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Neural Circuitry of Impaired Emotion Regulation in Substance Use Disorders

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Abstract

Impaired emotion regulation contributes to the development and severity of substance use disorders (substance disorders). This review summarizes the literature on alterations in emotion regulation neural circuitry in substance disorders, particularly in relation to disorders of negative affect (without substance disorder), and it presents promising areas of future research. Emotion regulation paradigms during functional magnetic resonance imaging are conceptualized into four dimensions: affect intensity and reactivity, affective modulation, cognitive modulation, and behavioral control. The neural circuitry associated with impaired emotion regulation is compared in individuals with and without substance disorders, with a focus on amygdala, insula, and prefrontal cortex activation and their functional and structural connectivity. Hypoactivation of the rostral anterior cingulate cortex/ventromedial prefrontal cortex (rACC/vmPFC) is the most consistent finding across studies, dimensions, and clinical populations (individuals with and without substance disorders). The same pattern is evident for regions in the cognitive control network (anterior cingulate and dorsal and ventrolateral prefrontal cortices) during cognitive modulation and behavioral control. These congruent findings are possibly related to attenuated functional and/or structural connectivity between the amygdala and insula and between the rACC/vmPFC and cognitive control network. Although increased amygdala and insula activation is associated with impaired emotion regulation in individuals without substance disorders, it is not consistently observed in substance disorders. Emotion regulation disturbances in substance disorders may therefore stem from impairments in prefrontal functioning, rather than excessive reactivity to emotional stimuli. Treatments for emotion regulation in individuals without substance disorders that normalize prefrontal functioning may offer greater efficacy for substance disorders than treatments that dampen reactivity.

The ability to monitor and control affect, or “emotion regulation,” refers to the processes by which individuals influence which emotions they have, when they have them, and how they experience and express these emotions (1). Impairments in emotion regulation contribute to substance use disorder (substance disorder) development, persistence, and severity. In adolescence, difficulties in emotion regulation may increase the likelihood of initiating, or perpetuating, substance use (2, 3), and adults with substance disorders have more emotion

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regulation difficulties than comparison subjects (see review in reference 4). Individuals who use substances to relieve negative affect develop addictive patterns of drug use more quickly (2, 5), and emotion regulation difficulties are associated with greater substance use severity in individuals in whom a substance disorder has already developed (6, 7). As impaired emotion regulation would render an individual with a substance disorder more vulnerable to cue-induced cravings or impulsive responding (1), it is not surprising that impaired emotion regulation predicts poor response to treatment (8, 9) and accentuates the risk of relapse during negative affect (10).

Although several well-established pharmacologic treatments for anxiety disorders, depressive disorders, and other disorders associated with impaired emotion regulation have been tested in substance disorders (11), most show little or no effect on substance use. Identifying the neural circuitry underlying impaired emotion regulation, and how it differs from the neural circuitry in those with emotion regulation difficulties without substance disorders, may help identify important treatment targets for substance disorders. Once identified, normalization of the neural underpinnings of impaired emotion regulation in individuals with substance disorders could serve as a proximal marker of the substance disorder's treatment response.

To provide a framework for identifying these alterations in neural circuitry, this review will first present different components of emotion regulation, the imaging tasks used to assess each component, and their associated neural circuitry. We will focus on studies that used task-based functional magnetic resonance imaging (fMRI) to examine functional connectivity (particularly resting state functional connectivity) and structural connectivity. The neural circuitry associated with impaired emotion regulation in individuals with dysregulated emotion without substance disorders (particularly anxiety, depressive, and borderline personality disorders) will be compared with the circuitry in people with substance disorders, with a focus on the amygdala, insula, and prefrontal cortex and associated networks. The review concludes with treatment implications and targets, limitations of the studies to date, and suggested future directions of research.

FOUR DIMENSIONS UNDERLYING EMOTION REGULATION

A number of conceptual approaches have been posited for emotion regulation (see reviews in references 1, 12–15). Although an in-depth discussion of these approaches is outside the scope of this review, we posit four dimensions of emotion regulation that are consistent with previous conceptual approaches. These dimensions—affect intensity/reactivity, affective modulation, cognitive modulation, and behavioral control—will provide an organizational schema to categorize the broad array of fMRI paradigms described (see reference 4). Commonly used self-report scales measuring emotion regulation can also be categorized into these four dimensions (see Table S1 in the data supplement accompanying the online version of this article), and impairments in all four of these dimensions are observed in substance disorders (4).

Affect Intensity/Reactivity

The initial affective response may occur outside of conscious awareness and prior to the engagement of most top-down modulatory processes (15, 16). Individuals with higher intensity (magnitude) and reactivity (degree of changeability) of affect may be more likely to suffer from emotional instability, especially if modulatory processes (described below) are not intact. Affect intensity/reactivity is tested by the rapid presentation (i.e., less than 2 seconds) of stressful, disturbing, or emotional cues. The short stimulus presentation timing induces intense affect but does not allow for a prominent regulatory response (17–22).

Affective Modulation and Cognitive Modulation

Two modulatory processes are involved in emotion regulation, each testable by distinct functional approaches and thus considered separately. These two strategies (affective modulation and cognitive modulation) roughly correspond to hot and cold executive functioning (23), implicit and explicit emotion regulation (14), and automatic and voluntary cognitive/behavioral emotion control (24), respectively. Affective modulation automatically engages processes that evaluate reward salience, assess environmental cues for potential threats, help with social and emotional functioning, and produce motivational biases in emotionally significant contexts. Cognitive modulation voluntarily engages processes involved in problem solving, strategic planning, and the conscious efforts to modulate internal affective states (13, 15, 16, 23).

Affective modulation tasks utilize paradigms exposing participants to prolonged (up to 2 minutes) exposure to negative cues, allowing for engagement of regulatory responses. Such tasks include reading a personalized stress script (25, 26) or a social stress task (Montreal Imaging Stress Task) (27), multiple negative stimuli presented over blocks of time (28), and cue conditioning, in which a neutral conditioned stimulus is paired with an unpleasant unconditioned stimulus, evoking a negative emotional response (29). Cognitive modulation tasks, which include “cognitive reappraisal” (16) and “reinterpretation” (30), require participants to use cognitive reframing techniques (reappraisal) to alter their emotional response to a stimulus (16, 30–35). For example, individuals may be shown negative images and asked to lessen the intensity of their emotional response (31).

Behavioral Control

Impulsivity refers to difficulties in regulating behavior. The behavioral control dimension is a subfacet of impulsivity related to engaging in a (maladaptive) behavior in the context of or in response to an intense emotion. Individuals with poor behavioral control are more likely to have a strong emotion “take over” their actions, corresponding to “negative urgency” (36) or “regulation” (16).

These tasks assess the effects of distracting affective stimuli. Examples include emotional go/no-go tasks (inhibition of prepotent responses are tested in the presence of emotionally distracting cues) (37), emotional oddball tasks (the ability to respond to an infrequent target is assessed in the setting of a disturbing cue) (38), emotional distractor tasks (threat-related distractors are presented during performance of simple cognitive tasks) (20, 39), conflict tasks (categorizing facial affect while ignoring overlaid affect label words) (40), and tasks of

expressive suppression (participants are asked to “keep their face still” while watching negative images) (30, 32).

NEURAL CIRCUITRY OF EMOTION REGULATION

Selected Regions of Focus

In the following sections, the neural circuitry of emotion regulation in psychiatric populations with and without substance disorders is reviewed. We focus on five brain regions or groups of regions based on their essential roles in evaluating threatening stimuli, emotional processing, emotion regulation, and behavioral control (15, 16, 41–44). These regions roughly fall within two functional categories—emotion-generating or emotion-processing regions, i.e., amygdala and insula—and three emotion regulatory regions—1) the dorsomedial PFC (dmPFC), including the dorsal anterior cingulate cortex (dACC) and the presupplementary and supplementary motor area; 2) the lateral PFC (lPFC), including the lateral orbitofrontal cortex (lOFC) and ventrolateral PFC (vlPFC); and 3) the rostral ACC/ventromedial PFC (rACC/vmPFC), including the perigenual ACC, subgenual ACC, and medial OFC (mOFC)] (Table 1, Figure 1A) (15, 16, 41–44). Two general characteristics of intact emotion regulation processes are that emotion-generating/processing regions are activated by negative emotional stimuli and that this neural response is dampened by emotion regulatory regions, automatically by the rACC/vmPFC and voluntarily by the dmPFC and lPFC (15, 16, 24, 42).

These brain areas are also components of neural “networks,” defined by the strength of the temporal correlation of low-frequency fMRI blood oxygen labeled dependent (BOLD) fluctuations between discrete anatomical regions (45). This review focuses on the described regions rather than networks because some regions in the network overlap and some regions may be activated in isolation of a network (Table 1). The dmPFC and lPFC are considered part of the cognitive (or executive) control network (35, 41), which plays a critical role in “the internal representation, maintenance, and updating of context information in the service of exerting control over thoughts and behavior” (42, 46). The dmPFC and insula are components of the “salience network” (42, 43), which activates in response to and integrates information concerning salient stimuli during cognitive control (41). (The dmPFC is considered part of both the cognitive control and salience networks.) The rACC/vmPFC is an integral component of the “default mode network,” which is actively engaged during rest, mind wandering, and self-referential introspective states and is deactivated when executive control is engaged (45, 47–49).

Connections between regions and/or networks can be assessed with functional or structural connectivity; the former assesses temporal coherence between regions, and the latter uses diffusion tensor imaging to assess white matter connection. Although measures of functional and structural connectivity are frequently correlated, the strength of correlation varies with the network examined (50). Connectivity between regions may occur via indirect pathways, and consequently, functional connectivity may be observed in the absence of structural connectivity. Functional, relative to structural, connectivity also varies more across time (50). Higher levels of fractional anisotropy and lower levels of mean diffusivity are both markers of greater white matter integrity.

Neural Circuitry of Emotion Regulation During fMRI Tasks

The rACC/vmPFC and dmPFC (dACC) are activated during tasks of all four dimensions of emotion regulation, consistent with rACC/vmPFC involvement in automatic regulation and inhibition of intense affect (15, 16, 24, 51) and the dmPFC dual role of responding to salient stimuli (dACC, in particular) and mediating cognitive control (41, 42). Activation of the lPFC is most notable during tasks of the latter three dimensions (27, 29, 31–35, 37, 39, 52). Emotion-generating/processing regions (amygdala and insula) are activated during tasks of affect intensity or reactivity (18–22), but inconsistently or rarely during affective or cognitive modulation tasks (27,29,31–35,52). The absence of consistent amygdala/insula activation during affective/cognitive modulation may result from down-regulation by regulatory regions (15, 16, 24, 35) or habituation to the repeated presentation of emotional stimuli (21, 53, 54). In contrast, the amygdala is often activated during behavioral control (32, 37, 40), presumably due to the effort required to control behavior, diminishing the availability of neural resources to attenuate emotional reactivity (32).

NEURAL CIRCUITRY IN DISORDERS OF NEGATIVE AFFECT

fMRI Tasks of Emotion Regulation

Affect intensity/reactivity—Anxiety and borderline personality disorders are associated with insula/amygdala hyperactivation during tasks of affect intensity/reactivity, and amygdala/insula activation is positively associated with self-reported negative valence of task stimuli (18, 21, 44, 53, 55, 56). In contrast, hypo-activation in the rACC/vmPFC and dmPFC is described in these disorders, with possibly greater hypoactivation in some diagnoses (generalized anxiety disorder, posttraumatic stress disorder [PTSD]) relative to others (panic and social phobia) (18, 21, 53, 55).

Affective modulation—Anxiety and depressive disorders are associated with greater amygdala and insula activation during tasks of affective modulation (21, 44, 51, 57). When participants recall unresolved life events, amygdala/insula hyperactivation is also observed in individuals with borderline personality (58). With respect to regulatory regions, PTSD is associated with lower activation in all regulatory regions in most (21, 57, 59), but not all (44), studies during these tasks. Depression, by contrast, is associated with hyperactivation in regulatory regions (59).

Cognitive modulation—Cognitive modulation tasks consistently reveal that individuals with higher anxiety levels or with anxiety disorders (31,34,60) or borderline personality disorder (56) experience increased activation in emotion-generating/processing regions and lower activation in all regulatory regions. Depression is associated with decreased activity in the lPFC (51). Hyperactivation in emotion-generating/processing regions, coupled with hypoactivation in regulatory areas during these tasks, may lead to difficulties in down-regulating intense emotion. Treatment of social anxiety disorder is associated with greater inverse dmPFC–amygdala connectivity and greater connectivity within regulatory regions (dmPFC–lPFC and dmPFC–rACC/vmPFC) during a cognitive modulation task (60), and improvement of depressive symptoms during treatment is also associated with greater activity in the lPFC (33).

Behavioral control—During tasks of behavioral control, higher subjective anxiety levels and anxiety disorder diagnoses are associated with heightened activation in emotion-generating/processing regions (40, 61) and attenuated activation in all regulatory regions (39, 40, 61). Impairment in amygdala–rACC/vmPFC anticorrelation (40) and lower connectivity between the insula and dmPFC are observed in individuals with anxiety disorders during behavioral control (62).

In summary (Figure 1B), greater problems with emotion regulation in individuals with disorders associated with negative affect (without substance disorders) are associated with hyperactivation in the amygdala/insula and hypoactivation in the rACC/vmPFC and dmPFC (specifically dACC) during tasks of affect intensity/reactivity and hyperactivation of the amygdala/insula and hypoactivation in regulatory regions (rACC/vmPFC, dmPFC, and lPFC) during tasks of affective modulation, cognitive modulation, and behavioral control.

Resting State Functional Connectivity and Structural Connectivity

Decreased resting state connectivity between emotion-generating/processing and regulatory regions is associated with disorders of emotion dysregulation. Resting state connectivity between the amygdala/insula and all three regulatory regions is lower in individuals with anxiety and depressive disorders relative to controls in most studies and improves with treatment (44, 63, 64). Structural connectivity is also impaired in disorders of emotion regulation. Trait anxiety, anxiety disorder, major depressive disorder, and borderline personality are associated with decreased fractional anisotropy or increased mean diffusivity in the uncinate fasciculus and cingulum (tracts connecting the amygdala/insula to regulatory regions and the amygdala to the insula) (20, 65–67).

Decreased within-regulatory region functional and structural connectivity are also associated with emotion dysregulation. Decreased resting state connectivity is observed between the rACC/vmPFC and dmPFC inveterans with PTSD relative to healthy combat veterans (68). Impaired interhemispheric connections among individuals with major depressive disorder also occur, evidenced by decreased fractional anisotropy with in the genu of the corpus callosum (69). Studies in individuals with anxiety disorders, however, demonstrated mixed results in the genu (65).

In summary, individuals with disorders of negative affect generally exhibit decreased resting state functional and structural connectivity between emotion-generating/processing regions and regulatory regions and, to some degree, within regulatory regions as well.

NEURAL CIRCUITRY OF EMOTION REGULATION IN SUBSTANCE USE DISORDERS

The emerging literature exploring the neural underpinnings of emotion regulation in substance disorders points to intriguing similarities—and differences—relative to individuals with disturbed emotion regulation but without substance disorders. While we will consider potential confounds, our goal is to highlight congruent findings that are shared among the various addictions. Moreover, we will report on differences that are associated with relapse risk (26, 70) and craving intensity (71). fMRI activation studies are summarized in Figure

1C, Table 2, and Table S2 in the online data supplement, and resting state functional and structural connectivity studies are summarized in Figure 1C, Tables 3 and 4, and online Table S3.

fMRI Tasks of Emotional Regulation

Affect intensity/reactivity—Amygdala hyperactivation is consistently observed in individuals with disorders of negative affect during tasks of affect intensity/reactivity (preceding section). In contrast, individuals with substance disorders show evidence of no activation, hypoactivation (72, 73), or hyperactivation (17, 72) of the amygdala during exposure to negative images in the International Affective Picture System (IAPS) (17) or facial expressions (72, 73). Insula activation is equally mixed, with no or hypoactivation (17, 72, 73) or hyperactivation (72) observed in substance disorders compared with controls. These disparate findings (even within the same cohort [72]) are evident even though all cited studies were conducted in individuals with alcohol use disorders (alcohol disorders) and the subjects had been abstinent for at least 2 weeks (17, 72, 73). Notably, two of these studies (17, 72) were small (11 subjects per group).

Similar to groups with disorders of negative affect without substance disorders, individuals with substance disorders show a dampening of the rACC/vmPFC and dmPFC. Decreased activation in the rACC/vmPFC during fear and disgust (72, 73) and in the dmPFC (dACC) during disgust (72) is observed in alcohol disorders. Therefore, diminished regulatory activity but not heightened activation in emotion-generating/processing regions is observed in substance disorders during tasks of affect intensity/reactivity.

Affective modulation—Affective modulation tasks in substance disorders are also not associated with the heightened activation of emotion-generating/processing regions observed in individuals with disorders of negative affect without substance disorders. In individuals (primarily male) with alcohol disorders (26, 74), opioid use disorders (opioid disorders) (28), and cocaine use disorders (cocaine disorders) (25, 75), tasks of affective modulation showed no change or dampened amygdala (25, 26, 28, 74, 75) and insula (25, 26, 28, 74) activation relative to controls. In contrast to a cohort of matched male participants with cocaine disorders who showed no amygdala and limited insula activation during a personalized stressful narrative, however, female participants demonstrated a marked response (75).

Attenuated activity in emotion regulatory regions during affective modulation, on the other hand, is again generally consistent with the observation of attenuated activation in individuals with disorders of negative affect without substance disorders. rACC/vmPFC activation was significantly lower in individuals with alcohol disorders than in control subjects (26, 74) and in individuals who relapsed earlier (26). Similar findings in other regulatory regions have been observed in most comparisons of people with substance disorders versus control subjects: hypoactivation was demonstrated in the dmPFC (dACC) in individuals with cocaine disorder (25) and in the lPFC in alcohol disorder (26), and lower activation in the lPFC predicted relapse in alcohol disorder (26). The exceptions to these findings include increased activation (lPFC) in women-only participants with cocaine

disorder (75) and increased dACC activation in both women and men with cocaine disorder (75).

Cognitive modulation—The only published study, to our knowledge, that assessed cognitive modulation in individuals with substance disorders asked participants to suppress a negative affective response during exposure to negative IAPS stimuli (76). These epochs were compared with periods when participants were asked to maintain their affective response. In individuals with cocaine disorders, suppression of affect resulted in reduced activation in both emotion-generating/processing regions (insula) and emotion-regulating regions (lPFC).

Behavioral control—When exposed to neutral distractor images while performing an emotional oddball task (requiring attendance to a target stimulus), individuals with borderline personality plus opioid disorder demonstrated less activation in both emotion-generating/processing regions (amygdala) and all three emotion-regulating regions, relative to individuals without either disorder (38). Findings in the amygdala are in contrast to the increase in activation that would be expected in individuals with borderline personality only.

Summary

The most consistent finding distinguishing people with substance disorders from healthy subjects, and often predictive of relapse, is hypoactivation in regulatory regions, particularly the rACC/vmPFC, during tasks of emotion regulation (with the exception of a single study in cocaine disorder [75]). These findings persist across dimensions and substance-disordered populations and mirror studies of individuals with anxiety, depressive disorders, and borderline personality disorder. Unlike the observed increase in amygdala/insula activation in individuals with impaired emotion regulation without substance disorders, however, activation in emotion-processing/generating regions is not reliably observed during emotion regulation in substance disorders. The critical caveat to these observations is an apparent gender effect. The only study assessing women separately (75) found increased activation of emotion-generating/processing regions in women but not men.

Resting State Functional and Structural Connectivity

The strength of resting state connectivity between the amygdala (77, 78) or insula (73, 77–80) and the rACC/vmPFC is weaker in individuals with substance disorder compared with controls, in individuals with a greater risk of relapse (70), and in individuals with heightened craving during withdrawal relative to those with less craving (71). Similarly, lower strength of resting state connectivity between the amygdala and the lPFC and dmPFC is observed in opioid disorders (78), between the insula and lPFC in alcohol and opioid disorders (73, 78, 81), and between the insula and dmPFC (78, 79) in opioid and cannabis disorders. Finally, lower insula–amygdala connectivity strength is observed in substance disorders (78).

Likewise, alterations in structural connectivity between emotion-generating/processing regions and regulatory regions and between the insula and amygdala are observed in substance disorders. Fractional anisotropy in the uncinate fasciculus (78, 82) and ventral amygdalofugal pathway (78) (amygdala–regulatory regions, amygdala–insula), anterior

corona radiata (amygdala–rACC)(83), internal capsule (amygdala–lPFC) (82, 84), and external capsule (amygdala–lPFC, amygdala–dmPFC) (78) is reduced in substance disorders compared with controls. Reduced fractional anisotropy of the extreme capsule (lPFC–insula) is also observed in substance disorders (85). One reported exception was in smokers; these individual showed increased fractional anisotropy in the internal capsule and cingulum (amygdala–regulatory regions). This was posited as related to a trajectory wherein there is increased fractional anisotropy at earlier ages, which decreases with more years of smoking and greater dependence (86).

Measures of resting state connectivity within regulatory regions are less consistent than results between emotion-generating/processing and regulatory regions. In alcohol disorder, connectivity is increased between the rACC/vmPFC and dACC but decreased between the dlPFC and dACC (81). Connectivity between the rACC/vmPFC and the lPFC is also attenuated in individuals who later relapse, relative to those who abstain (80).

In contrast, structural connectivity within and between regulatory regions is more consistently reduced in substance disorders relative to controls and in more severe substance disorders relative to those that are less severe. Except for some conflicting results in smokers (in the genu) (86, 87), fractional anisotropy within the frontal forceps (82), within the genu of the corpus callosum (78, 82, 88), and within the rostral body (87) is reduced in substance disorders. Decreased fractional anisotropy in the genu is also associated with a longer duration of substance disorder (89), and reduced fractional anisotropy in the genu and frontal forceps predicts relapse in alcohol disorder (82). Further, mean diffusivity of the genu of the corpus callosum is increased (90) in substance disorders. A number of studies assessing white matter integrity utilizing a region-of-interest approach have also demonstrated within-PFC reductions in white matter integrity in individuals with substance disorders, including reduced fractional anisotropy in lOFC (91) and in a region encompassing the cingulum and the right dACC (91). Duration of drug dependence negatively correlated with fractional anisotropy within the right mOFC (89).

In summary, individuals with substance disorders reliably demonstrate weakened strength of resting state connectivity between the amygdala/insula and regulatory regions, consistent with observations in individuals with disorders associated with negative affect. Decreased resting state functional connectivity is also generally observed between and within regulatory regions in substance disorders relative to controls. This weakening of functional connectivity strength may be caused by impairment in the integrity of white matter tracts.

POTENTIAL TREATMENT TARGETS

Routes of Dysfunction

Impaired functioning in rACC/vmPFC, dACC, lPFC—Unlike the augmented amygdala/insula reactivity observed in individuals with emotion regulation difficulties without substance disorders, individuals with substance disorders rarely exhibit hyperactivation in emotion-generating/processing regions during emotional provocation. This is consistent with reduced sensitivity to nondrug emotional stimuli in substance disorders (92), whereas emotion-generating/processing regions are highly reactive to drug

cues (26, 75, 92). Similar to what is commonly reported in individuals with emotion regulation difficulties without substance disorders, hypo-activation in PFC regulatory regions is reliably observed in substance disorders (rACC/vmPFC in all tasks of emotion regulation and the dmPFC and lPFC during affective modulation and cognitive modulation). Therefore, emotion regulation disturbances in substance disorders may stem primarily from impairments in PFC activation, as a direct result of disrupted neural functioning, rather than from excessive reactivity to negatively charged affective stimuli.

Decreased resting state functional and structural connectivity between amygdala/insula and PFC—Impairments in resting state connectivity and white matter tract integrity in individuals with substance disorders, in particular in connections between emotion-generating/processing regions and regulatory regions (rACC/vmPFC, lPFC, dmPFC) and between the insula and amygdala, may contribute to impaired down-regulation of emotion-generating/processing regions. However, disruptions in connectivity could also be the genesis of hypoactivation in regulatory regions in substance disorders. Proper engagement of PFC modulatory responses may depend on receiving information from the amygdala and/or insula; the primary deficit in emotion dysregulation may be delayed or weak communication from emotion-generating/processing regions to the PFC. In fact, individuals with anxiety disorders show delayed dlPFC and dmPFC activation during cognitive modulation tasks (60).

Hyperactivation in default mode network during rest/baseline—In substance disorders, task-induced rACC/vmPFC hypo-activation may reflect a relatively heightened fMRI signal during baseline or neutral periods (26, 74, 75). rACC/vmPFC (a primary locus of the default mode network) is active during rumination and self-monitoring but deactivated during outwardly focused cognitive tasks (47–49). Rumination is associated with unhappiness (47) and may be a form of emotionality itself; hyperactivation in this network could contribute to difficulties in emotion regulation in substance and other disorders. Heightened intraregional rACC/vmPFC connectivity has been observed in depression (93), and heightened within-network connectivity has been observed in alcohol disorders (94). Although our theory is more concerned with basal default mode network activity, it is still notable that difficulty “shutting down” the net work has been observed in PTSD (57), ADHD (48), and cocaine disorders (95).

Treatment Implications

It is not yet known which, if any, of the described alterations in substance disorders 1) reliably contributes to relapse risk and 2) will respond to treatment, particularly with respect to emotion regulation. Proposed avenues of future study are herein discussed.

Augment PFC activation during emotion regulation tasks—Treatments for emotion regulation in populations without substance disorders that normalize PFC function (increase task-related activation) may have greater efficacy for substance disorders than dampening reactivity in emotion-generating/processing regions, as the latter is generally not observed in substance disorders. Selective serotonin reuptake inhibitors (SSRIs) and benzodiazepines dampen amygdala, insula (96–98), and lOFC (97, 99) activity and are

useful in the treatment of disorders of negative affect without substance disorders but not particularly in the treatment of substance disorders (11). A caveat is that late-onset alcohol disorder—associated with heightened anxiety and higher rates of comorbid anxiety/depression—tends to respond better to SSRIs than does early-onset disorder (100), possibly suggesting a typology-specific difference in the reactivity of emotion-generating/processing regions. In contrast to SSRIs, norepinephrine reuptake inhibitors (e.g., reboxetine) increase activation in the dlPFC and dmPFC in response to negative stimuli (97). Norepinephrine reuptake inhibitors, as well as other medications that increase noradrenergic function (e.g., bupropion, tricyclic antidepressants, SNRIs such as venlafaxine) may, therefore, deserve further study for the treatment of substance disorders. Bupropion is already a mainstay of treatment for nicotine dependence, and although it has not proven reliably effective in the treatment of stimulant disorders (11), targeting individuals with PFC hypoactivation may improve its effectiveness. Similarly, modafinil, which is most beneficial in alcohol disorders with comorbid impairments in cognitive control (101), was reported to attenuate behavioral disinhibition in alcohol disorder while increasing dmPFC activation (102). Targeted studies focused on substance-disordered individuals with attenuated PFC activation during emotion regulation tasks may improve the effectiveness of both pharmacological and behavioral interventions.

Improve white matter tract integrity or resting state connectivity strength— Oxytocin enhances resting state connectivity between the amygdala and rACC/vmPFC (64) and is being investigated (preclinically) as a treatment for substance disorders (103). Cognitive-behavioral therapy for anxiety disorders increases connectivity within regulatory regions (dmPFC–rACC/vmPFC, dmPFC–lPFC) and increases anticorrelation between the amygdala and dmPFC during cognitive modulation tasks (60). Identifying either medications or psychosocial therapies that increase the strength of resting state functional connectivity or the integrity of white matter tracts between emotion-generating/processing and regulatory regions may, therefore, prove particularly useful in substance disorders.

Decrease default mode network activation at rest or increase deactivation during tasks—Finally, identifying treatments that ameliorate heightened basal activation in this network may also prove useful. Performing a complex task is known to deactivate the default mode network, and boredom is a well-accepted relapse trigger. Simply encouraging patients to “stay busy” may work, in part, by deactivating this network. Mindfulness is under investigation for the treatment of a variety of substance disorders (104) and may be working by means of this mechanism, as meditation decreases network activation (49, 105).

LIMITATIONS AND FUTURE WORK

This review has some notable limitations. First, the relatively comprehensive literature cited assessing the neural circuitry associated with negative affect in individuals without substance disorders is not matched by a commensurate literature in substance disorders. Second, more task-based studies in substance disorders are needed to further explore activation patterns within each dimension (especially in affect intensity/reactivity, cognitive modulation, and behavioral control). Third, most studies of emotion regulation in substance disorders have male majorities; those that included sufficient numbers of women to explore gender

differences observed stark gender contrasts (75). Consequently, further studies into the effects of gender on brain activation are required. Fourth, the quandary of whether the neural differences in individuals with substance disorders are a consequence of pre-existing vulnerabilities or of persistent substance use was not considered in this review. Nevertheless, almost all of the studies assessing neural activity evaluated individuals with substance disorders following at least two weeks of abstinence. Thus, even substance-induced alterations appear to persist beyond the initial withdrawal period and may therefore impact relapse risk and, subsequently, require treatment. Fifth, we focused our work on the insula, amygdala, and certain regions within the PFC and their interactions partially because they fell within relevant networks of interest. However, other regions also play key roles in emotion regulation, including the hippocampus, dorsal and ventral striatum, and posterior cingulate. Although not a focus of this review, these and other regions may be of equal importance in accounting for altered emotion regulation in substance disorder. Sixth, it will be important in future work to identify differences between different substances of abuse and at different stages of abstinence as well as premorbid alterations versus those that are substance-induced. Seventh, because substance disorder subtype may influence treatment response, future work could explore the relationships between subtype and alterations in emotion regulation circuitry, which could help in treatment matching efforts (11).

Finally, the extant literature did not allow us to assess the potential impact of comorbid psychiatric disorders associated with negative affect (e.g., depressive, borderline personality, posttraumatic stress, and other anxiety disorders) on disruptions in neural circuitry. Comorbid diagnoses could account for many of the similarities described between substance disorders and disorders of negative affect without substance disorders, as well as much of the variability reported in the substance disorder groups. Other comorbid disorders commonly observed in substance disorders and events associated with emotion dysregulation (e.g., attention deficit, bipolar, and conduct/antisocial disorders as well as childhood and adult trauma) could also play an important role in the alterations described. For example, similar to persons with substance use disorders, individuals with conduct disorder and callous-unemotional traits demonstrate a blunted amygdala response to emotional stimuli (106), individuals with ADHD histories show decreased activation in the amygdala, rACC/vmPFC, and lOFC during behavioral control (107), and those with trauma histories alone evidence decreased PFC activation during cognitive modulation relative to controls (108). The majority of the articles did not provide extensive details on the rates of these disorders in their samples (see Tables S2 and S3 in the online data supplement); these questions remain open for future exploration.

Identifying the root neural causes contributing to emotion regulation disturbances in substance disorders, the relationship of these disturbances to relapse, and approaches for normalizing these processes is imperative. Knowing the neural underpinnings will help us in efforts to match treatments, which may lead to improved treatment efficacy.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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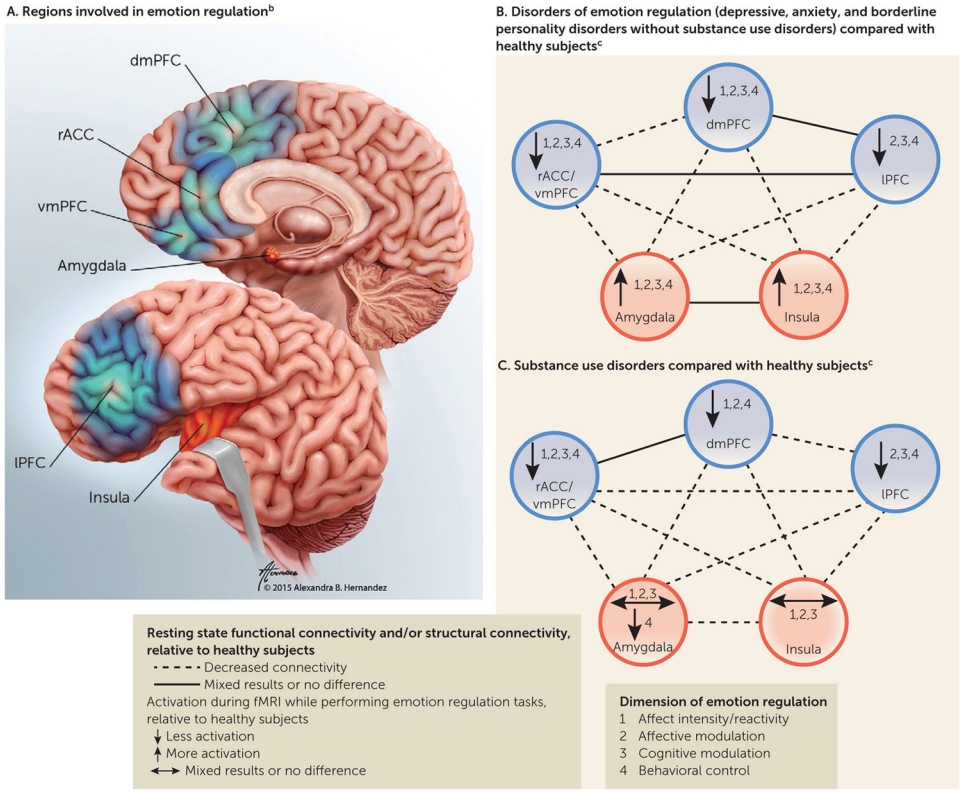

FIGURE 1.

Brain Regions Involved in Emotion Regulation and Alterations in Depressive, Anxiety, and Borderline Personality Disorders and in Substance Use Disorders[a]

[a]The dorsomedial prefrontal cortex (dmPFC) includes the dorsal anterior cingulate cortex (dACC), presupplementary motor area (preSMA), and supplementary motor area (SMA). The lateral prefrontal cortex (lPFC) includes the dorsolateral prefrontal cortex (dlPFC), ventrolateral prefrontal cortex (vlPFC), and lateral orbitofrontal cortex (lOFC). Other abbreviations: rostral anterior cingulate cortex (rACC), ventromedial prefrontal cortex (vmPFC).

[b]The illustration in part A is by Alexandra B. Hernandez of Gory Details (used by permission). Regions shaded in red are categorized as emotion-generating or emotion-processing regions; regions depicted in blue are categorized as regulatory regions. Further details about the roles of these regions in emotion regulation are specified in Table 1.

[c]Emotion regulation tasks were performed during functional magnetic resonance imaging.

TABLE 1

Brain Regions of Focus, Functional Role in Emotion Regulation, and Related Connections (White Matter Tracts) in Substance Use Disorders[a]

Region of Focus and Region With Functional Connections	Structurally Connected via
Emotion-generating and emotion-processing regions	
Amygdala[b]: assigns value to positive and negative emotional cues, is involved in fear conditioning, activates during stress and exposure to negative stimuli, generates fear response (21, 44)	
Insula	Ventrolateral branch of UF; ventral amygdalofugal pathway
dmPFC	Anteromedial branch of the UF; external capsule; cingulum
rACC/vmPFC	UF; cingulum; anterior corona radiata via the internal capsule; ventral amygdalofugal pathway; inferior thalamic peduncle/radiation
lPFC	Ventrolateral branch of UF; external capsule; cingulum
Amygdala	AC (interhemispheric connections)
Insula (SN)[c]: activates in response to salient stimuli (positive and negative cues), processes interoceptive information (ascending visceral inputs to insula) (42), activates during stress and exposure to negative stimuli, is involved in fear conditioning (21, 44)	
Amygdala	Ventrolateral branch of UF; ventral amygdalofugal pathway
dmPFC	Superior fronto-occipital fasciculus
rACC/vmPFC	Unnamed tracts (structural connectivity demonstrated through seed-based studies)
lPFC	Extreme capsule; short association fibers (fronto-insular tracts)
Insula	Midbody of the CC (interhemispheric connections)
Regulatory regions	
dmPFC[d] (includes dACC, preSMA, SMA) (CCN/ECN): activates in response to salient stimuli (positive and negative cues), is involved in performance monitoring/error monitoring, conflict processing, integrating emotional response during goal selection, response conflict, response execution (preSMA/SMA) (24,41,42,44)	
lPFC	Short association fibers (frontal aslant tract) (intrahemispheric connections)
dmPFC	Regions of the CC (genu, rostrum, rostral body, anterior midbody, midbody) (interhemispheric connections)
rACC/vmPFC	Short association fibers (interhemispheric connections)
lPFC[e] (includes dlPFC, vlPFC, lOFC) (CCN/ECN): involved in planning, selection of goals, sequencing, holding information online (dlPFC), response inhibition (especially vlPFC/lOFC), conscious/voluntary regulation of amygdala and insula activation (24, 41, 42, 44)	
dmPFC	Short association fibers (frontal aslant tract) (intrahemispheric connections)
lPFC	Regions of the CC (genu, rostrum, rostral body, anterior midbody) (interhemispheric connections)
rACC/vmPFC	Short association fibers (interhemispheric connections)
rACC/vmPFC[f] (includes rACC, vmPFC, mOFC, pgACC, sgACC) (DMN): is involved in the subjective valuation of cues (assigns motivational salience and encodes outcome expectancies during emotional decision making, determines motivational priorities), is involved in self-referential introspection (tags information as personally relevant), processes emotional conflict (15,48), mediates extinction	

Region of Focus and Region With Functional Connections	Structurally Connected via
(16), provides automatic/unconscious regulation of amygdala and insula activation (15, 24)	
dmPFC	Regions of the CC (genu, rostrum, rostral body) (interhemispheric connections)
rACC	Frontal forceps (interhemispheric connections)
lPFC	Short association fibers (frontal orbitopolar tract) (intrahemispheric connections)

[a] ***Abbreviations for networks***: cognitive control network (CCN) or alternatively named executive control network (ECN), default mode network (DMN), salience network (SN). ***Abbreviations for regions:*** dorsal anterior cingulate cortex (dACC), dorsolateral prefrontal cortex (dlPFC), dorsomedial prefrontal cortex (dmPFC), lateral prefrontal cortex (lPFC), lateral orbitofrontal cortex (lOFC), presupplementary motor area (preSMA), medial orbitofrontal cortex (mOFC), perigenual anterior cingulate cortex (pgACC), rostral anterior cingulate cortex (rACC), subgenual anterior cingulate cortex (sgACC), supplementary motor area (SMA), ventrolateral prefrontal cortex (vlPFC), ventromedial prefrontal cortex (vmPFC). ***Abbreviations for tracts:*** anterior commissure (AC), corpus callosum (CC), uncinate fasciculus (UF).

[b] Data are from references 15 and 21 (functional connections) and 78 and 109–112 (structural connections). Although amygdala–lPFC structural connectivity has been described, amygdala regulation by the lPFC likely occurs primarily via the insula, dmPFC, and/or rACC/vmPFC (15, 51).

[c] Data are from references 21,42 (functional connections) and 109 and 113–115 (structural connections). Unless otherwise mentioned, “insula” refers to the anterior portion of this region.

[d] Data are from references 15 (functional connections) and 109 and 116 (structural connections). The dACC is named an “emotion generating/processing region” (44) but also has important regulatory functions and is a “transition zone between limbic and frontal cortex” (41) and often coactivates with the preSMA and SMA, which regulate motor behavior (41). It is therefore named as a regulatory region in this review.

[e] Data are from references 15 (functional connections) and 116 and 117 (structural connections). Includes parts of Brodmann areas 6, 8, 9, 10, 11, 45, 46, and 47.

[f] Data are from references 15 (functional connections) and 116 and 117 (structural connections). Commissural pathways such as the CC connect “broadly similar regions” of the two hemispheres. Although usually commissural paths are thought to connect between homologous regions, this is not always the case. Sometimes nonhomologous regions are connected via commissural pathways, including the CC (109).

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TABLE 2

Differences Between Individuals With Substance Use Disorders and Control Subjects in Activation in Regions of Focus (Amygdala, Insula, lPFC, dmPFC, rACC/vmPFC) During Tasks of Emotion Regulation[a, b]

Study	Task	Stress Versus Baseline Contrast	Stress Versus Neutral Contrast	Overall Effect: Neutral Plus Stress[c]	Neutral Trials Only	Regions
Affect intensity/reactivity tasks						
Gilman et al. 2008 (17)	Negative or neutral pictures paired with alcohol or neutral beverages			AUD > controls		R amygdala
O'Daly et al. 2012[d] (73)	Fearful faces		AUD < controls			R amygdala
				AUD < controls		B insula (AUD with history of multiple detoxifications < AUD with history of single detoxification < controls); B middle/lOFC (AUD with history of multiple detoxifications < AUD with history of single detoxification and controls)
Salloum et al. 2007 (72)	Negative emotional faces	AUD < controls				Fear: L vmPFC/middle OFC, L rACC, L insula, R sgACC; disgust: L dlPFC, L dACC, L rACC, R amygdala, R insula
		AUD > controls				Disgust: L dlPFC; anger: L insula
Affective modulation tasks						
Potenza et al. 2012 (75)	Personalized script	Women only: cocaine use disorder > controls				B insula, dACC, L dlPFC, B amygdala, B posterolateral OFC (BA 47)
					Women only: cocaine use disorder > controls	L vlPFC/B posterolateral OFC (BA 47), vmPFC, B dlPFC, rACC
		Men only: cocaine use disorder > controls				L insula, dACC
					Men only: cocaine use disorder > controls	sgACC, rACC, B vmPFC, dACC, B insula, B amygdala, B vlPFC (BA 47), B dlPFC (lateral BA 10)
Seo et al. 2013 (26)	Personalized script	AUD < controls				L insula, dmPFC (BA 8, 9), L lOFC, B dlPFC (BA 6, 8), vmPFC, sgACC
					AUD > controls	vmPFC, sgACC
					AUD < controls	L lOFC, L insula, L dlPFC (BA 6, 8)
		Worse-outcome AUD < better-outcome AUD				rACC, vmPFC, R vlPFC

Study	Task	Stress Versus Baseline Contrast	Stress Versus Neutral Contrast	Overall Effect: Neutral Plus Stress[c]	Neutral Trials Only	Regions
					Worse-outcome AUD > better-outcome AUD	sgACC, vmPFC, rACC
Sinha et al. 2005 (25)	Personalized script	Cocaine use disorder < controls				dACC
Sinha et al. 2007 (118)	Personalized script	Worse-outcome cocaine use disorder > better-outcome cocaine use disorder				dmPFC/frontal pole (BA 9, 10)
Wang et al. 2010 (28)	Short negative stimuli (IAPS) in block design			Opioid use disorder < controls		R amygdala
Xu et al. 2013 (119)	Personalized script		Cocaine use disorder with higher-relapse-risk genotype (CG) > cocaine use disorder with lower-relapse-risk genotype (CC)			R amygdala
Yang et al. 2013 (74)	Conditioned paradigm		AUD < controls (AUD deactivated to high threat, controls did not)			rACC
		AUD < controls (AUD deactivated more than controls to high threat)				rACC
					AUD > controls (controls deactivated more than AUD to low threat)	rACC
Cognitive modulation tasks						
Albein-Urios et al. 2014 (76)	Reappraisal	Cocaine use disorder < controls				L dlPFC, L insula
Behavioral control tasks						
Smoski et al. 2011 (38)	Emotional oddball task		Opioid use disorder < controls			B amygdala, dACC, R dlPFC, L sgACC
		Opioid use disorder < controls				B amygdala, dACC
					Opioid use disorder > controls	dACC

Study	Task	Stress Versus Baseline Contrast	Stress Versus Neutral Contrast	Overall Effect: Neutral Plus Stress[c]	Neutral Trials Only	Regions
			Opioid use disorder > controls			L IFG/vlPFC (BA 45)

[a] ***Abbreviations for substance use disorders:*** alcohol use disorder (AUD), substance use disorder (SUD). ***Abbreviations for regions:*** dorsal anterior cingulate cortex (dACC), dorsolateral prefrontal cortex (dlPFC), inferior frontal gyrus (IFG), lateral prefrontal cortex (lPFC), lateral orbitofrontal cortex (lOFC), orbitofrontal cortex (OFC), presupplementary motor area (preSMA), medial orbitofrontal cortex (mOFC), perigenual anterior cingulate cortex (pgACC), rostral anterior cingulate cortex (rACC), subgenual anterior cingulate cortex (sgACC), supplementary motor area (SMA), ventrolateral prefrontal cortex (vlPFC), ventromedial prefrontal cortex (vmPFC). ***Other abbreviations:*** bilateral (B), Brodmann's area (BA), International Affective Picture System (IAPS), left (L), right (R).

[b] Further details about the individual studies (subject details, psychiatric comorbidities, exclusion criteria, tasks, analysis methods) can be found in Table S2 in the online data supplement. When laterality is not specified, the cluster crosses the midline. Findings for the insula are restricted to the anterior insula; findings observed in the posterior insula are not cited in the table.

[c] This column is included for studies in which an ANOVA was performed (group by condition, where group is SUD or controls and where condition is stress or neutral) and demonstrated an effect of group but not an effect of condition, indicating that, had a t test been performed comparing AUD to controls for the stress trials only, there may have still been a significant effect.

[d] Significant group-by-condition-by-task interaction. Explicit task: controls had activation and AUD had deactivation for all conditions. Implicit task: controls and AUD with a history of a single detoxification had minimal or no activation for all conditions. AUD with a history of multiple detoxifications had deactivation for neutral and 100% fear. AUD with a history of multiple detoxifications had activation for 50/50 fear/neutral.

TABLE 3

Differences Between Individuals With Substance Use Disorder and Control Subjects in Resting State Functional Connectivity in Regions of Focus (Amygdala, Insula, lPFC, dmPFC, rACC/vmPFC)[a, b]

Study	Seeds	Connectivity	Regions
Camchong et al. 2013 (80)	sgACC	Worse-outcome AUD < better-outcome AUD	sgACC–L dlPFC, sgACC–B insula
Gu et al. 2010 (77)	B amygdala, B rACC	Cocaine use disorder < controls	B amygdala–rACC, B rACC–R insula, B rACC–B amygdala
McHugh et al. 2014 (70)	L and R BL amygdala, L and R CM amygdala	Worse-outcome cocaine use disorder < better-outcome cocaine use disorder and controls	L CM amygdala–vmPFC/rACC
Müller-Oehering et al. 2014 (81)	dACC, B dlPFC	AUD > controls AUD < controls	dACC–B vmPFC B dlPFC–R dACC/insula
O'Daly et al. 2012 (73)	R and L insula, R and L amygdala	AUD < controls	L insula–L rACC (AUD with history of multiple detoxifications versus controls), L insula–L vmPFC (AUD with history of multiple detoxifications versus controls), L insula–R vlPFC (AUD with history of multiple detoxifications versus controls)
		AUD > controls	L insula–R vlPFC (AUD with history of single detoxification versus controls), L insula–L vmPFC (AUD with history of single detoxification versus controls)
		Positive correlation with number of past detoxifications (more detoxifications > fewer detoxifications)	L amygdala–L dlPFC
		Negative correlation with number of past detoxifications (more detoxifications < fewer detoxifications)	L insula–L vlPFC
Pujol et al. 2014 (79)	R and L insula, but authors report only R because L was similar	Cannabis use disorder < controls	R insula–dACC, R insula–rACC/vmPFC (more anticorrelated in cannabis use disorder than in controls)
Sutherland et al. 2013 (71)	R and L insula[c]	Nicotine use disorder with greater alexithymia and craving in withdrawal < nicotine use disorder with lower alexithymia and craving in withdrawal	R insula–sgACC/rACC
Upadhyay et al. 2010 (78)	B insula[d], B BL amygdala, B CM amygdala	Opioid use disorder < controls	B insula–B lOFC, B insula–vmPFC, B insula–B BL amygdala, B insula –dACC, B CM amygdala–rACC, B BL amygdala–B lOFC, B BL amygdala–dmPFC

[a] ***Abbreviations for substance use disorders:*** alcohol use disorder (AUD), substance use disorder (SUD). ***Abbreviations for regions:*** basolateral amygdala (BL amygdala), centromedial amygdala(CM amygdala), dorsal anterior cingulate cortex (dACC), dorsolateral prefrontal cortex(dlPFC), inferior frontal gyrus (IFG), lateral prefrontal cortex (lPFC), lateral orbitofrontal cortex (lOFC), orbitofrontal cortex (OFC), presupplementary motor area (preSMA), medial orbitofrontal cortex (mOFC), perigenual anterior cingulate cortex (pgACC), rostral anterior cingulate cortex (rACC), subgenual anterior cingulate cortex (sgACC), supplementary motor area (SMA), ventrolateral prefrontal cortex (vlPFC), ventromedial prefrontal cortex (vmPFC). ***Other abbreviations:*** bilateral (B), left (L), right (R).

[b] Directionality for all connectivity results was stated in most studies and, unless noted, was positive within individual groups (so in cases where group 1 was less than group 2, it was because connectivity was less, not that anticorrelation was greater in group 1). Further details about the individual studies (subjects, psychiatric comorbidities, exclusion criteria, tasks, analysis methods) can be found in Table S3 in the online data supplement. When laterality is not specified, the cluster crosses the midline. Findings for the insula are restricted to the anterior insula; findings observed in the posterior insula are not cited in the table.

[c] Only results from the anterior insula seed are reported in this table, but anterior, middle, and posterior seeds were used.

[d]Only results from the anterior insula seed are reported in this table, but anterior and posterior seeds were used.

TABLE 4

Differences Between Individuals With Substance Use Disorder and Control Subjects in Structural Connectivity in White Matter Tracts Connecting Regions of Focus (Amygdala, Insula, lPFC, dmPFC, rACC/vmPFC)[a, b]

Study	Tracts/Volumes of Interest (and Diffusion Tensor Imaging Measures)	Structural Connectivity	Substance Use Disorder Group	Control Group	Exclusion Criteria
Alhassoon et al. 2012 (88)	Body of CC, genu of CC (fractional anisotropy, radial diffusivity)	AUD < controls	15 abstinent AUD (15 male; mean age=51.4, SD=6); minimum 2 weeks abstinent; 11 smokers; 0 with other SUD	15 controls (15 male; mean age=51.8, SD=7.4); 3 smokers; 0 with SUD	Any axis I disorder except major depressive disorder, other SUD except nicotine or cannabis, not having "urine and blood assured sobriety for 2 weeks"
Durkee et al. 2013 (120)	AC (fractional anisotropy)	AUD/AUD+PTSD < controls	19 AUD (14 male; mean age=32.6, SD=7; 10 smokers, 1 cocaine use disorder, 1 cannabis use disorder, 2 major depressive disorder; 16 mean days abstinent before scan); 17 AUD +PTSD (9 male; mean age=37, SD=8.6; 11 smokers, 2 cocaine use disorder, 1 cannabis use disorder, 3 major depressive disorder; 24 mean days abstinent before scan)	19 controls (10 male; mean age=26, SD=4; 0 smokers)	Positive urine screen for drugs or positive breath alcohol reading at time of study; other axis I disorders not an exclusion
Harris et al. 2008 (91)	R lOFC, R cingulum in R dACC (fractional anisotropy)	AUD < controls	15 AUD (15 male; mean age=48, SD=13; 3 with history of tobacco dependence; abstinent minimum 4 weeks before MRI)	15 controls (15 male; mean age=56, SD=9); similar to AUD group on depression and anxiety measures	History of depression, schizophrenia, or other SUD
Hudkins et al. 2012 (86)	B cingulum, genu of CC, L internal capsule (fractional anisotropy)	Nicotine use disorder > controls	18 nicotine use disorder (10 male; mean age=33.7, SD=7.9)	18 controls (9 male; mean age=33, SD=10)	Any axis I disorder, dependence on alcohol or drug of abuse, positive drug test on day of scan
	L internal capsule, R cingulum (fractional anisotropy)	Negative correlation with level of dependence[c] (higher dependence < lower dependence)			
	R ACR, R cingulum (fractional anisotropy)	Negative correlation with cigarettes/day (more cigarettes<fewer cigarettes)			
Lane et al. 2010 (83)	B ACR (fractional anisotropy)	Cocaine use disorder < controls	15 cocaine use disorder (10 male; mean age=38.47, SD=2; 13 smokers, 9 other SUD [sedative 1, opiate 2, cannabis 5, hallucinogens 1, PCP 1, stimulant 2, alcohol 4])	18 controls (9 male; mean age=35, SD=2.6; 4 smokers, 0 other SUD)	Comorbid alcohol dependence, positive urine drug test on day of scan, DSM IV axis I disorders other than SUD
	Anterior body of CC (fractional anisotropy, mean λ_2 λ_3)	Cocaine use disorder < controls			
Lin et al. 2013 (87)	L genu of CC, L rostral body of CC (fractional anisotropy, axial diffusivity, radial diffusivity)	Heavy smokers < controls; positive correlation between years of regular smoking and diffusivity(radial diffusivity and mean diffusivity, not fractional anisotropy) (more smoking < less smoking)	34 heavy smokers (27 male; mean age=47, SD=7)	34 nonsmokers (28 male; mean age=47, SD=9)	Drug abuse or dependence, psychiatric disease (Mini International Neuropsychiatric Interview); no subjects were daily drinkers, had had social consequences of drinking, or had difficulty stopping drinking

Study	Tracts/Volumes of Interest (and Diffusion Tensor Imaging Measures)	Structural Connectivity	Substance Use Disorder Group	Control Group	Exclusion Criteria
Pfefferbaum et al. 2006 (90)	Genu of CC, body of CC (mean diffusivity)	AUD < controls	57 AUD (age stratified by gender: 40 male [mean age=53, SD=10], 17 female [mean age=50, SD=10]); recruited from rehab centers; mean days abstinent 92; 8 anxiety disorder, 15 mood disorder, 17 depressive disorders, 26 smokers	74 controls (age stratified by gender: 32 male [mean age=52, SD=14], 42 female [mean age=55, SD=12]; 2 smokers)	DSM IV axis I diagnosis of bipolar disorder or schizophrenia, history of non-alcohol substance dependence
Qiu et al. 2013 (89)	R OFC, CC, B thalamic radiation (fractional anisotropy)	Opioid use disorder < controls	18 short-duration opioid use disorder (18 male; mean age=35, SD=8; heroin use duration <10 years); 18 long-duration opioid use disorder (18 male; mean age=38, SD=4; heroin use duration 10–20 years); all regular smokers	16 controls (16 male; mean age=38, SD=4; all regular smokers)	Schizophrenia, bipolar disorder, ever used any other types of drugs
	B UF (radial diffusivity)	Opioid use disorder < controls			
	R OFC (fractional anisotropy)	Negative correlation with length of drug dependence (more years < fewer years)			
Sorg et al. 2012 (82)	Frontal forceps, genu of CC, anterior body of CC, B UF, L anterior internal capsule (fractional anisotropy, axial diffusivity, radial diffusivity)	AUD who relapsed < AUD who remained abstinent	29 AUD, abstinent at 6-month follow up (minimum 2 weeks sobriety) (28 male; mean age=48, SD=7; in patients; 21 smokers, 8 past SUD; mean BDI score=8, SD=7); 16 AUD who returned to heavy use (minimum 2 weeks sobriety) (16 male; mean age=48, SD=10; inpatients; 15 smokers, 2 past SUD; mean BDI score=11, SD=8)	30 controls (29 male; mean age=49, SD=10; 3 smokers; mean BDI score=3, SD=2; no history of axis I disorder)	DSM-IV diagnosis of non-alcohol SUD, hospitalization for a psychiatric condition that preceded AUD
Upadhyay et al. 2010 (78)	Ventral amygdalofugal pathway, B UF, B internal capsule, B external capsule, genu of CC, anterior midbody of CC, B anterior thalamic radiation (fractional anisotropy)	Opioid use disorder < controls	10 opioid use disorder (prescription opioid dependence; 7 male; mean age=29, SD=9; 0 smokers)	10 controls (7 male; mean age=30, SD=8; 0 smokers)	Positive urine screen at time of scan, chronic pain, dependence on other drugs including heroin and alcohol, other psychiatric disorders
Viswanath et al. 2015 (84)	CC, B internal capsule, B corona radiata (fractional anisotropy)	SUD < psychiatric controls	99 SUD (alcohol, tobacco, cannabis most prevalent; 64 male; mean age=30, SD=1; inpatients; mean average length of stay=45 days, SD=1; 40% depression, 53% anxiety, 14% bipolar, 37% personality disorder)	52 psychiatric controls (21 male; mean age=33, SD=2; 38% depression, 50% anxiety, 17% bipolar, 41% personality disorder)	
Yeh et al. 2009 (85)	R ACR, genu of CC, B UF, B internal capsule, B cingulum, R extreme capsule (fractional anisotropy)	AUD < controls	10 AUD (10 male; mean age=47, SD=7.6; mean days of abstinence=6, SD=3;10 chronic smokers, 2 with alcohol-induced mood disorder with depressive features, 1 with alcohol-induced psychotic disorder)	10 controls (10 male; mean age=42.7, SD=9.4; light drinkers, 2 smokers)	General psychiatric conditions, SUD other than nicotine
	Genu of CC (mean diffusivity)	Negative correlation with increased drinking (more drinks < fewer drinks)			

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[a] ***Abbreviations for substance use disorders:*** alcohol use disorder (AUD), substance use disorder (SUD). ***Abbreviations for regions:*** dorsal anterior cingulate cortex (dACC), lateral orbitofrontal cortex (lOFC), orbitofrontal cortex (OFC). ***Abbreviations for tracts:*** anterior commissure (AC), anterior corona radiata (ACR), corpus callosum (CC), uncinate fasciculus (UF). ***Other abbreviations:*** bilateral (B), Beck Depression Inventory (BDI), left (L), right (R).

[b] Eigenvalues (λ_2 λ_3) are both measures of diffusivity. Higher levels indicate less connectivity. This table summarizes only a selected sample of the many studies assessing structural connectivity in individuals with SUD. A more comprehensive list of studies that have assessed structural connectivity in individuals with SUD is provided in the supplemental materials. Findings in these additional studies support the themes summarized in this table and the main body of the text.

[c] Smoking dependence was measured by using the self-report Fagerström Test for Nicotine Dependence.

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