REVIEW

Endocannabinoid signaling in social functioning: an RDoC perspective

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Core deficits in social functioning are associated with various neuropsychiatric and neurodevelopmental disorders, yet biomarker identification and the development of effective pharmacological interventions has been limited. Recent data suggest the intriguing possibility that endogenous cannabinoids, a class of lipid neuromodulators generally implicated in the regulation of neurotransmitter release, may contribute to species-typical social functioning. Systematic study of the endogenous cannabinoid signaling could, therefore, yield novel approaches to understand the neurobiological underpinnings of atypical social functioning. This article provides a critical review of the major components of the endogenous cannabinoid system (for example, primary receptors and effectors—Δ9-tetrahydrocannabinol, cannabidiol, anandamide and 2-arachidonoylglycerol) and the contributions of cannabinoid signaling to social functioning. Data are evaluated in the context of Research Domain Criteria constructs (for example, anxiety, chronic stress, reward learning, motivation, declarative and working memory, affiliation and attachment, and social communication) to enable interrogation of endogenous cannabinoid signaling in social functioning across diagnostic categories. The empirical evidence reviewed strongly supports the role for dysregulated cannabinoid signaling in the pathophysiology of social functioning deficits observed in brain disorders, such as autism spectrum disorder, schizophrenia, major depressive disorder, posttraumatic stress disorder and bipolar disorder. Moreover, these findings indicate that the endogenous cannabinoid system holds exceptional promise as a biological marker of, and potential treatment target for, neuropsychiatric and neurodevelopmental disorders characterized by impairments in social functioning.

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INTRODUCTION

Social functioning impairments are frequently cited as core features of neuropsychiatric and neurodevelopmental disorders, yet progress in biomarker identification and development of targeted pharmacotherapies has been extremely limited. Delays in progress are attributed to social deficit heterogeneity and use of the Diagnostic and Statistical Manual of Mental Disorders (DSM) for investigational research.1–3 The DSM is a categorical classification system intended to provide clinicians with a common language for diagnosis, but its use in empirical research confers a 'top-down' design. Clinicians categorize patients phenomenologically using the DSM, then researchers attempt to identify pathophysiological mechanisms in patient-participants. However, congruence in phenomenology between patients does not necessarily signify similarity in endophenotypes or genotypes, confounding explicit links to pathology.4,5 To address the disparity in our current understanding of brain dysfunction with clinical phenomenology, a paradigm shift towards a dimensional 'bottom-up' design in research has been adopted. The Research Domain Criteria (RDoC) is a translational research approach that utilizes a matrix framework to facilitate studies that cut across diagnostic boundaries by probing functional constructs associated with neural circuits. The RDoC provides a comprehensive infrastructure to interrogate social functioning impairments and strongly emphasizes the appropriate experimental classification of patients to support direct translation of research findings for clinical use.2

Social competence is an emergent property, inter- and intra-dependent on functional integrity of three of the RDoC domains: negative valence systems, positive valence systems and cognitive systems. Initial stages of social interaction require overcoming negative valence systems (for example, fear, anxiety) to initiate the interaction and are reinforced by positive valence systems (for example, reward learning, reward valuation). Cognitive Systems (that is, attention, perception, working memory) guide the exchange after social interaction has commenced. Social process systems (that is, affiliation and attachment, social communication, perception of self and others) exert supramodal control to coordinate germane practices. Dysfunction in one construct intrinsically affects social information processing and impacts the ability to function typically. In addition, the RDoC framework encourages experimental inquiry at multiple levels of analysis (that is, genes, molecules, cells, circuits, physiology, behavior) to foster research within and across constructs, which fundamentally highlights neuromodulatory systems that operate in multiple constructs, such as the cannabinoid system. The functional heterogeneity of the endogenous cannabinoid system recapitulates the diversity of social functioning abilities in neuropsychiatric and neurodevelopmental disorder patients and parallels dimensional analysis of the RDoC.

The first reports on cannabinoid involvement in social functioning are from the nineteenth century psychiatrist Dr. Jacques Moreau de Tours for the treatment of distributed 'neurological...
dysregulation’ and ‘social alienation’.\textsuperscript{5–7} Dr. Moreau noted similarities from experiences in healthy humans after ingesting North African hashish (which contains ‘very high concentration of THC (∆9-tetrahydrocannabinol’\textsuperscript{6}) with the diversity of behaviors in neurological dysfunction.\textsuperscript{6} Moreover, first-person reports from hashish users detail traits that neatly map onto RDoC constructs: for example, ‘fluctuations of emotions’ (negative valence), extreme ‘happiness, excitement’ (positive valence), ‘errors of time and space…and illusions and hallucinations\textsuperscript{6} (arousal/regulatory), ‘irresistible impulses…and dissociation of ideas’ (cognitive domain).\textsuperscript{8,5} However, current research is focused on the use of inhibitors of endogenous cannabinoid degradation (to enhance signaling) in the study of reward-related processing in social interactions.\textsuperscript{10–14} The present article reviews the basic biology of the endogenous cannabinoid system and the roles of its relevant components across each RDoC construct as it pertains to social functioning. Data reviewed within each RDoC construct are applicable to multiple neuropsychiatric and neurodevelopmental disorders, the most notable of which are highlighted as exemplars at the conclusion of each section. With development of diagnostic assessments and treatment options for social functioning deficits limited due to inherent phenotypic heterogeneity, methodical research on the endogenous cannabinoid system has high potential to provide inroads in identifying underlying mechanisms shared across disorders.

ENDOCANNABINOID SIGNALING: EFFECTORS IN NEUROPSYCHIATRIC AND NEURODEVELOPMENTAL DISORDERS

Receptors
Cannabinergic effects is chiefly mediated by stimulation of cannabinoid receptors, type 1 and 2 (CB1R and CB2R),\textsuperscript{15} which are distributed throughout the central nervous system\textsuperscript{8,16} (see Table 1). Both types are seven-transmembrane G-protein-coupled receptors. These receptors stimulate \(G_{\alpha_i}\) proteins in the regulation of ion channels, inhibit adenylyl cyclase, which through downstream signaling increase cyclic AMP in the modulation of neurotransmission, activate protein kinase A to govern cellular function and regulate mitogen-activated protein kinases in control of transcriptional factors.\textsuperscript{8,17,18} Mainly expressed in presynaptic axonal segments of inhibitory and excitatory neurons of the brain, CB1Rs are implicated in regulation of synaptic strength.\textsuperscript{16,17} CB1Rs control the probability of neurotransmitter release at glutamate and \(\gamma\)-aminobutyric acid (GABA) synapses, mediating GABA suppression or glutamate release and reuptake,\textsuperscript{18,19} thereby contributing to the homeostatic maintenance of the brain’s excitatory-inhibitory balance.\textsuperscript{17,20,21} CB1R activation also suppresses release of serotonin, dopamine, acetylcholine and noradrenaline,\textsuperscript{18,21} thereby mediating the characteristic cognitive and antidepressant effects.\textsuperscript{16,18} CB2Rs, in contrast, were initially considered a peripheral nervous system receptor as they were originally from immune cells and gene expression levels were higher in inflammatory responses.\textsuperscript{15,22} The responses of brain CB2Rs was first detected after harm, insult or neuroinflammation, which breaks down the blood–brain barrier and allows for non-neuronal immunocytes to infiltrate the central nervous system, thereby increasing CB2R expression.\textsuperscript{23} Accordingly, expression levels of brain CB2R represent brain health,\textsuperscript{22,23} as very low expression indicates a fit brain.\textsuperscript{23,24} At homeostasis, low CB2R expression\textsuperscript{25} is observed in cell bodies and dendrites of neural progenitor cells, neurons, oligodendrocytes, astrocytes\textsuperscript{23,26} and stimulated microglia—‘resident macrophages of the central nervous system’.\textsuperscript{22} Activation of CB2Rs upregulates cell-surface factors in regeneration and degeneration, functions in migration and proliferation, as well as neural cell maturation and survival,\textsuperscript{16,25,27} but the underlying mechanisms remain unclear.

Ligands
Elucidation of the delta-9 double bond in plant-derived cannabinoid (phytocannabinoid), ∆9-tetrahydrocannabinol (THC), in the early 1960s instigated the search for endogenously synthesized cannabinoids (endocannabinoids) and led to the detection of anandamide (AEA) and 2-arachidonoylglycerol (2-AG).\textsuperscript{65,66} Each cannabinoid class and type is distinct in mechanisms of action, behavioral profiles and action in neural circuits. Phytocannabinoids are produced in secretory cells of glandular trichomes at high concentrations in unfertilized female Cannabis flowers. THC is a low potency partial agonist at CB1R and CB2R.\textsuperscript{6,65} The non-psychoactive analog of THC, cannabidiol (CBD), is of burgeoning clinical interest for its very low efficacy and partial agonism at CB1R and CB2R. At low molar concentrations, CBD acts as an antagonist or inverse agonist (particularly at CB2R) to limit THC effects and contributes to the upregulation of endogenous cannabinoid signaling.\textsuperscript{67} Clinically, CBD is a neuroprotectant used as an anti-inflammatory, anticonvulsant, antiepileptic and antipsychotic.\textsuperscript{67} CBD’s effects are attributed to the full agonism it exhibits for non-cannabinoid G-protein-coupled receptors (for example, peroxisome proliferator-activated and nuclear receptors) and interactions with serotoninergic, adenosinergic and vanilloid systems.\textsuperscript{8,15} Notably, the most efficacious therapies are observed with formulations combining THC and CBD (two to four times greater than single cannabinoid preparations)\textsuperscript{69} as CBD enhances the therapeutic action of THC by potentiating its psychotrophic effects, augmenting THC tolerability, and widening the therapeutic window.\textsuperscript{67} Enhanced efficacy is attributed to the entourage effect\textsuperscript{65,68} the synergistic action of the more than 480 biologically active and inactive compounds in Cannabis. It is likely that the as-yet identified major and minor cannabinoids in plant extracts may further enhance the therapeutic benefit observed with THC and CBD through improved stimulation of the endogenous cannabinoid system.\textsuperscript{65}

Endocannabinoids (eCBs) are small (< 400 Da) lipophilic activity-dependent retrograde messengers in the brain. Produced post-synaptically ‘on demand’ through de novo synthesis from membrane phospholipids in response to increased intracellular \(Ca^{2+}\) via depolarization,\textsuperscript{69} eCBs act presynaptically to inhibit GABA and glutamate release.\textsuperscript{17} The physiological endpoints of AEA and 2-AG are comparable to THC,\textsuperscript{69} but are functionally and temporally distinct from one another. AEA has high binding affinity (CB1R: \(K_i = 239\) nmol l\(^{-1}\), CB2R: 440 nmol l\(^{-1}\))\textsuperscript{70} but low efficacy for cannabinoid receptors. It is most active during steady-state conditions and regulates basal synaptic neurotransmission. Data from rodent autism spectrum disorder (ASD) models demonstrate that genetic mutations in the neuroligin gene disrupt tonic eCB signaling\textsuperscript{71} and intimate the importance of eCB signaling mode (tonic or phasic) in neurodevelopment and neuropsychiatric disorders. 2-AG is the more prevalent eCB (~4 nmol g\(^{-1}\) brain)\textsuperscript{70} and regulates synaptic plasticity.\textsuperscript{17,60} It is representative of ‘phasic’ signaling evoked in sustained depolarization. The greater overall efficacy and binding affinity of 2-AG (CB1R: \(K_i = 3424\) nmol l\(^{-1}\), CB2R: 1194 nmol l\(^{-1}\))\textsuperscript{70} particularly at CB2R\textsuperscript{72} is likely related to the enhanced native tone and role in adaptive response. Inactivation of AEA and 2-AG is primarily through enzymatic degradation. AEA is transported across the transmembrane proteins\textsuperscript{47,73} and hydrolyzed via fatty acid amide hydrolase (FAAH),\textsuperscript{67} whereas 2-AG can be hydrolyzed by FAAH or monoacylglycerol lipase.\textsuperscript{74}

ENDOCANNABINOID SIGNALING IN SOCIAL FUNCTIONING: AN RDOC PERSPECTIVE

The endocannabinoid system provides a consummate model to examine social functioning deficits across multiple clinical populations. The distribution of eCB components is congruent...
### Table 1. Endocannabinoid system component in RDoC domains

| RDoC construct | Mediating circuit | CB1R in circuitry | CB2R in circuitry | 2-AG | AEA |
|----------------|-------------------|-------------------|-------------------|------|-----|
| Anxiety        | Interprept: BNST, HPC, amygdala | BNST<sup>a</sup>, HPC, amygdala | Microglia<sup>b</sup>, VTA and NAc dopaminergic neurons | ↑ in brain → anxiolytic<sup>c</sup> | ↓ in brain → anxiogenic<sup>c</sup> |
| Chronic stress| HPA, amygdala—medial PFC—striatum<sup>d</sup> | PFC, HPC, NAc, amygdala | Rats: amygdala, HPC, PFC, hypothalamus<sup>e</sup> | ↓ in amygdala (via FAAH)<sup>f</sup> | ↑ in amygdala | PFC<sup>e</sup> |
| Motivation     | Orbitofrontal cortex, amygdala, VTA, NAc<sup>d</sup> | HPC, VTA and NAc dopaminergic neurons<sup>j</sup> | VTA dopaminergic neurons<sup>j</sup> | ↑ in NAc → ↑ dopamine<sup>c</sup> | ↑ in NAc | ↑ in NAc → ↑ dopamine<sup>c</sup> |
| Reward learning| VTA, NAc, PFC, hypothalamus, amygdala<sup>d</sup> | NAc medium spiny neurons, HPC, amygdala, VTA and NAc dopaminergic neurons, hypothalamus<sup>j</sup> | VTA dopaminergic neurons<sup>j</sup> | ↑ in NAc → ↑ dopamine<sup>c</sup> | ↑ in NAc | ↑ in NAc → ↑ dopamine<sup>c</sup> |
| Declarative memory | PFC, amygdala, HPC (dentate gyrus, CA1, CA3), VTA, NAc<sup>d</sup> | PFC, amygdala, GABAergic interneurons, HPC (dentate gyrus, CA1 and CA3)<sup>j</sup> | HPC interneuron | ↑ HPC CB1R binding → ↑ GABA<sup>j</sup> | ↓ | |
| Working memory | PFC—parietal—cingulate—thalamus—NAc, HPC<sup>j</sup> | NAc medium spiny neuron, GABAergic hippocampal interneurons<sup>j</sup> | HPC<sup>j</sup> | ↑ HPC CB2R binding → ↑ encoding/consolidation<sup>j</sup> | ↑ (via FAAH) | → ↑ acquisition<sup>j</sup> |
| Affiliation and attachment | Amygdala, VTA, NAc, PVN, SON, HPA, BNST<sup>j</sup> | PVN, SON, HPA, BNST<sup>j</sup>, amygdala, NAc<sup>j</sup> | HPC<sup>j</sup> | ↑ in HPC → ↓ care<sup>j</sup> | ↑ (via FAAH) | → ↑ acquisition<sup>j</sup> |
| Social communication | Amygdala, NAc, orbitofrontal cortex, cortico-basal ganglia-thalamo network<sup>j</sup> | HPC, amygdala, NAc<sup>j</sup> | Not yet known | ↑ in amygdala → ↓ play<sup>j</sup> | ↑ (via FAAH) | → ↑ USVs<sup>j</sup> |

Abbreviations: AEA, anandamide; 2-AG, 2-arachidonoylglycerol; BNST, bed nucleus of the stria terminalis; FAAH, fatty acid amide hydrolase; GABA, glutamate and γ-aminobutyric acid; HPA, hypothalamus–pituitary–adrenal gland axis; HPC, hippocampus; NAc, nucleus accumbens; PFC, prefrontal cortex; PVN, paraventricular nucleus; RDoC, Research Domain Criteria; SON, supraoptic nucleus; USV, ultrasonic vocalization; VTA, ventral tegmental area. CB1R is the most abundant G-protein-coupled receptor (highest levels/densities, lowest) in the mammalian brain, contributing to cannabinergic effects on movement, affective responding, cognition, temperature, appetite and neuroendocrine function<sup>g</sup>. Human mRNA expression for a CB2R isoform has been found in amygdala, striatum, HPC, cortex and cerebellum<sup>h</sup>, with rodents showing additional expression in the cerebral cortex, brain stem, thalamic nuclei and periaqueductal grey. AEA binding elicits sub-maximal receptor signaling, whereas 2-AG binds with much greater efficacy<sup>i</sup>, necessary to produce robust phasic signaling responses.
with affected neuroanatomy in neuropsychiatric and neurodevelopmental disorders with social functioning impairments (see Table 1). Changes in eCB components and function contribute to impairments in RDoC constructs critical to social behavior, resulting in a spectrum of atypical social endophenotypes. The next sections review the role of the eCB system in RDoC constructs subserving social functioning and which are characteristically observed as affected in neuropsychiatric and neurodevelopmental disorders.

**eCB SIGNALING AND NEGATIVE VALENCE SYSTEMS**

**Anxiety**

Anxiety, fear, and stress as terms are often semantically interchangeable, though each is independently characterized by the nature of the eliciting event and magnitude of response. Stressors impose a progressive pattern of dysfunction in social functioning, beginning as asociality and culminating in chronic stress. Overexpression of CB2Rs in mouse dorsal root ganglion. No significant change in CB2R expression was observed in three separate mouse lines, following exposure to chronic stressors, but without analogous data in humans, few conclusions can be made about CB2R function under chronic stress. Alterations in CB1R expression are concurrent with changes in eCB signaling in the hippocampus, striatum, dorsal raphe nucleus, hypothalamus, nucleus accumbens (NAC), PFC (at GABAergic terminals) and the amygdala. In the absence of stressors, AEA tone suppresses activity of the hypothalamic–pituitary–adrenal (HPA) axis (the chief modulator of the stress response) and disruption of this suppression initiates HPA-axis activation. Chronic stressor exposure impairs AEA signaling and elevates 2-AG content within the amygdala (and increases glucocorticoid hormone secretion), hippocampus, hypothalamus and PFC, likely due to altered FAAH and monoacylglycerol lipase-mediated hydrolysis, as the synthesis of these eCBs is unimpaired. Glucocorticoid feedback inhibition of HPA-axis activity is suggested to occur on two temporal scales, rapidly via the PFC and 2-AG tone enhancement, or less rapidly via negative feedback inhibition at the paraventricular nucleus of the hypothalamus. Glucocorticoids then normalize the amygdalar AEA levels to support basal HPA function. The enhancement of 2-AG signaling is perceived as an attempt to habituate to the chronic stress exposure and may be crucial in understanding how to properly engage eCB signaling in the modulation of the HPA axis to guarantee a positive adaptive response. However, the presence of a mechanism to examine maladaptive responses to chronic stress exposure highlights novel areas for social deficits in which exposure to a chronic stressor is unavoidable (for example, social anxiety and mood disorders).

**eCB SIGNALING AND POSITIVE VALENCE SYSTEMS**

**Reward learning**

Reward attainment is one of the only RDoC constructs to explicitly detail eCBs as candidate modulators of reward learning, valuation and processing. Recent data linking reward and social neuropeptides with eCBs highlight a novel, potential intervention specific to social functioning deficits. Adaptive reinforcement of social interactions requires long-term synaptic plasticity at excitatory synapses of the NAc and is dependent on oxytocin (OT), a neuropeptide that regulates prosocial behavior and its dysregulation has been implicated in social impairments. In the examination of neural circuits of socialization, Wei et al. demonstrated an obligatory role of AEA in a socially isolated rodent model. Salience and reward were modulated by AEA mobilization in the NAc and hippocampus via activation of OT receptors by endogenously released OT following social contact. Additional experiments to control for the anxiogenic induction of AEA release during stressful social situations found the observed effects were independent of the stress response and specific to social reward. Data suggest that OT acts as a social reinforcement signal to induce long-term depression in medium spiny neurons and requires specific activation of CB1Rs by AEA to regulate social incentive salience. These preclinical data provide insight into the mechanisms associated with OT in social functioning in clinical populations. If improvement in social functioning requires OT-evoked AEA signaling as data suggest, then enhancement of OT to improve social deficits must be sufficient to engage AEA mobilization for proper functioning of the neural circuit. Researchers have advocated that these findings are of particular relevance to ASD, although these results can also be broadly applied to neuropsychiatric disorders characterized by dysregulated OT and impaired social functioning (for example, schizophrenia and mood, anxiety, or personality disorders).
Social motivation leads to enhancement of social development by promoting social interactions. Abnormal motivation precludes proficient social interaction and has negative consequences on the acquisition of higher-order social abilities. The inability to separate motivation from social interest has contributed to the assumption that deficits in social functioning are a cause of disrupted social interest, as opposed to a consequence of them. Motivation is necessary to attend to social information, seek and engage in social interaction, as well as foster and maintain social bonds, whereas interest does not necessitate action. Individual differences in social motivation are associated with alterations in the activity of neurocircuitry that overlap with reward learning; high social motivation is correlated with enhanced activation of the amygdala and orbital frontal cortex, whereas weaker activation is related to lower social motivation. Opioid and dopaminergic neurons in the ventral tegmental area have complementary roles in motivated behaviors and require eCB signaling to fine-tune dopamine release in incentive-related reward learning. Concomitantly, enhanced motivation is observed following CB1R stimulation and with increased AEA signaling in the amygdala, NAc and dorsal striatum and 2-AG in the NAc. Diminished motivation is associated with CB1R blockade. Wei et al. suggest increased AEA content in the forebrain in animal models of ASD can ameliorate social motivation deficits. Extending previous results in rats in which modulation of CB1R or genetic removal of FAAH negatively impacted social interactions, researchers examined the influence of AEA on social behaviors via FAAH modulation. A social approach task and elevated plus maze were used to assess the effects of increased AEA (via FAAH inhibition) on social motivation in BTBR mice (an idiopathic ASD model with known deficits in social approach, reciprocal social interaction, and juvenile play) and Fragile X Syndrome mice (a syndromic ASD model with persistent social approach deficits). Increased AEA signaling in the forebrains of ASD mouse models correlated with increased time in the social chamber and prefrerential interaction with novel animals compared with untreated and control mice. Effects were not associated with decreased anxiogenic responses, as no change in behavior on the elevated plus maze was observed. Improved prosocial behaviors were ‘generalizable’ and suggest common neural circuitry of social motivation between idiopathic and syndromic ASD.

**eCB SIGNALING AND COGNITIVE SYSTEMS**

**Declarative memory**

Declarative memory (that is, encoding, consolidation, storage and retrieval of factual information) supports social interactions by providing biographical and episodic recall. It functions as a store of experience-outcomes and integrates previous conclusions with new input, as well as emotion, motivation and perception. of experience-outcomes and integrates previous conclusions with new input, as well as emotion, motivation and perception. Explicit control of eCB signaling in declarative memory for social functioning deficits must account for individual differences in abilities. Brain disorders characterized by difficulties in uncontrolled recall (for example, ASD, posttraumatic stress disorder, phobia disorders) may benefit from control over extinction, whereas disrupting short-term memory consolidation may be advantageous for other disorders (for example, OCD, anxiety disorders).

**Working memory**

More immediate information processing involves working memory, which actively maintains and updates relevant information, but is capacity-limited. In social interactions, working memory tracks social information, like the characteristics of, or relationships among, people necessary to competently socially interact. THC exposure in humans negatively impacts working memory via CB1R activation and inhibition of AEA reuptake. Correspondingly, rodent models with upregulated CB1R expression in the PFC, as well as CB1R knockout mice, demonstrate changes in cognitive flexibility. Low doses of CB1R antagonists improved task switching (a measure of cognitive flexibility) and inhibitory control via inhibition of PFC glutamatergic activity, whereas CB1R agonists increased impulsive behaviors. A neuroimaging study suggests that THC impacts activity in cerebral inhibition response circuits causing increased hyperactivity in the PFC and anterior cingulate cortices. Acute administration of THC reduces response inhibition (that is, increases behavioral impulsivity) and causes hyperactivity at dopaminergic synapses in the PFC. Data from animal models suggest that cannabinoid signaling interacts with dopaminergic, GABAergic and glutamatergic pathways to mediate behavioral changes. Data in FAAH knockout mice demonstrate that AEA-biased tone improves acquisition in working memory tasks, but the effects are transient and do not persist into later trials. This evidence suggests that strategies to improve components of working memory (for disorders such as prosopagnosia, schizophrenia and/or depression) should focus on control of AEA tone and local modulation of 2-AG signaling.
bonding. Valproate-exposed rats, another animal model of social deficits used in ASD research, demonstrate similarly reduced sociability, but changes in CB1R expression were also correlated with reduced hippocampal 2-AG expression.98 Moreover, after social play, increased AEA and 2-AG levels in the NAC and the amygdala were observed.12,88 These data demonstrate that perturbation of eCB signaling is an elegant potential causal effector in the regulation of maternal care and affiliative behaviors. These results are pertinent to better understanding how cannabinoid modulation contributes to the neurocircuitry of psychiatric disorders related to early-life adversity, such as depression, bipolar disorder and schizophrenia.56,96

Social communication
In humans, high concentrations of cannabinoid receptors are found in the left hemisphere cortical regions that are associated with verbal language function.16,18 which suggests a role for eCB signaling in social communication. However, current findings only supports a role for eCB signaling in nonverbal motor-related aspects of social communication (that is, eye-gaze or body language). Genetic variants (that is, single-nucleotide polymorphisms) in CB1Rs are correlated with greater gaze duration to happy faces and are considered a quantitative endophenotype for communicative deficits, particularly in ASD research.99 Animal models of social communication impairments demonstrate a direct connection to cannabinergic function, which interacts with theforkhead box protein family.58 Interestingly, FOXP are instrumental in ultrasonic vocalizations (USVs) production and vocal learning.58,100 In rodents, USVs serve a communicatory function to elicit social interaction61,62 or to share socially relevant information with known conspecifics.63 Moreover, USVs are developmental- and context-dependent62 relating identity, emotionality,51–63 receptivity to affiliative and sexual behaviors, and changes in the environment.56 Persistent activation of CB1R, via agonists or inhibitors of enzymatic degradation, decrease emission of USVs in rodent pups. Cannabinoids modulate USVs induced by maternal separation in pups,61 whereas in adult rodents, cannabinoids increase the emission of USVs when exposed to anxiogenic stimuli.51,63 Moreover, CB1R knockout mice have low USV emission throughout development,56 which parallels the communication impairments associated with disorders such as ASD.62 For clinical populations with impairments in language acquisition, especially nonverbal patients with social deficits, cannabinergic modulation of USVs offers a novel and viable area of biomedical intervention in support of communication acquisition and development.59,60,100

CONCLUSIONS
The diversity of social functioning deficits present in neuropsychiatric and neurodevelopmental disorders confounds the efficacy and specificity of treatment for affected individuals. However, the recent shift in psychiatric research towards examining the underlying dysregulated neural circuits of brain disorders has allowed consideration herein of novel aspects of the functionally diverse eCB signaling system. This article reviewed the eCB signaling system and the role of its components (that is, cannabinoid receptors, functional ligands) in varied, but convergent, RDoC domains of social functioning. From a molecular level of analysis, the cannabinoid system is implicated in negative and positive valence systems to restore homeostatic balance, increase the salience of reward learning and motivate social interactions. Behavioral and physiological effects of the eCB system are observed in cognitive systems. Social process systems show evidence of cannabinergic modulation, and as an emergent domain, rely on appropriate eCB function in the aforementioned RDoC domains. Although further work is needed to clarify the discrete roles of cannabinoid signaling in each RDoC domain, the extant evidence strongly supports the contribution of dysregulated cannabinoid signaling to the pathophysiology of social functioning impairments. With regard to the development of pharmacological interventions, although there is a diverse set of methods to enhance endogenous signaling or receptor stimulation in vivo, the lack of evidence on direct endocannabinoid (AEA or 2-AG)66 highlights the need for further research. Moreover, in the pursuit of precision health,7 although each component of the eCB system can be targeted for therapeutic development, appropriate targeting with respect to the intersection of the eCB system and a disorder’s neurocircuitry must be carefully considered to achieve optimal outcomes. It is clear, though, that the eCB system holds exceptional promise as a biological marker of, and treatment target6 for, neuropsychiatric and neurodevelopmental disorders characterized by pronounced abnormalities in social functioning.

CONFLICT OF INTEREST
The authors declare no conflict of interest.

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