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Review Article

Psycho-Behavioral Spiral of Disturbances in Prosocial Behavior, Stress Response, and Self-Regulation in Substance-Related and Addictive Disorders

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Abstract Studies on neuropathological changes in substance-related and addictive disorders (SRADs) suggest that substance abuse or pathological gambling induces persistent abnormalities in the brain reward system that compromise emotional, decision making, and stress responses. Moreover, the enhancement of cortisol secretion resulting from long-term hyperactivation of the stress response is thought to impair the self-regulating system that controls emotion and executive function. In contrast, oxytocin induces prosocial behavior, attenuates the stress response, and reduces addictive behaviors in laboratory animals and humans. Prosocial behavior, a major coping response for stress in humans, is believed to be related to reward system function. Cognitive-behavioral therapy (CBT) is reported to lessen some symptoms of SRADs by affecting the function of the prefrontal cortex. Taken together these findings suggest that abnormalities of the reward system trigger the psycho-behavioral spiral of disturbances in prosocial behavior, the stress response, and self-regulation that are associated with SRADs. It is proposed that CBT in combination with drugs known to modulate prosocial behavior and the stress response could be of therapeutic value in the treatment of SRADs.

Keywords addictive substance use; pathological gambling; self-regulation; stress response; prosocial behavior; oxytocin; cognitive-behavioral therapy

Abbreviations ACTH, adrenocorticotropic hormone; ASD, autism spectrum disorder; AVP, arginine-vasopressin; BED, binge-eating disorder; BMI, body mass index; CBT, cognitive-behavioral therapy; CREB, cyclic AMP response element-binding protein; CRH, corticotropin releasing hormone; DLPFC, dorsolateral prefrontal cortex; fMRI, functional magnetic resonance imaging; HPA axis, hypothalamic-pituitary-adrenal axis; IL, interleukin; NAc, nucleus accumbens; PVN, paraventricular nucleus; rTMS, repetitive Transcranial Magnetic Stimulation; SON, supraoptic nucleus; SRADs, substance-related and addictive disorders; tDCS, transcranial Direct Current Stimulation; VLPFC, ventrolateral prefrontal cortex; VMPFC, ventromedial prefrontal cortex; VTA, ventral tegmental area.

1. Introduction

"Fight-or-flight" is a key stress response that mobilizes the organism to confront or flee from a threat [1]. Recent psychological studies suggest that "tend-and-befriend," which is associated with positive affiliative contacts and peer bonding, is another important response to stress [2]. It has also been found that prosocial behavior can also improve health and well-being by activating brain systems regulated by the prefrontal cortex [3]. This brain region, especially the DLPFC, integrates information from the other brain areas and coordinates responses through top-down processing [4]. This regulation is crucial in humans for self-regulation of behavioral responses [4]. We have previously hypothesized that disturbances in the self-regulation system are a common feature of psychiatric conditions, and that they underlie the emotional and social cognitive abnormalities associated with mood disorders, schizophrenia, and ASD [5,6,7].

SRADs include drug abuse and compulsive gambling [8]. Some major hypotheses concerning the brain structures associated with SRADs are summarized in Table 1. While SRADs are characterized by a complex set of psychological and biological features, the condition can be viewed as a consequence of aberrant learning that results from disturbances in the reward, emotional, decision making, and stress response systems. Although it is generally believed that these systems all interact with the self-regulation system, including the DLPFC top-down control process, their interactions in this regard have yet to be defined. The aim of this review is to consolidate existing hypotheses into a coherent theory that can be tested in an attempt to develop and further refine therapeutic approaches for the treatment of SRADs and related conditions.

2. Brain systems associated with SRADs

2.1. Reward system

It is well established that the dopamine pathway from the VTA to the NAc is an essential component of the reward system and that this pathway is under the influence of endogenous opioid, cannabinoid, and glutamate systems [18,19]. There have been many studies indicating that addictive substances increase NAc activity [18,19].

Table 1: Major hypotheses of SRADs.

Psychological backgrounds
✓ Self-regulation failure underlies behavioral problems including addictive substance use and pathological gambling [9].
✓ Self-medication for emotional states as well as for a range of psychiatric problems is associated with substance abuse [10].
Biological alterations in the brain
✓ Activation of the pathway from the VTA to the NAc is related to SRADs [11,12,13].
✓ Positive-reinforcement mechanisms are important for establishing drug-seeking habits and reinstating them quickly after periods of abstinence [11].
✓ Negative-reinforcement mechanisms become most obvious in the late stages of SRADs. The combination of decreases in reward neurotransmitter function and recruitment of brain stress systems provides a powerful motivation for compulsive drug-seeking behavior [14].
✓ The signaling of reward prediction errors by dopamine neurons is associated with SRADs. Dopamine neurons encode the discrepancy between reward predictions and information about the actual reward received (the reward prediction error) and broadcast this signal to downstream brain regions involved in reward learning [15].
✓ SRADs are related to a habit-based learning which is an aberrant form of learning and mediated by maladaptive recruitment of certain memory systems in the brain. Addictive substance users lose VMPFC function to resist substance use [16].
✓ SRADs are associated with disturbances in the decision making system which consists of an impulsive amygdala system and a reflective VMPFC system [17].

Clinical studies have revealed an alcohol-induced reduction in the binding of [^{11}C]raclopride, a D2 receptor antagonist, in the NAc of moderate drinkers [20] and that there is a greater gray matter density in the NAc in recreational cannabis users than in control subjects [21]. It has also been reported that patients with alcohol-related disorders display a significant reduction in NAc volume [22], and a post-mortem study revealed that myelin basic protein-immunoreactive oligodendrocytes are reduced in the NAc of individuals known to have chronically abused cocaine [23]. fMRI studies have shown that, relative to healthy controls, gambling disorder patients show a reduction of NAc activity when exposed to gambling cues [24,25]. These results suggest that addictive drug use or recreational gambling initially overwhelm the VTA-NAc pathway, with continued drug abuse or gambling resulting in the hypofunction of this pathway and NAc atrophy [18,19,22,26].

A diffusion tensor imaging study conducted to investigate brain anatomical connectivity revealed that a period of regular cannabis use is positively correlated with the degree of white matter impairment in the fornix-fimbria, corpus callosum, and commissural fibers [27]. Fractional anisotropy values, which reflect the deviation from pure isotropic diffusion of water mobility, in the corpus callosum are negatively correlated with the severity of a gambling disorder [28]. Furthermore, it has been reported that impairments of the reward system can lead to disturbances in motivation (wanting rather than liking) or reward prediction [15,29]. These findings suggest that addictive substance use or pathological gambling progressively induce a structural disconnectivity in brain regions associated with behavioral self-regulation.

2.2. Emotional system

Abnormalities of the reward system are thought to induce emotional system dysfunction and a negative emotional state [30]. The amygdala and hippocampus are two important regions in the emotional system [31,32], with neural pathways connecting these to the NAc [32,33]. Overall, the limbic system, which is a key regulator of emotional response, is composed of the amygdala, hippocampus, mammillary bodies, anterior thalamus, anterior cingulate cortex (ACC), and prefrontal cortex [32]. There is a significant increase in amygdalar volume in casual cannabis users [21], while hippocampal and amygdala volumes are reduced in those with cannabis-related disorders [34]. The volumes of the amygdala and hippocampus are smaller than normal controls in gambling disorder patients [35]. Overall, the volumes of the amygdala and hippocampus are negatively correlated with the amount of cannabis use or severity of cannabis-related disorders [36]. Thus it is possible that drug- or gambling-induced increases in NAc activity affect the amygdala and hippocampus, decreasing the volumes of these brain regions in those with SRADs.

Anxiety is a common withdrawal symptom associated with SRADs [37]. Moreover, an alcohol cue significantly induces higher anxiety scores in patients with alcohol-related disorders compared to healthy subjects, even though there is no significant difference in baseline anxiety scores between these groups [38]. Also, patients with alcohol-related disorders are impaired in their ability to recognize facial emotion [39]. Compared to controls, gambling disorder patients show impaired emotional intensity, lack of emotional clarity, and strong impulsivity, all of which are possibly related to deficits in emotion regulation [40,41]. It seems likely that reduced volumes of the amygdala and hippocampus seen with these conditions may contribute to the deficit in emotional responses observed in SRAD patients.

2.3. Decision making system

A dysfunction in decision making system is another hallmark of SRADs [42]. VMPFC plays a pivotal role in

regulating an emotional response, a response to immediate reward, and decision making [43,44,45]. Chronic use of cocaine, opioids or heroin leads to a decrease in the linkage between the amygdala and VMPFC [46,47,48]. On the other hand, the results of several fMRI studies indicate that resting-state overconnectivity between the NAc and VMPFC occurs in pathological gamblers and chronic users of cocaine or heroin [49,50,51]. Moreover, it has been reported that hypoactivity of the NAc-VMPFC pathway is induced by a cocaine cue in chronic cocaine users [50]. In patients with an alcohol-related or gambling disorder, VMPFC activity is increased under neutral-relaxing condition but attenuated in trials of stress, alcohol cue or gambling cue [24,38,52]. Also, VMPFC activity correlates negatively with the severity of gambling disorder [24], and Iowa Gambling Task performances and VMPFC activity during the task are diminished in these patients [53,54]. Furthermore, the volume of VMPFC is reduced in patients with cannabis-related disorders [55].

These results suggest that with SRADs the VMPFC activity is regulated by the NAc rather than by the amygdala. This makes it appear likely that hyperactivity of the NAc-VMPFC connection associated with SRADs initially causes an increase in VMPFC activity which in turn results in the dysfunction and atrophy of this region of the prefrontal cortex. Alterations in VMPFC appear to be associated with anxiety symptoms, the response to an immediate reward associated with gambling and substance abuse, and a decline in the decision making needed to prevent addictive behaviors. In accord with earlier hypotheses it appears that SRADs are associated with a dysregulation between the VMPFC and dorsal striatum, disrupting behavioral habits [56]. However, it remains unclear as to why functional hyperactivity between the NAc and VMPFC is induced under neutral-relaxing condition, while hypoactivity occurs under cue conditions in SRAD patients. Additional work is necessary to clarify the differences in the structural and functional interactions between the reward, emotional, decision making, and regulation systems under these two conditions.

2.4. Self-regulation system

The DLPFC top-down control plays an important role in self-regulation [4]. This brain region integrates information from various brain areas to ensure appropriate planning and action [4]. Impairments of self-regulation are likely associated with behavioral problems, including substance abuse and pathological gambling [9,57].

In healthy subjects, the activity in the DLPFC and of the DLPFC-VMPFC pathway is increased when making a choice, especially if the choice involves a delayed reward [58]. Because DLPFC activity is negatively correlated with VMPFC activity in successful decision-making trials [59], it appears that the increase in DLPFC activity causes inhibition of VMPFC activity. In gambling disorder patients, DLPFC activity increases with cravings initiated by exposure to gambling-related cues [60, 61]. Patients with gambling disorder have pronounced decision-making deficits in gambling-related tasks [62], with the Wisconsin Card Sorting Test (WCST) score, a measure of DLPFC activity, reportedly diminished in these subjects [63]. Furthermore, the volume of the DLPFC is up to 20% lower in patients with alcohol-related disorders compared to controls, and the volume is negatively correlated with the period of alcohol use [64,65].

These findings indicate that, in SRAD patients experiencing cravings, DLPFC initially attenuates the VMPFC hyperactivity caused by the increase in NAc activity. Subsequently, dysregulation between the DLPFC and VMPFC appears to occur, leading to a decline in the quality of decision making which promotes addictive substance use or pathological gambling. Noël et al. hypothesize that SRADs are likely related to a dysfunction of the insula, a brain region that plays a key role in "pulling" and "steering" the human towards appropriate goal objects [66]. This hypothesis is reasonable given the known functional connectivity between the DLPFC and insula [67,68]. Decision making may be altered with stress because the brain regions implicated in this thought process are sensitive to stress-induced changes [69].

2.5. Stress response system

Abnormalities of the stress response system as well as the reward system are implicated in the development of SRADs [30]. CRH and AVP are principal components of the HPA axis, an essential element of the stress response [70, 71]. Whereas CRH is synthesized in the hypothalamic PVN, AVP is assembled in the PVN and SON of the hypothalamus [71]. Both CRH and AVP stimulate the release of ACTH [71].

IL-1β plays an important role in stress-related HPA axis function by inducing secretion of glucocorticoids which in turn inhibit production of proinflammatory cytokines and mediators, thereby forming a negative feedback loop [70, 72]. The blood levels of IL-1β in chronic cocaine users correlate positively with the severity of SRADs [73]. Social light drinkers display an increase in salivary cortisol levels when administered a relatively high dose of alcohol, whereas alcohol administration causes no change in salivary cortisol levels in social heavy drinkers [74]. Whereas salivary cortisol levels are significantly elevated by speech stress in healthy control subjects, salivary cortisol levels are unchanged in patients with alcohol-related and stimulant-related disorders [75]. Recreational gamblers show significantly increased salivary cortisol levels after viewing gambling and rollercoaster videos, while gambling disorder patients display no increase in

salivary cortisol levels with this type of video stimulus [76]. No correlation was found between the severity of SRADs and plasma levels of proinflammatory cytokines such as tumor necrosis factor (TNF)-α and IL-6 [73]. From these results it can be speculated that addictive substance abuse or pathological gambling increases production of IL-1β which in turn can induce hyperactivation and the subsequent blunting of the HPA axis that is associated with a reduced production of proinflammatory cytokines. It should be noted, however, that several studies indicate higher blood cortisol concentrations in patients with alcohol-related disorders as compared to healthy controls [77,78], suggesting that blunting of the HPA axis does not occur in these patients. Further studies on the relationship between the severity of SARD and HPA axis activity are needed to define more precisely the relationship between the disorder and this critical element of the stress response.

2.6. Interaction between the self-regulation and the stress response systems

In monkeys, injection of the α_{2A}-adrenoceptor agonist guanfacine into the DLPFC improves working memory, whereas phenylephrine, an α_1-adrenoceptor agonist, impairs it [79]. Dexmedetomidine, an α_2-adrenoceptor agonist, suppresses conditioned fear responses and decreases the memory retrieval-induced expression of c-Fos and CREB in mouse amygdala, while the suppression of the fear responses is absent in α_{2A}-adrenoceptor knockout mice [80]. In addition, it has been reported that injection of phenylephrine into the amygdala increases serum ACTH and corticosterone levels in rats [81]. Based on these data, Arnsten and colleagues suggest a mechanism to explain the underlying regulation of the DLPFC and amygdala in the regulation of the HPA axis. These investigators posit that low or moderate levels of noradrenaline release stimulate higher affinity α_{2A}-adrenoceptors and thereby maintain DLPFC function while attenuating amygdalar activity under nonstressed arousal conditions [82]. On the other hand, the higher levels of noradrenaline release that occur under uncontrollable stress activate low affinity α_1-adrenoceptors, thereby reducing DLPFC activity while maintaining amygdalar functioning [82]. Although hypothalamic control of HPA axis function, including glucocorticoid secretion, is normally related to diurnal and metabolic signals, such data indicate that the DLPFC or amygdala can influence HPA axis activity when an arousal signal or social stress information, such as craving, is sent from the lower brain regions to cortical regions via noradrenergic neurons [83, 84]. It is also known that the hippocampus plays a pivotal role in HPA axis functions [85]. As mentioned above, there is functional interaction among the hippocampus, amygdala, NAc, VMPFC, and ACC which allows them to be regulated by DLPFC top-down processing [4,5,6,7]. Given this, it is likely that HPA axis function is initially controlled by the DLPFC and subsequently, with the development of SRADs, by the amygdala and hippocampus.

Dopamine is also associated with the regulation of the HPA axis. It is probable that low or moderate levels of dopamine release maintain DLPFC activity, while higher levels of dopamine reduce the activity of this brain region [83]. The positive correlation between plasma cortisol levels and the NAc response to gambling cues in gambling disorder patients [86] suggests that NAc can influence HPA axis function via the amygdala in SRAD patients. Moreover, glucocorticoids increase brain tissue vulnerability to neurotoxicity [87]. Indeed, chronic glucocorticoid administration, or repeated exposure to stress, induces apical dendritic atrophy in the rat prefrontal cortex [88,89].

Accumulation of these data has led to the hypothesis that pathological gambling, addictive substance use, and craving induce large increases in noradrenaline and dopamine release which, in turn, directly impair self-regulation in the DLPFC. In addition, addictive behaviors and craving can lead to persistent cortisol secretion and the consequent DLPFC disturbances or atrophy associated with this response. It is probable that dysfunction of the DLPFC results in dysregulation of the reward, emotional, decision making, and stress response systems, while sustained hyperactivation of the HPA axis causes a blunting of the stress response (Figure 1).

3. Therapeutic approaches to normalizing self-regulation disturbances

3.1. Oxytocin and stress response

The fight-or-flight response is dependent upon a functioning noradrenergic system [90,91]. On the other hand, tend-and-befriend activity is associated with oxytocin and related hormones/neurotransmitters [2]. Outside the brain, oxytocin is synthesized in the uterus, placenta, amnion, corpus luteum, testis, and heart [92]. Uterine contraction is thought to be caused by oxytocin synthesized in the intrauterine tissues, such as the maternal decidua and the fetal amnion and chorion [92]. In brain, oxytocin is synthesized in magnocellular neurons in the PVN and SON of the hypothalamus and released from the pituitary gland into the general circulation [92,93]. Oxytocin neurons project from the PVN to several brain regions, including the amygdala, hippocampus, NAc, VTA, and brain stem [94].

In a double-blind, placebo-controlled clinical study, intranasal administration of oxytocin significantly reduced the stress response and salivary cortisol levels in male and female subjects subjected to stress [95,96]. It has also been found that intranasal oxytocin decreases blood ACTH levels induced by social isolation in female monkeys [97] and that oxytocin knockout female mice have an increase

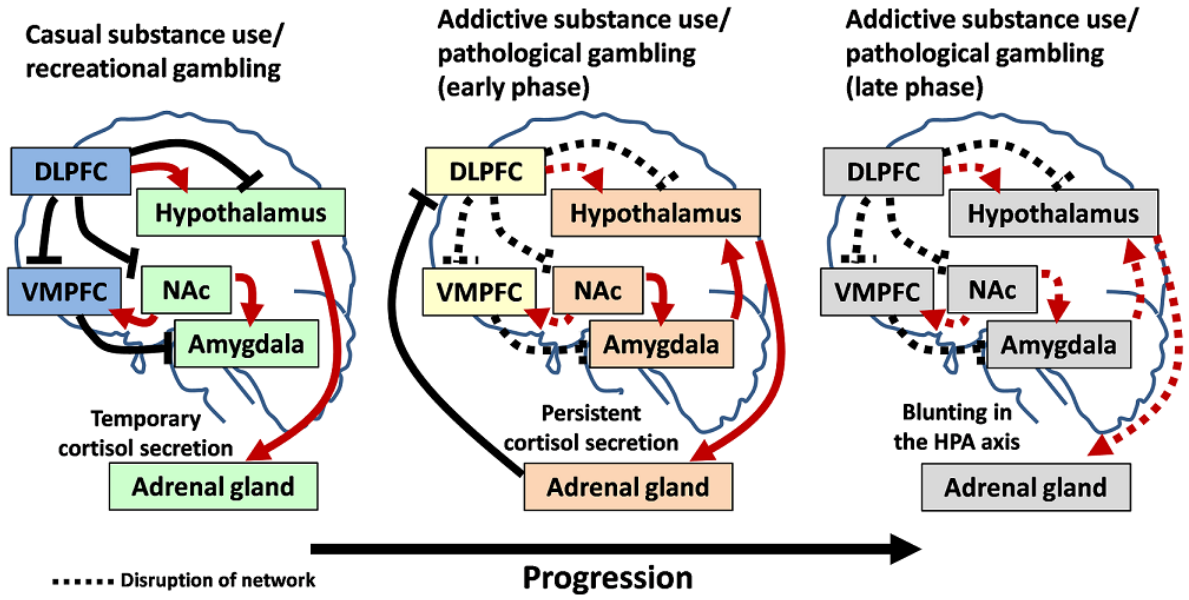

Figure 1: Hypothetical model of neural network abnormalities in SRADs. The DLPFC regulates casual substance use and recreational gambling appropriately. On the other hand, in the early phase of SRADs, addictive substance use or pathological gambling likely induce hyperactivation of the NAc (reward system), thereby leading to disturbances in the amygdala (emotional system) and VMPFC (decision making system). Increases in brain noradrenaline and dopamine levels can directly impair functions of the DLPFC that plays a key role in the self-regulation system. In addition, persistent cortisol secretion due to long-term hyperactivation of the amygdala and HPA axis (stress response system) appears to result in DLPFC dysfunction. In the late phase, dysfunction and atrophy of each brain region can eventually occur accompanying with blunted functions of the HPA axis.

in their corticosterone concentrations in the blood and attenuate c-Fos expression in oxytocin-positive neurons of the amygdala during stress [98]. These results suggest that oxytocin modulates the stress response via the HPA axis and amygdala in both males and females.

3.2. Oxytocin and prosocial behavior

Blood oxytocin levels in postpartum human females are related to maternal bonding behaviors [99]. Female rats that exhibit a consistently higher pup licking/grooming than a group of low licking/grooming animals show increases in PVN oxytocin expression and oxytocin-positive cell projections from the PVN to VTA [100]. High pup licking/grooming rats show greater increases in dopamine signaling in the NAc during bouts of pup licking/grooming [100]. The difference in maternal behavior between these two groups of rats is abolished following VTA injection of [β-mercapto-β, β-cyclopentamethylene-propionyl^1, O-Me-Tyr^2, Orn^8]-oxytocin, an oxytocin receptor antagonist [100], indicating that activation of the VTA oxytocin receptor regulates dopamine release in the NAc. In female prairie voles, blockade of the NAc oxytocin receptor prevents partner preferences induced by quinpirole, a D2 receptor agonist [101]. As blockade of D2, but not D1, receptors attenuates oxytocin-induced partner preferences, it appears that concurrent activation of NAc D2 and oxytocin receptors is essential for pair-bond formation in females of this species [101]. Considering that dopamine binds to both D1 and D2 receptors with low and high affinity, respectively [102], it is suggested that the moderate oxytocin-induced increase in the levels of dopamine release in the NAc plays an important role in parental behavior and pair-bonding in females.

In human males and their firstborn children, oxytocin levels in the saliva of fathers who show parenting behaviors are parallel to those of their children [103]. Intranasal administration of oxytocin improves mind-reading performance in males as compared with placebo controls [104]. Healthy male subjects engage in more prosocial behavior than controls when they experience acute social stress [105]. Thus it is likely that oxytocin can evoke prosocial and parental behaviors and attenuate the stress response in both human males and females.

3.3. Conflicting actions of oxytocin

Several double-blind, placebo-controlled studies have generated conflicting data concerning the effects of oxytocin. For example, intranasal administration of oxytocin increases envy and schadenfreude (gloating) in human females and males [106]. Oxytocin induces an increment

in perceived social stress without alterations in salivary cortisol levels in male humans [107] and drives a defensive, but not offensive, aggression towards competing out-groups, while a tend-and-befriend response to in-groups is found in male humans [108]. Therefore, it is possible that the responses to oxytocin are context-dependent or that oxytocin affects males and females differently with regard to certain behaviors [109, 110].

Because oxytocin has a chemical structure closely related to AVP, it is not surprising that there is an interaction between oxytocin and AVP systems [92, 93]. It is thought that oxytocin facilitates approach behavior by overcoming natural avoidance of proximity and inhibition of defensive behavior, while AVP is implicated in male-typical social behaviors such as aggression, pair-bond formation, and courtship [111]. Furthermore, oxytocin decreases activity in the amygdala and HPA axis, whereas AVP increases activity in both brain areas [71, 95, 96, 112]. Accordingly, it is possible that an endogenous balance between oxytocin and AVP receptor activation regulates prosocial behavior and the stress response [93]. It is unclear what, if any, effect oxytocin has on these behaviors through an interaction with the AVP system.

3.4. Oxytocin and addictive behavior

Although oxytocin can modulate dopamine neurotransmission in the NAc, no detectable subjective changes are noted by normal humans following intranasal administration of this hormone [113]. On the other hand, oxytocin significantly inhibits the acquisition of methamphetamine-induced conditioned place preference (CPP) and abolishes the reinstatement of CPP induced by stress in mice [114]. These effects are antagonized by atosiban, an oxytocin receptor antagonist [114]. Oxytocin reduces methamphetamine self-administration, reinstatement of methamphetamine-seeking behavior, and methamphetamine-induced hyperactivity in rats [115]. Furthermore, oxytocin-treated rats show a reduction of anxiety-like behaviors and in alcohol consumption, and enhancement of social interaction as compared to controls [116]. Given these responses in laboratory animals, it is possible that oxytocin may be of value in treating similar symptoms in SRAD patients.

3.5. CBT and self-regulation system

CBT is reported to be an effective treatment for major depressive disorder, schizophrenia, and chronic pain [117, 118, 119]. Likewise, CBT promotes reduction of gambling scores in combination with Gamblers Anonymous referral [120]. A meta-analysis revealed that psychosocial treatments such as CBT, contingency management, and their combination are efficacious as treatments for SRADs, especially for cannabis users [121]. It is reported that DLPFC activity and its connectivity with the cerebellum predict responsiveness to CBT for psychosis in schizophrenia [117]. An 11-week CBT intervention for coping with chronic pain induced an increase in DLPFC volume in conjunction with a reduction in pain catastrophizing [118]. CBT also improves executive functions that are dampened in anxious elderly adults [122]. Furthermore, noninvasive neurostimulation of the DLPFC, such as rTMS and tDCS, decreases cravings in SRAD patients [123]. These results suggest that improvement of DLPFC top-down control is a critical factor in therapeutic response to CBT. Thus, CBT in combination with drugs capable of modulating prosocial behavior and the stress response may provide therapeutic benefits for SRAD patients who have self-regulation deficits and a blunted stress response (Figure 2).

4. Comparison with other psychiatric disorders

4.1. Mood disorders, ASD, and schizophrenia

The area under the 24-hour time-concentration curve (AUC) of blood cortisol is significantly higher in patients with bipolar disorder than controls [124]. Patients with major depressive disorder show a significantly higher awakening response of salivary cortisol as compared to healthy subjects, while salivary cortisol levels in the dexamethasone suppression test do not differ between these two groups [125]. There is no association between depression characteristics and salivary cortisol levels [125]. Markedly enhanced blood or salivary cortisol response were found in ASD children when exposed to social stress [126, 127]. In schizophrenia patients, salivary cortisol secretion was slightly increased by exposure to stress [128]. Therefore, it is unlikely that a significant blunting in the HPA axis occurs in patients with mood disorders, ASD, and schizophrenia.

On the other hand, hyperactivation of possible initiating brain regions of mood disorders, ASD, and schizophrenia patients can induce M1 polarization of microglia which produces proinflammatory cytokines and chemokines including IL-6, TNF-α, and CC-chemokine ligand (CCL)-2 [5, 6, 7]. It is likely that M1 polarization of microglia is persistent under inhibition in the M2 state and that imbalance of M1/M2 microglia subsequently leads to disturbances in the DLPFC [5, 6, 7]. Taken together, imbalance between pro- and anti-inflammatory subsets of microglia appears to mainly contribute to self-regulation system disturbances in mood disorders, ASD, and schizophrenia in contrast to SRADs.

4.2. BED

BED is characterized by uncontrolled consumption of large amounts of food in the absence of inappropriate compensatory methods [8]. A genotype analysis shows that BED is significantly related to polymorphism D2 gene which reflects enhanced dopamine neurotransmission [129]. In obese patients with BED but not in those without BED, food stimuli significantly increase dopamine levels in

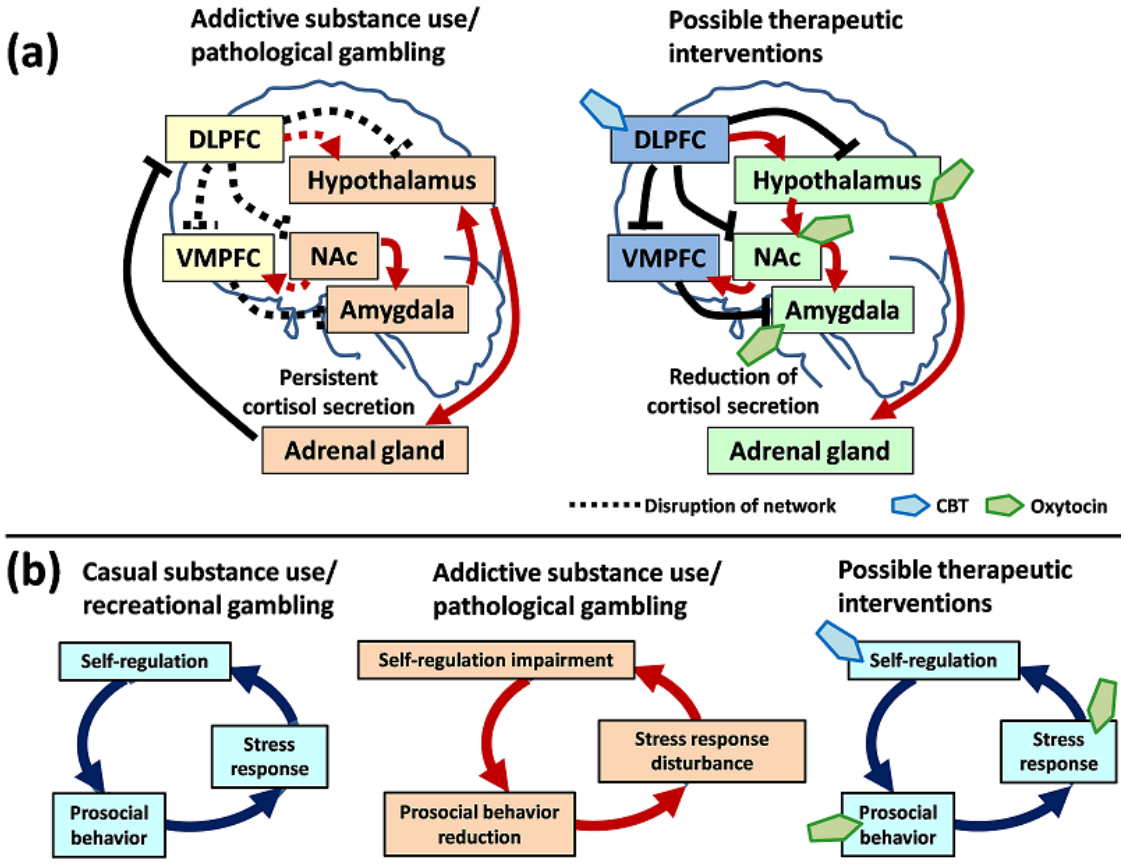

Figure 2: Possible therapeutic interventions on SRADs. (a) Oxytocin can attenuate the stress response and induce prosocial behavior via hypothalamus, amygdala, and NAc, while CBT likely improves functions of the DLPFC which plays a pivotal role in the self-regulation system. (b) It is possible that stress response disturbance, prosocial behavior reduction, and self-regulation impairment form a psycho-behavioral spiral in SRADs. CBT in combination with drugs capable of modulating prosocial behavior and the stress response may provide a therapeutic effect on SRADs.

the dorsal striatum that plays a key role in behavioral habits and the increased dopamine levels in this brain area are significantly correlated with binge-eating scores but not with BMI [130]. Social stress increased serum cortisol levels in normal weight controls and obese patients without BED, while a blunted cortisol response was observed in the BED group [131]. From these results, it is likely that higher levels of dopamine release in the reward and behavioral habit systems continuously induce hyperactivation of the HPA axis, which is predominantly associated with disturbances in self-regulation system in BED with similarity to SRADs. In contrast, imbalance between pro- and anti-inflammatory subsets of microglia appears to primarily contribute to dysregulation of the DLPFC for feeding behavior in obesity without BED [6].

5. Conclusion

In this review, I summarize current understandings of brain alterations in SRADs and provide a novel hypothesis concerning development of SRADs. It is likely that the oxytocin and dopamine systems in the brain are closely related to the stress response and prosocial behavior. Substance abuse or pathological gambling can induce robust dopamine release associated with persistent activation of the VTA-NAc pathway and HPA axis, subsequently leading to stress response disturbance and prosocial behavior reduction. Persistent hyperactivation of the HPA axis probably induces long-term cortisol secretion, which can predominantly impair function of the self-regulation system. Self-regulation impairment resulting from cortisol oversecretion appears to occur in BED similar to SRADs. On the other hand, it is likely that neuroinflammation mediated by imbalance between M1 and M2 microglia mainly causes impairment of self-regulation in obesity, mood disorders, ASD, and schizophrenia. Therefore, drugs capable of modulating stress response and prosocial behavior seem to afford favorable approaches for treatment of SRADs and BED, whereas drugs that can improve imbalance between pro- and anti-inflammatory subsets of microglia may be effective interventions in obesity, mood

disorders, ASD, and schizophrenia. CBT in combination with such drugs possibly provides a superior therapeutic effect on these psychiatric disorders commonly.

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