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Impaired self-awareness in human addiction: Deficient attribution of personal relevance

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Abstract

Compromised self-awareness of illness-related deficits and behaviors in psychopathology (e.g., schizophrenia) has been associated with deficient functioning of cortical midline regions including the ventromedial prefrontal cortex (vmPFC), implicated in personal relevance. Here, we review and critically analyze recent evidence to suggest that vmPFC abnormalities could similarly underlie deficient tagging of personal relevance in drug addiction, evidenced by a constellation of behaviors encompassing drug-biased attention, negative outcome insensitivity, self-report/behavior dissociation, and social inappropriateness. This novel framework might clarify, for example, why drug-addicted individuals often ruin long-standing relationships or forego important job opportunities while continuing to engage in uncontrolled drug-taking. Therapeutic interventions targeting personal relevance and associated vmPFC functioning could enhance self-awareness and facilitate more adaptive behavior in this chronically relapsing psychopathology.

Keywords

self-awareness; insight; addiction; fMRI; rostral anterior cingulate cortex; ventromedial prefrontal cortex; cortical midline regions; self-processing; personal relevance; RDoC criteria

Self-Awareness in Drug Addiction

Drug addiction is characterized by compromised decision-making and behavioral monitoring, and inflexibility in modifying previously-rewarded behaviors that no longer produce favorable outcomes (1). We previously posited that these compromises in addiction might embody a core deficit in insight and self-awareness, attributable to abnormalities in select brain regions including the anterior cingulate cortex (ACC) (2). The current opinion

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Disclosure/Conflict of Interest

None declared.

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article supports, yet refines this hypothesis. In particular, we posit that, as with other neuropsychiatric disorders of impaired self-awareness (e.g., schizophrenia, Alzheimer's disease, focal brain lesions), impairments of self-awareness in addiction may reflect an underlying abnormality in the attribution of personal relevance to salient stimuli (for a more extended definition of self-awareness, see Box 1). We further posit that this deficit could be undergirded by aberrant functioning of the prefrontal cortical (PFC) midline regions traditionally implicated in self-related processing. Such dysfunction may culminate in elevated personal relevance of drug contexts, but not of other important contexts (e.g., ongoing behavior, social cognition). We place special emphasis on the ACC, especially of its more rostral (also referred to as perigenual) aspects (rACC) [Brodmann Areas (BA) 24, 32], extending ventrally and anteriorly to include portions of the ventromedial prefrontal cortex (vmPFC) (BAs 10, 11, 25) (Figure 1). [For a discussion of a broader self-awareness network (e.g., inclusive of more lateral regions such as the insula), see Box 2.] Because impaired self-awareness is typically associated with increased severity and poorer prognosis across multiple diseases (3), this topic has both theoretical and clinical importance.

Box 1

New emphasis for the definition of self-awareness in addiction

Deficits in self-awareness can range from complete denial of the entire illness to more specific metacognitive awareness deficits of individual disease-specific symptoms, impairments, or performance, and may vary between psychopathologies (3). For example, self-awareness impairments are more severe in schizophrenia than in mood disorders (54). In drug addiction, consistent with its overall neuropsychological profile (55), self-awareness impairments are anticipated to be relatively mild.

Here, we operationalize self-awareness impairment as the failure to ascribe personal relevance or significance to internal or external stimuli or events that have implications for the self – be they environmental cues/feedback, interoceptive sensations, or ongoing behavior. This operationalization is distinct from other related concepts that may be conflated with self-awareness, such as self-attribution processes, self-monitoring, and self-consciousness, personal agency, consciousness/alertness, interoception, or alexithymia. These related concepts may be distinguished from our current self-awareness formulation according to the following. (A) *Motivation*: Self-attribution is generally invoked to explain avenues that individuals use to preserve and enhance self-esteem (e.g., ascribing positive outcomes to skill and negative outcomes to bad luck) (56). Likewise, self-monitoring (57) and self-consciousness (58) are dispositional tendencies in which the motivation is to present the self favorably to others. Here, we view the actual expression of self-awareness deficits as being motivationally agnostic or ambivalent. Deficient oversight of one's behavior (e.g., error awareness) or insensitivity to negative outcomes (e.g., money loss) may occur despite sufficient task motivation and compliance with task demands. (B) *Cognition*: Personal agency reflects the dispositional tendency to understand one's behavior in terms of its consequences and implications (i.e., *why* a behavior is executed) or, alternatively, in terms of its details or mechanics (i.e., *how* a behavior is executed) (59). With self-awareness, the focus is on whether a particular behavior, when executed, is meaningful to the self. (C) *Attention*:

Consciousness generally refers to the degree of alertness to one's environment (e.g., ranging from coma, sleep, daydreaming, to full task engagement). In our formulation, self-awareness deficits may, but need not, entail a lapse in consciousness. A self-awareness deficit could presumably occur, for example, during an immersive, highly engaging experience that promotes "flow" or "dissociation," such as during gambling (60). (D) *Scope*: Interoception and alexithymia are probably most closely related to our concept of self-awareness. However, our formulation goes beyond awareness of bodily sensations (interoception) or emotions (alexithymia) to also include awareness of ongoing behavior and its designation as important to the self.

Box 2

Beyond focal deficits: rACC/vmPFC functional connectivity and its disruption in drug addiction

A full understanding of impaired self-awareness in addiction is likely to require, beyond focal rACC/vmPFC deficits, investigation of circuit-level deficits. An important tool in this effort is task- and resting-state functional connectivity, which can examine functional interactions between the rACC/vmPFC and the larger brain network implicated in personal relevance, possibly pointing to additional regions that contribute to self-awareness dysfunction. Functional connectivity studies often define a certain number of *a priori* seed regions and subsequently examine, either at rest or during a specified task event, all the regions in the brain where the fMRI signal covaries with those seeds. In prior resting-state studies, positive functional connectivity has been observed between the rACC/vmPFC with the insula, striatum, and (most prominently) large swaths of the entire medial PFC [ventral to dorsal, sometimes extending laterally into the orbitofrontal cortex (OFC)] (61, 62). In prior task-based studies using multiple social-cognitive paradigms, increased rACC/vmPFC connectivity was reported with the posterior cingulate cortex (PCC) [when participants judged the self-relevance of personality traits (63)], the striatum [when participants viewed positively-valenced words high in self-relevance in further positive correlation with state self-esteem (64)], and the temporal-parietal junction (TPJ) [when participants mentalized about others' emotions versus intentions (65)]. Meta-analyses across various task domains have confirmed rACC/vmPFC connectivity with the PCC (66, 67), while also highlighting additional regions of connection (e.g., striatum, medial PFC, hippocampus, amygdala) (66). Importantly for the current topic, many of the regions identified in these functional connectivity studies and meta-analyses (e.g., PCC, TPJ, insula) have been similarly observed in previous activation meta-analyses of self-relevant processing and social cognition (4, 68–70).

Also importantly, some of these same rACC/vmPFC connections are altered in drug addiction. For example, opiate-addicted individuals had higher resting-state connectivity between the rACC and the ventral striatum, but lower connectivity between the vmPFC and lateral OFC (71). Cocaine-addicted individuals showed reduced resting-state connectivity between the rACC with the posterior insula and large clusters encompassing portions of the amygdala, hippocampus, and parahippocampal gyrus (72). Reduced vmPFC-insula connectivity also correlated with higher alexithymia in smokers (73).

Nevertheless, and suggesting the need for a more nuanced interpretation of this connection, other studies showed that vmPFC-insula connectivity was reduced (or rendered more negative) by varenicline (74) or mindfulness training (75). Given the insula's hypothesized function of mediating interoception (76) and its critical association with drug craving (77, 78), vmPFC-insula connectivity might be an especially important contributor to dysfunctional self-awareness.

The rACC/vmPFC: Emotionally Tagging Stimuli for Personal Relevance

The rACC (and adjacent anterior medial PFC) forms part of the network that supports self-related processing, with the specific hypothesized function of tagging stimuli as being personally relevant (4, 5). This region is involved in generating the affective response that may occur shortly after error commission (6) and in resolving emotional conflict (7). Relatedly, the rACC activates during the experience of negative self-conscious emotions including embarrassment (8), and after receiving emotion-laden feedback (9). The rACC is also implicated in one's sense of agency, activating when individuals gamble for themselves versus when a computer gambles for them (10). The rACC activates even when, through mental imagery, neutral stimuli become associated with the self (11).

This perspective extends ventrally to the vmPFC, which participates in the highly related function of appraising or representing the personal value/significance of self-related information (12). For example, the vmPFC activated when participants imagined objects belonging to them versus when they imagined objects belonging to someone else (13, 14). This region also showed a descending level of engagement when participants were asked to think about a personally relevant target (one's mother), an intermediately relevant target (George Bush), and a non-personally relevant target (Cinderella), respectively (15). This hypothesized function of the vmPFC squares well with the more generally recognized roles of this region in computing or representing the subjective value of various types of stimuli (16–18).

Linking Personal Relevance with Self-Awareness in Psychopathology

Compromised self-awareness in psychopathology may be driven by disorder-specific abnormalities in the rACC/vmPFC (4). When individuals with schizophrenia reflected on themselves, contrasted with when they reflected on others, a correlation emerged between vmPFC activation and better cognitive insight, as measured by self-awareness that one's strange mental experiences may have been fictitious (19). In Alzheimer's disease, patients with more self-awareness of their illness-related deficits showed more rACC/vmPFC activity during a go/no-go task than those with less self-awareness (20). Patients with lesions to the vmPFC overestimate their own ability, compared with informants' ratings, to self-monitor their own behavior and adaptively adjust their actions (21).

This framework may also extend to depression and anxiety disorders. In an interesting dissociation that underscores the rACC's role in tagging information as personally relevant, depressed participants had increased rACC activation during inhibition of negative, but not positive, words (22). In another dissociation, healthy controls and individuals with social

phobia (who fear being negatively evaluated by others) were exposed to evaluative phrases that were presented either in the first person (e.g., “I’m ugly”) or in the second person (e.g., “You’re ugly”). Healthy controls had higher vmPFC activity during first- versus second-person phrases, whereas individuals with social phobia had higher vmPFC activity during the reverse contrast (23) – presumably of high personal relevance to this psychopathology.

Neural Correlates of Self-Awareness in Drug Addiction

Increased rACC/vmPFC Activity to Drug-Related Stimuli

In drug addiction, one could expect similarly increased rACC/vmPFC activation to addiction-associated cues, which are likely tagged with high personal relevance. Recent neuroimaging meta-analyses of multiple substances support this idea (24–26) (Figure 2A–C). [For a comprehensive list of the neural correlates of cue-reactivity, see (24–27).] Such personal relevance could be tracking individual differences in craving and/or immediate desire for the drug. In a study of cocaine-addicted individuals who completed a monetarily-rewarded drug word task, a positive correlation emerged between rACC activity and task-induced cocaine craving during the most personally relevant task condition (i.e., drug word presentation in tandem with a high monetary reward for correct performance) (28) (Figure 2D). A similar correlation emerged between rACC/vmPFC activation and self-reported craving across multiple studies of alcoholism (25). Relatedly, smoking-related cues elicited activation in the rACC/vmPFC in smokers who expected to smoke immediately but not in those who expected to wait for hours to smoke (29). These cue-elicited, personally-relevant activations could be tracking individual differences in addiction severity. The degree of rACC/vmPFC activation to smoking-related cues, compared with neutral cues, was greater for highly addicted smokers than for controls, problem gamblers, and even smokers with lower nicotine dependence (30).

Decreased rACC/vmPFC Activity to Non-Drug Related Stimuli

Another potential manifestation of impaired self-awareness/personal relevance in drug addiction involves the processing of non-drug related cues, such as behavioral monitoring during task performance. Cocaine abusers had less rACC activation than controls while performing a modified Stroop task that required monitoring and correction of errors; less rACC activation also correlated with more frequent cocaine use (31). In another study, cannabis abusers and controls completed the Error Awareness Task, a modified go/no-go task that asks participants trial-by-trial to signal when they have committed an error. Cannabis users showed a specific deficit in error awareness (i.e., despite comparable total errors), which was associated with hypoactivity in the dorsal ACC (extending to rACC) (32). One recent study of individuals with a range of problematic drinking levels (up to and including dependence) showed a negative relationship between error-related activity in the rACC on a go/no-go task and alcohol use severity (33). In our work, we found that cocaine abusers with impaired self-awareness, as demonstrated by their inability to monitor their own choice behavior (34, 35), had lower error-related activity in the rACC on a classical Stroop task relative to both controls and cocaine abusers whose self-awareness (choice awareness) was intact (Figure 3A); similarly to (31), this reduced activation correlated with more frequent cocaine use (36). These findings could collectively indicate that errors fail to

engender the appropriate tagging of personal relevance or emotional significance in addicted individuals.

Another dysfunctional process in addiction that involves the rACC/vmPFC is risky decision-making, with the outcomes of risky decisions appearing to lack appropriate personal relevance. Compared with controls, treatment-seeking methamphetamine-addicted individuals had lower bilateral rACC activation during a risky decision-making task; this effect further correlated with increased choosing of risky options following a loss (37) (Figure 3B–3C). During another risky decision-making task (the Iowa Gambling Task), controls had greater rACC/vmPFC activity than marijuana users in response to initial losses, and this loss-elicited activity in the rACC/vmPFC was associated with better performance later in the task (38). Thus, addicted individuals may persist in risk-taking behavior due to impaired awareness into the potential loss that could be incurred due to further risky or disadvantageous behavior (39).

A third area of impairment in addiction that might be related to rACC/vmPFC abnormalities is social cognition. In an interesting recent study, participants were instructed to follow or not follow the gaze of an unfamiliar virtual character. Although pupil dilation, a proxy of task engagement, was higher during mutual gazing in all participants, this effect was attenuated in the cocaine-addicted individuals (40). In a subsample of these participants who completed functional magnetic resonance imaging (fMRI) during this paradigm, controls had more activity in the rACC/vmPFC than did cocaine-addicted individuals during the mutual gaze condition (Figure 3D) (40). This study suggests that addicted individuals perceive social interactions as being less engaging, novel, rewarding, or personally relevant, with potential far-reaching consequences for real-life interpersonal relationships.

rACC/vmPFC Associations with Clinical Outcome

The rACC/vmPFC has also been examined vis-à-vis clinical outcomes. Relative to recently abstinent cocaine-addicted individuals (1–5 weeks abstinent) and controls, long-term abstinent cocaine-addicted individuals (40–102 weeks abstinent) showed the highest rostral and dorsal ACC activity on a go/no-go task (41). Similarly, we reported that 6-month abstinent treatment-seekers had the highest rACC activation on a rewarded drug-word task, compared with active cocaine abusers and controls (42). In another study in which participants responded to the border color that surrounded unpleasant, neutral, and smoking images, ex-smokers (~12 months abstinent) activated the rACC/vmPFC more strongly than current smokers and controls during all task conditions (43). [But see (44), where alcoholics who relapsed, versus those who remained abstinent, had increased vmPFC activation to alcohol cues.] Because in many of these studies rACC activity exceeded that of controls, one interpretation, which awaits empirical testing, is that rACC activity is marking *accentuated* personal relevance because of the desire to avoid drug-related cues or to sustain vigilance about relapse.

Implications for Potential Remediation

The rACC/vmPFC could provide a therapeutic target to enhance self-awareness in drug addiction. Traditional cognitive-behavioral therapy (CBT) could be complemented, or

possibly even augmented, by interventions aimed at fortifying self-awareness and/or rACC/vmPFC functioning. Indeed, mindfulness training has shown promise in modulating functioning of cortical midline structures (45), and mindfulness in alcoholics has been associated with less difficulty resisting the urge to drink (46). Similarly, pharmacological studies have revealed rACC/vmPFC normalizations in smokers who received varenicline or bupropion (47, 48) and cocaine-addicted individuals who received methylphenidate (49).

Presenting personally-relevant content could also engage self-awareness circuitry while fostering a commitment to change among addicted individuals not yet indicating a readiness to seek treatment. The rACC/vmPFC was more engaged when participants were presented with high-tailored smoking cessation messages (i.e., describing the participant's own smoking behavior) than low-tailored (generic) smoking cessation messages (50). Such activation during tailored messaging, though located slightly more dorsally, also predicted smoking abstinence 4 months later (51).

In all interventions, it may be important to selectively enhance the rACC/vmPFC response to non-drug (but not drug) reinforcers. As a parallel, standard CBT in depressed individuals decreased rACC/vmPFC activity when thinking about negative aspects of the self and enhanced activity in this region when thinking about positive aspects of the self (52). To avoid inducing self-criticism, rumination, or anxiety (53), it may also be important to tailor the degree of self-awareness enhancement to each individual.

Concluding Remarks

We proposed that impaired self-awareness in drug addiction may reflect dysfunction of the rACC/vmPFC, thought to underlie the attribution of personal relevance to behavior or stimuli in one's environment that have implications for the self. Although important questions remain (Box 3), we contend that studying self-awareness vis-à-vis personal relevance in addiction may uncover core features in the basic phenomenology and clinical outcome of this disease, such as helping to clarify why drug-addicted individuals, in service of drug-seeking, could ruin longstanding personal relationships, forego important job opportunities, and engage in risky and unhealthy behaviors – all activities and contexts that ought to (but seem not to) engender a high degree of personal relevance. Our proposal also highlights this deficit and associated brain region as a novel and specific therapeutic target for possibly raising self-awareness and facilitating more adaptive behavior, such as enhancing the addicted individual's capacity to identify and adaptively cope with situations that trigger craving or induce relapse. More broadly, this approach could provide a novel phenotype that links addiction with other neuropsychiatric disorders of impaired self-awareness, potentially spurring the development of novel treatment approaches that cut across traditional diagnostic labels.

Box 3

Outstanding questions for future research

- What paradigms can be developed that target deficits in self-awareness and personal relevance in addiction, which do not rely on self-reports or memory

(i.e., instead incorporating online objective behavior or neural measures)? One interesting direction would be to cross self-relevance and drug-related contexts. For example, in a 2×2 design, study participants could view pictures of a family member/close friend (versus a stranger), with each of these individuals using drugs (versus not using drugs). This design would allow a fine-grained test of whether the rACC/vmPFC activates more strongly to the close other or the drug context, and in addition whether the drug context potentiates rACC/vmPFC activation to the close other (i.e., whether activation would be especially strong when viewing the close other who is using drugs). This design would also help clarify if rACC/vmPFC functioning in addiction is fundamentally abnormal (i.e., operating differently than controls) or whether it is simply ascribing “healthy” personal relevance to the “wrong” (drug-related) stimuli.

- What is the direction of association between self-awareness impairment and addiction symptomatology (i.e., does self-awareness precede or follow the addiction)? For example, negative emotionality (neuroticism) is a risk factor for substance use (79) and is associated with cortical midline dysfunction (80), which could be exacerbated by chronic drug use; when viewed in this light, self-awareness impairment, via negative emotionality, could predate and contribute to the manifestation of addiction. Nevertheless, several lines of more direct evidence in cocaine abusers suggest that self-awareness is a symptom, rather than an antecedent, of addiction: (A) rACC dysfunction as related to impaired self-awareness correlated with frequency of recent cocaine use (past 30 days) (36); (B) a different marker of more recent cocaine use (cocaine-positive urine screens versus cocaine-negative urine screens) correlated with higher drug-seeking on tasks of simulated drug choice (34); (C) impaired self-awareness was associated with a specific deficit in monitoring of choice for cocaine stimuli, not with a general compromise in behavioral monitoring (35); and (D) drug treatment and/or abstinence is associated with rACC/vmPFC functional recovery (42) – although the direct link between rACC/vmPFC recovery and increased self-awareness remains to be tested. Nevertheless, such evidence, while informative, cannot effectively adjudicate between the competing hypotheses of whether dysfunctional self-awareness predates, follows, or exacerbates the addiction syndrome. To address this fundamental question, future studies are needed that incorporate longitudinal designs (e.g., studying youth prior to addiction onset) and/or familial designs (e.g., studying non-addicted siblings).

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Highlights

- Compromised self-awareness predicts severe disease and poor prognosis.
- We suggest similar self-awareness impairments in human drug addiction.
- This deficit is traced to ventromedial prefrontal cortex (vmPFC) functioning.
- Treatment approaches to target self-awareness and vmPFC functioning are raised.

Figure 1.

Converging meta-analyses showing the rACC/vmPFC association with personal relevance in health. Across multiple fMRI studies, research points to a self-to-other gradient that extends along the midline from ventral PFC to dorsal PFC, with the more ventral PFC regions respond more preferentially to self-processing (and very close others). For example, the rACC is activated to the contrasts (A) self>close other, self>public other, and their conjunction [adapted from (68), with permission from Elsevier]; and (B–C) self-reflection>baseline and self-reflection>other-reflection, respectively [adapted from (4), with permission from Elsevier].

Figure 2.

Increased rACC/vmPFC response to drug stimuli in drug addiction, perhaps suggesting high personal relevance of the stimuli. (A–C) Meta-analyses showing rACC activation to drug>neutral stimuli as revealed in studies of (A–B) smokers and (C) alcohol abusers [adapted, respectively, from (25), (24), and (26), with respective permissions from John Wiley and Sons, Elsevier, and John Wiley and Sons]. (D) During an incentivized drug word task, the higher the fMRI activity during the most salient task condition (where drug words were presented, and where there was a high monetary reward available for correct performance), the higher was the self-reported task-induced cocaine craving [adapted from (28), with permission from the National Academy of Sciences].

Figure 3.

Decreased rACC/vmPFC response, perhaps suggesting low personal relevance, to non-drug stimuli in drug addiction. (A) Cocaine-addicted individuals who lacked knowledge of their cocaine-choice behavior (i.e., in the Figure, those characterized as the “Impaired” group) had decreased rACC activity to the fMRI contrast error>correct on a classical color-word Stroop task; neither “Controls” nor even “Intact” cocaine-addicted individuals exhibited this decreased activity [data from (36)]. (B) Methamphetamine-addicted individuals had lower bilateral rACC activity during a risky decision-making task across all decisions; and (C) the lower the activity in the right rACC, the more times a risky choice was selected following a loss [adapted from (37), with permission from John Wiley and Sons]. (D) Compared with healthy controls, cocaine-addicted individuals had less rACC/vmPFC activity during a social interaction task [adapted from (40), with permission from the National Academy of Sciences].