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HOT TOPIC

Alexithymia and Addiction: A Review and Preliminary Data Suggesting Neurobiological Links to Reward/Loss Processing

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Abstract Alexithymia, characterized by impairments in emotional awareness, is common among individuals with substance use disorders. Research on alexithymia suggests that it is a trait that may contribute to substance dependence. This paper will review alexithymia as it relates to substance use and substance use disorders, considering its potential role in the maintenance and treatment of these disorders. We will then describe how neural correlates associated with alexithymia may shed light on how alexithymia relates to addiction. Finally, we present preliminary fMRI data that examines how alexithymia may relate to the neurobiological correlates of reward/loss processing in individuals with cocaine dependence. While preliminary, these findings suggest a role of alexithymia in reward anticipation in cocaine-dependent individuals.

Keywords Alexithymia · fMRI · Reward processing · Emotion · Substance abuse · Addiction

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Introduction

Emotional dysregulation has been well described in the addictions literature. For example, substance-dependent individuals who reported primary use of different substances, including 3, 4-methylenedioxymethamphetamine (MDMA), opiates, and alcohol [1, 2], demonstrated impaired perception of emotional faces. Cocaine-dependent individuals did not properly modulate inhibitory control by emotion when given emotional images during a Go/NoGo task [3], and polysubstance-dependent individuals showed subjective emotional processing impairments in response to emotional pictures [4]. Imaging of cocaine-using populations has revealed hypoactivation in the dorsolateral prefrontal cortex (DLPFC), thalamus, and striatum in response to pleasant and unpleasant pictures [5], suggesting a role for emotional processing difficulties in response to natural reinforcers and thus potentially contributing to drug dependence.

Several aspects of emotional dysregulation in substance users may relate to alexithymia, which is characterized by a diminished ability to identify, define, and explain one's own emotions, as well as a tendency to externalize feelings and experiences [6••]. Given increasing interest and recent research reports in this area, we will review research on alexithymia and the addiction with the purpose of highlighting how neuroscience may shed light on the relationship between alexithymia and addiction and its treatment. First, we will briefly summarize data on rates of alexithymia among samples of individuals with substance-use disorders. Next, we will review the literature describing emotional processing difficulties and alexithymia in substance-dependent individuals, including stability of alexithymia over time and relationship to treatment outcomes. We will briefly review the mental illnesses that commonly co-occur in individuals with substance-use disorders with an aim toward understanding if

the presence of these co-occurring disorders may relate to alexithymia in substance-use disorders. Finally, we will focus on potential mechanisms of how alexithymia may contribute to substance-use disorders, including alexithymia's relationship to craving and the neural correlates of alexithymia in both healthy and substance-using populations. We will conclude by presenting preliminary data exploring how alexithymia relates to the neural correlates of reward and loss processing in cocaine-dependent individuals as an illustration of how alexithymia may influence reward and loss anticipation in this population.

Alexithymia Overview

Alexithymia was first described in 1973 by Sifneos, who described it in a population of patients with psychosomatic illnesses. Patients presented with "…a relative constriction in emotional functioning, poverty of fantasy life, and inability to find appropriate words to describe their emotions" [7]. These characteristics were further examined and refined into an alexithymia construct [6••]. Today, alexithymia is typically measured with the Toronto alexithymia scale (TAS-20) [8•]. The TAS-20 has been validated in multiple populations, including healthy individuals and those with addictive, eating, anxiety, mood, psychotic, and somatoform disorders [8•, 9•, 10, 11•, 12]. The TAS-20 is a 20-item self-report scale, graded using a five-point Likert scale, that provides total scores (ranging from 20 to 100) and has three factors that reflect the original description of alexithymia by Sifneos, including difficulty describing feelings, difficulty identifying feelings, and externalization. While there is some disagreement over whether alexithymia should be considered as a dimensional or categorical variable [13], in general, scores above 61 on the TAS-20 tend to be considered clinically significant for alexithymia [14]. Alexithymia in otherwise healthy populations is nevertheless still associated with affect. Increased alexithymia in males is associated with increased intensity of positive affect and increased frequency of negative affect, and the authors suggest that this finding is symptomatic of a cognitive deficit in the processing of emotional information [15]. Another study in healthy Italian university students found an association between avoidant-coping strategies, negative emotionality, and alexithymia, suggesting that alexithymia may be adopted as a method of coping with negative affect or as a method of avoiding negative emotions [16].

Individuals with alexithymia have been found to have poorer regulation of their emotions, to the extent that their mental and physical health is adversely affected [17], possibly due to a state of hyperarousal relating to difficulties in identifying or describing their emotions and adequately reacting to or modulating them [18••]. A tendency to externalize may also lead to a diminished fantasy life and a preoccupation with external detail. Indeed, those with alexithymia have poorer abilities to mentally recreate emotions [19]. Further, imaging work has revealed that those with alexithymia have reduced activation in brain areas related to mentalizing, including the temporoparietal junction and dorsomedial prefrontal cortex, as well as lower scores on questionnaires related to mentalizing [20]. Together, these findings suggest poorer empathy and theory of mind in individuals with high degrees of alexithymia. However, other recent work has suggested that alexithymia is closely related to psychiatric symptoms and may be a measure of distress and an indicator of negative affect in psychiatric populations [21]. Alexithymia is closely related to the concept of emotional intelligence [22], which offers resilience to negative life events [23], thus suggesting that individuals with low alexithymia would exhibit more resilience. Consistently, individuals high in alexithymia tend to report more severe post-traumatic stress disorder (PTSD) after negative life events [24, 25]. Individuals with alexithymia have been reported to encounter more interpersonal problems and have reduced social support [26]. Alexithymia has also been associated with anxiety and depressive disorders [27, 28]. Taken together, alexithymia is linked with multiple comorbidities, including substance-use disorders.

Alexithymia and Addiction

Rates of alexithymia in the general population are estimated to range between 6 and 10 % [29, 30], but alexithymia is more frequently observed in individuals with substance-use disorders. As many as 78 % of individuals with alcohol-use disorders have been reported to have some level of alexithymia [31], with percentages typically in the range of 45 to 67 % [32••]. Alexithymia has also been associated with a family history of alcoholism [33]. Individuals with illicit drug use disorders also frequently exhibit alexithymia, with 42 % in one study and 50 % in another meeting the criteria for alexithymia [11•, 34]. When compared to non-addicted individuals, those with substance-use disorders more frequently exhibit alexithymia [35]. Alexithymia is also frequently seen in participants who are undergoing drug abuse treatment [36], and research has suggested that alexithymia itself may be a difficult characteristic to change.

Alexithymia as an Enduring or Malleable Characteristic

Data exist suggesting alexithymia is a pre-existing trait that may promote substance use, and alexithymia is associated with negative affect and ahedonia [28, 37, 38] which are themselves associated with substance use [39]. Alexithymia in healthy populations appears stable, as evidenced by good

relative and absolute stability of alexithymia in a large sample after an 11-year follow-up period [40•]. If alexithymia predates the onset of drug use, then the high rates of alexithymia among individuals with substance-use disorders may be explained by the use of drugs or alcohol to relieve the emotional dysregulation associated with alexithymia [41]. In social drinkers, alexithymia may predict alcohol consumption [42]. In adolescents, the children of individuals with alcohol-use problems demonstrate increased alexithymia that interacts with executive dysfunction in a manner that may raise the risk for future substance use [43]. In addition, if alexithymia were brought upon by drug dependence, then cessation of use may reduce alexithymia symptoms. However, alexithymia did not change over an 8-week course of treatment using computerized cognitive-behavioral therapy (CBT) [44•]. Similarly, other treatment comparison studies in populations with cocaine-use disorder [45] and polysubstance-use disorders [46] also revealed no change in alexithymia scores over time, regardless of the type of treatment delivered. Alexithymia also remained stable over a 6-week course of treatment in individuals with polysubstance-use disorders [47•]. The same study revealed a correlation between a component of alexithymia (the "difficulty describing feelings" factor on the TAS-20) and family history of substance-use problems, suggesting that alexithymia may exist as a vulnerability factor. Additionally, alexithymic features have been frequently observed in males at high genetic risk for alcoholism [48]. Finally, in a study of alexithymia as a trait or state phenomenon that examined identifying feelings, describing feelings, and externalization factors separately in substance-dependent individuals [49], during withdrawal from alcohol, two of the three factors remained stable, and scores in all three alexithymia factors following withdrawal were similar to those at baseline after consideration of the influences of depression and anxiety.

Some data also suggest that alexithymia may not be a stable trait. Alexithymia scores changed over time during detoxification in 101 and in 187 substance-abusing individuals who were stratified into low, medium, and high alexithymic groups based on the TAS-20 [50, 51]. The changes followed a pattern that suggested regression toward the mean, even though alexithymia scores appeared largely stable across the entire sample [50, 51].

Implications for Substance-Abuse Treatment

Alexithymia may interfere with treatment success, as individuals for whom it is difficult to recognize and describe emotional states may not be able to adequately regulate these states or recognize their relationship to initiation or maintenance of drug use. Alexithymia status at treatment intake has been related prospectively to treatment outcomes at 15 months in a cohort ($n = 46$) of individuals with alcohol-use disorders, with high alexithymia associated with poorer outcomes [52]. In 60 men with alcohol-use disorders in outpatient treatment, those with higher alexithymia reported more episodes of relapse after 1 year than those with low levels of alexithymia [53]. In another sample of 230 outpatients being treated for substance-use disorders, those with higher alexithymia also showed poorer treatment adherence, which may underlie poorer treatment outcome [54]. Alexithymia status may be helpful in assigning patients to particular treatments. Computerized cognitive behavioral therapy (CBT4CBT) has been shown to be more helpful in alexithymic individuals [44•], perhaps because computerized delivery may be more amenable than person-to-person therapy given social difficulties and anxieties that individuals with alexithymia may encounter.

It should be noted that not all studies have found associations between alexithymia and treatment outcome. In a study involving a cohort of 100 individuals with alcohol-use disorders, no effects of alexithymia were seen on treatment outcome, as indicated by self-reports of use 30 days after cessation of an inpatient treatment program that consisted of a combination of motivational interviewing (MI) and CBT approaches delivered in group therapy [55]. Nonetheless, the preponderance of data suggests that alexithymia warrants consideration in treatment development efforts for addictions.

Alexithymia, Substance-Use Disorders, and Co-Occurring Mental Illness

Questions exist regarding alexithymia's relationship to the development or maintenance of addictions, including whether alexithymia is a trait/characteristic that leads to substance-use problems or whether it arises or worsens secondary to substance-use problems. Substance-use disorders are associated with affective disorders, and alexithymia is seen in association with depressive [56, 57] and anxiety [58] disorders. It is possible that alexithymia may be prevalent in substance-use disorders simply because alexithymia is commonly observed in affective disorders that often accompany substance-use disorders. Thus, alexithymic individuals may seek to relieve depression or anxiety brought about by alexithymia by turning to alcohol or drug use [59]. However, alexithymia may represent a separable construct from depression [60], consistent with observations that not all individuals with co-occurring alexithymia and substance dependence demonstrate affective disorders [44•]. Alexithymia may also be associated with affect and cognitive regulation regardless of the presence of other mental illnesses. While the notion of lack of emotional awareness does not itself seem an intuitive cause of distress, the diminished ability to identify emotions, and the tendency of alexithymia individuals to instead identify emotion as physiological distress [61], may lead to alexithymic individuals

turning to drug use to alleviate this distress [62]. Indeed, the literature on alexithymia has reported a link between alexithymia and a chronically elevated stress response [63•], perhaps because an inability to identify negative emotion makes such emotions harder to regulate. The decoupling between physiological stress response and the awareness of emotion may make the stress response itself more salient.

It is still an open question; however, if this increased, stress encourages substance use. Evidence in heavy drinkers suggests that stress in alexithymic individuals does not necessarily contribute to heavy drinking behavior [64], although stress itself has been shown to be associated with substance use [65]. If alexithymia, as has been discussed above, is truly associated with drug use initiation via stress, it may be more related to poorer regulation of stress due to poorer emotional intelligence, which has also been identified as a predictor of alcohol and substance use [66]. Individuals with alexithymia demonstrate more displacement behaviors, such as self-grooming and scratching, that may indicate a failure to regulate distress [67]. Alexithymic individuals show reduced executive function capabilities, with reductions in performance across multiple domains of executive function, including inhibition [68]. It is possible that alexithymia may contribute to substance use via mechanisms related to reduced inhibition and regulation of powerful urges like craving.

Alexithymia and Craving

Factors other than mood regulation (e.g., craving) warrant consideration when understanding the relationship between alexithymia and substance-use disorders. Research suggests links between alexithymia and craving for drugs or alcohol, although the directionality has not been consistent across studies. Negative associations between alexithymia and subjective measures of craving for alcohol in response to alcohol cues have been reported among individuals with alcohol dependence [69], whereas positive associations between alexithymia and cue-induced craving for methamphetamine have been reported among individuals with methamphetamine dependence [70]. Heavy alcohol users with alexithymia report more alcohol craving, compulsive drinking urges, and obsessive thoughts about alcohol [71], and this relationship between craving and alexithymia appears to be maintained over 12 weeks [36].

Neural Correlates of Alexithymia

Most imaging studies of the neural correlates of alexithymia have focused upon how alexithymia may relate to neural responses to emotional stimuli. Regions that may be hypothesized to be associated with alexithymia due to their role in emotional awareness and in subjective responses to emotional stimuli include the insula, anterior cingulate cortex (ACC), amygdala, and striatum [72–74]. A review of the neurobiology of alexithymia when individuals were given emotional tasks (regardless of emotional valence) has identified the dorsal ACC as relating to alexithymia, with negatively valenced stimuli-linking alexithymia to responses in the amygdala, premotor areas, and dorsomedial prefrontal cortex and positively valenced stimuli-linking alexithymia to responses in the insula and precuneus [75••]. The findings suggest that alexithymia may relate to poor emotional regulation, reduced awareness of positive affect, and poorer empathic abilities [75••]. In a study that explicitly examined alexithymic and non-alexithymic individuals on subjective and neural responses to painful pictures designed to elicit feelings of empathy [76], individuals with higher levels of alexithymia showed a different pattern of activation compared to those with lower levels of alexithymia. Those with high alexithymia showed lower activation in the insula, left DLPFC, dorsal pons, cerebellum, and left caudal ACC in response to painful pictures, and greater activation in the right insula and inferior frontal gyrus (IFG) compared with individuals with lower scores on the TAS-20. In addition, individuals with higher alexithymia reported lower scores on a questionnaire related to mature empathy, suggesting that those individuals with higher TAS-20 scores have poorer emotion-regulatory abilities. In another study that examined differently valenced images, individuals with higher alexithymia as compared to those with lower alexithymia showed increased activation in the ACC, mediofrontal cortex, and middle frontal gyrus in response to positive stimuli, and decreased activation was observed in the left mediofrontal-paracingulate in response to negative stimuli [77]. This pattern of altered neural activation was proposed to provide a neural mechanism for poorer emotional regulation in alexithymic individuals.

Few studies have examined relationships between alexithymia and neural measures in addictions. In tobacco smokers, alexithymia was associated with subjective measures of tobacco craving, and that this relationship was mediated by functional connectivity between the right anterior insula and ventromedial prefrontal cortex [78•]. Alexithymia was also examined in a population of cocaine-dependent adults [79] using a task that involved guided imagery exposure to stressful situations. Alexithymic cocaine-dependent men demonstrated a positive correlation between scores on the TAS-20 and activation in the right putamen and middle frontal cortex. Alexithymic cocaine-dependent women demonstrated a negative correlation between scores on the TAS-20 and activation in the right amygdala, thalamus, putamen, and left frontal and bilateral cortices. As suggested above, alexithymia may play a key role in the modulation of emotional responses to different kinds of stimuli, and this may hold especially true in substance-dependent individuals.

Alexithymia and Reward/Loss Processing

Given the emotional responses that rewards and losses elicit, it is possible that alexithymia may relate to these processes in addictions. A widely used means of studying the neural correlates of reward and loss processing in groups with and without addictions involves use of the monetary incentive delay task (MIDT) [80••, 81, 82, 83•]. The MIDT can parse prospect, anticipation, and outcome phases [80••, 81, 82]. This work has revealed that in healthy populations, reward anticipation is associated with activation in the nucleus accumbens/ventral striatum, while reward receipt has been associated with activation in the frontal-medial cortex including the ventromedial prefrontal cortex (VMPFC). Anticipation of punishments has been shown to activate the ACC and thalamus [84].

In cocaine-dependent individuals compared to non-addicted comparison subjects, greater activation was observed during reward receipt in the bilateral ventral striatum, right caudate, and right insula; increased activation during reward prospect was also observed in the left and right ventral striatum and right insula [85]. In other work, cocaine use was linked to reduced activation in the right caudate during reward anticipation [86]. In a third study, current cocaine users as compared to control subjects showed reduced activation of the amygdala, ACC, parahippocampal gyrus, and ventral tegmental area (VTA) during loss prospect, and less activation of the right insula during loss anticipation [87]. During reward prospect, current users showed relatively reduced activity of the right parahippocampal gyrus [87]. Thus, regions implicated in alexithymia, including the ACC and insula, have also been linked to reward processing in cocaine-use disorders, raising the question of whether alexithymia is related to brain activations when cocaine-dependent individuals process rewards. Such relationships may have implications for prevention and treatment strategies for cocaine-use disorder and other addictions.

A Pilot Study of Alexithymia and Reward Processing

To address this question, we explored alexithymia's relationship to neural correlates of reward processing in cocaine-dependent individuals. We examined pilot data from an 8-week randomized clinical trial [88] in which 12 methadone-maintained individuals who met current DSM-IV criteria for cocaine dependence completed both the TAS-20 [9•] and an fMRI MIDT scanning session. Individuals' self-reports of how they felt after winning or losing money were also obtained. The prospect or processing of receiving rewards or avoiding punishments may fail to elicit appropriate responses in individuals with alexithymia, or individuals with alexithymia may fail to respond to more intense signals relating to reward, and this may be reflected in neural activations during reward processing. We hypothesized that alexithymia would be associated with lower ratings of self-reported enjoyment of rewards and disappointment associated with losses. Given that alexithymia was correlated previously with cue-induced craving in stimulant users [70], we hypothesized that alexithymia in cocaine-dependent, methadone-maintained individuals would be associated with increased neural activation in response to reward prospect and anticipation, notably in areas previously indicated to be associated with reward anticipation, including the insula and striatum. We also hypothesized that alexithymia would be associated with decreased neural activation in these areas in response to both reward and loss outcomes, as increased alexithymia may be associated with blunting of or difficulties in recognizing emotional responses to positive or negative outcomes.

Demographic and drug use information for participants are as follows: average age was 39.42 years (SD = 11.3). Participants averaged 11.67 years (SD = 1.3) of education. Average years of use of drugs were cocaine 10.4 (SD = 5.9), opiates 9.0 (SD = 6.6), alcohol 10.3 (SD = 9.7), and marijuana 8.9 (SD = 8.6). Two participants presented with a current diagnosis of generalized anxiety disorder (GAD) according to the DSM-IV, and three reported episodes of GAD in their lifetime, for a total of three participants who had reported a current or previous history of anxiety disorders. Two participants also reported the presence of previous episodes of major depression throughout their lifetime, but none had a current diagnosis.

At intake, participants were assessed using a battery which included the TAS-20 [9•], the structured clinical interview for DSM-IV [89], and the addiction severity index [90]. fMRI data were acquired during the performance of an event-related MIDT, modified from the original design [80••], and described in detail previously [81]. At the end of each of the two trials of the MIDT, participants were asked by the experimenter how they felt, on a scale of 1 to 5 (1 = very unhappy, 2 = slightly unhappy, 3 = neither, 4 = slightly happy, 5 = very happy) about winning, losing, not winning, or not losing specific dollar amounts.

All participants were scanned at the Yale Magnetic Resonance Research Center (MRCC) using a 3-Tesla Siemens Trio MRI system and consistent with previous MID task studies done by our group [91]. Consistent with previous MID task studies [82, 85, 91], win and loss events were contrasted with their analogous neutral event (e.g., "LOSE US$0") at the single-subject level. Group-level random effects models using these contrasts were then conducted to explore whole-brain correlational analyses related to TAS-20 scores. Statistical maps were voxel-level-thresholded at $p < .01$ prior to undergoing cluster-based family-wise error correction (pFWE < .05).

The mean score on the TAS-20 for the 12 cocaine-dependent individuals included in this study was 58.8 (SD

Table 1 Findings from whole-brain correlational analyses of bold responses and alexithymia scores (as assessed using the Toronto alexithymia scale (TAS-20)) among methadone-maintained, cocaine-dependent individuals

A1 Loss									
Cluster	Areas	Hemisphere	BA	k	X	Y	Z	Z-score	*p* value
	Thalamus Midbrain	L, R		418	−6	−37	−41	5.9	FWE < .01
	Brainstem								
	Pons								
	Inferior frontal gyrus Middle frontal gyrus	R	46, 6	320	39	8	28	6.26	FWE < .01
	Precentral gyrus								
	Premotor/supplementary motor area								
	DLPFC								
A1 Win									
Cluster	Areas		BA	K	X	Y	Z	Z-value	p value
	Pons Brainstem	L, R		195	−3	−22	−23	5.7	FWE < .01
	Midbrain								
	Inferior frontal gyrus Middle frontal gyrus	R	46, 13	508	39	8	16	6.06	FWE < .01
	Insula								
	DLPFC								
	Thalamus Parahippocampal gyrus	L, R		432	−15	−16	7	7.6	FWE < .01
	Caudate								
	Midbrain								

BA Brodmann area, *k* cluster size, *L* left, *R* right, *DLPFC* dorsolateral prefrontal cortex

4.7). Scores ranged between 53 and 65. Five individuals had scores in the "alexithymia" range (cutoff score >60), and seven had scores in the "possible alexithymia" range (score between 51 and 60). No individuals scored in the "non-alexithymia" range. Cutoff values followed the approach outlined in [56].

Participants' subjective responses were averaged over the two trials for each condition. Variability of responses was low within conditions, i.e., participants all reported a "4" or "5" for "happy" or "very happy" when they won US$5. When comparing between conditions, i.e., between WON US$5 or DID NOT WIN US$5, means differed significantly (*p* values

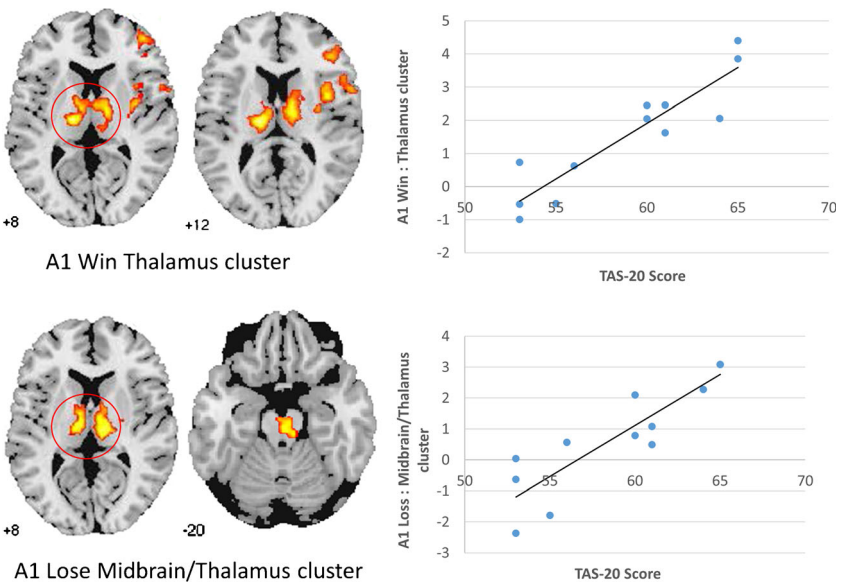

Fig. 1 Neural activations in midbrain clusters associated with TAS-20 scores during the prospect of reward and loss (A1 win and A1 loss) phases of the MID task. The *scatter plots* show the relationship between activation of the midbrain cluster and score on the TAS-20

<.001) except between WIN US$0 vs DID NOT WIN US$0 ($p > 0.3$) and LOSE US$0 vs DID NOT LOSE US$0 ($p > 0.7$). Subjective ratings were not correlated with TAS-20 scores.

Whole-brain correlational analyses revealed positive associations between scores on the TAS-20 and neural activations during the prospect phase for both rewards and losses (A1 phase; pFWE <.01; details in Table 1). During loss prospect, regions of the thalamus, midbrain, IFG, and DLPFC were implicated. During reward prospect, regions of the caudate, thalamus, midbrain, insula, IFG, and DLPFC were implicated (Fig. 1). There were no significant correlations between alexithymia and activation for the anticipation phase or for the outcome phases for either reward or loss.

Conclusions and Future Directions

Our findings were partially supportive of our hypotheses that alexithymia would be associated with neural correlates of reward processing, although the correlations were limited to reward and loss prospect phases. Activity within multiple clusters was positively correlated with alexithymia during the prospect period of both reward and loss phases (A1), including the insula, midbrain, and pons, the inferior and middle frontal gyri, and DLPFC. An additional cluster with activation in the thalamus and caudate was found during reward prospect. However, we found no correlations between alexithymia and neural activations in response to reward or loss anticipation or receipt or between alexithymia and subjective response data. This suggests that some of the neural relationships with alexithymia may not be represented in self-reported responses, and future studies involving larger samples may be warranted.

Previous imaging work, including work using the MIDT, has implicated the thalamus and caudate, as well as the insula and mesial prefrontal cortex, as regions associated with reward processing and cocaine-use disorders [87, 92]. The insula is also associated with interoceptive and emotional processing [74]. Activity was correlated with alexithymia in these regions during the reward prospect phase and was specifically associated with the thalamus and caudate during reward prospect, which resonates with the idea that reward may be pursued in order to offset negative affect associated with alexithymia, although this possibility warrants further direct testing.

Our findings also resonate with those from the previously discussed study of non-methadone-maintained, cocaine-dependent individuals [79]. While we were not powered to examine gender-related patterns of associations as in the prior study, overlapping regions were implicated across studies (including the thalamus and regions of the frontal cortex being related to alexithymia). Similarly, regions of the insula were related to alexithymia in both in our work and in a prior study that examined how alexithymia related to craving in methamphetamine users [70]. Taken together, the findings suggest a possible role for alexithymia in influencing neural processes underlying not only emotion and motivation but also reward and loss processing in cocaine-addicted populations.

To our knowledge, this is the first study to explore the neural correlates of alexithymia in methadone-maintained cocaine-dependent individuals during MIDT performance. Findings from this preliminary study should be interpreted within the context of the small sample size ($n = 12$). While there was a distributed range of TAS-20 scores, scores were high overall and no individuals in this cohort were classified as non-alexithymic. Thus, findings may have differed had fMRI data from individuals with a wider range of TAS-20 scores been available. In addition, a larger sample of participants with a wider range of alexithymia scores may have revealed differences in subjective responses, and a larger sample would have allowed for investigations of other factors, including severity of substance use, methadone dosage, or psychiatric symptoms. Additionally, although the sample was largely free of affective disorders and might suggest that the findings are independent of these, a larger and more diverse sample is needed to ascertain relationships between alexithymia, neural activations relating to reward/loss processing, and affective disorders in addicted populations.

While novel, our findings of a positive association between alexithymia scores and neural responses during the prospect phase of processing of reward and loss parallel the existing literature on alexithymia, emotional processing, and relationships with neural activations during the performance of emotional tasks in both addicted and non-substance-using populations. These findings of neuroimaging correlates implicate neural anatomy affected by alexithymia, suggesting a link between alexithymia and neural correlates of reward and loss processing and possibly to persistent drug use. Future work could investigate these relationships in larger samples, as well as links between alexithymia and cocaine-cue craving and alexithymia and mood, and the neural correlates thereof, in addicted populations.

Our neuroimaging findings also illustrate the importance of a more rigorous examination of alexithymia itself. Future work should examine each aspect of the alexithymia construct, including emotion definition, identification, and externalization, in an aim to determine if each of these factors may have different neural correlates or contribute in different ways to alexithymia. More in-depth examination of how each of these factors may be differently associated with substance use is also warranted.

Compliance with Ethical Standards

Conflict of Interest Kristen P. Morie, Sarah W. Yip, Charla Nich, and Karen Hunkele declare that they have no conflict of interest.

Kathleen M. Carroll is a consultant to CBT4CBT LLC, which makes CBT4CBT available to qualified clinical providers and organizations on a commercial basis. Dr. Carroll works with Yale University to manage any potential conflicts of interest.

Marc N. Potenza has consulted for Ironwood, Lundbeck, Shire, INSYS and Rivermend Health; has received research support from Mohegan Sun Casino, the National Center for Responsible Gaming, and Pfizer pharmaceuticals; has participated in surveys, mailings, or telephone consultations related to drug addiction, impulse control disorders, or other health topics; has consulted for law offices and the federal public defender's office in issues related to impulse control disorders; provides clinical care in the Connecticut Department of Mental Health and Addiction Services Problem Gambling Services Program; has performed grant reviews for the National Institutes of Health and other agencies; has guest-edited journal sections; has given academic lectures in grand rounds, CME events, and other clinical or scientific venues; and has generated books or book chapters for publishers of mental health texts.

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Contributors Dr. Carroll was principal investigator of the trial and wrote the protocol. Dr. Potenza oversaw the fMRI component of the study. Dr. Morie with Ms. Hunkele and Nich and Dr. Yip undertook the statistical analysis. Dr. Morie wrote the first draft of the paper. All authors contributed to the editorial process and have approved the final submitted version of the manuscript.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

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