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Brain default-mode network dysfunction in addiction

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ABSTRACT

Aberrant patterns of brain functional connectivity in the default mode network (DMN) have been observed across different classes of substance use disorder (SUD) and are associated with craving and relapse. In addicted individuals resting functional connectivity (RSFC) of the anterior DMN, which participates in attribution of personal value and emotional regulation, tends to be decreased, whereas RSFC of the posterior DMN, which directs attention to the internal world, tends to be increased. Aberrant RSFC within the DMN is believed to contribute to impaired self-awareness, negative emotions and to ruminations in addiction. Additionally, the disrupted connectivity between DMN and cortical regions involved with executive function, memory and emotion could be critical to drug-taking regardless of negative consequences and to stress-triggered relapse. At the system level, the dynamics of DMN interactions with the executive control and the salience networks are also disturbed in addiction. The DMN is prominently engaged during the withdrawal and preoccupation phases of the addiction cycle at the expense of the executive control network and with an enhanced participation of the salience network. In contrast, DMN prominence appears to be transitorily decreased during the intoxication phases. There is also growing evidence that disruption of the DMN in addiction reflects in part changes in dopaminergic, glutamatergic, and GABAergic signaling associated with acute and chronic drug use. Findings are starting to reveal DMN RSFC as a potential biomarker for predicting clinical outcomes in SUD and identify the DMN as a promising target for the treatment of addiction.

1. Introduction

Substance use disorder (SUD) is defined as a chronically relapsing disorder, characterized by compulsive drug-seeking behavior, loss of control in restricting intake, and emergence of a negative emotional state (e.g. dysphoria, anxiety, irritability) during withdrawal (Volkow et al., 2016). Drugs enhance dopaminergic signaling in reward regions of the brain (ventral tegmental area, nucleus accumbens) exerting strong reinforcing effects (intoxication phase) that condition the individual and motivate him/her to seek the drug in the future (Volkow et al., 2017). Continued and excessive drug use leads to neuroadaptations that reduce the sensitivity of the reward system and enhance the sensitivity of stress systems in the extended amygdala facilitating the emergence of negative emotions (withdrawal; Koob and Volkow, 2016). In parallel, neuroadaptations in striatal and cortical dopaminergic projections mediated through glutamatergic and GABAergic synaptic neuroplasticity (Volkow and Morales, 2015), impair executive function, including the capacity to exert self-regulation over emotions and desire for drugs (craving). This facilitates rumination and obsessive thinking about drugs (during preoccupation phase) that leads to relapse and compulsive drug taking despite adverse consequences (Volkow et al., 2016). Numerous preclinical and brain imaging studies have characterized the neurobiological mechanisms underlying these three recurring phases of the addiction cycle (Koob and Volkow, 2016). Findings are also emerging on how dopaminergic (DA), glutamatergic and GABAergic adaptations influence the communication between functional brain networks implicated in addiction (McCutcheon et al., 2019).

In the last decade, resting-state functional connectivity (RSFC) neuroimaging studies have expanded our understanding of the neurocircuitry implicated in the addiction cycle. RSFC studies, rather than examining brain activation while participants perform specific tasks, investigate the functional communication between different brain regions in a task-free condition. Impressively an individual's RSFC map can be used to predict their brain activation patterns during task performance (Tambini et al., 2010). Unlike experimental paradigm, which can cause variations in neural reactivity due to study-specific factors such as

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targeted sensory modality or length and type of cue presentation in drug cue reactivity paradigms (see review Jasinska et al., 2014), resting-state allows easier comparisons of data across independent studies and laboratories. Several methodologies have been developed for the analyses of RSFC images and applied to compare the brains from addicted individuals to that of non-addicted controls. The two most frequently use approaches are seed-based analysis that designates specific brain regions as seeds, and whole-brain analysis that extracts patterns of connectivity across the whole brain (e.g. independent component analysis (ICA) and functional connectivity density mapping (FCDM)) (Box 1 discusses methodology).

The default mode network (DMN) is a large-scale functional brain network that generally exhibits higher activity at rest (passive states) than during task performance. However, this common notion has been challenged by accumulating evidence showing that the DMN is actively involved in goal-directed tasks when internally directed/self-related cognition is required (Andrews-Hanna et al., 2010a; Buckner and Carroll, 2007). For example, the DMN was engaged when participants were required to retrieve episodic and autobiographical memory, to plan for personal future, to understand the behavior and thoughts of others, to appraise emotional information and to reflect upon one's self (Andrews-Hanna, 2012; Buckner et al., 2008; Spreng et al., 2009). The multiple components underlying self-related thoughts (e.g. personal significance, temporal and spatial orientation) are supported by different interacting subsystems of the DMN (Andrews-Hanna et al., 2014). Although the DMN is not fully defined, some regions are consistently revealed by different techniques and can be roughly divided into three components: a midline core network, a medial temporal subsystem (MTL-DMN) and a dorsal medial prefrontal subsystem (dMPFC-DMN) (Andrews-Hanna et al., 2010b; Fox et al., 2005; Golland et al., 2008; Greicius et al., 2003).

The midline core network comprised of the medial prefrontal cortex (MPFC) and the posterior cingulate cortex and precuneus (PCC/Precuneus), emerges in constructing personal meaning from salient events (Andrews-Hanna et al., 2014). Of note, MPFC and PCC have distinct contributions to self-related processes, emotion and evaluation (see Box 2 for more details). Remarkably, findings from the "1000 Functional Connectomes" project showed that the strongest functional connectivity hubs in the brain are located in the DMN midline core (MPFC and PCC/Precuneus) (Buckner et al., 2009; Tomasi and Volkow, 2011a). Through distributed connectivity throughout the brain, the DMN midline core presumably integrates information from various cortical areas to evaluate personal relevance and to facilitate self-related decision-making (Andrews-Hanna et al., 2010b; Gusnard et al., 2001b; Sutherland et al., 2012).

Both MTL-DMN and dMPFC-DMN subsystems are strongly connected with the midline core DMN (Andrews-Hanna et al., 2010b; Fox et al., 2005; Golland et al., 2008; Greicius et al., 2003). The MTL-DMN comprises medial temporal lobe (hippocampus, parahippocampal cortex), medial parietal cortex (retrosplenial cortex), the inferior parietal lobe (IPL comprising the angular gyrus and the posterior supramarginal gyrus) and ventromedial PFC (vMPFC) and becomes active when decisions involve constructing a mental scene based on memory (Andrews-Hanna et al., 2010b). The dMPFC-DMN comprises the dorsal medial prefrontal cortex (dMPFC), the temporoparietal junction and the lateral temporal cortex extending to the temporal pole (Andrews-Hanna et al., 2010b). The dMPFC-DMN allows individuals to process information in a meta-cognitive manner and is involved in social cognition (e.g. understanding the mental states of others), self-reflection and conceptual processing (Andrews-Hanna et al., 2014). For the specific role of regions involved in each subsystem please refer to the review from

Box 1
Analytic approaches in RSFC

Different approaches are applied to analyze RSFC. Here we focus on three of the most frequently-used approaches: seed-based analysis, independent component analysis (ICA) and functional connectivity density mapping (FCDM), and separately discuss their strengths and limitations.

Seed-based analysis is an hypothesis-driven method and is advantageous when there is strong theoretical support for selecting regions of interest for seed-voxel correlation analyses (Biswal et al., 1995; Uddin et al., 2009). Seed-based analysis is the simplest method to study functional connectivity. It provides a direct answer to specific questions about functional connectivity (i.e. which regions are most strongly connected with seed regions) and the results are easier to interpret relative to other methods (Cole et al., 2010b). However, seed-based analysis tends to reveal seed-specific rather than whole-brain networks (Buckner et al., 2008). Compared to whole-brain analysis such as ICA or FCDM, seed-based analysis has the potential of under-representing the data by disregarding alternative connectivity pathways. Furthermore, differences in seed selection (seed size, location and shape) can increase the variability of the connectivity patterns and make comparison across studies more difficult (Cole et al., 2010b).

ICA is a data-driven approach to identify synchronous brain networks by estimating spatially independent components from fMRI data (Beckmann et al., 2005; Damoiseaux et al., 2006). In contrast to seed-based analysis, ICA simultaneously examines the synchrony of the MRI signals in the whole brain. However, the number of imaging volumes and the choice of the number of components to be estimated influences the networks identified (Kiviniemi et al., 2009). An increasing number of components has the potential of splitting networks into multiple components, which might represent sub-systems with separate functions (Seeley et al., 2007) that makes the biological interpretations more complex (Cole et al., 2010b). In contrast to seed-based analysis, ICA quantifies the changes of intra- and inter-network connectivity at the network level. For example, ICA identifies regions that display altered synchrony with the other parts of the network (intra-network connectivity) or assesses changed dynamics between different networks (inter-network connectivity). ICA alone, however, cannot answer questions such as 1) whether lower synchrony of dMPFC with the rest of DMN in SUD depends on connectivity between dMPFC and PCC or between dMPFC and lateral parietal areas or 2) whether altered DMN-SN RSFC is determined by changes of anterior DMN-SN or posterior DMN-SN. To further characterize such contributions requires combination of ICA with seed-based methodologies.

FCDM is a data-driven method to map degree, the number of connections between voxels in the brain (Tomasi and Volkow, 2010). FCDM identifies regions with high connectivity or 'hubs', in graph theory terminology. Local (lFCD) maps are useful to study functional segregation and global (gFCD) maps are valuable to assess the long-range hubs necessary for functional integration across the brain (Tomasi and Volkow, 2011a). For example, comparing lFCD and gFCD, the DMN showed a higher proportion of long-range than short-range hubs, while regions involved in ECN have a relatively weaker representation of global than local FCD hubs at rest (Tomasi and Volkow, 2011a). FCDM can be used to guide the selection of seed regions for seed-based analyses (Tomasi and Volkow, 2011b). However, FCDM does not assess the directionality of the functional connectivity given by the strength of each voxel's connections. Nevertheless, FCDM and seed-based analysis are complimentary: FCDM can guide the seed selection process, and seed-based correlation analysis can be used to assess the directionality of the functional connectivity (Tomasi and Volkow, 2012).

Box 2
The role of the anterior and posterior midline core

The anterior midline core, particularly the ventromedial PFC (vMPFC) has extensive connectivity with the rest of the DMN (e.g. PCC, MTL) as well as the ventral limbic system and with subcortical regions involved in affect modulation (Andrews-Hanna et al., 2010b; Roy et al., 2012). The vMPFC is associated with the attribution of personal value. Activity increases in this region when processing personal information, making decisions pertaining to people who are important to us, and when processing emotional information with personal relevance (Benoit et al., 2010; Krienen et al., 2010; Wager et al., 2009).

The dorsal medial prefrontal cortex (dMPFC) can be distinguished from the vMPC by its role in cognitive processing. Of note, dMPFC is also a key structure in the dorsal medial prefrontal DMN subsystem involved in metacognitive processes (Andrews-Hanna et al., 2010b). The activity in the dMPFC increased during a task that required internally directed cognition (i.e. self-referential judgment). Meanwhile, the activity decreased in the vMPFC (Gusnard et al., 2001a), consistent with a competitive relationship between cognitive and emotional processing that might be subserved by these separate regions (Drevets and Raichle, 1998; Goel and Dolan, 2003).

The PCC is functionally heterogenous (Leech et al., 2011). While the ventral PCC shows strong functional connectivity to the rest of the DMN and engages in nearly all self-generated tasks, the dorsal PCC shows higher connectivity to frontoparietal networks of cognitive control (Leech et al., 2012) and stronger anti-correlation with attentional network (Chen et al., 2017) compared to ventral PCC. The ventral and dorsal PCC are intensely connected with each other and the broader PCC is proposed to play a role in directing attention to the internal world (Leech and Sharp, 2014) and relaying internal information for further evaluation (e.g. evaluated by vMPFC) (Andrews-Hanna et al., 2014).

Andrews-Hanna et al. (2014). Even though studies have tried to delineate the distinct functions of DMN subcomponents, it is important to keep in mind that DMN subsystems are highly integrated and co-activate as a whole during most self-generated experiences (Andrews-Hanna, 2012) and therefore, a clear differentiation of function is difficult. For example, the PCC (midline core network) works interactively with the hippocampal formation and parietal areas (MTL-DMN) for recollection of prior experiences (Vincent et al., 2006).

The DMN has been implicated in multiple brain diseases (Gusnard et al., 2001b; Raichle et al., 2001; Uddin et al., 2009) including SUD (Ding et al., 2015; He et al., 2018; Huang et al., 2014; Li et al., 2014a; Li et al., 2015c; Wang et al., 2016). Altered DMN function in neurological and psychiatric disorders has been associated with compromised cognitive functions (Leech and Sharp, 2014; Zhang and Raichle, 2010), rumination (Whitfield-Gabrieli and Ford, 2012) and emotional dysregulation (Hahn et al., 2011). Furthermore, DMN strongly interacts with subcortical areas and other large-scale networks most prominently with the executive control network (ECN) and the salience network (SN) (Raichle, 2015; Spreng et al., 2012). Dynamic interactions between the DMN and other networks influence cognition and emotion, affecting attentional performance and impulsivity (Fox et al., 2005; Shannon et al., 2011). In SUD increasing evidence indicates that both aberrant DMN function and disturbed interaction with other networks impair cognitive and affective processes that contribute to craving and relapse. Because resting functional networks are highly reproducible across laboratories it has allowed the integration of images from independent investigators (Jovicich et al., 2016; Pinter et al., 2016) and facilitated their evaluation as potential biomarkers of brain diseases and treatment outcomes (Greicius et al., 2004; Whitfield-Gabrieli et al., 2009).

This review summarizes findings from studies of RSFC of the DMN across different classes of SUD and discusses how these alterations contribute to the clinical presentation, outcomes, and vulnerability in addiction. Prior review papers on RSFC of the DMN have so far mostly concentrated on a specific type of SUD (Ieong and Yuan, 2017; Pandria et al., 2018; Sutherland et al., 2012) whereas here we aim to compare findings across different SUD to identify common patterns of DMN changes (Zilverstand et al., 2018). As the strength of RSFC has a direct influence on brain activation during task performance (Hampson et al., 2006; Kelly et al., 2008; Seeley et al., 2007; Tambini et al., 2010), this review also includes relevant studies on task-induced DMN activities. Specifically, in this review we summarize findings on: 1) altered RSFC within the DMN (local system); 2) altered RSFC interactions between DMN and other large-scale networks (global network interactions); 3) role of DA, glutamate and GABA in modulating the DMN and its disruption in SUD; 4) the interplay between the DA reward circuitry and the DMN in the three phases of the addiction cycle (i.e. drug intoxication, withdrawal and preoccupation); 5) the implications of the DMN as a potential biomarker of SUD and as a target for the treatment of addiction; and 6) research opportunities to advance our understanding of the DMN in SUD.

2. Midline core of DMN in addiction

The brain regions that constitute the midline core of DMN are among the most researched in neuroimaging studies of addiction (Table 1). Drug abuse has profound effects on both anterior (MPFC including the dMPFC, the rostral anterior cingulate (rACC) and parts of the anterior MPFC and vMPFC) and posterior DMN (PCC/Precuneus), which are presumed to have distinct functions but work interactively with one another (Gusnard et al., 2001b) (Fig. 1).

2.1. Midline core of DMN at resting state

Studies of resting baseline activity that measured glucose metabolic rate (a marker of brain function) reported an association between higher activity in regions of the anterior and posterior DMN and the personality trait of positive emotionality, which is considered a protective factor for SUD (Volkow et al., 2011a). In contrast, studies of resting brain glucose metabolism have found significant reductions in MPFC activity in cocaine abusers (Volkow et al., 1992, 1991), alcoholics (Volkow et al., 1997b), methamphetamine (Volkow et al., 2001) and cannabis abusers (Wiers et al., 2016a) when studied during the withdrawal/detoxification phase. Using ICA, lower synchrony of the dMPFC with other regions of the DMN was reported in recently detoxed medication-free, heroin-dependent individuals relative to controls (Li et al., 2016), which was associated with heroin craving. The MPFC, especially the vMPFC, encompassing the ventral anterior cingulate cortex (vACC) and the medial orbitofrontal cortex (mOFC) is recognized as a central component of the valuation system of the brain (Bartra et al., 2013). The MPFC participates in emotional processing, decision-making (Fuster, 1988), salience attribution (Goldstein and Volkow, 2011) and is implicated in the dysregulation of the reward and motivation circuits in addiction (Volkow et al., 2003, 1992).

Changes in the posterior DMN have also been reported in SUD. A case study reported complete loss of interest in smoking after a patient with a cigarette smoking history suffered an intracerebral hemorrhage in the PCC (Jarraya et al., 2010). Using ICA, higher synchrony of PCC with other parts of the DMN was found in 24-h abstinent alcohol-dependent

Table 1
Summary of fMRI findings of changes within the midline core of DMN in drug abusers at rest and during tasks.

DMN	Drug used	Resting state	References	During tasks	References
Anterior DMN	cannabis	↓ right MPFC connectivity, active user (MJ: n = 19; MJ + MDD: n = 20)	Osuch et al. (2016)		
	heroin	↓ dMPFC connectivity, detoxified, male (n = 27)	Li et al. (2016)		
	nicotine			↑drug cue-reactivity in OFC/rostral ACC in quitting-unmotivated smokers (n = 43; quitting-motivated: n = 47)	Wilson et al. (2012)
				↑drug cue-reactivity in OFC/rostral ACC with higher nicotine dependence, 16–18 h abstinence (n = 18)	Goudriaan et al. (2010)
	cocaine			↓error-preceding vMPFC activation (SST task), two weeks abstinence (n = 23)	Bednarski et al. (2011)
				↓cue-reactivity (cocaine vs. neutral cue) in OFC and rostral/ventral ACC active user, male (n = 20)	(Tomasi et al., 2015b)
	alcohol			↑drug cue-reactivity in OFC, 1–3 weeks abstinence, Male (n = 10)	Hermann et al. (2006)
Posterior DMN	alcohol	↑PCC connectivity, 24 h abstinence, mainly male (n = 25)	Zhu et al. (2017)	↑PCC activation (stroop task) early and sustained remission, male (n = 18)	Schulte et al. (2012)
		↓Precuneus connectivity density, active user, male (n = 16)	Shokri-Kojori et al. (2017)		
		↓Precuneus connectivity active user, mostly male (n = 28)	Vergara et al. (2017)		
		After 90 min: ↓Precuneus & PCC connectivity acute administration, male (n = 14)	Weber et al. (2014)		
	cannabis	↑PCC connectivity, one-month abstinence, male (n = 28)	Pujol et al. (2014)		
		↑right precuneus connectivity active user with early-onset vs. late-onset (MJ: n = 19; MJ + MDD: n = 20)	Osuch et al. (2016)		
	heroin	↑left precuneus connectivity relapse vs. abstinence during MMT, mainly male (n = 13)	(Li et al., 2015b)		
		↓ PCC connectivity, during heroin-assisted treatment for at least 6 months (n = 20)	Schmidt et al. (2015)		
	cocaine			↓error-preceding PCC activation (SST task), two weeks abstinence (n = 23)	Bednarski et al. (2011)
				↑drug cue-reactivity in PCC, active user, mostly male (n = 17)	Garavan et al. (2000)
				↑cue-reactivity (cocaine vs. food cue) in precuneus and posterior cingulum active user, male (n = 20)	(Tomasi et al., 2015b)
	nicotine	↓ PCC activity, acute administration (n = 19 non-smoker)	Tanabe et al. (2011)	↑PCC activation in the abstinent (24 h) vs. sated state (WM task) (n = 73)	Falcone et al. (2014)
	cannabis + nicotine	no changes (vs. controls), 72 h abstinence from cannabis and 12 h abstinence from nicotine, male (n = 26)	Filbey et al. (2018)		
Anterior-posterior DMN connectivity	alcohol	↓ PCC-MPFC connectivity (early remission vs. sustained remission), male (n = 26)	Müller-Oehring et al. (2015)		
	nicotine	↓ PCC-MPFC connectivity, acute users, male (n = 15)	Tang et al. (2016)		
		↓ PCC-vACC/MOFC	Wetherill et al. (2015)		
		↑PCC-lateral frontal poles connectivity, active user (n = 24, nicotine + cannabis: n = 23)			
	heroin	↓ PCC-MPFC connectivity, active user Male (n = 14)	Ma et al. (2015)		
	cannabis	↓ PCC-MPFC connectivity, active user (n = 19, cannabis + nicotine: n = 23)	Wetherill et al. (2015)		

PCC: Posterior Cingulate Cortex, **MPFC:** Medial Prefrontal Cortex, **OFC:** Orbitofrontal Cortex, **ACC:** Anterior Cingulate Cortex, **MMT:** Methadone Maintenance Treatment, **WM:** Working Memory, **SST:** Stop Signal Task, **MJ:** Marijuana, **MDD:** Major Depression Disorder.

patients (Zhu et al., 2017) compared to controls. Early-onset cannabis users had greater RSFC within DMN comprising the right precuneus compared to late-onset users (Osuch et al., 2016). Compared to abstinent patients, relapsed heroin users had higher synchrony between the posterior DMN and the rest of the DMN (Li et al., 2015b). Intriguingly, using seed-based analysis (seed located on the boundary between ventral and dorsal PCC), chronic cannabis users showed increased RSFC within ventral PCC, which is strongly connected to the rest of DMN and reduced RSFC within dorsal PCC, which is strongly connected with frontoparietal networks (Leech et al., 2012; Pujol et al., 2014). Still, findings are not always consistent. For example, using ICA, lower synchrony of PCC with other parts of DMN was observed in heroin abusers on long term

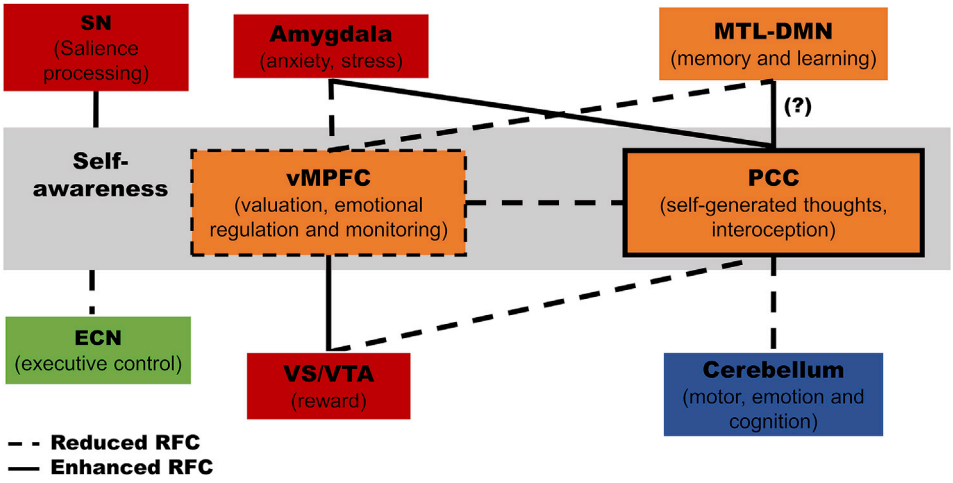

Fig. 1. Summary of resting functional connectivity in drug-addicted individuals. RSFC within the midline core of DMN (denoted in semi-transparent grey color) and between DMN and other brain regions and networks (ECN and SN) is changed in drug abusers. Dashed line/frame delineates reduced connectivity and solid line/frame depicts enhanced connectivity. Question mark in the brackets indicates inconsistent findings. Note that the amygdala and the VS are considered by some to be part of the SN.

maintenance with heroin when given an acute placebo (but not when given acute heroin) compared to controls (Schmidt et al., 2015). Using FCDM, active heavy drinkers exhibited reduced FCD in DMN; and in PCC the reduced FCD was associated with worse cognitive performance (Shokri-Kojori et al., 2017). These inconsistent findings could reflect concurrent use of multiple drugs, stage in the addiction cycle when scanning was performed, and the different analytic approaches used to measure RSFC (Box 1). Co-morbid substance use, which is very frequent in SUD, can affect connectivity in a more complex manner (Filbey et al., 2018; Vergara et al., 2017). For example, using ICA, it was shown that individuals with concomitant use of nicotine and cannabis had greater synchrony of posterior DMN with other parts of DMN than those with isolated cannabis or nicotine use (Filbey et al., 2018; Wetherill et al., 2015) and also greater synchrony of anterior DMN than those who only used nicotine (Filbey et al., 2018). The PCC is involved in directing attention to the internal world and its activity and connectivity are attenuated when attention is directed from internal thoughts towards external stimuli (Buckner et al., 2008; Buckner and Carroll, 2007; Small et al., 2003). In general, hyper-synchrony of PCC with other parts of DMN during abstinence might underlie the ruminatory behavior that can result in distress and unhappiness (Killingsworth and Gilbert, 2010).

The MPFC and PCC are structurally (Greicius et al., 2009) and functionally (Buckner et al., 2008) connected. Both of them are recruited for self-related thoughts, though in distinctive functions (Box 2 for more discussion). The PCC/precuneus appears to direct attention to internal and external information (Andrews-Hanna et al., 2014) and relays this information to the anterior DMN, which is implicated in continuously monitoring the internal states, imparting emotional and personal valence to it (Abraham, 2013; Moeller and Goldstein, 2014). In general, a pattern of functional hypoconnectivity within the midline core (reduced anterior-posterior DMN connectivity) has been reported in SUD (Vergara et al., 2017) including alcoholics (Müller-Oehring et al., 2015), smokers (Tang et al., 2016), heroin-dependent (Ma et al., 2015) and cannabis-dependent individuals (Wetherill et al., 2015). Reduced anterior-posterior DMN connectivity has been associated with impaired self-awareness (Carhart-Harris et al., 2012), which in SUD is characterized by failure to ascribe personal relevance or significance to internal or external stimuli that have implications for the self, such as interoception, environmental cues and feedback of ongoing behavior (Moeller and Goldstein, 2014). Impaired self-awareness in SUD contributes to uncontrolled drug-taking despite negative consequences and to their seemingly paradoxical reduced sensitivity to the rewarding effects of drugs (Volkow and Morales, 2015). In sated tobacco smokers the connectivity between vMPFC and PCC was decreased, whereas connectivity between the bilateral frontopolar cortex and PCC was enhanced after acute nicotine administration (Wetherill et al., 2015). The vMPFC and the frontopolar cortex are engaged in affective (Blair, 2007; Li et al., 2014b; Margulies et al., 2007) and cognitive control processing (Moayedi et al., 2015) respectively. Therefore, lower PCC connectivity with vMPFC could interfere with emotionally regulated cognitive control and decision-making (Hutcherson et al., 2012; Wetherill et al., 2015) while the increased frontopolar connectivity after acute nicotine could underlie nicotine's improvement of attention and memory (Heishman et al., 2010; Wetherill et al., 2015).

In sum, most studies in drug-addicted individuals show decreased anterior DMN function and RSFC between anterior DMN particularly vMPFC and posterior DMN. In contrast, elevated function of posterior DMN has been reported in abstinent drug users, though reduction has been reported by some studies. RSFC changes within the DMN correlate with increased craving and relapse in SUD (Li et al., 2016; Li et al., 2015b). The aberrant RSFC in drug abusers could underlie their impairments in self-awareness, emotional dysregulation and the increases in self-related thoughts during abstinence.

2.2. *Midline core of DMN during task performance*

The DMN is postulated to modulate activity in task-positive networks (Uddin et al., 2009). DMN activity (McKiernan et al., 2003; Shulman et al., 1997) and connectivity (Fransson, 2006) decrease during goal-directed task performance (without requirement of internal contents), which typically occurs in association with increased activation in task-relevant regions, such as dorsal anterior cingulate cortex (dACC) and lateral PFC (Fransson, 2006; Tomasi et al., 2006). Failure to suppress DMN activity during task performance, coupled with decreased task-evoked activation in prefrontal areas is associated with impaired cognitive performance (i.e. slower RTs, increased errors) in healthy controls (Polli et al., 2005; Weissman et al., 2006).

When exposed to drug-related stimuli, addicted individuals showed increased activity in anterior (Engelmann et al., 2012; Moeller and Goldstein, 2014; Volkow et al., 2005) and posterior DMN (Garavan et al., 2000; Vollstädt-Klein et al., 2011). Drug and cue-evoked increases in anterior DMN activity were positively related to craving and relapse in cocaine abusers (Volkow et al., 2005), alcoholics (Seo et al., 2013) and in smokers to the expectation of immediate smoking (Wilson et al., 2012) and nicotine dependence (Goudriaan et al., 2010). The vMPFC participates in emotional processing and its reduced activation during cognitive task performances is thought to reflect a dynamic interplay between cognitive and emotional processes (Drevets and Raichle, 1998; Goel and Dolan, 2003). This role of the vMPFC relies on its dense connectivity to the limbic system (Roy et al., 2012), and to executive network regions such as the dorsolateral PFC (Hare et al., 2009). Enhanced activity in anterior DMN in drug abusers exposed to cues might accordingly indicate increased emotional involvement to

drug-related stimuli, which are ascribed with high personal relevance at the expense of cognitive control over craving. Indeed, successful cognitive inhibition of craving in cocaine abusers when exposed to cocaine-cues was associated with lower activation of the right mOFC, a subregion of the vMPFC (Gourley et al., 2016) and higher activation of the right inferior frontal cortex, which is involved in a wide range of executive control processes (Volkow et al., 2010a). Intriguingly, a recent study found that the vMPFC participated in extinction learning of drug-related cues and was impaired in cocaine abusers in whom it correlated with craving (Konova et al., 2019). As the vMPFC updates the value of cues, its disruption may mediate the inability to discontinue drug use despite reduced pleasure from the drug and its multiple negative consequences (Konova et al., 2019; Volkow and Fowler, 2000).

In comparison, reduced posterior DMN activity during external-oriented tasks is presumably linked to shifting attention from self-related thoughts to external stimuli (Andrews-Hanna et al., 2014). In SUD participants drug-cues compared to food-cues elicited higher activity in posterior DMN (precuneus/PCC) (Fig. 2), which could reflect greater internal-directed attention triggered by drug cues than by other reinforcers (Tomasi et al., 2015b).

For non-drug related stimuli, a study in alcoholics reported failure to exhibit PCC deactivation in an inhibitory task as observed in controls (Schulte et al., 2012). Likewise, smokers displayed less suppression of PCC activity in a working memory task when they were in the abstinent states as compared to satiety (Falcone et al., 2014) and reduced suppression of PCC predicted early smoking relapse (Loughead et al., 2015). During the stop signal task, healthy controls showed activation of bilateral precuneus, PCC and vMPFC preceding errors, while these error-predicting activations were not observed in cocaine-dependent individuals (Bednarski et al., 2011; Li et al., 2010).

Furthermore, the effect size of error-preceding vMPFC activation was inversely correlated with years of cocaine use (Bednarski et al., 2011). Enhanced vMPFC deactivation was associated with improved inhibitory control and better self-control (Matuskey et al., 2013). Overall, failed suppression of DMN activity during tasks in SUD has been associated with increased drug-cue reactivity and with impaired cognitive control (Bednarski et al., 2011; Garavan et al., 2000; Matuskey et al., 2013; Volkow et al., 2005; Vollstädt-Klein et al., 2011). The compromised cognition in addiction might result in part from impairments in their ability to loosen emotional involvement for cognitive control processes and for directing attention from self-generated thoughts to external stimuli, mediated by disrupted activity in anterior and posterior DMN, respectively.

3. Midline core DMN connectivity with medial temporal DMN (MTL-DMN) in addiction

The MTL-DMN subsystem is reliably activated by past and future autobiographical thought and episodic/contextual retrieval (Andrews-Hanna et al., 2010b; Davidson et al., 2008). Differences of RSFC within the MTL-DMN reflected the degree of experienced spontaneous thoughts about personal past and future: Individuals who experienced more such thoughts exhibited higher RSFC within MTL-DMN (Andrews-Hanna et al., 2010a). Midline core DMN strongly interacts with the MTL-DMN subsystem (Andrews-Hanna et al., 2010b; Buckner et al., 2008) and is profoundly involved when retrieving memory that has personal relevance. For instance, midline core DMN had greater activity when individuals retrieved autobiographical events that happened in the external world compared to previously-imagined autobiographical events (Summerfield et al., 2009). The midline core was also consistently co-activated by simulation of personal future thought (Andrews-Hanna et al., 2010b), especially in a familiar context where they have past experience (Szpunar et al., 2009).

Changes on connectivity between midline core DMN and MTL-DMN in SUD have been implicated in the conditioning of internal affective states with the experience of drug intake (Volkow et al., 2003; White, 1996). However, the specific pattern of connectivity disruption is not consistent across studies. For example, whereas studies in heroin-dependent individuals reported lower PCC/precuneus connectivity with parahippocampal area (Ma et al., 2015; Wetherill et al., 2015), studies in alcohol abusers reported greater PCC connectivity with right hippocampus (Müller-Oehring et al., 2015). Conflicting findings probably reflect in part differences on how concurrent use of drugs were controlled. For example, while one study revealed greater synchrony between parahippocampal area and other parts of DMN in cannabis users using ICA (Osuch et al., 2016), another study, that controlled for the use of nicotine and alcohol in cannabis users, reported lower PCC-parahippocampal connectivity (Wetherill et al., 2015). Regarding connectivity between anterior DMN and medial temporal lobe, cocaine-addicted individuals displayed decreased RSFC between rACC (extending ventrally and anteriorly to vMPFC), and hippocampus/parahippocampal gyrus using seed-based analyses (Gu et al., 2010).

The IPL appears to participate in attention and recollective aspects of episodic memory (Corbetta et al., 2000; Davidson et al., 2008; Seghier, 2013; Wheeler and Buckner, 2004; Zhang and Li, 2014). Young binge drinkers showed higher RSFC (assessed by magnetoencephalography (MEG)) between IPL and DMN (both MFC and PCC) than controls in delta, theta and beta frequency bands (Correas et al., 2016), which might reflect the influence of their previous drinking experiences. Also due to its intense connectivity to PCC, the posterior IPL (pIPL) is thought to engage in self-referential processing by directing attention to the internal world during resting-state (Laird et al., 2009). Brain lesions involving right angular gyrus, which is located in pIPL (Seghier, 2013) and PCC typically interfere with body awareness (Mesulam, 1990, 1981). Increased angular gyrus connectivity with precuneus in smokers was

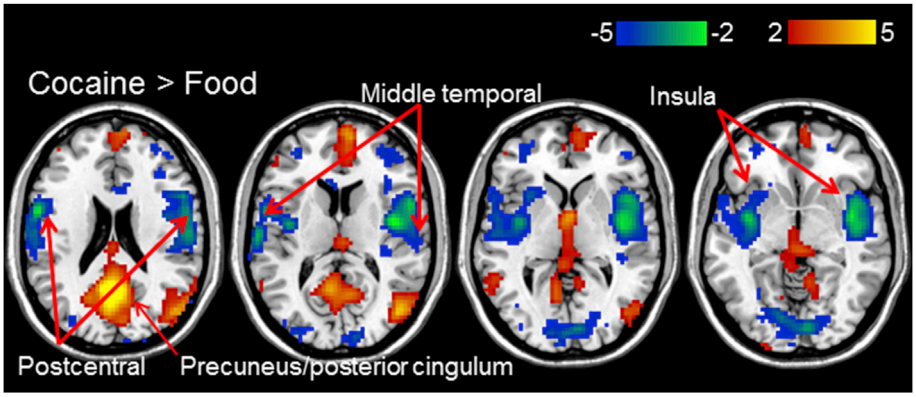

Fig. 2. Statistical significance of differential activation responses to drug cues vs. food cues in SUD. In SUD participants, drug cues compared to food cues, elicited higher activity in the posterior DMN (precuneus and PCC) whereas they elicited less activation in MTL and insula. Modified with permission based on Figure 7 of Tomasi et al. (2015b)..

associated with nicotine dependence severity (Vergara et al., 2017). Enhanced interoception and somesthesis might elicit the urge to smoke in individuals with severe nicotine dependence.

Remarkably, smoking seems to have the opposite effect on IPL-posterior DMN and IPL-anterior DMN connectivity. Unlike enhanced IPL-PCC connectivity, IPL-MPFC connectivity was reduced in smokers (Tang et al., 2016). Given the role of MPFC in representing personal value (Andrews-Hanna et al., 2014) and affective meaning (Roy et al., 2012), the IPL-MPFC connectivity might affect the personal salience assigned to the retrieved memory and impede recall for the best action including the emotional response to specific events and circumstance from past experiences (Euston et al., 2012). Lower IPL-MPFC connectivity thus might bias decision-making in smokers leading to risky behavior and further drug use (Briggs et al., 2015).

Taken together, reduced connectivity between anterior DMN and MTL-DMN (including medial temporal lobe and IPL) might intrude decision-making by affecting the attribution of personal relevance to the retrieved episodic memory. Even though the findings of MTL-DMN with posterior DMN connectivity are inconsistent, its disruption might interfere with recollecting autobiographical information in SUDs and contribute to conditioning of emotional states that are associated with drug taking (Fig. 1).

4. Midline core DMN connectivity with the dorsal medial prefrontal DMN (dMPFC-DMN) in addiction

The dMPFC-DMN, including dMPFC, temporoparietal junction and lateral temporal cortex/temporal pole (Andrews-Hanna et al., 2010b) plays an important role in mentalizing and conceptual processing that relate to social cognition (Andrews-Hanna et al., 2014). Weaker RSFC between right temporal pole and MPFC was revealed in non-treatment-seeking cocaine users and predicted their relapse status in five months (Geng et al., 2017). In contrast, greater RSFC between lateral temporal lobe (middle temporal gyrus and temporal pole) and PCC was shown in alcohol abusers (Müller-Oehring et al., 2015). Both cocaine (Preller et al., 2014) and alcohol abusers (Bora and Zorlu, 2017; Freeman et al., 2018) showed deficits in social cognition including facial emotion recognition and in inferring the mental states of others. Though there are few studies on the involvement of the dMPFC-DMN in addiction there is increased recognition that impaired social cognitive processing interferes with social function and is an important factor jeopardizing recovery in addiction (Kroll et al., 2018).

5. Midline core DMN connectivity with subcortical regions in addiction

The midline core DMN has widespread connectivity with subcortical areas including cerebellum, amygdala and striatum (note that some include the amygdala and striatum as part of the SN discussed below (Borsook et al., 2013; Seeley et al., 2007)). Altered connectivity from DMN to subcortical regions might contribute to cognitive, emotional and reward-related dysregulation in SUD (Koob and Volkow, 2016; Volkow et al., 2003) (Fig. 1).

Lower RSFC between PCC and cerebellar regions was reported in alcoholics (Chanraud et al., 2011), in cannabis- and nicotine-dependent individuals (Wetherill et al., 2015) when compared to controls. Stronger RSFC correlated with longer sobriety in alcoholics (Chanraud et al., 2011). In addition to motor functions, the cerebellum participates in executive control, salience detection and memory/self-reflection (Habas et al., 2009; Strick et al., 2009). Recently a direct excitatory projection between the cerebellum and the ventral tegmental area (VTA), which is key brain region involved with drug reward and addiction, was reported in mice (Carta et al., 2019). Cerebellar lesions or dysfunction can lead to cognitive and emotional impairments (Riva et al., 2013; Stoodley and Schmahmann, 2018). Accordingly, there is extensive evidence of cerebellar involvement in addiction (Moreno-Rius and Miquel, 2017; Moulton et al., 2014). For example, cerebellar activation is associated with cue-induced craving in addicted individuals (Li et al., 2015a; Tomasi et al., 2015b) and this activation decreased with chronic drug use (Tomasi et al., 2015b). Interestingly, a study in participants with internet gaming disorder showed that those with childhood attention deficit hyperactivity disorder (ADHD) had aberrant PCC-cerebellum RSFC, which correlated with self-reported impulsiveness (Lee et al., 2017). Thus, decreased connectivity between DMN and cerebellum in SUD might not only contribute to disturbed motor functions (Yalachkov et al., 2010) but also to cognitive and emotional deficits associated with craving and drug-taking (Moreno-Rius and Miquel, 2017; Moulton et al., 2014).

The vMPFC is heavily connected with the amygdala and other limbic structures (Gusnard et al., 2001b). The amygdala is involved in fast, negative emotional reactions such as fear and anxiety, which can be regulated through slower cortical input (LeDoux, 1995). Lower RSFC between MPFC and amygdala has been repeatedly reported in SUD including decreased amygdala connectivity with vMPFC/rACC in cocaine (Gu et al., 2010), heroine (Wang et al., 2010) and prescription-opioid use disorders (Upadhyay et al., 2010). Furthermore, greater reduction in amygdala-vMPFC connectivity was associated with longer periods of opioid use (Upadhyay et al., 2010) and increased risk of relapse (McHugh et al., 2014). The vMPFC has been posited to suppress amygdala activity (Foland-Ross et al., 2010; Hariri et al., 2003; Kim et al., 2011b) alleviating emotional distress (Ochsner et al., 2004). Indeed, diminished amygdala-vMPFC connectivity has been related to higher anxiety levels both in non-clinical groups (Dincheva et al., 2015; Kim et al., 2011a; Pezawas et al., 2005) and individuals with neuropsychiatric disorders (Hahn et al., 2011; Motzkin et al., 2011; Phan et al., 2009). The extended amygdala underlies the withdrawal/negative affect stage in the addiction cycle (Koob and Volkow, 2016). Lower connectivity between amygdala and MPFC could increase the sensitivity to stress and anxiety in SUD, which in turn could contribute to drug-taking as a means to temporarily reduce tension and anxiety (Berlin and Hollander, 2014). Meanwhile, abstinent heroin abusers (Xie et al., 2011) and smokers (Shen et al., 2017) showed an attenuated negative correlation between amygdala and posterior DMN (precuneus) that might underlie increased internal-directed attention and ruminatory behavior, and contribute to distress and unhappiness (Killingsworth and Gilbert, 2010). Thus, higher amygdala-posterior DMN connectivity might enhance the amygdala reactivity and impulsivity while lower amygdala-anterior DMN disrupts the regulation of negative affect mediated by amygdala.

The ventral striatum (VS) is modulated by DA projections from the VTA and plays an essential role in the reward and motivation circuit in addiction (Mitchell et al., 2012; Volkow et al., 2007, 2003). Increased RSFC between VS and vMPFC has been reported in heroin (Ma et al., 2010) and cocaine users (Wilcox et al., 2011), and in alcoholics it was associated with higher trait anxiety scores (Müller-Oehring et al., 2015). In contrast, lower connectivity between VS and posterior DMN was observed in chronic cocaine users (Wilcox et al., 2011). The opposite patterns of connectivity of VS to anterior and posterior DMN in SUD might contribute to the opposite pattern of RSFC within anterior and posterior DMN (i.e. decreased in anterior DMN and increased in posterior DMN) as well as the decreased RSFC between them. Moreover, cocaine abusers who were successful in cognitively inhibiting craving when exposed to cocaine cues exhibited an associated decrease in activity of vMPFC and VS along with increased activity of the right inferior frontal cortex, which is fundamental for inhibition of motor, cognitive and emotional responses (Volkow et al., 2010a).

The dorsal striatum (DS) is modulated by DA projections mostly from the substantia nigra and is implicated in motor (mostly putamen) and cognitive control (mostly caudate) processes (Balleine and O'Doherty, 2010; Graybiel, 2008; Seamans and Yang, 2004). Alcoholics showed weaker caudate-PCC RSFC than controls (Müller-Oehring et al., 2015) and weaker connectivity between putamen and MPFC during an inhibition task that was associated with greater alcohol dependence severity (Courtney et al., 2013).

Overall, RSFC between midline core DMN and subcortical areas is disrupted in SUD and the anterior and posterior DMN tend to show opposite patterns of RSFC changes. There is evidence that aberrant RSFC between midline core DMN and subcortical areas enhances negative emotion, impairs cognitive inhibition, increases craving and contributes to relapse in SUD. However, the specific role of the various connectivity tracts remains unclear and requires further investigation.

6. Interactions between DMN and the ECN and SN in addiction

Large-scale networks and their dynamic interactions is necessary for proper brain function (Bressler and Menon, 2010; van den Heuvel and Hulshoff Pol, 2010). Disrupted interaction between DMN and other functional networks has been reported in addiction (Li et al., 2018; Liang et al., 2015; Shahbabaie et al., 2018). One of the most investigated networks is the frontoparietal ECN, which is associated with top-down cognitive control functions including attentional control, working memory, cognitive flexibility and decision making (Cole et al., 2013; Seeley et al., 2007). Cocaine-dependent individuals showed reduced connectivity between PCC and ECN (Liang et al., 2015). Also, heroin-dependent individuals had lower connectivity between dMPFC and left dorsolateral PFC (dlPFC: key node of ECN), which was associated with relapse (Li et al., 2018). Larger negative coupling between DMN and ECN (networks identified by ICA) after nicotine replacement therapy in abstinent smokers was associated with greater reduction in withdrawal symptoms and in cognitive impairments (Cole et al., 2010a).

The SN, which directs attention to salient events (Seeley et al., 2007) is primarily comprised of the anterior insula and dACC (Menon and Uddin, 2010; Uddin, 2015), though the amygdala and striatum are also considered to be part of the SN (Borsook et al., 2013). The insula detects salient events and initiates appropriate control processing for them (Craig, 2009, 2002; Menon and Uddin, 2010). There is evidence that the anterior insula mediates dynamic activity between DMN and ECN flexibly directing attention to internal or external events (Fedota et al., 2018; Sridharan et al., 2008). During abstinence, impaired cognitive performance might result from a shift of activity from ECN towards DMN. Conversely, acute nicotine administration in nicotine smokers biases processing from the DMN to the ECN (Sutherland et al., 2012). Cannabis- and heroin-dependent individuals who were required to refrain from drug use before scanning showed increased connectivity between PCC and right anterior insula, which was related to duration of cannabis (Pujol et al., 2014; Wetherill et al., 2015) and heroin use (Li et al., 2013). Increased connectivity between PCC and insula, which plays a key role in interoceptive awareness, perception and consciousness (Caseras et al., 2013; Craig, 2009; Critchley et al., 2004; Gasquoine, 2014), might render addicted individuals more sensitive to visceral sensations, stress and negative emotions promoting craving (Naqvi and Bechara, 2010, 2009). On the other hand, a study that used graph theory analysis, which defines modules as groups of nodes that are highly connected with each other reported altered modularity in DMN and SN in cocaine abusers (Newman and Girvan, 2004). Specifically, cocaine abusers showed decreased inter-module connectivity between DMN and SN (contributed by reduced rACC connectivity to the SN module comprised of dACC and insula, and reduced insula connectivity to the DMN module comprised of rACC, MPFC, superior frontal cortex, inferior temporal lobe and PCC/precuneus) (Liang et al., 2015). These findings are seemingly inconsistent with those obtained using seed-based analyses. However, this might reflect satiation: in the study by Liang and colleagues, cocaine users were not required to discontinue their cocaine use and nicotine smoking was allowed before scanning, which might have shifted processing away from DMN to ECN, diminishing insula-DMN connectivity (Sutherland et al., 2012).

There is evidence of a dual role of dACC in interoceptive processing (co-activated with insula) (Critchley et al., 2004) and in conflict monitoring (Kerns et al., 2004; Ridderinkhof et al., 2004). Chronic drug use affects the RSFC between dACC and different subregions of anterior DMN. Compared to controls, chronic heroin users on methadone treatment showed reduced RSFC between dACC and ventral part of MPFC (vACC) (Ma et al., 2010). Greater coupling between dACC and dMPFC was found in relapsed heroin users relative to early remission and control groups (Li et al., 2018).

In general, chronic drug use disrupts dynamics between DMN and the SN and ECN. Disrupted DMN-SN connectivity might contribute to the enhanced salience towards drug cues and shifting attention to internal thoughts and emotions. Disrupted DMN-ECN connectivity might interfere with the ability to disengage attention from internal rumination and desires making it difficult for patients to recruit attention and cognitive resources for processing external stimuli.

7. Acute effects of drugs on DMN

Acute drug administration tends to result in an opposite pattern of RSFC of the DMN to that observed in abstinent addicted individuals. Acute administration of nicotine (Tanabe et al., 2011) and the psychostimulant dexamphetamine (Schrantee et al., 2016) attenuated the RSFC and activity within PCC and enhanced the DMN connectivity to ECN for external events. Acute opioids increased cerebral blood flow (CBF) in the anterior DMN (Khalili-Mahani et al., 2011; MacIntosh et al., 2008; Schlaepfer et al., 1998) and decreased CBF in the MTL and amygdala, which might reduce negative affect during opioid intoxication in opioid addicted individuals. Notably, drug-induced changes in RSFC of DMN vary as a function of time of intoxication (Weber et al., 2014). For example, the effect of acute alcohol on DMN connectivity differed at 60 min when PCC connectivity with cerebellum, thalamus, cingulate, parahippocampus and inferior parietal lobule was increased and connectivity with middle frontal and postcentral gyri was decreased compared to 90 min post-consumption when connectivity was only decreased (Weber et al., 2014). Also, the effect of acute drug administration differs between naive drug users and addicted individuals (Shokri-Kojori et al., 2017; Volkow et al., 1996). Delta 9 tetrahydrocannabinol (THC), main psychoactive component of cannabis, increased anterior DMN metabolism in chronic users but not in inexperienced users (Volkow et al., 1996).

In sum, acute drug use has distinct effects in chronic than in occasional or naive drug users, in chronic users but not in controls, acute drug intoxication tends to enhance activity in anterior DMN activity while suppressing activity in posterior DMN. These effects are dynamic and change as a function of the time of intoxication.

8. Dopaminergic modulation of DMN and its relevance to SUD

There is accumulating evidence that DA modulates DMN activity and connectivity at rest and during task performance (Liu et al., 2010; Sambataro et al., 2013; Tomasi et al., 2009) (Fig. 3). Patients with dopaminergic dysfunctions such as Parkinson's disease and ADHD display abnormalities in DMN RSFC and in DMN deactivation during executive performance, which are associated with poorer cognitive performances including working memory, cognitive flexibility and attention (Fassbender et al., 2009; Manza et al., 2016; Peterson et al., 2009; van Eimeren et al., 2009).

Changes in the dopaminergic system in addiction have been well-documented (Koob and Volkow, 2016; Volkow et al., 2002; Volkow et al., 2009b; Volkow et al., 2014a,b; Volkow et al., 2017). Acute drug administration and exposure to drug-cues trigger increases in extracellular DA concentration in striatum (Volkow et al., 2006b; Wong et al., 2006). Long-term drug use results in reduced striatal DA D2 receptor (D2R) availability and in decreased DA release, which contributes to the attenuated sensitivity to reward and reduced motivation for non-drug related stimuli and activities in addicted individuals (See review Volkow et al., 2017, 2009). Drug-addicted individuals display connectivity alterations between DMN and regions in the dopaminergic system including midbrain (where VTA and substantia nigra are located) and

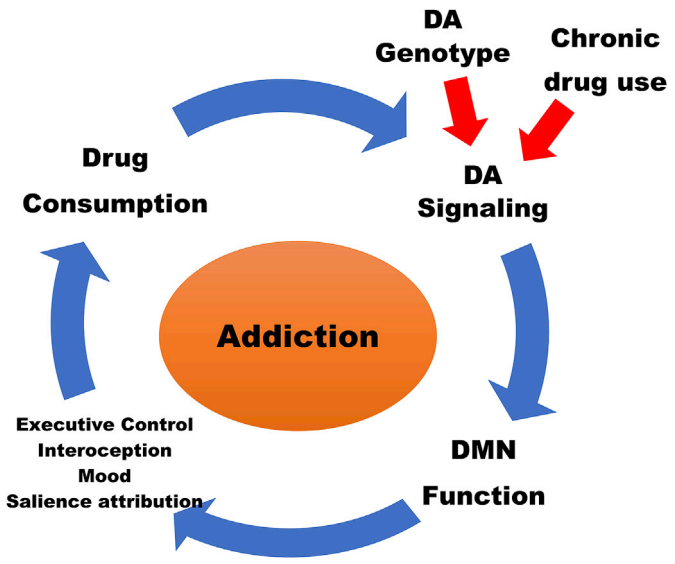

Fig. 3. Model of contributions of dopaminergic dysregulation to aberrant DMN underlying addiction. DA genotypes, which increase risk to addiction and DA dysfunction caused by chronic drug use have been associated with altered DMN function and functional connectivity. Altered DMN functional connectivity contributes to relapse by affecting cognitive (including self-regulation) and emotional processing, salience attribution and enhancing interoceptive awareness of drug craving and discomfort in drug-addicted individuals.

striatum (VS and DS) at rest (Ma et al., 2010; Müller-Oehring et al., 2015; Wilcox et al., 2011) and during task performance (Courtney et al., 2013; Tomasi et al., 2010).

In active cocaine users the higher posterior DMN activation for cocaine cues compared to food-cues was negatively associated with striatal D2/D3R availability (Tomasi et al., 2015b), consistent with a role of striatal DA signaling in modulating reactivity of the DMN. Drug-addicted individuals with lower striatal D2R availability might experience more drug-evoked self-related thoughts mediated by higher activity in precuneus and PCC (Buckner et al., 2008; Buckner and Carroll, 2007; Small et al., 2003). Moreover, reductions of striatal D2R availability in detoxified alcoholics were associated with alcohol craving severity and with greater cue-elicited activation of MPFC and ACC (Heinz et al., 2004), which is essential to emotional processing and salience attribution (Mitchell et al., 2012; Seo et al., 2013). Remarkably, reduced striatal D2R availability in addicted individuals has been associated with lower baseline activity in MPFC and ACC (including mOFC, vACC and dACC) (Volkow et al., 2006a, 2001, 1993), which has been thought to underlie impairments in emotional self-regulation and compulsive drug taking in addiction (Rolls, 2000; Saxena et al., 2002; Volkow et al., 2009b). At rest "tonic" DA neuronal firing is dominant and maintains the baseline DA levels that set the DA system's responsiveness threshold (Grace, 1991) and influence the DMN (Nagano-Saito et al., 2017), the ECN (Hagerty et al., 2018) and the SN (McCutcheon et al., 2019). Therefore, higher striatal D2R levels might protect against cue-induced craving by setting higher responsiveness threshold in anterior DMN regions in response to "phasic" DA neuronal firing triggered by drug-cues and by enhancing the function of the ECN and SN. Indeed, high levels of D2Rs in striatum have been observed in unaffected members of alcoholic families who were not alcoholics and who displayed normal baseline activity in regions of DMN (including vMPFC and vOFC), ECN (dlPFC) and SN (insula and dACC) (Volkow et al., 2006a). In all, higher striatal D2R availability might facilitate posterior DMN deactivation, attenuating self-referential processing while increasing the responsiveness threshold of the DMN for drug-cue reactivity. However, in alcoholics (Hermann et al., 2006) and abstinent smokers (Luijten et al., 2012) the acute administration of low doses of D2R antagonist drugs (400 mg amisulpiride and 2 mg haloperidol, respectively), reduced the hyperactivation of MPFC and dACC induced by drug-cues, though the opposite effect or smaller reduction was found in healthy controls. The reason for the attenuation of DMN reactivity to drug-cues with D2R antagonists is unclear but could reflect the use of low doses, which predominantly antagonize presynaptic D2R, thereby enhancing DA release (Perrault et al., 1997). Overall, the findings from these studies are consistent with DA's role in modulating the DMN including its reactivity to drug-cues in addiction.

Despite sparse direct studies, findings in healthy controls and animal studies support the potential relationship between changes in DA modulation and DMN in drug abusers in non-drug related cognitive tasks. In young healthy controls reduced striatal DA synthesis correlated with decreased PCC/Precuneus deactivations during a working memory task (Braskie et al., 2011). Mirroring this, transient DA depletion reduced task-related suppression of DMN (MPFC, PCC, medial temporal lobe) resulting in poorer performance in a set-shifting task (Nagano-Saito et al., 2008). The DA receptor agonist apomorphine, which mainly binds to D2R, enhanced the correlation between task complexity and deactivation of vMPFC (Nagano-Saito et al., 2009). Based on these findings, the decreased striatal DA signaling induced by chronic drug administration is consistent with its contribution to the attenuated deactivation of DMN during task performance in drug-addicted individuals (Lerman et al., 2014; Schulte et al., 2012).

DA transporters (DAT) are responsible for removing the extracellular DA release back into the terminal and their function is affected by several drugs (review Volkow et al., 2009b). Studies have shown that DAT availability, presumably by regulating extracellular DA, modulates DMN activity (Minzenberg et al., 2011; Tomasi et al., 2011, 2009). Individuals with higher striatal DAT availability, and hence greater synaptic DA removal, had lower deactivation of DMN during an attention task (Tomasi et al., 2009). The DAT inhibitor modafinil, which increases extracellular DA (Volkow et al., 2009a) enhanced task-induced DMN deactivation especially vMPFC, facilitating sensorimotor processing (Minzenberg et al., 2011). Similarly, methylphenidate (MPH), which also increases DA by blocking DAT (Volkow et al., 2009a), increased PCC deactivation during working memory and visual attention tasks (Tomasi et al., 2011) and reduced RSFC between VS and MPFC (Ramaekers et al., 2013). In cocaine abusers striatal DAT is elevated during the first few days of withdrawal (Malison et al., 1998; Wang et al., 1997), which might contribute to altered DMN activity during task performance (Bednarski et al., 2011). Supporting this, MPH restored the abnormal activation of DMN regions in cocaine-dependent individuals (Matuskey et al., 2013). In contrast, reduced DAT availability has been reported in other SUDs including alcohol, cigarettes, methamphetamine, heroin, and nicotine/cannabis (Leroy et al., 2012; Shi et al., 2008; Volkow et al., 2015; Yen et al., 2015; Yuan et al., 2017). However, despite the differences in DAT availability, individuals with cocaine (Martinez et al., 2007; Volkow et al., 1997a; Volkow et al., 2014a,b), alcohol (Volkow et al., 2007), cannabis (van de Giessen et al., 2017; Volkow et al., 2014a,b) and methamphetamine use disorders (Wang et al., 2012) showed decreased striatal DA release, which suggests that in some instances DAT down-regulation in addiction might reflect an adaptation to overcome reduced DA release.

Additionally, DA-related genetic variants, which confer vulnerability to addiction contribute to inter-individual differences in DMN. Prominent among them is the gene that encodes for Catechol-O-methyl transferase (*COMT*) an enzyme that degrades catecholamines including DA and plays a central role in DA's modulation of the PFC (Bearden et al., 2004; Chen et al., 2004; Gothelf et al., 2005). *COMT* Val^{158} is associated with a greater risk for addiction (Lachman, 2008) including methamphetamine, nicotine and polysubstance abuse (Beuten et al., 2006; Herman et al., 2013; Li et al., 2004; Vandenbergh et al., 1997). Compared with non- Val^{158} carriers, homozygous Val^{158} individuals who presumably have lower DA signaling in PFC and higher phasic DA in subcortical areas showed a significant decrease in RSFC between prefrontal regions

and PCC/restrosplenial cortices (Bilder et al., 2004; Liu et al., 2010) that is reminiscent of what has been reported in drug abusers (Ma et al., 2015; Müller-Oehring et al., 2015; Tang et al., 2016; Wetherill et al., 2015). As the anterior and posterior DMN are critical for emotion and executive function (Blair, 2007; Li et al., 2014b; Moayedi et al., 2015), the restricted midline core connectivity might account for reduced reward sensitivity (Wichers et al., 2008) and poor executive control (Egan et al., 2001; Loughead et al., 2009) in Val^{158} carriers making them more prone to drug abuse.

Likewise, the DA D2R gene (*DRD2*) single-nucleotide polymorphism rs1076560 genotype is linked to opioid, alcohol and cocaine addiction (Clarke et al., 2014; Moyer et al., 2011; Sasabe et al., 2007). T carriers who express fewer D2R presynaptic auto-receptors exhibit worse cognitive performance and have higher risk for addiction (Clarke et al., 2014; Moyer et al., 2011; Sasabe et al., 2007; Sasabe and Ishiura, 2010; Zhang et al., 2007). Interestingly, using ICA, T carriers displayed enhanced local connectivity strength in PCC within posterior DMN (i.e. increased synchrony between PCC and other regions within the posterior DMN) and decreased local connectivity strength in MPFC within anterior DMN during a working memory task, which were associated with connectivity strength in DS and VS respectively (Sambataro et al., 2013). Increased internal-directed attention reflected by enhanced PCC involvement and diminished emotional modulation by MPFC interfere with external-oriented cognitive function (Andrews-Hanna et al., 2014; Cavanna and Trimble, 2006; Moreno-López et al., 2012) and might explain the higher vulnerability of T carriers to addiction.

9. DMN and the DA reward circuitry in the three stages of addiction

Acute and chronic drug use differentially affects anterior and posterior DMN, and we propose that this results in an imbalance between them, which likely contributes to addiction. As discussed above DMN impairments in addiction are likely to reflect in part disruption of DA signaling in particular in the DA reward system. Accordingly, we expand our discussion of how an imbalance between anterior and posterior DMN would contribute to exaggerated incentive salience of drug and drug-cues, negative affect when not under the intoxicating effects of the drug and to compromised executive function in the three stages of addiction (i.e. binge/intoxication, withdrawal/negative affect and preoccupation/anticipation stage) (Koob and Volkow, 2016) and its relationship to the DA reward circuitry (Fig. 4).

In the binge/intoxication stage, the rewarding effects of drugs are largely mediated by activation of the ascending DA reward system (VTA to VS and to MPFC). Exposure to the drug and to drug-cues increases phasic DA release resulting in VS activation, which is associated with the "high" and "euphoria", and MPFC activation, which is associated with saliency attribution and enhanced motivation to procure the drug (Koob and Volkow, 2016; Volkow et al., 2011b). In contrast to enhancement of the anterior DMN, which is a recognized target of DA projections from VTA, acute drug use suppresses the posterior DMN (Schrantee et al., 2016; Tanabe et al., 2011), which while not as extensively studied as the anterior DMN, also expresses D2R and D3R (Nagano-Saito et al., 2009) and is modulated by DA (Birn et al., 2018). Interestingly, studies in healthy individuals have provided evidence that DA signaling in DS might counterbalance the influence of DA signaling in the VS for the modulation of the DMN. Specifically, while performing a visual attention task, the caudate to VS D2R availability modulated activation of the posterior DMN such that the higher the caudate to VS D2R availability the greater the activation of the posterior DMN, whereas the putamen to VS D2R modulated activation of the anterior DMN such that the higher the putamen to VS D2R the greater the activation of the anterior DMN (Tomasi et al., 2016). The counterbalance between the DS and VS D2R signaling appears to be disrupted in cannabis abusers (Tomasi et al., 2015a), which might contribute to anterior-posterior DMN imbalance and altered DMN activation during drug intoxication (Volkow et al., 1996).

Chronic drug use decreases the activity of the DA reward system and results in a reduced sensitivity to rewards (Garavan et al., 2000; Volkow et al., 2010b). During withdrawal, the decreases in both DA release and D2R availability result in a reduced inhibition of D2R-expressing medium spiny neurons (MSN) in striatum (since DA binding to D2R, which are Gi coupled, inhibits MSN), which signal aversions (Hikida et al., 2013; Zhu

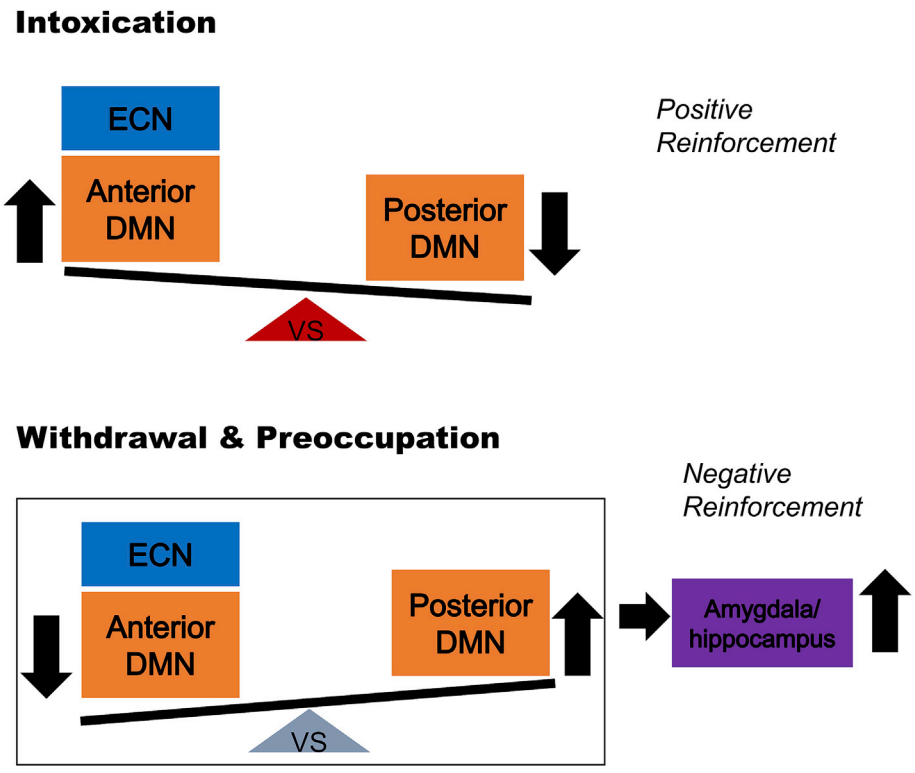

Fig. 4. Imbalance between anterior and posterior DMN caused by altered DA-related reward function in addiction. During the binge-intoxication stage, the rewarding effects of drug (red) are mediated by activation of the DA reward system projecting from the VTA (and to a lesser extent the substantia nigra) into the VS (and to a lesser extent the DS) and the PFC including regions from the anterior DMN and regions from the ECN while suppressing the function of posterior DMN shifting attention to external stimuli. Chronic drug use however decreases the activity of the brain DA reward system (grey) of addicted individuals resulting in opposite effects than during acute drug intoxication. Reduced emotional control (mediated by anterior DMN) and increased self-referential processing (mediated by posterior DMN) can enhance ruminatory behaviors and negative affect (mediated by amygdala and habenula and decreased dopaminergic signaling in VS) during withdrawal and contribute to negative reinforcement of drug use. Lower baseline activity of anterior DMN exaggerates the reactivity to drug cues. Along with compromised cognitive control (mediated by ECN), it facilitates craving and relapsing behavior in the preoccupation stage of the addiction cycle.

et al., 2016) and impair motivation (Soares-Cunha et al., 2016). In parallel, changes in the extended amygdala and habenula, which indirectly inhibit DA neuronal firing (Lammel et al., 2012) contribute to an enhanced sensitivity to stress, to anhedonia and dysphoria, all of which act as negative reinforcers for drug consumption as a means to temporarily escape the aversive state (Koob et al., 2014).

Chronic drug use has opposite effect on DMN (i.e. reduced involvement of anterior DMN and increased engagement of posterior DMN) compared to acute drug use, which might contribute to the predominance of anti-reward systems during the withdrawal/negative affect stage (Koob and Le Moal, 2008). Increased posterior DMN involvement, PCC-amygdala and PCC-insula RSFC, could promote ruminatory behaviors and negative emotional states. Meanwhile, because of compromised function of the anterior DMN and its reduced connectivity to the posterior DMN and amygdala, the negative emotional state cannot be inhibited, interfering with abstinence and flexible decision-making (Koob and Volkow, 2016).

Excessive salience to drug-related cues and decreases in the ability to inhibit maladaptive behavior facilitate relapse behavior in the preoccupation stage (Goldstein and Volkow, 2011; Volkow et al., 2003). In drug-addicted individuals, disruption of the anterior DMN enhances the reactivity to drug cues and interferes with the involvement of executive control (through ECN) (Wilcox et al., 2011). Cue-induced craving as well as affective responses to negative emotional stimuli such as stress can therefore not be suppressed leading to repeated drug-taking behavior. Acute drug administration can temporarily reduce the imbalance between anterior and posterior DMN in addicted individuals. Indeed, the anterior to posterior ratio of CBF increased after intravenous infusion of THC in cannabis users (Mathew et al., 2002). In healthy controls, lower engagement of MPFC was correlated with greater recruitment of PCC (Sambataro et al., 2013). Continued drug use exacerbates the imbalance of anterior-posterior DMN by decreasing the baseline activity of the anterior DMN and enhancing the engagement of the posterior DMN disrupting the flexibility of DMN in the long-term (Li et al., 2016; Volkow et al., 2001; Zhu et al., 2017).

10. Glutamatergic and GABAergic neurotransmission and its relationship to DMN in SUD

Brain imaging studies using magnetic resonance spectroscopy (MRS) to compare addicted individuals with controls have reported lower brain glutamate and/or Glx (glutamate + glutamine) and lower GABA concentrations most consistently in the SN (for a review, see Moeller et al., 2016), and DMN including PCC, precuneus and dMPFC (Crocker et al., 2014; Ke et al., 2004; O'Neill et al., 2014). Reduced glutamatergic and GABAergic neurotransmission were associated with higher craving, increased drug-seeking, worse cognitive functions and more years of drug use (Abé et al., 2013; Ernst and Chang, 2008; O'Neill et al., 2014). In healthy participants, glutamate levels were positively correlated with inter-regional functional connectivity during tasks and at rest, while GABA concentrations were negatively correlated with task-induced regional activation (Duncan et al., 2014). Glutamate concentrations in the anterior DMN were positively correlated with BOLD responses in the SN (Duncan et al., 2011). Ketamine, an NMDA antagonist, reduced the anticorrelation between task-positive networks and DMN in a working memory task (Anticevic et al., 2012). Referring to intra-network effects, GABA concentration in anterior DMN (Northoff et al., 2007) and in PCC/precuneus (Hu et al., 2013) was positively associated with task-induced deactivation in these regions, while glutamate/Glx concentration showed opposite effects (Hu et al., 2013; Witt et al., 2018).

In terms of resting-state, higher glutamate concentrations increased DMN RSFC whereas GABA reduced it. The ratio of glutamate to GABA in the posterior DMN positively correlated with intra-DMN RSFC (Kapogiannis et al., 2013). In contrast, during the resting periods of a task (removing task effects instead of using a pure resting-state design), glutamate to GABA ratio negatively correlated with intra-DMN RSFC and with the anticorrelation between DMN and SN/ECN, which mediates task-induced PCC deactivation (Gu et al., 2019). Furthermore, glutamate levels in MPFC had opposite effects on MPFC connectivity to subcortical areas in the eyes-open vs the eyes-closed conditions: positive association for eyes-open and negative for eyes-closed (Duncan et al., 2013). Although the relationship between glutamatergic and GABAergic modulation of DMN has been researched in healthy controls, limited work has been done in SUD. Notably, the effects of MPFC glutamatergic and GABAergic neurotransmission on the DMN differed between adolescents with narcolepsy and healthy individuals (Witt et al., 2018). Investigation in SUD is needed.

11. Clinical implications of the DMN in addiction

The DMN might have potential value as a biomarker to predict addiction risk and response to treatment. For example, a generalizable machine learning approach successfully classified individuals with a cocaine use disorder and controls using several clusters that included DMN (Mete et al., 2016). Furthermore, anterior DMN baseline activity is associated with striatal D2R availability, a predictor for drug abuse risk (Rolls, 2000; Saxena et al., 2002; Volkow et al., 2009b). Since resting-state imaging has lower costs and risks compared to positron emission tomography (PET), it is more amenable for potential clinical use as a biomarker for SUD especially in adolescence, which is a target group for prevention efforts. The DMN could also be a target for therapeutic interventions. A recent study found that modulation of DMN RSFC induced by transcranial direct current stimulation decreased craving in abstinent methamphetamine users (Shahbabaie et al., 2018). Therapeutic effects from nicotine replacement on the relief of withdrawal symptoms in abstinent smokers were associated with stronger anticorrelation between DMN and ECN (Cole et al., 2010a). Notably, behavioral interventions (e.g. motivational interviewing, cognitive behavioral therapy, mindfulness training) that are able to successfully reduce drug use, target self-referential processing and affect DMN activity (Thayer and Feldstein Ewing, 2016). For example, mindfulness-based interventions that emphasize awareness of internal states and bodily sensations (Bowen et al., 2014; Thayer and Feldstein Ewing, 2016), decreased the activity in precuneus and MPFC (DeWitt et al., 2015; Froeliger et al., 2017; Ives-Deliperi et al., 2011). This training presumably brings drug use related decision-making into conscious awareness, mitigating compulsive drug intake (Witkiewitz et al., 2014). Also, the skills learned from the intervention are believed to help cope with negative affect, which is a factor that contributes to initial drug use (de Dios et al., 2012).

12. Conclusions and future directions

Alterations of the DMN have been reported in addicted individuals across different drug classes and have been associated with craving, negative mood and relapse. It is believed that increased self-generated thoughts, deteriorated emotional regulation and valuation of internal states result in attenuated self-awareness and negative affect in SUD. Apart from this, DMN integrates information from various brain regions for self-related decisions and this function is impaired due to disrupted DMN connectivity to other large-scale networks. The prominent engagement of DMN during withdrawal and anticipation phases enhances self-referential processing and prevents cognitive control mediated by ECN while impairing emotional flexibility mediated by the SN. Furthermore, growing evidence shows that aberrant DMN is associated with dysfunction of the DA reward system, which is impaired in drug addiction and necessary for motivation (Volkow et al., 2017). Further, the DMN is modulated by glutamatergic and GABAergic neurotransmission, which are also disrupted in SUD (Abé et al., 2013; Ernst and Chang, 2008; O'Neill et al., 2014). Still, the question remains of how these changes in neurotransmission modulate the connectivity within the DMN and its connectivity to other regions and networks in addicted individuals across the different stages of the addiction cycle.

Because of limited sample sizes and the greater focus on males with SUD than on females (Table 1) gender differences in DMN have been overlooked. In healthy adults, men and women differ in RSFC of DMN. For example, greater connectivity between the ventral precuneus and the hippocampus/parahippocampus was observed in men compared to women (Zhang and Li, 2014). Gender also influences the acute responses to drugs of abuse, as well as the progression of brain changes with repeated drug use that result in addiction (Becker, 2016; Becker et al., 2017) and future studies are needed to assess the role of gender on the effects of drugs on DMN. Prospective studies of DMN connectivity during brain development (Khundrakpam et al., 2019) and the effects of adversity on these trajectories are also needed to investigate the DMN's role in the vulnerability for SUD and other mental illnesses. It is also increasingly recognized that sleep is disrupted in SUD and contributes to relapse (Angarita et al., 2016). In healthy participants decreased habitual sleep duration (Khalsa et al., 2016) and sleep deprivation reduces striatal D2R (Volkow et al., 2012, 2008) and markedly affects RSFC of DMN and its connectivity to other regions (Chen et al., 2018; De Havas et al., 2012; Kaufmann et al., 2016; Xu et al., 2018). Lower striatal D2R availability correlated with reduced deactivation of the anterior DMN during performance of an attention task (Volkow et al., 2009b). There is also evidence that reduced sleep exacerbates DA deficits in addiction (i.e. reduces striatal D2/D3R availability) (Wiers et al., 2016b.). Therefore, drug-induced impairments in sleep might influence DMN in SUD in part through its downregulation of striatal D2R availability. On the other hand, altered DMN in SUD might further deteriorate sleep problems as changes of DMN RSFC in turn affects the sleep-wake cycle (Tagliazucchi and van Someren, 2017) aggravating addiction. Co-morbidities with psychiatric disorder such as depression, anxiety, ADHD and schizophrenia (Dixon et al., 1991; Santucci, 2012; Wu and Blazer, 2014) affect brain function, behavior and clinical outcomes in addiction. Though studies have started to assess DMN differences between drug abusers with and without such comorbidities (Osuch et al., 2016), this remains a key area for future investigation.

Conflicts of interest

None.

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