems supporting the cognitive down- and up-regulation of negative emotion. NeuroImage. 2004; 23(2):483–499. [PubMed: 15488398]

Parrott, a C.; Garnham, NJ.; Wesnes, K.; Pincock, C. Cigarette smoking and abstinence: comparative effects upon cognitive task performance and mood state over 24 hours. Human Psychopharmacology: Clinical and Experimental. 1996; 11:391–400.

Paulus MP. Decision-making dysfunctions in psychiatry--altered homeostatic processing? Science. 2007; 318:602–606. [PubMed: 17962553]

Paulus MP, Stein MB. An insular view of anxiety. Biological Psychiatry. 2006; 60:383–387. [PubMed: 16780813]

Pezawas L, Meyer-Lindenberg A, Drabant EM, Verchinski BA, Munoz KE, Kolachana BS, Egan MF, Mattay VS, Hariri AR, Weinberger DR. 5-HTTLPR polymorphism impacts human cingulate-amygdala interactions: a genetic susceptibility mechanism for depression. Nature Neuroscience. 2005; 8:828–834.

Phan KL, Orlichenko A, Boyd E, Angstadta M, Coccarod EF, Liberzona I, Arfanakis K. Preliminary evidence of white matter abnormality in the uncinate fasciculus in generalized social anxiety disorder. Biological Psychiatry. 2009; 66:691–694. [PubMed: 19362707]

Phillips ML, Drevets WC, Rauch SL, Lane R. Neurobiology of emotion perception I: the neural basis of normal emotion perception. Biological Psychiatry. 2003; 54:504–514. [PubMed: 12946879]

Prado J, Weissman DH. Heightened interactions between a key default-mode region and a key task-positive region are linked to suboptimal current performance but to enhanced future performance. NeuroImage. 2011; 56:2276–2282. [PubMed: 21440073]

Raichle ME, MacLeod AM, Snyder AZ, Powers WJ, Gusnard DA, Shulman GL. A default mode of brain function. Proceedings of the National Academy of Sciences USA. 2001; 98:676–682.

Redish. Addiction as a computational process gone awry. Science. 2004; 306:1944–1947. [PubMed: 15591205]

Rombouts SARB, Barkhof F, Goekoop R, Stam CJ, Scheltens P. Altered resting state networks in mild cognitive impairment and mild Alzheimer's disease: an fMRI study. Human Brain Mapping. 2005; 26:231–239. [PubMed: 15954139]

Schacter DL, Addis DR, Buckner RL. Remembering the past to imagine the future: the prospective brain. Nature reviews. Neuroscience. 2007; 8:657–661. [PubMed: 17700624]

Seeley WW, Menon V, Schatzberg AF, Keller J, Glover GH, Kenna H, Reiss AL, Greicius MD. Dissociable intrinsic connectivity networks for salience processing and executive control. Journal of Neuroscience. 2007; 27:2349–2356. [PubMed: 17329432]

Sestieri C, Corbetta M, Romani GL, Shulman GL. Episodic memory retrieval, parietal cortex, and the default mode network: functional and topographic analyses. Journal of Neuroscience. 2011; 31:4407–4420. [PubMed: 21430142]

Sheline YI, Price JL, Yan Z, Mintun M a. Resting-state functional MRI in depression unmasks increased connectivity between networks via the dorsal nexus. Proceedings of the National Academy of Sciences USA. 2010; 107:11020–11025.

Smith SM, Fox PT, Miller KL, Glahn DC, Fox PM, Mackay CE, Filippini N, Watkins KE, Toro R, Laird AR, Beckmann CF. Correspondence of the brain's functional architecture during activation and rest. Proceedings of the National Academy of Sciences USA. 2009; 106:13040–13045.

Smith SM, Miller KL, Salimi-Khorshidi G, Webster M, Beckmann CF, Nichols TE, Ramsey JD, Woolrich MW. Network modelling methods for FMRI. NeuroImage. 2011; 54(2):875–891. [PubMed: 20817103]

Sonuga-Barke EJS, Castellanos FX. Spontaneous attentional fluctuations in impaired states and pathological conditions: a neurobiological hypothesis. Neuroscience and Biobehavioral Reviews. 2007; 31:977–986. [PubMed: 17445893]

Spreng RN, Mar RA, Kim AS. The common neural basis of autobiographical memory, prospection, navigation, theory of mind and the default mode: a quantitative meta-analysis. Journal of Cognitive Neuroscience. 2009; 21(3):489–510. [PubMed: 18510452]

Sridharan D, Levitin DJ, Menon V. A critical role for the right fronto-insular cortex in switching between central-executive and default-mode networks. Proceedings of the National Academy of Sciences USA. 2008; 105:12569–12574.

Stein EA, Pankiewicz J, Harsch HH, Cho JK, Fuller SA, Hoffmann RG, Hawkins M, Rao SM, Bandettini PA, Bloom AS. Nicotine-induced limbic cortical activation in the human brain: a functional MRI study. American Journal of Psychiatry. 1998; 155:1009–1015. [PubMed: 9699686]

Stein JL, Wiedholz LM, Bassett DS, Weinberger DR, Zink CF, Mattay VS, Meyer-Lindenberg A. A validated network of effective amygdala connectivity. Neuroimage. 2007; 36:736–745. [PubMed: 17475514]

Tagliazucchi E, Balenzuela P, Fraiman D, Chialvo DR. Brain resting state is disrupted in chronic back pain patients. Neuroscience Letters. 2010; 485:26–31. [PubMed: 20800649]

Tambini A, Ketz N, Davachi L. Enhanced brain correlations during rest are related to memory for recent experiences. Neuron. 2010; 65:280–290. [PubMed: 20152133]

Tanabe J, Nyberg E, Martin LF, Martin J, Cordes D, Kronberg E, Tregellas JR. Nicotine effects on default mode network during resting state. Psychopharmacology. 2011; 216:287–295. [PubMed: 21331518]

Taylor KS, Seminowicz DA, Davis KD. Two systems of resting state connectivity between the insula and cingulate cortex. Human Brain Mapping. 2009; 30:2731–2745. [PubMed: 19072897]

Tian L, Jiang T, Wang Y, Zang Y, He Y, Liang M, Sui M, Cao Q, Hu S, Peng M, Zhuo Y. Altered resting-state functional connectivity patterns of anterior cingulate cortex in adolescents with attention deficit hyperactivity disorder. Neuroscience Letters. 2006; 400:39–43. [PubMed: 16510242]

Tomasi D, Volkow ND, Wang R, Carrillo JH, Maloney T, Alia-Klein N, Woicik P a, Telang F, Goldstein RZ. Disrupted functional connectivity with dopaminergic midbrain in cocaine abusers. PLoS ONE. 2010; 5:e11509. [PubMed: 20634975]

Uddin LQ, Kelly AMC, Biswal BB, Castellanos FX, Milham MP. Functional connectivity of default mode network components: correlation, anticorrelation and causality. Human Brain Mapping. 2008; 30:625–637. [PubMed: 18219617]

Uddin LQ, Menon V. The anterior insula in autism: under-connected and under-examined. Neuroscience and Biobehavioral Reviews. 2009; 33:1198–1203. [PubMed: 19538989]

Uddin LQ, Supekar KS, Ryali S, Menon V. Dynamic reconfiguration of structural and functional connectivity across core neurocognitive brain networks with development. The Journal of Neuroscience. 2011; 31(50):18578–18589. [PubMed: 22171056]

Upadhyay J, Maleki N, Potter J, Elman I, Rudrauf D, Knudsen J, Wallin D, Pendse G, McDonald L, Griffin M, Anderson J, Nutile L, Renshaw P, Weiss R, Becerra L, Borsook D. Alterations in brain structure and functional connectivity in prescription opioid-dependent patients. Brain. 2010; 133:2098–2114. [PubMed: 20558415]

Verdejo-García A, Lawrence AJ, Clark L. Impulsivity as a vulnerability marker for substance-use disorders: review of findings from high-risk research, problem gamblers and genetic association studies. Neuroscience and Biobehavioral Reviews. 2008; 32:777–810. [PubMed: 18295884]

Wang K, Jiang T, Liang M, Wang L, Tian L, Zhang X, Li K, Liu Z. Discriminative analysis of early Alzheimer's disease based on two intrinsically anti-correlated networks with resting-state fMRI. Medical Image Computing and Computer-Assisted Intervention. 2006; 9:340–347. [PubMed: 17354790]

Wang Z, Faith M, Patterson F, Tang K, Kerrin K, Wileyto EP, Detre J a, Lerman C. Neural substrates of abstinence-induced cigarette cravings in chronic smokers. Journal of Neuroscience. 2007; 27:14035–14040. [PubMed: 18094242]

Wang W, Wang YR, Qin W, Yuan K, Tian J, Li Q, Yang LY, Lu L, Guo YM. Changes in functional connectivity of ventral anterior cingulate cortex in heroin abusers. Chinese Medical Journal (English). 2010; 123(12):1582–1588.

Weinstein, a; Greif, J.; Yemini, Z.; Lerman, H.; Weizman, a; Even-Sapir, E. Attenuation of cue-induced smoking urges and brain reward activity in smokers treated successfully with bupropion. Journal of Psychopharmacology. 2010; 24:829–838. [PubMed: 19648219]

Weissman DH, Roberts KC, Visscher KM, Woldorff MG. The neural bases of momentary lapses in attention. Nature Neuroscience. 2006; 9:971–978.

Wilcox CE, Teshiba TM, Merideth F, Ling J, Mayer AR. Enhanced cue reactivity and fronto-striatal functional connectivity in cocaine use disorders. Drug and Alcohol Dependence. 2011; 115:137–144. [PubMed: 21466926]

Williamson P. Are anticorrelated networks in the brain relevant to schizophrenia? Schizophrenia Bulletin. 2007; 33:994–1003. [PubMed: 17493957]

Wise RA. Dopamine and reward: the anhedonia hypothesis 30 years on. Neurotoxicity Research. 2008; 14:169–183. [PubMed: 19073424]

Xie C, Li S, Shao Y, Fu L, Goveas J, Ye E, Li W, Cohen AD, Chen G, Zhang Z, Yang Z. Indentification of hyperactive intrinsic amygdala network connectivity associated with impulsivity in abstinent heroin addicts. Behavioral Brain Research. 2011; 216:639–646.

Yuan K, Qin W, Dong M, Liu J, Sun J, Liu P, Zhang Y, et al. Gray matter deficits and resting-state abnormalities in abstinent heroin-dependent individuals. Neuroscience Letters. 2010; 482(2): 101–105. [PubMed: 20621162]

Yuan Y, Zhu Z, Shi J, Zou Z, Yuan F, Liu Y, Lee TMC, et al. Gray matter density negatively correlates with duration of heroin use in young lifetime heroin-dependent individuals. Brain and Cognition. 2009; 71(3):223–228. [PubMed: 19775795]

Zhang X, Salmeron BJ, Ross TJ, Gu H, Geng X, Yang Y, Stein EA. Anatomical differences and network characteristics underlying smoking cue reactivity. Neuroimage. 2011; 54(1):131–141. [PubMed: 20688176]

Zhou Y, Liang M, Tian L, Wang K, Hao Y, Liu H, Liu Z, Jiang T. Functional disintegration in paranoid schizophrenia using resting-state fMRI. Schizophrenia Research. 2007; 97:194–205. [PubMed: 17628434]

Zhou Y, Yu C, Zheng H, Liu Y, Song M, Qin W, Li K, Jiang T. Increased neural resources recruitment in the intrinsic organization in major depression. Journal of Affective Disorders. 2010; 121:220–230. [PubMed: 19541369]

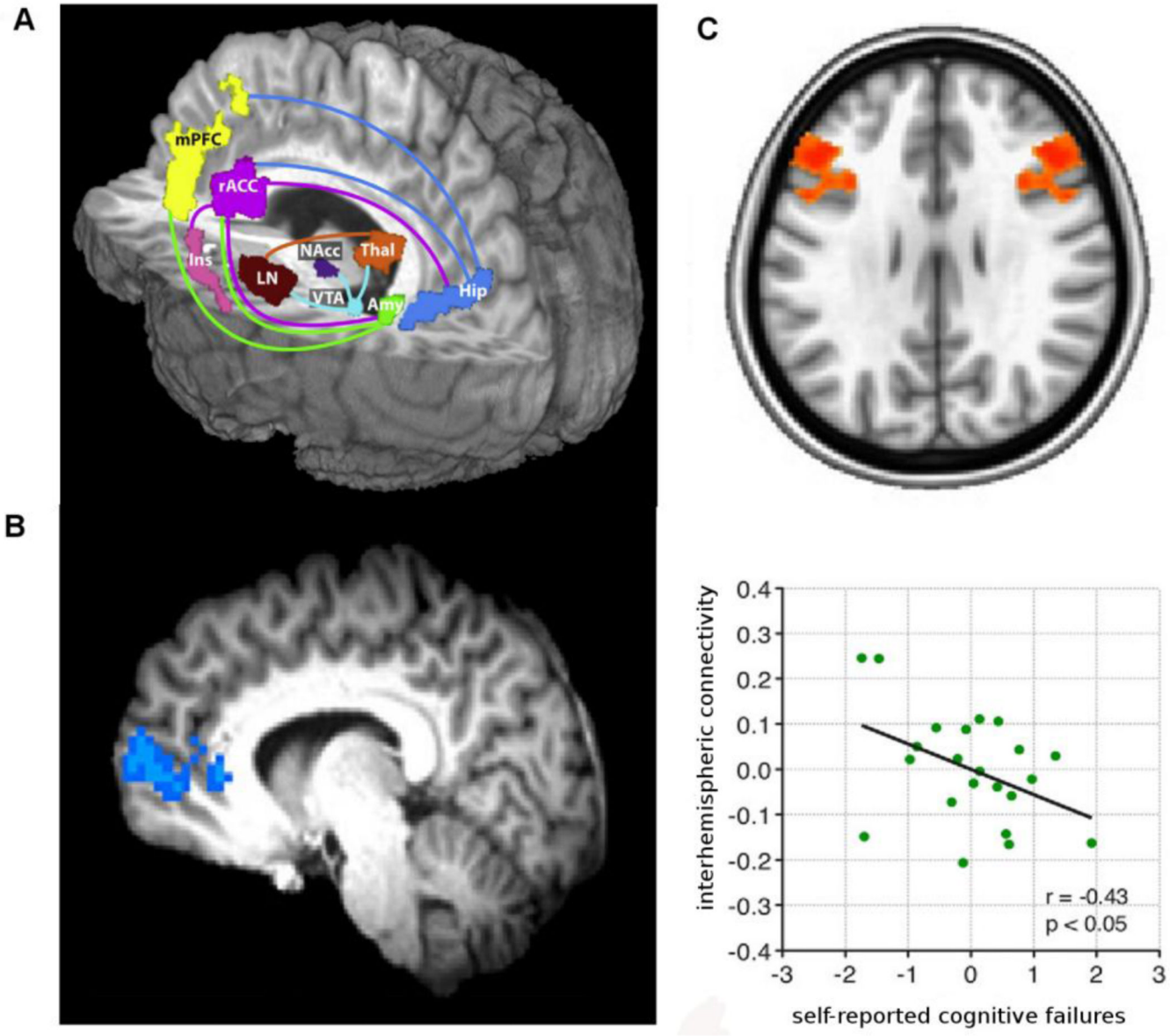

Figure 1.

(A) Summary of regions showing reduced rsFC strength with MCL seed regions in cocaine-users relative to matched non-using controls (Reproduced from Gu et al., 2010). (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 (Reproduced from Gu et al., 2010). (C) Top right displays a difference map showing stronger interhemispheric connectivity between lateral PFC regions among non-using controls relative to cocaine-users. Bottom right shows self-reported cognitive failures as a function of reduced lateral PFC interhemispheric connectivity (reproduced from Kelly et al., 2011).

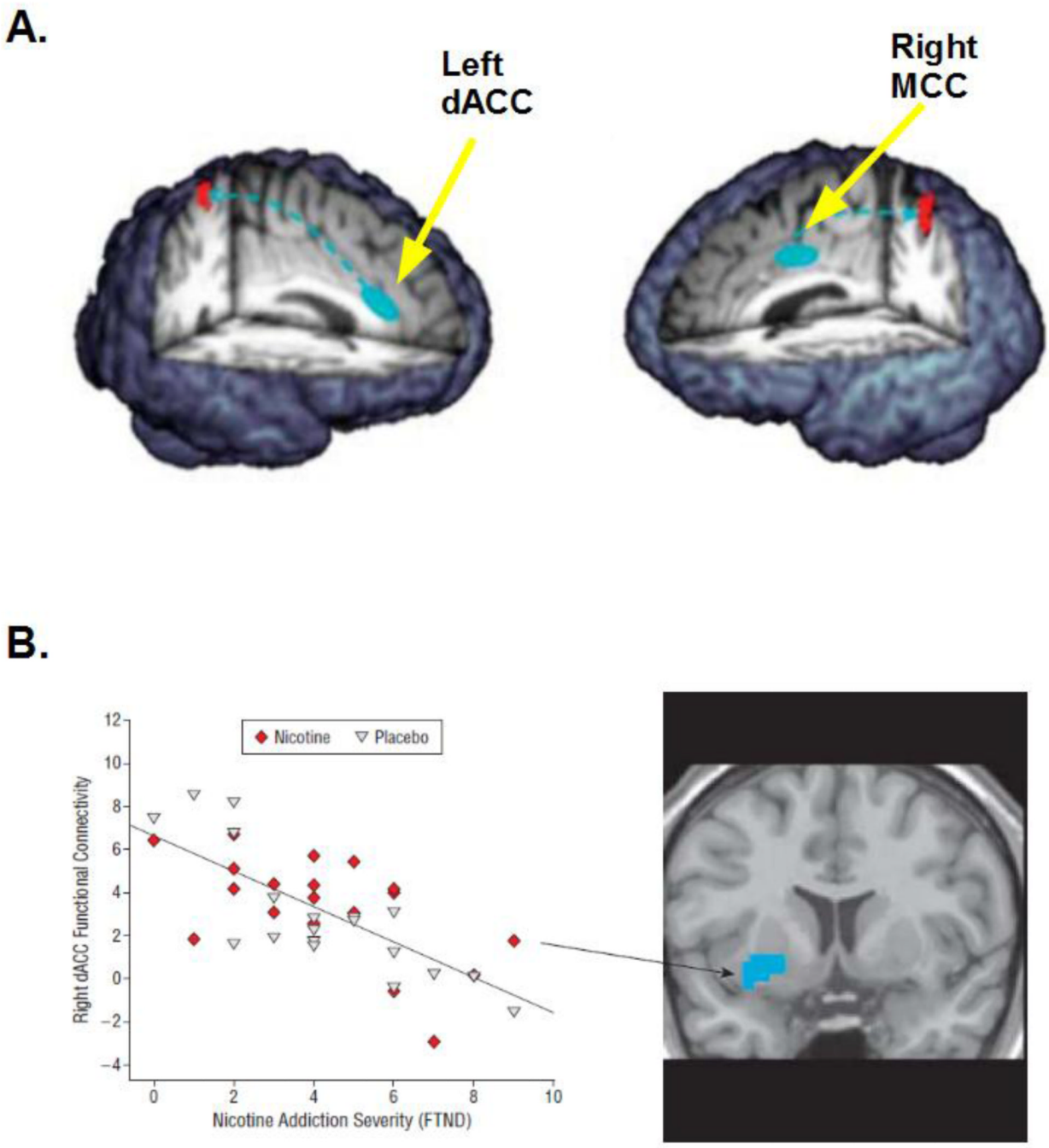

Figure 2.

State and trait components of nicotine addiction. (A) Two of the seven resting state networks that showed enhanced connectivity under nicotine relative to placebo administration in minimally deprived (~4.5hrs) smokers. Left image shows enhanced rsFC between a dorsal ACC (dACC) seed (blue oval) and a region encompassing the superior parietal lobe and post-central gyrus. Right image shows enhanced rsFC between a mid cingulate cortex (MCC) seed and a region encompassing the post-central gyrus and inferior parietal lobe. (B) Negative correlation between scores on the Fagerström Test for Nicotine Dependence (FTND) and rsFC strength in smokers between the right striatum (blue) and a dACC seed in

minimally deprived (grey triangles) and nicotine sated (red diamonds) conditions. (Reproduced from Hong et al., 2009).

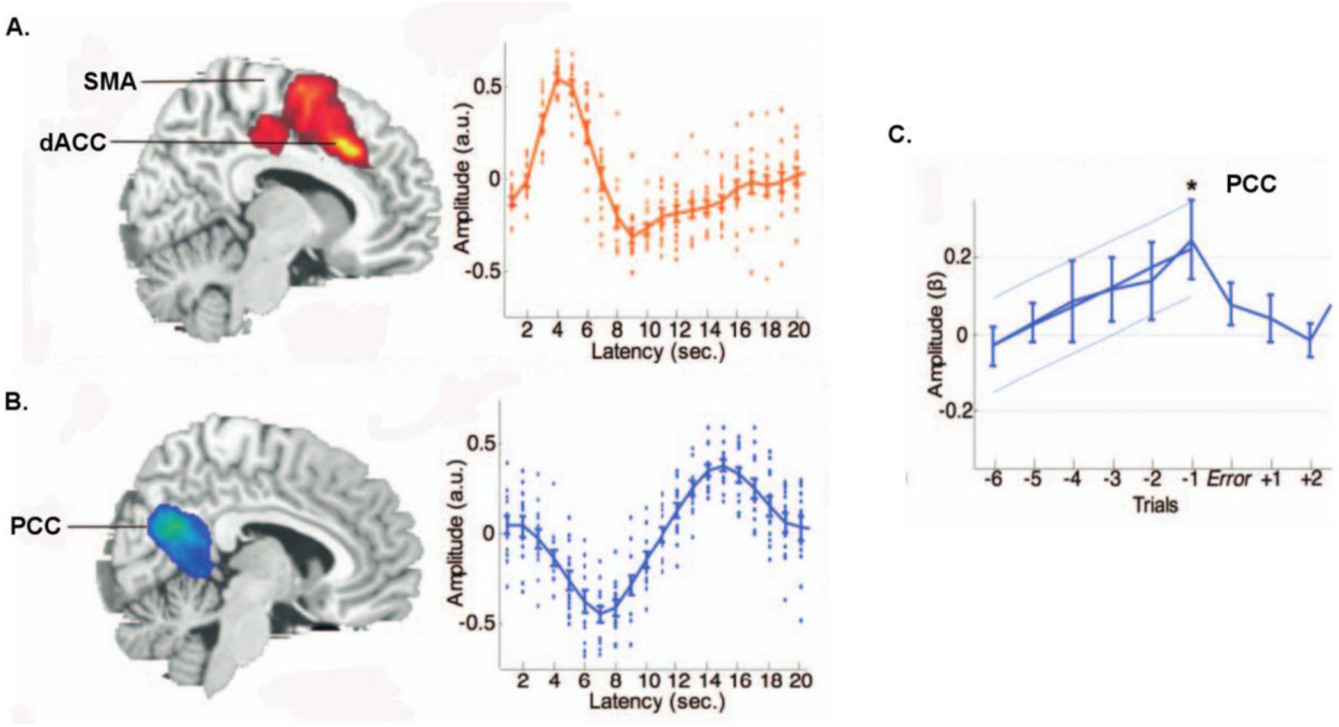

Figure 3.

Two components derived from a spatial Independent Components Analysis of BOLD activity during performance of a speeded flanker task. (A) A “task positive” component that includes the dorsal ACC and supplementary motor area (pictured in red/yellow) as well as the anterior insula and dorsal premotor area (not pictured), showing a pattern of activation consistent with engagement of these regions in performance monitoring. (B) A “task negative” component that includes the PCC (pictured in blue/green), precuneus and retrosplenial cortex (not pictured) showing task-related deactivation consistent with the identification of these regions as part of the default-mode network. (C) Activity in the “task negative” component shows a linear increase in activity preceding response errors (Reproduced from Eichele et al., 2008).

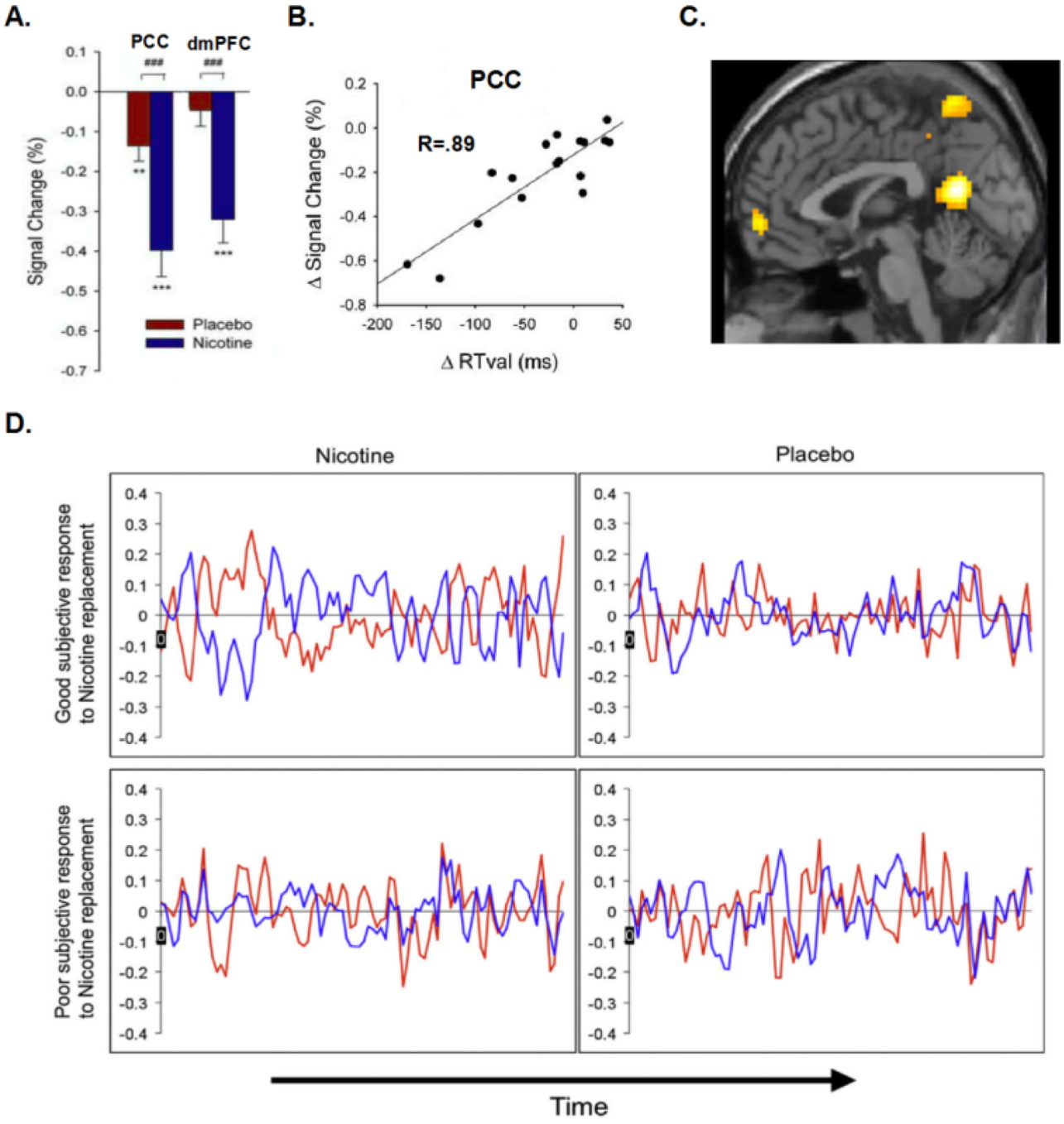

Figure 4.

Nicotine's impact on default-mode functioning. (A) Nicotine enhanced deactivation in DMN regions (PCC, dmPFC) in minimally deprived (~3 hrs) smokers under nicotine (relative to placebo) administration during a spatial attention task. (B) Nicotine-induced deactivation in the PCC correlates with reduced reaction time (difference values reflect Nicotine - Placebo). (Reproduced from Hahn et al., 2007). (C) Nicotine (relative to pre-nicotine baseline) reduced activity in DMN regions (vmPFC, PCC, precuneus) of non-smokers (Reproduced from Tanabe et al., 2011). (D) Example time-courses of DMN (blue) and ECN (red) activity during the resting state under nicotine and placebo conditions in two abstinent (~12 hrs) smokers. Top graphs illustrate enhanced negative coupling between the DMN and ECN

following nicotine in an individual reporting decreased withdrawal symptoms following nicotine replacement. Bottom graphs show little change in DMN-ECN coupling following nicotine administration in an individual reporting no change in withdrawal symptoms (Reproduced from Cole et al 2010).

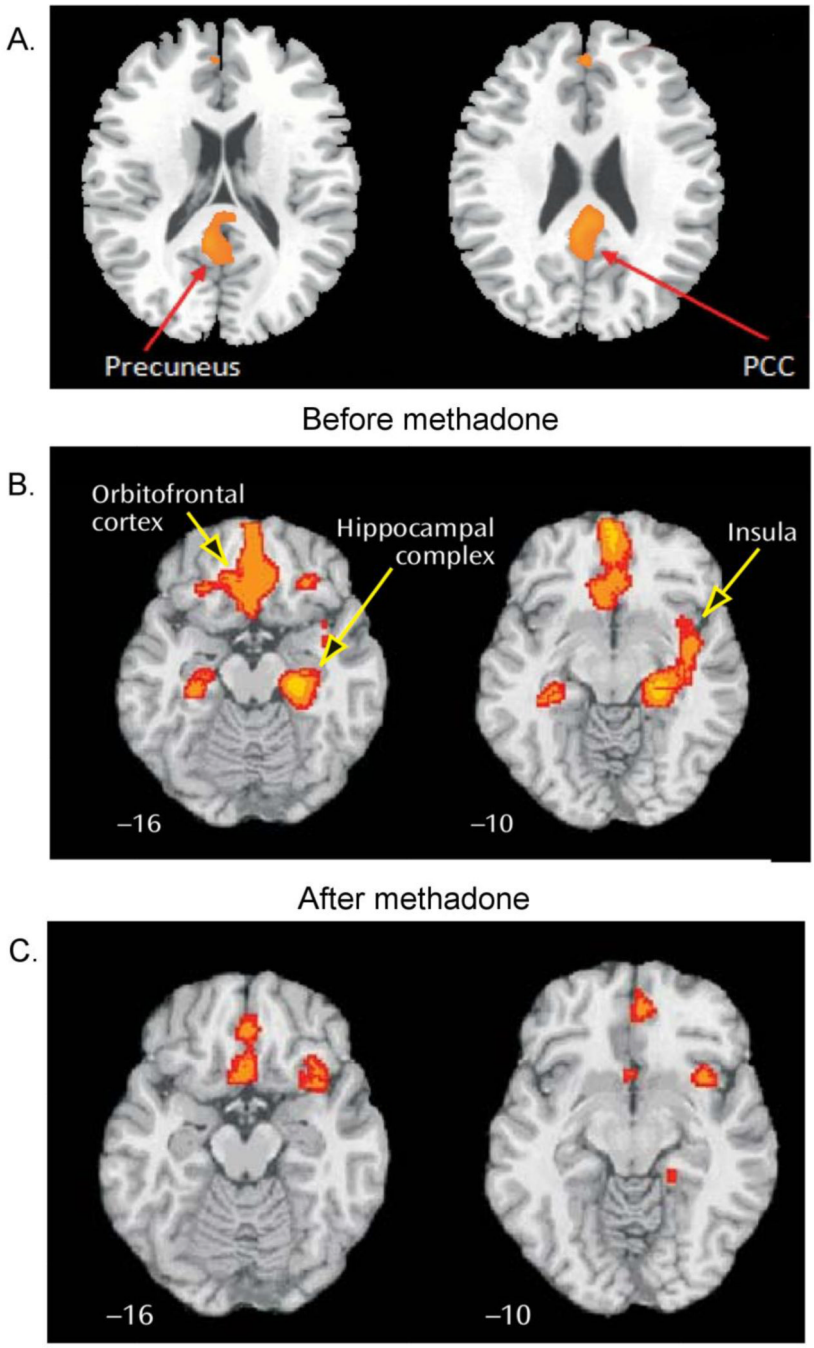

Figure 5.
Increased activity in DMN regions in response to cues. (A) BOLD activation in DMN regions (PCC, precuneus) to heroin-related versus neutral cues in opioid-dependent individuals (Reproduced from Wang et al., 2010). (B,C). Heroin-related cues increase BOLD activation in DMN regions (vmPFC, hippocampus) and the insula immediately prior to and after a methadone dose in opioid-dependent individuals (Reproduced from Langelben et al. 2008).

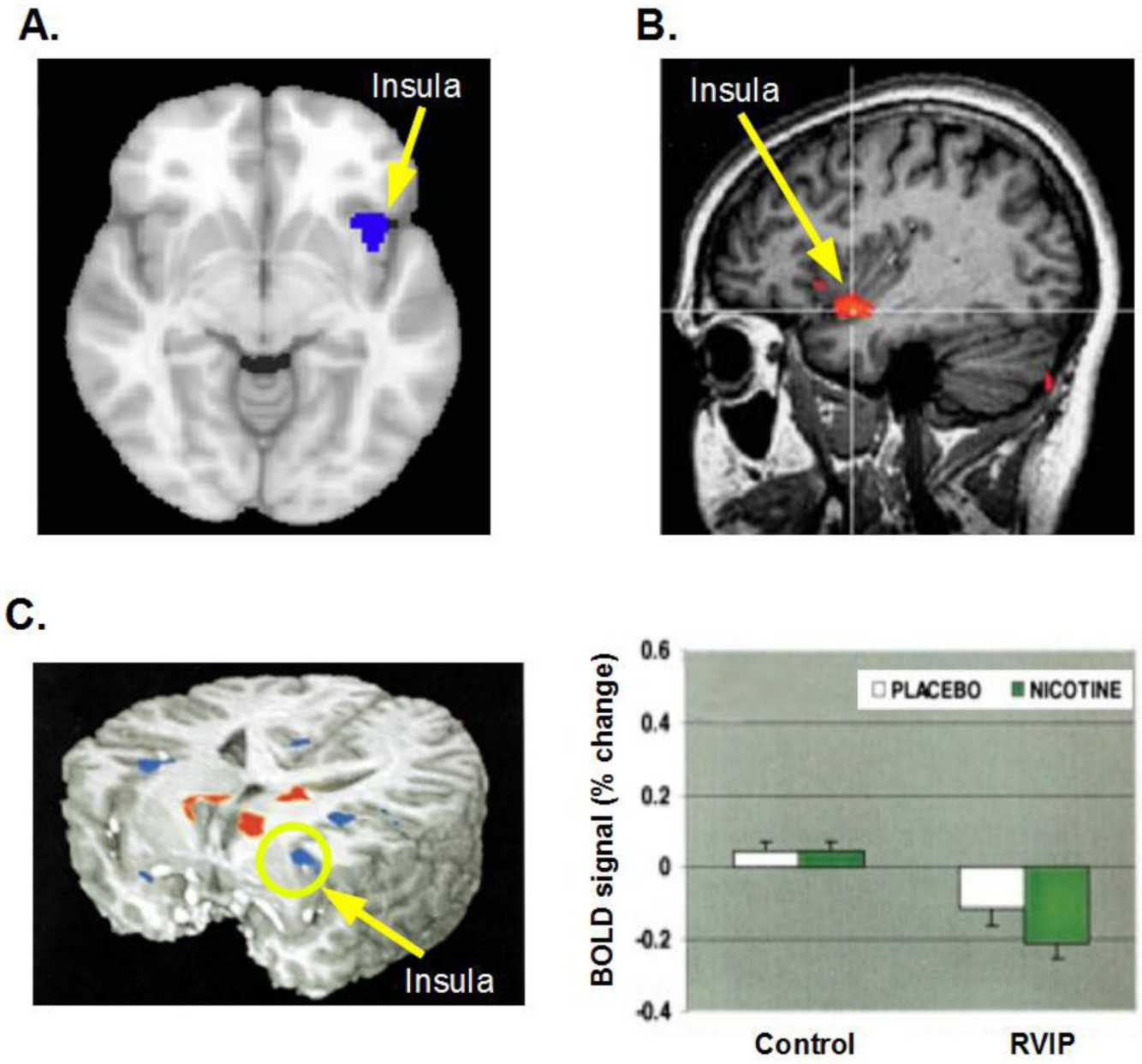

Figure 6.

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. (Reproduced from Zhang et al., 2010) (B) Increased insula activity to smoking-related versus neutral cues is positively correlated with attention to smoking-cues in an affective Stroop task. (Reproduced from Janes et al., 2010). (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 hrs) smokers. (Reproduced from Lawrence et al., 2002).

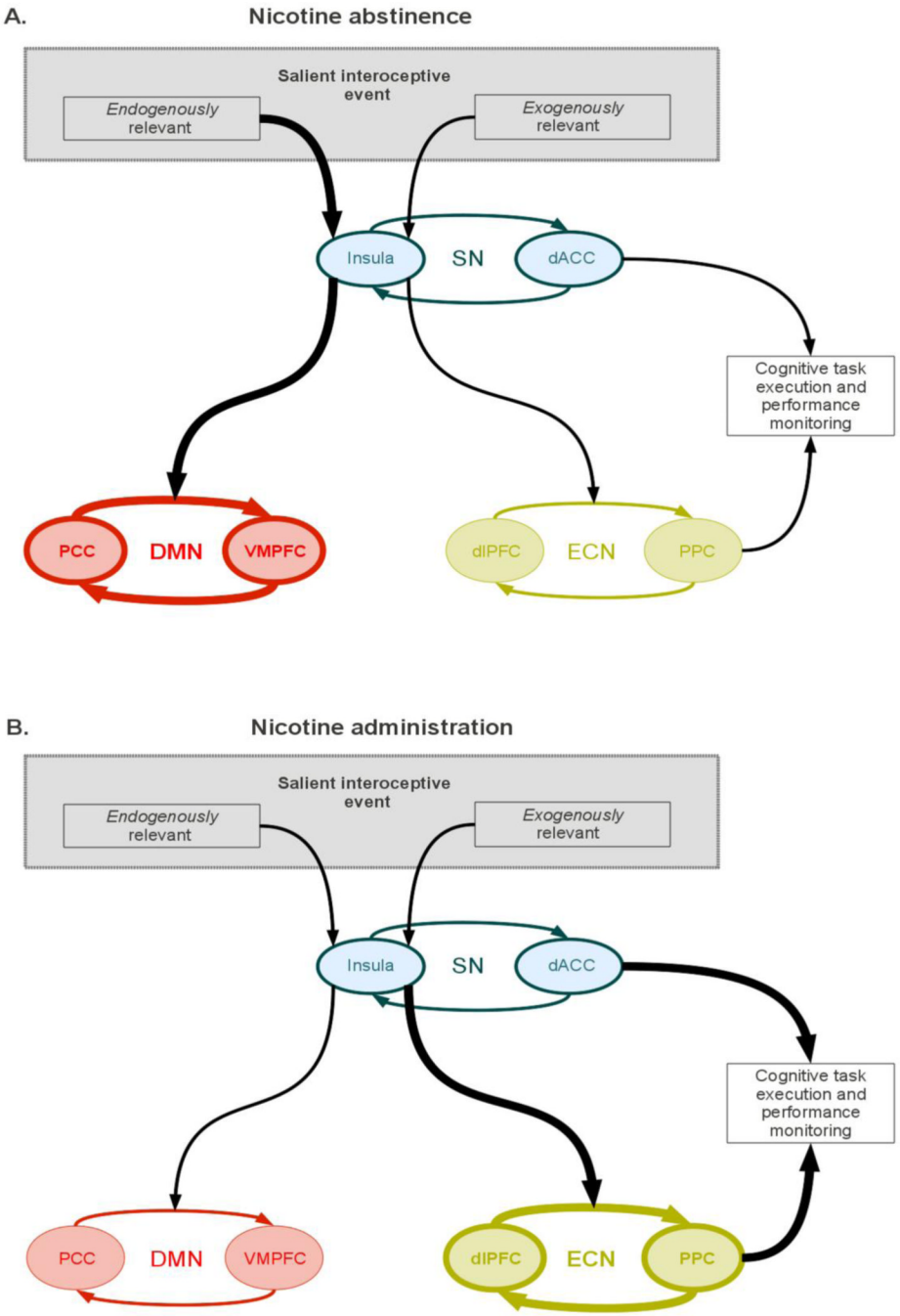

Figure 7.

A proposed model of activity within and between the 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.