



HHS Public Access

Author manuscript

Am J Drug Alcohol Abuse. Author manuscript; available in PMC 2016 January 29.

Published in final edited form as:

Am J Drug Alcohol Abuse. 2015 ; 41(5): 374–381. doi:10.3109/00952990.2015.1049701.

The hyper-sentient addict: an exteroception model of addiction

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Abstract

Background—Exteroception involves processes related to the perception of environmental stimuli important for an organism's ability to adapt to its environment. As such, exteroception plays a critical role in conditioned response. In addiction, behavioral and neuroimaging studies show that the conditioned response to drug-related cues is often associated with alterations in brain regions including the precuneus/posterior cingulate cortex, an important node within the default mode network dedicated to processes such as self-monitoring.

Objective—This review aimed to summarize the growing, but largely fragmented, literature that supports a central role of exteroceptive processes in addiction.

Methods—We performed a systematic review of empirical research via PubMed and Google Scholar with keywords including 'addiction', 'exteroception', 'precuneus', and 'self-awareness', to identify human behavioral and neuroimaging studies that report mechanisms of self-awareness in healthy populations, and altered selfawareness processes, specifically exteroception, in addicted populations.

Results—Results demonstrate that exteroceptive processes play a critical role in conditioned cue response in addiction and serve as targets for interventions such as mindfulness training. Further, a hub of the default mode network, namely, the precuneus, is (i) consistently implicated in exteroceptive processes, and (ii) widely demonstrated to have increased activation and connectivity in addicted populations.

Conclusion—Heightened exteroceptive processes may underlie cue-elicited craving, which in turn may lead to the maintenance and worsening of substance use disorders. An exteroception model of addiction provides a testable framework from which novel targets for interventions can be identified.

Keywords

Addiction; default mode network; exteroception; posterior cingulated cortex; precuneus; self-monitoring

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Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this paper.

Introduction

From a biochemical perspective, the mechanisms of drugseeking behavior are attributable to mesolimbic regions, specifically dopaminergic projections of the nucleus accumbens (1). Hence, models of addiction primarily revolve around functions related to the mesolimbic-dopaminergic pathway, such as the cognitive processing of reward and motivation. Animal research, however, has shown that lesioning these regions does not fully abate all drug-seeking behavior (2), implying involvement of other neurocircuitry and processes that contribute to the sequela of addiction. For example, repeated drug use has shown to attenuate frontal regulation of behavior that is associated with impulsivity and compulsive drug taking (3). Additionally, a seminal paper in patients with insula damage demonstrated important contributions of the insula, and consequently interoceptive processes in nicotine dependence (4). These findings propose that evaluative processes relating to internal physiological states or memory thereof are important cognitive processes related to addiction processes.

Two signaling sources for sentience: interoception and exteroception

Sources for sentience or sensory awareness can be parsed based on whether the neuronal signaling codes for *internal* bodily states (interoception) or the *external* environment (exteroception). In the addiction literature, of the two sources, interoception has been a topic of keen interest. Since Naqvi and Bechara's insular model of addiction (4), most of the literature related to sensory awareness and drug use has focused on interoceptive processes (e.g. using to avoid physiological withdrawal). Specifically, fMRI studies have demonstrated greater insula activity after presentation of cigarette (5) cocaine (6) alcohol (7) and heroin (8) cues in their respective using populations, indicating heightened internal awareness in the presence of these stimuli. In all, these studies suggest that the primary contribution of insula activity and interoceptive processes in drug addiction is in monitoring internal, bodily states such as craving or urge to consume a substance (9). In concordance with the aforementioned study in which insula-lesioned patients demonstrated significantly reduced craving for tobacco (4,10,11) these results indicate an important role of the insula in monitoring internal states that drive drug-seeking behavior.

As with interoception, drug craving can also be driven by exteroceptive processes (11,12). In contrast to sensory awareness of internal body states, exteroception refers to sensory awareness of stimuli outside of the body. In the context of drug-craving, heightened exteroception may occur under positive or negative valence. For example, heightened awareness of negative external stressors (e.g. an exam) may drive an individual to use a drug (negative valence). An example of positive valence are drug cues or paraphernalia that signal the impending pleasurable experience from drug use. This heightened awareness to conditioned drug cues, also referred to as cue-elicited craving, is one of the key mechanisms that leads to drug-seeking behavior. To date, the literature has focused largely on this positive incentivization, and, as such, is the focus of our proposed model of exteroception of addiction.

Exteroceptive processes have been postulated to lie within posterior cortical midline structures (pCMS), particularly the precuneus (13–17), which are considered fundamental regions in the perception of the physical body in space (18–21). In this light, pCMS regions are critical for bottom-up sensory processing that contributes to the initial recognition and assignment of salience to external stimuli. This subsequently affects top-down processes within frontal areas of the brain such as decision-making. Exteroception may also be modulated by other processes, including those that relate to the evaluation of self-relevant information. While exteroception refers to the perception of all external stimuli, the stimuli's relevance to the self is processed by the Relevance Detector Network (RDN) with the amygdala as its primary node (22). In the RDN, the amygdala serves as the gateway through which external information (via exteroception) is tagged as self-relevant via emotional arousal. In this light, the amygdala has been referred to as a “quick and dirty” evaluation of salient stimuli (23) and as such may be the first stage of self-relevant processing. This first level of self-relevant detection may then be integrated in pCMS regions. Dysfunction of this relevance detection system has been described as possibly displaying an aberrant “priority mapping” of salient stimuli in which inappropriate stimuli become tagged as self-relevant (24). In the context of addiction, this would involve heightened exteroception on drug-relevant stimuli.

While the construct of exteroception has yet to be tested empirically in the context of addiction, it conceptually will involve exteroceptive awareness with afferent and efferent projections from RDN (self-relevant evaluation) and integration of information, self-projection (self-referential processing in future scenarios), as well as exteroceptive enhancement via reward-motivation signaling, all of which then influence downstream behavioral outcomes (see proposed model in Figure 1). In this model, we acknowledge that affective salience and episodic memory associated with the evaluation of self-relevant cues likely contribute to a heightened sensory awareness of drug-related cues, and in this way further influence downstream behavioral outcomes such as drug use. This is based on the notion that the individual's self-defined concept of the drug stimuli is tightly woven with the experiences evoked by the cues resulting in changes in sensory awareness. The corresponding neural regions in this model overlap with those previously outlined in a meta-analysis (25) suggesting that these heterogeneous processes lie primarily in cortical midline structures such as the dorsomedial prefrontal cortex (DMPFC), posterior cingulate cortex (PCC) and the precuneus. Notably, of these regions, the precuneus is more widely-reported across different paradigms such as cue-reactivity (20), self-centered mental imagery (26) and across different addicted populations (15–17,27).

Exteroception and the default mode network

Given that interoceptive and exteroceptive processes lie in cortical midline structures (CMS), it is therefore of interest that the CMS also play a role in the default mode network (DMN). The DMN consists of heterogeneous processes related to self-monitoring such as self-awareness and self-relevant processing; i.e. thoughts and knowledge about the self, and mentalization of experiences related to the self (25,28–30). Consequently, the DMN has been implicated in behaviors related to addiction such as impaired insight; either decreased awareness of one's self (9), or decreased awareness of stimuli relevant to one's self (31).

By and large, the DMN has been attributed to monitoring of internal states, such as in interoceptive processes. These include collecting and monitoring information about the self in order to plan behavior responses to internal stimuli (20,32). However, others suggest that sub-regions of the DMN have unique contributions of self-monitoring that are not specific to representations of the internal self. For example, Gusnard and Raichle (33) proposed functionally distinct sub regions of the DMN consisting of the medial prefrontal cortex (similar to anterior CMS) as well as the posterior medial cortex (similar to posterior CMS). This model posits that the DMN's role in monitoring of internal states is primarily via medial prefrontal cortex. Meanwhile, the posterior medial cortex, (specifically posterior cingulate, precuneus and retrosplenial cortex) was described to be primarily involved in monitoring the outside world; i.e. exteroception. The authors cited evidence of these regions' involvement in visuospatial processing to support this notion and further stated that the posterior cingulate gyrus has an evaluative role of what is being monitored. From this, they concluded that gathering (and evaluating) information about the external world is a defining feature of the DMN.

Monitoring and evaluating the external world via the DMN not only provides information about the external environment but also appears to heavily influence the sense of self. In a meta-analysis of fMRI studies, Schilbach and colleagues (34) showed remarkable overlap between regions of DMN and regions involved in social cognition, i.e. relating the self to others and the outside world. Additionally, a recent study using transcranial magnetic stimulation (TMS) sought to separate regions involved specifically in self-awareness and those which may be involved in both self-awareness and the DMN (30). TMS was applied to both medial prefrontal cortex as well as bilateral parietal cortex while participants performed a task involving “self-relevant” stimuli and “other” stimuli. The results showed that TMS interruption of cortical activation only disrupted task performance when applied to parietal regions, but not the medial prefrontal cortex. The authors suggested this to be evidence that while self-referential processing shares regions with the DMN, they do not completely overlap. This is in line with Gusnard and Raichle's suggestion that sub-regions of the DMN are specifically involved in such self-referential or exteroceptive processes. Notably, subsequent studies reveal activation in medial prefrontal cortex specific to self-referential processing (35,36). Thus, the degree to which regions of self-referential processing overlap with the DMN requires further investigation.

Taken together, the specific loci for exteroception may be in posterior, midline hubs of the default mode network, i.e. posterior cingulate cortex and precuneus, with likely contributions from medial prefrontal cortex and initial, amygdala relevance detection input. Their role in monitoring and evaluating the outside world, as well as in processing self-relevant information in the context of social cognition, suggest that these are the neural substrates for evaluating self-relevant information in the outside world.

Exteroception and addiction

The primary contribution of exteroception in addiction is in the hyper-sensitivity (sensory awareness) to external cues deemed self-relevant. In substance abusers, external cues associated with their drug of choice have heightened relevance, and, therefore, “turn up the

volume” of exteroceptors (regions dedicated to processing external stimuli) (14). Moreover, memory and affective processes can also modulate relevance (37–39). Neuroimaging studies provide concordant findings that support the contributions of exteroception in symptoms of addiction. For example, increased neural response to drug cues in the precuneus have been observed in different substance abusing populations and have been associated with symptoms of addiction, such as risky decision-making and problems related to substance use (40–43). Although increased activation observed in the precuneus was not directly addressed in these studies, it may reflect heightened sensory awareness in individuals with substance use disorders (SUDs) in response to cues. In a seed-based region of interest (ROI) study of functional connectivity comparing cannabis users and healthy controls, cannabis users demonstrated greater connectivity in brain regions associated with self-referential processing including ventral posterior cingulate cortex (PCC), anterior left insula, and bilateral supramarginal gyri (15). In cannabis users, ventral PCC-insula connectivity correlated with quantity of cannabis used, which suggests a role of exteroception in the onset and maintenance of substance use. Given that no directionality of this connection is implied (PCC-to-insula or insula-to-PCC), this association may speak to the integration of interoceptive and exteroceptive signaling that may, in turn, contribute to behaviors related to addiction, such as craving. Thus, in the context of addiction, aberrant connectivity/activation in exteroception regions may signal a bias for which external cues are being evaluated as self-relevant. This is illustrated in studies whereby response to drug cues is greater than response to salient non-drug stimuli (44,45). In all drug users, the meaning of drug-related cues is such that the drug and the drug user's sense of self become inextricably linked. In sum, we propose that processes of exteroception are hijacked such that drug cues become increased in self-relevance through a feedback loop involving heightened sensory awareness in the presence of relevant drug cues. While this model describes the process through which an individual transitions to a substance use disorder, we cannot discount the possibility that there may be enhanced exteroception (46,47) that is premorbid to substance use. Moreover, it is also likely that pre-morbid conditions of hyper-exteroception are exacerbated by exposure to substances. In which case, repeated conditioning of the rewarding experience with the drug cues may then titrate the individual's exteroceptors to the drug cues, thereby, making the cues more self-relevant.

It is possible that impaired attribution of self-relevance in drug-addicted individuals may result in a behavioral bias towards (i.e. error monitoring and appraisal) drug cues observed in the anterior cingulate gyrus and ventromedial prefrontal cortex (9). In the context of our present model, this behavioral bias would come into play in the downstream behavioral response after an initial exteroceptive bias to tag drug cues as relevant to one's sense of self. Importantly, identifying one's self with the drug of choice is a product of continued substance abuse. In this light, altered exteroceptive processes influence behavioral monitoring (see Figure 1) which in turn exacerbates the exteroceptive bias towards drug cues and thus contributes to the maintenance of drug use and relapse.

Roles of the precuneus in exteroception

The precuneus is considered a functional core of the DMN, although its specificity for exteroceptive processes is unique from other DMN-related processes. As a core of the

DMN, it has been suggested that the precuneus may be highly adaptable, given the DMN's involvement in wide-ranging cognitive processes (33,48) (see Table 1). Thus, besides awareness of external stimuli, exteroceptive processes in the precuneus may also contribute to self-referential processes in future scenarios or “self-projection” (26). Theoretically, self-projection plays a critical role in higher-order decision-making (see [20] for review) as it evaluates the self in future scenarios. These simulations would be based largely on memory of past experiences through connections with medial temporal lobe regions for the consolidation and retrieval of memories. Such self-projections may influence reward-motivation processes during continued drug use by triggering a cue-elicited craving (i.e. imagining oneself using a drug of choice) or during abstinence via imagined behavioral changes (e.g. motivation to engage in intervention strategies). As such, these self-projections present a modifiable target for intervention.

Self-referential processes have also been examined using paradigms that require individuals to adopt either a first person or third person view of themselves. In these imaging studies, increased activation in the precuneus for third-person compared to first-person view was found (49). Activation of the precuneus in the context of such task demands is shown consistently across a number of paradigms. In a meta-analysis that investigated the neural substrates of theory of mind, Schurz and colleagues (50) observed increased activation in the precuneus in tasks related to false beliefs, rational actions, and, trait judgment. Each of these tasks, the researchers argued, required the individual to make judgments either about persons and the world around them, or about those persons' own perceptions of the world around them. These consistent findings have led researchers to suggest that the precuneus is a key region of mental imagery related to the perception of other individuals (20). Adopting the perception of other individuals helps formulate one's own perception, and contributes to the evaluation process during exteroception. In sum, as an integrated hub of a putative exteroception network, we propose that the precuneus may be a vulnerable target in addiction.

Modifying exteroception during addiction treatment

Activation of exteroceptive regions in the brain (i.e. precuneus) has also been observed in treatment studies for SUDs. With the goal of identifying mechanisms of change following cognitive reappraisal, Brody et al. (2007) examined response to cues in tobacco users trained to crave nicotine or resist the urge (crave vs. resist conditions) (51). Results showed greater activation in the precuneus during the crave condition for nicotine cues (vs. neutral cues), and that subjective craving levels also correlated with precuneus activation. Interestingly, precuneus activation was also greater during the resist condition vs. crave condition for nicotine cues. It is important to note that while instructions to resist craving do not explicitly tap into cognitive reappraisal strategies, individuals commonly report using such strategies in order to resist. Given the role of the precuneus in exteroceptive processes, these findings further support the idea that (i) self-relevant drug cues enhance exteroception response, and that (ii) cognitive reappraisal (i.e. resist condition) target exteroceptive processes, specifically self-referencing, as reflected by increased activation in precuneus when trying to resist. Thus, current interventions in addiction implicate reductions in self-relevant processing of drug cues.

In addition to cognitive reappraisal, mindfulness training (MT) is another treatment approach that targets behavior change via exteroception mechanisms (in addition to interoception). MT involves focusing attention in the present moment, without judgment of internal or external experiences (52). It has been shown to reduce craving for nicotine dependence (53), alcohol (54) and marijuana craving (55,56), and leads to a reduction in relapse rates for substance use (57). While cognitive reappraisal techniques involve self-awareness regions coming online to engage in self-referential reappraisal of a scenario/stimuli, MT appears to involve disengaging from subjective, evaluative experience. Interestingly, the integrity of these self-awareness regions is closely tied to success in mindfulness strategies.

fMRI studies show that mindfulness meditation is associated with decreases in BOLD signal in the precuneus and anterior insula that was attributed to successful “deidentification” or non-subjective judgments and perceptions associated with mindfulness (58). Concordant findings have also been reported in terms of increased connectivity and network efficiency of the precuneus within the DMN during mindfulness, as well as activation in precuneus associated with successful treatment using motivational interviewing; another popular cognitive intervention strategy (59–61). These latter findings suggest that optimal network connectivity in exteroception regions, specifically the precuneus, leads to greater success in disengaging from evaluative thinking during mindfulness meditation. Thus, the extent to which addictive behaviors stem from a dysregulation of exteroception would be crucial for identifying mechanisms of change as well as for predicting treatment response.

Conclusions

In this review, we introduce the construct of exteroception as evaluative processes of self-relevant external cues that integrate self-projections to guide behavior. Our review of the literature suggests that the addiction process increases sensitivity of exteroceptors to drug-related cues, and may be the underlying mechanism for cue-elicited craving. It is also possible that heightened exteroceptive processes may be a vulnerability factor for addiction. Evidence from treatment studies provides support for the importance of evaluating the self and external stimuli, such as in cognitive reappraisal and mindfulness training. Success likely depends upon the extent to which the exteroceptive regions of addicted individuals can be re-trained. Successful re-training would cause drug-related cues to be perceived as less relevant to the self, and therefore less integral to the recovered drug-user's sense of self. In sum, models of addiction should take into account these exteroceptive processes, given (i) behavioral and neuroimaging evidence for their role in addictive behavior, and (ii) that these processes underlie mechanisms of change following psychosocial treatment.

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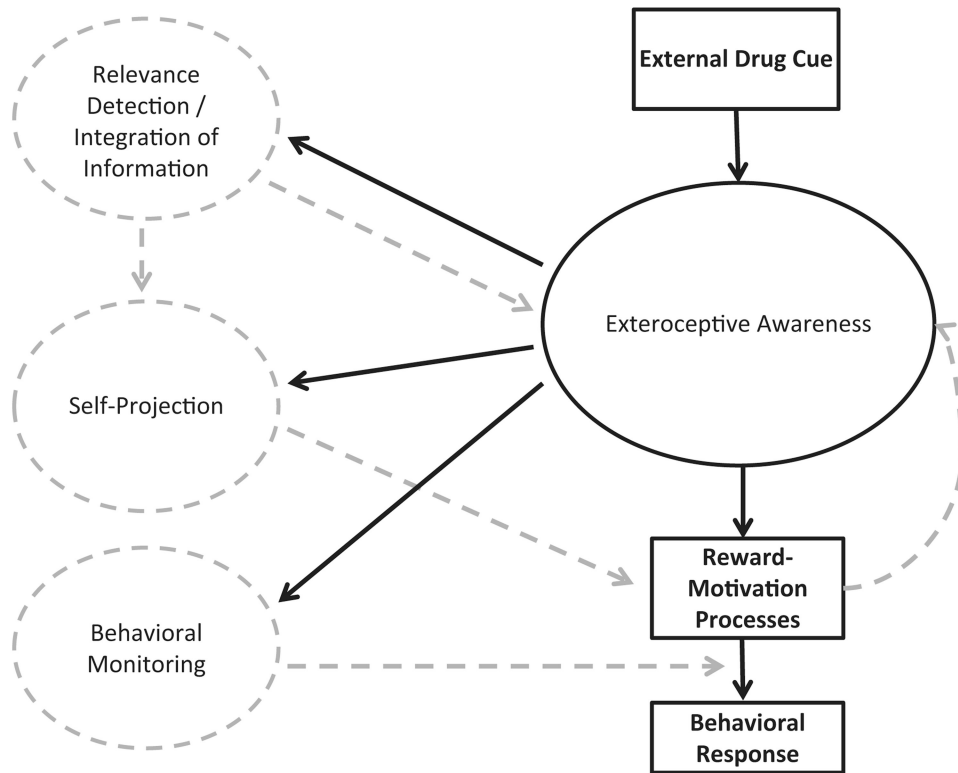


Figure 1.

An exteroception model of addiction. In this proposed exteroception model of addiction, we suggest that processing of drug cues in the reward-motivation system (or final common pathway) (1) leading to a behavioral response is influenced by (i) *Exteroceptive awareness* of salient cues within the precuneus (path shown in black). Grayed lines indicate modulatory paths whereby evaluation of the exteroception signal may be further processed for (ii) *Relevance* – cues are tagged as self-relevant via rapid detection within the amygdala as well as integration of information via precuneus/posterior cingulate area. The path between exteroceptive awareness (precuneus) and the reward-motivation processes (mesocorticolimbic) can also be modulated by (iii) *Self-projection* – self-referential processing in future scenarios that is a viable target for cognitive strategies, e.g. reappraisal, and, (iv) *Behavioral monitoring* – occurs after stimuli are tagged as self-relevant in anterior/frontal regions (anterior cingulate, mPFC) and guides the behavioral response. Finally, signaling during reward-motivation processes can enhance exteroceptive awareness for drug cues via feedback loop, thereby increasing exteroceptive awareness for drug cues.

Table 1

Human studies reporting the putative role of the precuneus in exteroceptive processes.

Authors	Modality	Participants	Putative mechanism of precuneus
Grant et al. (17)	PET <ul style="list-style-type: none"> Cue-elicited craving task 	13 cocaine abusers vs. 5 healthy controls	<ul style="list-style-type: none"> Cocaine users demonstrated greater precuneus rCMRglc signal in response to cocaine cues compared to neutral cues.
Shulman et al. (48)	PET <ul style="list-style-type: none"> Passive viewing vs. active judgment-making of visual stimuli 	9 PET studies including 132 healthy adults total	<ul style="list-style-type: none"> Decreased activity in precuneus during active judgment-making compared to passive viewing
Greicius et al. (65)	fMRI <ul style="list-style-type: none"> Resting state functional connectivity 	14 healthy participants	<ul style="list-style-type: none"> Precuneus was functionally correlated with ventral anterior cingulate cortex Precuneus activity was inversely correlated with dlPFC and vlPFC activity.
Tapert et al. (15)	fMRI <ul style="list-style-type: none"> Cue-reactivity task 	15 adolescents with alcohol use disorders	<ul style="list-style-type: none"> Greater activity in the precuneus when viewing alcohol-related pictures compared to neutral beverage pictures
Vogeley et al. (49)	fMRI <ul style="list-style-type: none"> Object-counting task from first- and third-person perspectives 	11 healthy males	<ul style="list-style-type: none"> Greater activity in precuneus in a third person perspective compared to a first person perspective
Fox et al. (66)	fMRI <ul style="list-style-type: none"> conjunction analysis between resting state 	10 healthy controls	<ul style="list-style-type: none"> Conjunction analysis between three resting conditions showed that precuneus activity was correlated with DMN (task-negative brain regions).
Brody et al. (51)	fMRI <ul style="list-style-type: none"> Cue-resist task 	42 adult smokers	<ul style="list-style-type: none"> Greater precuneus activity in the cue-resist condition vs. the neutral condition, and also the cue-resist condition vs. the cue-crave condition.
McClernon et al. (16)	fMRI <ul style="list-style-type: none"> Cue-reactivity task 	18 adult smokers	<ul style="list-style-type: none"> Greater activation in precuneus when viewing smoking cues compared to control cues.
Lou, Luber, Stanford, Lisanby (30)	Transcranial Magnetic Stimulation (TMS) in bilateral parietal cortex (angular gyrus) During self-referential task	18 healthy subjects	<ul style="list-style-type: none"> TMS disrupted self-referential effect in the precuneus.
Claus et al. (42)	fMRI <ul style="list-style-type: none"> Functional connectivity during alcohol taste cues 	326 heavy drinking individuals	<ul style="list-style-type: none"> AUD severity correlated with activity in precuneus Impaired Control Scale (failure in control over drinking subscale) score was positively associated with alcohol > juice contrast in precuneus Treatment-seeking participants had greater precuneus activity in alcohol > juice conditions Years of drinking positively correlated with alcohol > juice activity in precuneus

Authors	Modality	Participants	Putative mechanism of precuneus
Ersche et al. (67)	sMRI	50 sibling pairs discordant for stimulant dependence vs. 50 healthy controls	<ul style="list-style-type: none"> Decreased gray matter in precuneus in stimulant-dependent individuals compared to their healthy siblings, as well as healthy controls.
Feldstein Ewing et al. (68)	fMRI <ul style="list-style-type: none"> Cannabis cue-exposure task 	41 adolescent cannabis users	<ul style="list-style-type: none"> Adolescents with rs6311 C/C allele had greater cannabis-cue-induced precuneus activity than those with C/T and T/T alleles Rs6311 T allele carriers had negative correlations between anxiety score and cannabis-cue-induced precuneus activity
Filbey et al. (62)	fMRI <ul style="list-style-type: none"> High-calorie cue exposure task 	32 overweight (BMI > 25) adults	<ul style="list-style-type: none"> Greater activation in a cluster including the precuneus after high-calorie cue compared to water Precuneus activity correlated with Binge Eating Scale score, and sugar content of personally-relevant high-calorie cue
Claus et al. (64)	fMRI <ul style="list-style-type: none"> Nicotine cue-exposure task with appetitive control (i.e. food) cues 	116 adult smokers	<ul style="list-style-type: none"> Precuneus activity correlated with Fagerstrom test for nicotine dependence (FTND) scores Increased connectivity between precuneus and left insula during smoking > food cues Increased connectivity with right Orbitofrontal Cortex (rOFC) in food > smoking contrast
Feldstein Ewing et al. (63)	fMRI <ul style="list-style-type: none"> Exposure to change talk vs. counterchange talk during a cue-exposure task 	43 adolescent cannabis users	<ul style="list-style-type: none"> Activity in the precuneus during change talk cannabis-cue condition (vs. counterchange talk and neutral cue conditions) Negative relationship between precuneus activity during change talk (but not counterchange talk) and cannabis use upon follow-up
Pujol et al. (27)	fMRI <ul style="list-style-type: none"> Resting state functional Connectivity 	28 male cannabis users vs. 29 healthy controls	<ul style="list-style-type: none"> Cannabis users had reduced functional connectivity in the junction of dPCC/precuneus than controls
DeWitt et al. (69)	fMRI <ul style="list-style-type: none"> Resting state functional connectivity 	18 risk-taking adolescents (RT), 18 non-risk-taking adolescents (NR1)	<ul style="list-style-type: none"> Greater connectivity between amygdala and left precuneus in RT compared to NRT
Filbey and Dunlop (70)	fMRI <ul style="list-style-type: none"> Functional connectivity during cue-reactivity 	71 cannabis users	<ul style="list-style-type: none"> Dependent cannabis users demonstrated greater connectivity between anterior cingulate gyrus and precuneus during cannabis cue (vs. neutral cue) Non-dependent cannabis users demonstrated greater connectivity between OFC and precuneus during cannabis cue (versus neutral cue)
Utevsy et al. (71)	fMRI conjunction analysis between:	209 healthy participants	<ul style="list-style-type: none"> Precuneus had increased functional connectivity with right frontoparietal network (rFPN) at rest, compared with

Authors	Modality	Participants	Putative mechanism of precuneus
	<ul style="list-style-type: none"> • incentivized response-time task • financial decision making task • simple valuation task. • resting state 		<p>all three tasks as determined by a conjunction analysis.</p> <ul style="list-style-type: none"> • At rest, precuneus had greater functional connectivity with DMN compared to rFPN, indicating greater role in resting states.

DMN, default mode network; dPCC, dorsal posterior cingulate cortex.

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