CHAPTER FIVE

Neurotransmitters and Intermittent Explosive Disorder

Royce J. Lee, Emil F. Coccaro
Clinical Neuroscience & Psychopharmacology Research Unit, Department of Psychiatry and Behavioral Neuroscience, Pritzker School of Medicine, University of Chicago, Chicago, IL, United States

Contents

Introduction 87
Relevance of Social-Emotional Information Processing and Predictive Encoding 88
The Role of Neuromodulators in Impulsive Aggression and IED 89
- Serotonin and Impulsive Aggression 90
- Norepinephrine and Impulsive Aggression 95
- Dopamine and Impulsive Aggression 95
- Glutamate 97
- Gamma-Aminobutyric Acid 97

Neuropeptides and Impulsive Aggression 98
- Oxytocin 98
- Vasopressin 99
- Substance P 100
- Neuropeptide Y 100

Neuroinflammation 100
Summary 102
References 103

Introduction

How does disturbed neural signaling lead to impulsive aggression and IED? The dominant theory remains the serotonergic hypothesis. Over the last 2 decades, an exponentially expanding literature from the clinical neurosciences has helped us to understand how variation in serotonin signaling triggers aggressive outbursts. At the same time, research has followed threads of connection from serotonin signaling in the synapse to a wide brain network and further out into the body's immune and metabolic systems. The issue of neurotransmission in IED, as with other neuropsychiatric disorders, is increasingly seen from a systems neuroscience perspective.

Intermittent Explosive Disorder
https://doi.org/10.1016/B978-0-12-813858-8.00005-X

This chapter will summarize what we know about neurotransmitters in IED within a coherent conceptual model of disturbed neural circuit function that incorporates neurotransmitters, neuromodulators, and other signaling molecules.

Relevance of Social-Emotional Information Processing and Predictive Encoding

The role of neurotransmission in IED is complex and not reducible to a "chemical imbalance." This is due, in part, to the fact that brain signaling molecules do not always have a specific relationship to single instances or even recurrent patterns of behavior. The computational functions of the brain are complex enough that often the same signaling molecule involved in one circuit may be present in another circuit with opposite action. An example of this may be the role of dopamine signaling in the direct and indirect pathways of the striatum or the role of GABAergic signaling in hidden layer networks. Whereas intuitive models can be simple to understand, they may lack the sophistication required when applied to complex systems. Given the relevance of serotonergic function to IED, an impactful model would need to include markers of serotonin function in conjunction with other biological and psychological factors. Here we would propose a *social-emotional information processing (SEIP)/predictive coding* theory in order to organize the existing knowledge on neurotransmitters in impulsive aggression in a biologically plausible framework. To explain the model next two paragraphs will define SEIP and predictive coding.

SEIP was developed to understand the cycle of cognitions and actions of aggression in children (Crick & Dodge, 1994; Dodge, 1993). In the SEIP model, there are six phases of the aggressive response: (1) social information encoding, (2) attribution of the intent of the behavior of the other participant in the social interaction, (3) clarification of goals, (4) response generation, (5) response evaluation, and (6) response enactment. Evidence supports the validity of the SEIP model in adults with impulsive aggression. Adults with IED have reduced encoding of social cues (Coccaro, Lee, & Kavoussi, 2009; Coccaro, Noblett, & McCloskey, 2009), heightened hostile attribution and intensified negative emotional response (Coccaro, Fanning, & Lee, 2016; Coccaro, Keedy, et al., 2016; Coccaro, Lee, et al., 2016; Coccaro, Lee, & Gozal, 2016), and a bias to choose directly, or relationally, aggressive responses to socially ambiguous cues. Although biological correlates of SEIP stages have been identified, how these stages are

dynamically coded by the brain is difficult to study without modeling approaches. *Predictive coding* provides such a model.

Predictive encoding, first developed as a computational model of consciousness (Friston, Stephan, Montague, & Rolan, 2014), has been applied to the function of the NMDA receptor (Corlett, Honey, & Fletcher, 2016) and brain circuits in psychosis (Sterzer et al., 2018). In the predictive encoding model, cortical brain networks learn and develop through a form of Bayesian inference. Cortical brain network activity is dedicated to generating probabilistic predictions that are updated by new sensory data, informing the next prediction in a recurrent loop. What is being predicted? For humans, who are social mammals, reward and stressors are among the most powerful engines of behavior. Such processes are codified in the brain through the frontostriatal circuits computing temporal difference (TD) error (Wolpert, Doya, & Kawato, 2003).

In humans with impulsive aggression, dysfunction in three brain circuits has been identified. These three circuits are part of a *SEIP/predictive coding* brain network. These include: (1) Ventral prefrontal-amygdala circuits that include the insula and periaqueductal gray involved in fear learning (Coccaro, Fanning, et al., 2016; Coccaro, Keedy, et al., 2016; Coccaro, Lee, Breen, & Irwin, 2015; Coccaro, Lee, et al., 2016; Coccaro, Lee, & Gozal, 2016; Coccaro, Lee, McCloskey, Csernansky, & Wang, 2015; McCloskey et al., 2016), (2) frontostriatal circuits involved in reinforcement learning and cognitive control (Chen, Muggleton, & Chang, 2014; Endrass, Schuermann, Roepke, Kessler-Scheil, & Kathmann, 2016; Heritage & Benning, 2012), and (3) frontoparietal circuits involved in social cognition (Lee et al., 2016). Function of the ventral prefrontal-amygdala circuits corresponds with negative emotional response and encoding of social-emotional information. Function of frontostriatal circuits corresponds with clarification of goals, response generation, and response evaluation (Kogo & Trengove, 2015). Function of the frontoparietal circuits corresponds to attribution of intent in social interaction. Neurotransmitters and neuromodulators play both universal and context-specific roles in all three of these *SEIP/predictive coding* circuits.

The Role of Neuromodulators in Impulsive Aggression and IED

Having broadly reviewed the neural circuit topology implicated in impulsive aggression and IED, it is now possible to intelligently explore

how neurotransmitter and neuromodulator function in these circuits plays its role. With respect to the monoamine neurotransmitters and acetylcholine, Kenji Doya has proposed the Metalearning hypothesis of neuromodulator function in learning (Doya, 2002). It proposes that (1) dopamine signals the temporal difference error, acting as a global learning signal; (2) serotonin controls delay discounting, weighing the balance between short- and long-term reward predictions and thus modifying the dopaminergic learning signal; (3) norepinephrine controls surprise, or arousal; and (4) acetylcholine controls the balance between memory encoding, or learning rate, and memory stability.

Serotonin and Impulsive Aggression

According to the Metalearning theory, serotonin signaling in the brain has a computational role in delay discounting. This involves suppression of reflexive actions under stress and a way of weighing the future compared with today. Experimental data are supportive of the role of serotonin in delay discounting. In human, studies using tryptophan depletion have confirmed that serotonin increases delayed reward discounting in humans (Schweighofer et al., 2008), likely by modifying the dopaminergic temporal difference learning signal in the striatum (Tanaka et al., 2007). How does 5-HT accomplish this?

5-HT neurons in the cortex arise from the rostral 5-HT system, whose cell bodies reside in the midbrain and rostral pons (Piñeyro & Blier, 1999). Cortical neurons, even nonserotonergic neurons, contain 5-HT receptors. Serotonergic signaling is at its global low during REM sleep, is higher in deep sleep, and most active while awake and active. Stress results in marked increases in the release of brain 5-HT (Amat, Matus-Amat, Watkins, & Maier, 1998), and thus it would not be unreasonable to consider serotonin as part of the stress response. Two major subtypes, 5-HT_{1A} and 5-HT_{2A} receptors, are expressed in the majority of prefrontal pyramidal cell neurons and are frequently colocalized (Amargós-Bosch et al., 2004). Cortical excitatory activity is modulated by the predominantly inhibitory 5-HT_{1A} and mixed inhibitory/excitatory 5-HT_2 receptor (Amargós-Bosch et al., 2004). (Aghajanian & Marek, 1997; Jakab & Goldman-Rakic, 1998). 5-HT2a/c receptors are localized in nearly all glutamatergic neurons in the prefrontal cortex (Weber & Andrade, 2010), and are thus ideally distributed to modulate excitatory glutamatergic signaling in the brain. In animal models, disruptions of 5-HT impair delay discounting (Mobini, Chiang,

Ho, Bradshaw, & Szabadi, 2000) and reversal learning (Clarke et al., 2005; Clarke, Walker, Dalley, Robbings, & Roberts, 2007). 5-HT modulation of reward may also occur more directly, as striatal 5-HT2 receptors have been found to inhibit dopamine efflux (Ng, Lee, & Wong, 1999).

Initial human explorations of the serotonin system and aggression involved measurement of 5-hydroxyinoleacetic acid (5-HIAA), the metabolite of 5-HT. First related to suicidal behavior (Åsberg, 1997), low 5-HIAA levels in the cerebrospinal fluid levels were then associated with impulsive aggression (Brown, Goodwin, Ballenger, Goyer, & Major, 1979; Linnoila et al., 1983; Virkkunen, Nuutila, Goodwin, & Linnoila, 1987). Combined with the prescient clinical observation that impulsive aggression was encountered in the personality disordered population, the relationship of the serotonergic system was systematically tested with a series of 5-HT receptor subtype-specific drugs, using neuroendocrine measures as a biological readout of receptor sensitivity. The conclusion of this body of work was that $5\text{-HT}_{2a/c}$ receptor sensitivity is blunted in impulsive aggression (Coccaro, Kavoussi, Cooper, & Hauger, 1997; Coccaro, Kavoussi, & Hauger, 1997; reviewed in Yanowitch & Coccaro, 2011). The findings from pharmacochallenge studies have been confirmed in a meta-analytic review of 171 studies of the serotonin-aggression relationship, with pharmacochallenge studies yielding the strongest ($r=-0.21$), and CSF 5-HIAA concentration studies yielding the smallest ($r=-0.06$) effect size (Duke, Bègue, Bell, & Eisenlohr-Moul, 2013).

These first findings highlighted an important paradox: CSF 5-HIAA level decreases would suggest decreased serotonin signaling in aggression. On the other hand, blunted postsynaptic receptor function likely reflects chronically enhanced serotonin signaling. Is serotonergic function increased or decreased in IED? We will review both sides of the argument.

The strongest evidence for low serotonin signaling in impulsive aggression comes from experimental work in humans manipulating serotonin availability. In humans, depletion of the molecular precursor to serotonin, tryptophan, affects brain function in frontoamygdala circuits. Tryptophan depletion enhances amygdala activation to fearful face stimuli in subjects (Cools et al., 2005), enhances recognition of fearful faces in healthy controls (Harmer, Rogers, Tunbridge, Cowen, & Goodwin, 2003), and causes more severe mood induction following a stressor (Richell, Deakin, & Anderson, 2005). Mixed results have been seen regarding the effects of serotonergic depletion on response inhibition, a subtype of impulsivity (Dougherty, Richard, James, & Mathias, 2010; Rubia et al., 2005). Instead, serotonergic

depletion interferes with delay discounting (Dougherty et al., 2010). These alterations in emotion processing and behavioral inhibition explain how tryptophan depletion increases aggressive responding in simulated social provocations (Bjork, Dougherty, Moeller, & Swann, 2000; Bond, Wingrove, & Critchlow, 2001; Cleare & Bond, 1995; Marsh, Dougherty, Moeller, Swann, & Spiga, 2002).

Individuals with IED are particularly susceptible to the effects of tryptophan depletion on mood and affective reactivity, with increased anger and subjectively perceived intensity of angry emotional faces (Lee, Gill, Chen, McCloskey, & Coccaro, 2012). It thus seems that IED is associated with a vulnerability to the effects of low serotonergic tone on the regulation of anger and perception of angry faces. Given the evidence of compromised ventral prefrontal cortical-amygdala connectivity in IED (Coccaro, McCloskey, Fitzgerald, & Phan, 2007), the findings from the acute tryptophan depletion study suggest that serotonin alters social behavior by affecting ventral prefrontal-amygdala functional connectivity. Indeed, a recent tryptophan depletion study in impulsive aggressive individuals confirms this, finding that tryptophan depletion is associated with diminished connectivity between the ventral prefrontal cortex and amygdala (Passamonti et al., 2012). These findings are bolstered by research in borderline personality disorder subjects finding that uptake of a PET radioligand for the 5-HT precursor, tryptophan, is inversely correlated with measures of impulsivity (Leyton et al., 2001). Chronic administration of the serotonin precursor molecule tryptophan has been found to decrease aggressive behavior in healthy controls (Moskowitz, Pinard, Zuroff, Annable, & Young, 2003).

Another body of work finds evidence for enhanced serotonergic signaling in impulsive aggression. A genetic polymorphism of the monoamine oxidase A associated with low activity (thus predicting a decreased rate of serotonergic breakdown) has been associated with impulsive aggression (Chester et al., 2015). Interestingly, measurement of brain MAO activity with a radioactive pet ligand similarly finds that low MAO-A activity is associated with aggression (Alia-Klein et al., 2008). Metabolic PET brain imaging, when used in conjunction with pharmacochallenge with the 5-$HT_{2a/c}$ agonist fenfluramine, has revealed that impulsive aggressive personality disordered patients have a blunted metabolic response in the prefrontal cortex (Siever et al., 1999). These findings have been replicated in subsequent experiments using fenfluramine (Soloff, Meltzer, Greer, Constantine, & Kelly, 1999) and later with the 5-$HT_{2a/c}$ agonist metachlorophenylpiperizine (m-CPP; New et al., 2002). When probed directly

with a radioligand for the 5-HT_{2a} receptor, [(11)C]MDL100907, impulsive aggression has been found to be associated with downregulation of brain 5-HT_{2a} receptor expression (Rosell et al., 2010). Such downregulation has also been found with the 5-HT_{1A} receptor using the radioligand [c-11] WAY-100635 (Parsey et al., 2002). A neuroendocrine study of postsynaptic 5-HT_{1a} sensitivity similarly found evidence of reduced sensitivity in impulsive aggression (Almeida, Lee, & Coccaro, 2010). Findings of blunted 5-$HT_{2a/c}$ receptor expression are generally interpreted as reflecting compensatory downregulation of postsynaptic receptors in response to increased synaptic 5-HT release (Jørgensen et al., 2016; Meyer et al., 2001).

Consistent with the hypothesis that increased serotonergic signaling is associated with aggression, atypical antipsychotic drugs have been found to reduce anger and aggression in borderline personality disorder (Black et al., 2014; Zanarini, Frankenburg, & Parachini, 2004). Because olanzapine and quetiapine have numerous other pharmacological actions outside of 5-HT_{2a} receptor antagonism, follow-up research with a specific 5-HT_{2a} receptor antagonist in impulsive aggression would be of interest to confirm the importance of this receptor subtype.

The basic science literature has generally confirmed the relevance of serotonin signaling to aggressive behavior, but has had difficulty with discerning the direction of effect of serotonin. Most evidence supports the view that the 5-HT_{1a} has an important role, but what remains unclear is the association is due to increased or decreased postsynaptic 5-HT_{1a} signaling (De Boer & Koolhaas, 2005).

We have reviewed two bodies of replicated but seeming paradoxical findings regarding serotonergic signaling in impulsive aggression. The most likely explanation for this is that 5-HT_{1a} and 5-$HT_{2a/c}$ signaling are separable signals with distinct roles in shaping brain activity and thus behavior. The evidence suggests that impulsive aggression is likely inhibited by 5-HT_{1a} and facilitated by 5-$HT_{2a/c}$ neuromodulation. Distinct roles for these two signaling pathways have been hypothesized for stress reactivity, with 5-HT_{1A} signaling proposed to mediate passive coping while 5-$HT_{2a/c}$ signaling proposed to mediate active coping (Carhart-Harris & Nutt, 2017).

The action of selective serotonin reuptake inhibitor (SSRI) medications illustrates the complexity of the serotonergic system through dual modulation of 5-HT_{1a} and 5-$HT_{2a/c}$ signaling. Chronic SSRI treatment reduces cortical 5-HT_{2a} binding, likely through postsynaptic receptor desensitization (Peremans et al., 2005). However, the antidepressant actions of SSRI treatment are thought to depend on increased 5-HT_{1a} signaling in the

dentate gyrus of the hippocampus (Samuels et al., 2015). In humans, blocking the degradation of serotonin with serotonin reuptake inhibitors (SSRI) has been found to reduce impulsive aggression in IED. In a randomized, double-blind, placebo-controlled trial of the SSRI fluoxetine, fluoxetine was found to be superior to placebo in reducing verbal aggression in IED patients (Coccaro, Lee, et al., 2009; Coccaro, Noblett, et al., 2009). More severely aggressive subjects, who were also more likely to have blunted 5-HT receptor sensitivity to d-fenfluramine, were less likely to improve with fluoxetine treatment (Coccaro et al., 2007). Fluoxetine has similarly found to reduce aggressive behavior in depressed patients with anger attacks (Fava et al., 1993). The therapeutic effect of SSRI treatment of aggression may be by increasing OFC activity. PET brain imaging in conjunction with open-label fluoxetine treatment in 10 BPD-IED patients revealed that fluoxetine treatment was associated with an increase in OFC metabolism (New et al., 2004). Increased OFC activity may be due to 5-HT_{2a} desensitization, as preclinical research has found that chronic treatment with citalopram reduces cortical 5-HT_{2a} binding (Peremans et al., 2005), releasing the OFC from inhibitory modulation by 5-HT_{2A} (Bergqvist, Dong, & Blier, 1999). The effects of SSRI administration on aggression may not be restricted to the prefrontal cortex. A recent study of the effects of acute administration of the SSRI citalopram on the neural response to emotional face stimuli found that citalopram dosing was associated with increased activity in the left TPJ in IED compared with healthy control individuals (Cremers, Lee, Keedy, Phan, & Coccaro, 2015). Such effects could indicate that SSRI treatment may reduce aggression by increasing mentalizing ability and could be conceptualized as an extension of the Metalearning model of serotonin function into the sphere of social interaction. SSRIs may also reduce aggression by altering the time course of angry emotional responses to stimuli, consistent with the effects of tryptophan depletion on anger. A recent computational study modeled frustration in motor learning by adapting the Rescorla-Wagner learning rule (Grzyb, Boedecker, Asada, Pobil, & Smith, 2011). In this model, prediction error (P_e) at the current time ($P_e(t+1)$) is based on modification of prediction error at a previous time point $P_e(t)$ by the outcome of action (A_0) after the previous time point and a frustration factor E_f. This frustration factor is modeled as a leaky integrator ($df/dt = -L^*f + A_0$) with an onset and decay time, such that $P_e(t+1) = P_e(t) + (P_e(t) - A_0)^*E_f$. One can see that according to this model, frustration, or anger, can increase prediction error in a time-dependent fashion. This prediction error would drive motor action. In this section, we have posited

that 5-HT tone affects the magnitude of the frustration (anger) function as well as the computation of past prediction error through delay discounting. In real-world terms, this translates to serotonin decreasing anger intensity and increasing future reward sensitivity in the context of social interaction.

Norepinephrine and Impulsive Aggression

As norepinephrine (NE) is released in acute stress (Berridge & Waterhouse, 2003), it is plausibly linked to aggressive behavior. Frustration causes norepinephrine release in the right amygdala (Young & Williams, 2010). Via release from cell groups A6 and A4 in the locus coeruleus, projections of noradrenergic neurons to the cortex increase cortical arousal through effects on alpha-1 and alpha-2 noradrenergic receptors. Behaviorally this results in vigilance and reaction speed. According to the Metalearning hypothesis, norepinephrine mediates the effect of surprise on decision-making and motor behavior, favoring the exploration of new motor responses over habitual and older motor responses (Doya, 2002). While alpha-2 receptor sensitivity is not altered in impulsive aggression (Coccaro & Kavoussi, 2010), CSF levels of the norepinephrine metabolite 3-methoxy-5-hydroxyphenylglycol (MHPG) have been positively correlated with aggression in adult males with personality disorders (Brown et al., 1979) and adults with depression (Placidi et al., 2001; Prochazka & Ågren, 2003). Aggressive individuals show higher plasma norepinephrine release during aggressive responding, albeit without baseline differences. This means that peripheral norepinephrine release may be triggered by frustration or anger, and is not necessarily the cause of aggressive behavior (Gerra et al., 1997). On the other hand, treatment with antidepressant medications that increase norepinephrine worsens aggression in personality disordered patients (Soloff, George, Nathan, Schulz, & Perel, 1986).

Dopamine and Impulsive Aggression

Given the central role of dopamine in temporal difference learning in the Metalearning model, it would be expected to play an important role in aggressive behavior. However, the role of dopamine in aggression is complex. Low levels of striatal dopamine release signal worse than expected outcomes, which would be predicted to cause frustration. Consistent with this, human studies of the homovanillic acid (HVA), the major metabolite of dopamine, has found decreased levels of CSF HVA in impulsive aggression

(Coccaro & Lee, 2010; Linnoila et al., 1983; Virkkunen et al., 1987) and decreased DA storage capacity in the striatum/midbrain (Schlüter et al., 2013). PET imaging has been utilized to measure dynamic and regional brain dopamine release. A study using 6-[18F]-fluoro-L-DOPA PET imaging during a modified Point Subtraction Aggression Paradigm (PSAP) session found to be decreased dopamine release to be associated with aggressive responding after provocation (Schlüter et al., 2013). Another PET study, also conducted during the PSAP, showed that male patients with comorbid BPD-IED showed lower striatal glucose metabolism as measured by (18)-flouro-deoxyglucose (FDG) PET imaging (Perez-Rodriguez et al., 2012).

The regulation of aggression behavior, beyond that of external stimulus evaluation, may involve striatal circuits involved in decision-making. Externalizing psychopathology (Hall, Bernat, & Patrick, 2007) and violent offending (Vila-Ballo, Hdez-Lafuente, Rostan, Cunillera, & Rodriguez-Fornells, 2014) have both been associated with decreased amplitude of the Error-Related Negativity, an ERP that is elicited by the commission of errors. Likewise, BPD has been associated with decreased feedback-related negativity (FRN), a stimulus-locked ERP, and to positive and negative outcomes (Endrass et al., 2016). These neurophysiological findings suggest that dopamine does not undergo the phasic dips that would signal error and could help to regulate aggression. Thus dopamine release may decrease sensitivity to frustration or anger, which would in turn reduce aggression. An fMRI study of the Point-Subtraction Paradigm (PSAP) in aggressive children with Attention Deficit Hyperactivity Disorder (ADHD) and control children found that aggressive children failed to show normative activation of the anterior cingulate region during aggressive responding (Bubenzer-Busch et al., 2016). A separate study in normal subjects found a similar normative result: aggressive responding, this time during the Taylor Aggression Paradigm, was associated with anterior cingulate activation (Beyer, Münte, Göttlich, & Krämer, 2014). The interaction of dopamine and serotonin would also be expected to be of importance given the potential role of delay discounting in social behavior, as has recently been reviewed (Seo, Patrick, & Kennealy, 2008). In summary, the role of dopamine signaling in impulsive aggression and IED is not clear. Some evidence associates aggressive behavior with decreased levels of brain dopamine. Other evidence suggests that phasic dips in dopamine that would be expected to regulate behavior are lacking in humans with impulsive aggression.

Glutamate

Activation of all three circuits implicated in impulsive aggression requires excitation of pyramidal cell neurons and release of glutamate. Furthermore, glutamatergic neurotransmission includes the machinery of neuroplasticity, the molecular process of Hebbian learning. It is thus safe to say that glutamatergic signaling is implicated in all behavior, including aggression (Vekovischeva et al., 2004). CSF glutamate concentrations correlate positively with measures of both aggression and impulsivity in personality disordered and healthy control study participants (Coccaro, Lee, & Vezina, 2013). Given the presence of a global signal of increased excitatory neurotransmitter signaling, this finding seems to support the multicircuit model of aggression posited in this chapter. Namely, the finding that multiple brain circuits are hyperactive in response to social cues in IED and impulsive aggression is the likely explanation of increased glutamate.

Gamma-Aminobutyric Acid

Gamma-aminobutyric acid (GABA) is the major inhibitory neurotransmitter in the brain. GABA is also important in shaping the oscillations of the local field potential that help to coordinate brain communication (Lozano-Soldevilla, 2018; Mann & Mody, 2010). Preclinical studies have shown that aggressive animals have reduced brain GABA levels and of glutamic acid decarboxylase (GAD), the enzyme that catalyzes glutamate into GABA. In humans, we have previously discovered an inverse relationship between impulsivity and CSF GABA levels, but no relationship specifically with aggression (Lee, Ferris, Van der Kar, & Coccaro, 2009). These results are largely consistent with a large body of work finding that benzodiazepine drugs, which are allosteric modulators of the GABA-A receptor, are associated with behavioral disinhibition (Cowdry & Gardner, 1988) and aggression (Albrecht et al., 2014). Work in animal models has linked benzodiazepine-facilitated aggression to alpha-2 GABA-A receptor expression, confirming the direct and expected pharmacodynamics effect of benzodiazepine drug on aggression (Newman et al., 2015). It is known that benzodiazepine drug administration in humans causes a global reduction in brain metabolic activity (Wang et al., 1998). These reductions were strongest in the thalamus and occipital cortex, but include brain regions in the proposed three circuit model of aggression, such as the frontal cortex, parietal cortex, and basal ganglia.

Neuropeptides and Impulsive Aggression

Neuropeptides are protein-like molecules released in the brain to play a neuromodulator role on neural signaling. Unlike the monoamine neuromodulators and neurotransmitters, neuropeptide expression and release have a relatively high specificity for regional circuit distribution and behavioral effect. However, like other neuromodulators, they act on metabotropic receptors to depolarize or hyperpolarize the postsynaptic neuron.

Oxytocin

Oxytocin acts on a single oxytocin receptor subtype, a metabotropic G-protein-linked receptor. In humans, oxytocin receptors have recently been confirmed to be expressed in the gyrus rectus of the orbitofrontal cortex and ventral and subgenual anterior cingulate cortex but not the insula or olfactory cortex (Rogers et al., 2018). Previous work localized oxytocin binding sites to the forebrain, lateral septal nucleus, hypothalamus, and globus pallidus (Loup, Tribollet, Dubois-Dauphin, & Dreifuss, 1991). The distribution is consistent with the known role of oxytocin in enhancing the salience of social information. Preclinical work with the social neuropeptides has linked the expression of oxytocin and vasopressin to prosocial behaviors (Caldwell & Albers, 2016). Although oxytocin has been purported to suppress anxiety, in preclinical models the effect of oxytocin on behavior is context dependent, as is seen with social modulation of oxytocin effects on fear conditioning (Guzmán et al., 2013). In humans, CSF oxytocin levels are inversely correlated with life history of aggression measures in adults with impulsive aggression (Lee et al., 2009). In the periphery, plasma levels of oxytocin have been found to be inversely related to aggression in individuals with BPD (Bertsch et al., 2013; Bertsch, Schmidinger, Neumann, & Herpetz, 2013). Intranasal oxytocin has also been found to reduce amygdala activation to threatening faces in females with BPD (Bertsch, Schmidinger, et al., 2013). Surprisingly, administration of intranasal oxytocin to humans increases, rather than decreases, aggressive responding in simulated social interaction (Ne'eman, Perach-Barzilay, Fischer-Shofty, Atias, & Shamay-Tsoory, 2016). In our laboratory, intranasal oxytocin failed to exhibit the expected antiaggressive effect on the Point Subtraction Paradigm (PSAP). However, an indirect "cybernetic" effect of oxytocin was found in decreasing computer confederate aggression,

likely via a tendency of subjects when given oxytocin to increase defensive "C" button presses (Lee, 2014). Work in healthy humans has recently confirmed that intranasal oxytocin does not reduce behavioral aggression (Romney, Hahn-Holbrook, Norman, Moore, & Holt-Lunstad, 2018). In summary, oxytocin has a confirmed role in signaling the salience of social cues in the environment, and thus might be expected to predict social reward and thus facilitate predictive encoding of that reward. The weight of evidence suggests that in facilitating social behavior, oxytocin should reduce aggressive behavior. However, findings from the experimental literature reveal that the increased salience of social cues may not always translate to a reduction in aggressive behavior, perhaps due to frustration of predicted social reward.

Vasopressin

Vasopressin binds to three subtypes of G-protein-linked metabotropic receptors in the brain and periphery (Ring, 2005): the V1a, V1b, and V2 receptors. The V1a receptor is found in the limbic system and cortex, while the V1b is located in the limbic system and pituitary gland. The V2 receptor is localized in the kidney and is not thought to play a neuromodulator role in the brain. In humans, vasopressin receptors have been localized to the agranular insular cortex, the frontal operculum, primary olfactory cortex, and the subgenual cingulate gyrus (Rogers et al., 2018), as well as the amygdala, bed nucleus of the stria terminalis, thalamus, hippocampus, and medal septal nucleus (Loup et al., 1991). A large body of work has revealed a direct link between vasopressin signaling and both offensive and defensive aggressive behavior (Albers, 2012). In humans, genetic variation of the vasopressin V1a receptor has been found to predict differences in metabolic reactivity of the amygdala to emotional face stimuli (Meyer-Lindenberg et al., 2009). CSF levels of vasopressin are positively correlated with life history of aggression in adults with and without personality disorder (Coccaro, Kavoussi, Hauger, Cooper, & Ferris, 1998). A novel vasopressin V1a receptor antagonist has been found to reduce the brain response to repeated emotional face stimuli, suggesting the social behavior may be shaped by pharmacological blockade of vasopressin receptors (Lee et al., 2013). In summary, vasopressin has been found to signal the salience of social cues. This signaling would be expected to enhance encoding of social emotional information. Although work in animal models and some work in humans would predict that vasopressin promotes aggressive behavior, and blocking it with antagonists should reduce it, experimental evidence for this is so far lacking.

Substance P

The endogenous receptor for substance P is the Neurokinin-1 (NK1) receptor. NK-1 receptors are widely distributed in the CNS and include expression in the limbic system (Yip & Chahl, 2001). In animal models, substance P promotes aggression via activation of NK1 receptors in the hypothalamus and amygdala (Bhatt, TR, & Siegel, 2003; Han, Shaikh, & Siegel, 1996). Pharmacological blockade of the NK1 receptor reduces defensive aggression in cats (Shaikh & Siegel, 1994). In humans, CSF levels of substance P is correlated with life history of aggression (Coccaro, Lee, Owens, Kinkead, & Nemeroff, 2012).

Neuropeptide Y

Neuropeptide Y (NPY) is synthesized in GABA inhibitory neurons and acts on Y1, Y2, Y4, and Y5 G-protein-linked receptors as a neuromodulator. NPY is expressed in the amygdala, hypothalamus, hippocampus, basal ganglia, and brainstem (Robinson & Thiele, 2017). NYP has established roles in feeding, control of metabolism and fat deposition, stress reactivity, and anxiety. Its role in a multitude of behaviors has been conceptualized as promoter of stress resilience (Reichmann & Holzer, 2016). Somewhat counterintuitively, work in animal models has revealed that stimulation of Y1 receptors is associated with increased aggression (Karl et al., 2004; Kask & Harro, 2000; Rutkoski, Lerant, Nolte, Westberry, & Levenson, 2002). Consistent with this finding, in humans, CSF NPY concentration positively correlated with life history of aggression (Coccaro et al., 2012).

Neuroinflammation

Brain activity is tightly linked to immune system function. Why this is so is not completely understood. One possibility is that the process of neuroplasticity requires the immune systems for the clearance of synaptic proteins. Hebbian plasticity, a use-dependent shaping of neural function, utilizes multiple components of the immune system to target synapse and neurons (Mottahedin et al., 2017). Sleep, which takes up a large portion of mammalian life, may have in fact evolved to assist in the processing of this metabolic load. By taking brain inputs and outputs offline, sleep permits the immune system to enhance relevant synapses through long-term potentiation (LTP) and degrade irrelevant synapses through long-term depression (LTD) (Tononi & Cirelli, 2014). Crosstalk between the immune system

and the brain involves multiple signaling pathways, including acetylcholine (Rosas-Ballina & Tracey, 2009) and serotonin (Pelletier & Siegel, 2009). It is also known that cytokines, proteins released by immune system B and T cells, have direct effects on behavior due to their neuromodulator function in the brain. Inflammatory cytokines such as Interleukin 1β (IL-1β; Hassanain, Zalcman, Bhatt, & Siegel, 2003) and Interleukin 2 (IL-2; Bhatt & Siegel, 2006) modulate aggressive behavior in animals (i.e., defensive-rage aggression model in cat)

In humans, impulsive aggression is associated with increased peripheral expression of IL-6 and both peripheral and central C reactive protein (Coccaro, Lee, Breen, et al., 2015; Coccaro, Lee, & Coussons-Read, 2014; Coccaro, Lee, McCloskey, et al., 2015). Impulsive aggression has also been associated with increased oxidative stress, as evidenced by elevated 8-hydroxy-2'-deoxyguanosine and 8-isoprostane in impulsive aggression (Coccaro, Fanning, et al., 2016; Coccaro, Keedy, et al., 2016; Coccaro, Lee, et al., 2016; Coccaro, Lee, & Gozal, 2016). Immune activation in impulsive aggression extends into the brain. Impulsive aggression is associated with elevations in CSF levels of CSF CRP (Coccaro, Lee, & Coussons-Read, 2015a) and soluble CSF sIL-1RII receptor protein (Coccaro, Lee, & Coussons-Read, 2015b). The presence of normal levels of the tryptophan metabolite kynurenine in the CSF of adults with IED suggests that neuroinflammation does not affect aggression by decreasing serotonin synthesis (Coccaro, Fanning, et al., 2016; Coccaro, Keedy, et al., 2016; Coccaro, Lee, et al., 2016; Coccaro, Lee, & Gozal, 2016).

The endocannabinoid system, whose signaling molecules can cross the blood-brain barrier, is a vast signaling network that is ideally situated to provide crosstalk between brain and immune signaling pathways. There is a rich animal literature linking endocannabinoid signaling and aggression (Kolla & Mishra, 2018). Cannabinoid receptors are expressed in microglial and glial cells involved in neuroinflammation (Walter & Stella, 2004). Cannabinoid CB1 receptors are the most widely expressed metabotropic receptor in the brain (Herkenham et al., 1990). Full CB1 agonists are associated with extreme aggression (Kolla & Mishra, 2018). One of the major endogenous endocannabinoids is anandamide, or *N*-arachidonoylethanolamine (AEA). AEA is synthesized from arachidonic acid and essential fatty acids and acts as a neuromodulator in the brain. AEA levels have been found to be inversely related to affective intensity in human with and without personality disorder (Coccaro, Hill, Robinson, & Lee, 2018) but were not related to aggression specifically.

According to the *SEIP/predictive coding* model, coordinated brain activity is shaped through neuroplastic processes to enhance the predictive ability of the social brain. This process appears to result in metabolic stress as reflected in immune system activation. More work needs to be done in this exciting area of neuroscience to more completely understand the clinical relevance of neuroinflammation in impulsive aggression. It is not yet clear how the scientific understanding of the complex signaling networks in neuroinflammation will lead to new therapeutic approaches. It appears that currently available medications, such as fluoxetine and valproate, do not reduce inflammation in impulsive aggressive subjects (Coccaro, Lee, Breen, et al., 2015; Coccaro, Lee, McCloskey, et al., 2015). If immune activation plays a causal role, then targeting neuroinflammation with antiinflammatory medications may be a promising approach. On the other hand, if immune activation is stress related, it is possible that attempts to halt inflammation may be too late in the causal pathway.

Summary

This review of neurotransmitter and neuromodulator abnormalities in impulsive aggression has placed the body of research in a model of brain function relevant to IED. According to this *SEIP/predictive coding* framework, neurotransmitters and neuromodulators have a role as signaling molecules in circuits that enable social interaction. These circuits both facilitate and restrain aggressive responding. Depending on the balance of stress demands on the system and its biological vulnerabilities, variability can be seen in the balance of facilitation versus restraining of aggression. Neurobiological research has pointed to disturbed serotonin signaling in impulsive aggression. Impulsive aggression is indeed caused by serotonin dysregulation but in distinct, receptor-specific pathways. Recent research has not provided evidence to the contrary, but has rather expanded the network of connections to serotonin to distributed brain circuits and even out into the body in immune and intracellular signaling cascades. In total, the resulting neurobiological portrait of IED is of a person with a lifelong history of angry outbursts, with evidence of disturbed, stress-related 5-HT signaling. This 5-HT dysfunction worsens the very system that can regulate stress reactivity, centered on hubs in the prefrontal cortex. Contributing to this positive feedback loop may be an overtaxed immune system, tasked with cleaning up the metabolically costly synaptic downsides of stress.

Despite progress in understanding the basic biological mechanism of IED, many unanswered questions remain regarding the role of neurotransmitters and neuromodulators. The task is daunting, because the brain is an enormously complicated system; its functions are not captured simply. System-based approaches have increasingly been called on in the treatment of other complex medical disorders and will likely be required to understand and treat IED. Neurotransmitter and neuromodulator signaling systems have a key role in how brain circuits learn about social interaction over time. This work can be considered as part of the larger effort to understand IED as a brain-based disorder of interpersonal reactivity.

References

Aghajanian, G. K., & Marek, G. J. (1997). Serotonin induces excitatory postsynaptic potentials in apical dendrites of neocortical pyramidal cells. *Neuropharmacology*, *36*(4–5), 589–599.

Albers, H. E. (2012). The regulation of social recognition, social communication and aggression: Vasopressin in the social behavior neural network. *Hormones and Behavior*, *61*(3), 283–292.

Albrecht, B., Staiger, P. K., Hall, K., Miller, P., Best, D., & Lubman, D. I. (2014). Benzodiazepine use and aggressive behaviour: A systematic review. *The Australian and New Zealand Journal of Psychiatry*, *48*, 1096–1114.

Alia-Klein, N., Goldstein, R. Z., Kriplani, A., Logan, J., Tomasi, D., Williams, B., et al. (2008). Brain monoamine oxidase A activity predicts trait aggression. *Journal of Neuroscience*, *28*(19), 5099–5104.

Almeida, M., Lee, R., & Coccaro, E. F. (2010). Cortisol responses to ipsapirone challenge correlate with aggression, while basal cortisol levels correlate with impulsivity, in personality disorder and healthy volunteer subjects. *Journal of Psychiatric Research*, *44*(14), 874–880.

Amargós-Bosch, M., Bortolozzi, A., Puig, M., Serrats, J., Adell, A., & Artigas, F. (2004). Co-expression and In vivo interaction of serotonin1A and serotonin2a receptors in pyramidal neurons of pre-frontal cortex. *Cerebral Cortex*, *14*(3), 281–299.

Amat, J., Matus-Amat, P., Watkins, L. R., & Maier, S. F. (1998). Escapable and inescapable stress differentially and selectively alter extracellular levels of 5-HT in the ventral hippocampus and dorsal periaqueductal gray of the rat. *Brain Research*, *797*(1), 12–22.

Åsberg, M. (1997). Neurotransmitters and suicidal behavior. The evidence from cerebrospinal fluid studies. *Annals of the New York Academy of Sciences*, *836*, 158–181.

Bergqvist, P. B., Dong, J., & Blier, P. (1999). Effect of atypical antipsychotic drugs on 5-HT2 receptors in the rat orbito-frontal cortex: An in vivo electrophysiological study. *Psychopharmacology*, *143*(1), 89–96.

Berridge, C. W., & Waterhouse, B. D. (2003). The locus coeruleus-noradrenergic system: Modulation of behavioral state and state-dependent cognitive processes. *Brain Research Reviews*, *42*(1), 33–84.

Bertsch, K., Gamer, M., Schmidt, B., Schmidinger, I., Walther, S., Kästel, T., et al. (2013). Oxytocin and reduction of social threat hypersensitivity in women with borderline personality disorder. *American Journal of Psychiatry*, *170*(10), 1169–1177.

Bertsch, K., Schmidinger, I., Neumann, I. D., & Herpetz, S. C. (2013). Reduced plasma oxytocin levels in female patients with borderline personality disorder. *Hormones and Behavior*, *63*(3), 424–429.

Beyer, F., Münte, T. F., Göttlich, M., & Krämer, U. M. (2014). Orbitofrontal cortex reactivity to angry facial expression in a social interaction correlates with aggressive behavior. *Cerebral Cortex*, 3057–3063.

Bhatt, S., & Siegel, A. (2006). Potentiating role of interleukin 2 (IL-2) receptors in the midbrain periaqueductal gray (PAG) upon defensive rage behavior in the cat: Role of neurokinin NK(1) receptors. *Behavioural Brain Research*, *167*, 251–260.

Bhatt, S., TR, G., & Siegel, A. (2003). NK1 receptors in the medial hypothalamus potentiate defensive rage behavior elicited from the midbrain periaqueductal gray of the cat. *Brain Research*, *966*, 54–64.

Bjork, J. M., Dougherty, D. M., Moeller, F. G., & Swann, A. C. (2000). Differential behavioral effects of plasma tryptophan depletion and loading in aggressive and nonaggressive men. *Neuropsychopharmacology*, *22*(4), 357–369.

Black, D. W., Zanarini, M. C., Romine, A., Shaw, M., Allen, J., & Schulz, S. C. (2014). Comparison of low and moderate dosages of extended-release quetiapine in borderline personality disorder: A randomized, double-blind, placebo-controlled trial. *The American Journal of Psychiatry*, *171*(11), 1174–1182.

Bond, A. J., Wingrove, J., & Critchlow, D. G. (2001). Tryptophan depletion increases aggression in women during the premenstrual phase. *Psychopharmacology*, *156*(4), 477–480.

Brown, G. L., Goodwin, F. K., Ballenger, J. C., Goyer, P. F., & Major, L. F. (1979). Aggression in humans correlates with cerebrospinal fluid amine metabolites. *Psychiatry Research*, *1*(2), 131–139.

Bubenzer-Busch, S., Herpertz-Dahlmann, B., Kuzmanovic, B., Gaber, T. J., Helmbold, K., Ullisch, M. G., et al. (2016). Neural correlates of reactive aggression in children with attention-deficit/hyperactivity disorder and comorbid disruptive behaviour disorders. *Acta Psychiatrica Scandinavica*, *133*(4), 310–323.

Caldwell, H. K., & Albers, H. E. (2016). Oxytocin, vasopressin, and the motivational forces that drive social behaviors. *Current Topics in Behavioral Neurosciences*, *27*, 51–103.

Carhart-Harris, R. L., & Nutt, D. J. (2017). Serotonin and brain function: A tale of two receptors. *Journal of Psychopharmacology*, *31*(9), 1091–1120.

Chen, C. Y., Muggleton, N. G., & Chang, J. R. (2014). Inefficiency of post-error adjustment in impulsive violent offenders. *NeuroReport*, *25*(13), 1024–1029.

Chester, D. S., DeWall, C. N., Derefinko, K. J., Estus, S., Peters, J. R., Lynam, D. R., et al. (2015). Monoamine oxidase A (MAOA) genotype predicts greater aggression through impulsive reactivity to negative affect. *Behavioural Brain Research*, *283*, 97–101.

Clarke, H. F., Walker, S. C., Crofts, H. S., Dalley, J. W., Robbins, T. W., & Roberts, A. C. (2005). Prefrontal serotonin depletion affects reversal learning but not attentional set shifting. *The Journal of Neuroscience*, *25*(2), 532–538.

Clarke, H. F., Walker, S. C., Dalley, J. W., Robbings, T. W., & Roberts, A. C. (2007). Cognitive inflexibility after prefrontal serotonin depletion is behaviorally and neurochemically specific. *Cerebral Cortex*, *17*(1), 18–27.

Cleare, A. J., & Bond, A. J. (1995). The effect of tryptophan depletion and enhancement on subjective and behavioural aggression in normal male subjects. *Psychopharmacology*, *118*(1), 72–81.

Coccaro, E. F., Fanning, J., & Lee, R. (2016). Development of a social emotional information processing assessment for adults (SEIP-Q). *Aggressive Behavior*.

Coccaro, E. F., Hill, M. N., Robinson, L., & Lee, R. J. (2018). Circulating endocannabinoids and affect regulation in human subjects. *Psychoneuroendocrinology*, *92*, 66–71.

Coccaro, E. F., & Kavoussi, R. J. (2010). GH response to intravenous clonidine challenge: Absence of relationship with behavioral irritability, aggression, or impulsivity in human subjects. *Psychiatry Research*, *178*(2), 443–445.

Coccaro, E. F., Kavoussi, R. J., Cooper, T. B., & Hauger, R. L. (1997). Central serotonin activity and aggression: Inverse relationship with prolactin response to d-fenfluramine,

but not CSF 5-HIAA concentration, in human subjects. *American Journal of Psychiatry*, *154*(10), 1430–1435.
Coccaro, E. F., Kavoussi, R. J., & Hauger, R. L. (1997). Serotonin function and antiaggressive responses to fluoxetine: A pilot study. *Biological Psychiatry*, *42*, 546–552.
Coccaro, E. F., Kavoussi, R. J., Hauger, R. L., Cooper, T. B., & Ferris, C. F. (1998). Cerebrospinal fluid vasopressin levels: Correlates with aggression and serotonin function in personality-disordered subjects. *Archives of General Psychiatry*, *55*(8), 708–714.
Coccaro, E. F., Keedy, S. K., Gorka, S. M., King, A. C., Fanning, J. R., Lee, R. J., et al. (2016). Differential fMRI BOLD responses in amygdala in intermittent explosive disorder as a function of past Alcohol Use Disorder. *Psychiatry Research: Neuroimaging*, *257*, 5–10.
Coccaro, E. F., & Lee, R. (2010). Cerebrospinal fluid 5-hydroxyindolacetic acid and homovanillic acid: Reciprocal relationships with impulsive aggression in human subjects. *Journal of Neural Transmission (Vienna)*, *117*, 241–248.
Coccaro, E. F., Lee, R., Breen, E. C., & Irwin, M. R. (2015). Inflammatory markers and chronic exposure to fluoxetine, divalproex, and placebo in intermittent explosive disorder. *Psychiatry Research*, *229*(3), 844–849.
Coccaro, E. F., Lee, R., & Coussons-Read, M. (2014). Elevated plasma inflammatory markers in individuals with intermittent explosive disorder and correlation with aggression in humans. *JAMA Psychiatry*, *71*, 158–165.
Coccaro, E. F., Lee, R., & Coussons-Read, M. (2015a). Cerebrospinal fluid and plasma C-reactive protein and aggression in personality-disordered subjects: A pilot study. *Journal of Neural Transmission*, *122*(2), 321–326.
Coccaro, E. F., Lee, R., & Coussons-Read, M. (2015b). Cerebrospinal fluid inflammatory cytokines and aggression in personality disordered subjects. *International Journal of Neuropsychopharmacology*, *18*(7).
Coccaro, E. F., Lee, R., Fanning, J. R., Fuchs, D., Goiny, M., Erhardt, S., et al. (2016). Tryptophan, kynurenine, and kynurenine metabolites: Relationship to lifetime aggression and inflammatory markers in human subjects. *Psychoneuroendocrinology*, *71*, 189–196.
Coccaro, E. F., Lee, R., & Gozal, D. (2016). Elevated plasma oxidative stress markers in individuals with intermittent explosive disorder and correlation with aggression in humans. *Biological Psychiatry*, *79*(2), 127–135.
Coccaro, E. F., Lee, R., McCloskey, M., Csernansky, J. G., & Wang, L. (2015). Morphometric analysis of amygdla and hippocampus shape in impulsively aggressive and healthy control subjects. *Journal of Psychiatric Research*, *69*, 80–86.
Coccaro, E. F., Lee, R., Owens, M. J., Kinkead, B., & Nemeroff, C. B. (2012). Cerebrospinal fluid substance P-like immunoreactivity correlates with aggression in personality disordered subjects. *Biological Psychiatry*, *72*, 238–243.
Coccaro, E. F., Lee, R. J., & Kavoussi, R. J. (2009). A double-blind, randomized, placebo-controlled trial of fluoxetine in patients with intermittent explosive disorder. *Journal of Clinical Psychiatry*, *70*(5), 653–662.
Coccaro, E. F., Lee, R., & Vezina, P. (2013). Cerebrospinal fluid glutamate concentration correlates with impulsive aggression in human subjects. *Journal of Psychiatric Research*, *47*, 1247–1253.
Coccaro, E. F., McCloskey, M. S., Fitzgerald, D. A., & Phan, K. L. (2007). Amygdala and orbitofrontal reactivity to social threat in individuals with impulsive aggression. *Biological Psychiatry*, *62*, 168–178.
Coccaro, E. F., Noblett, K. L., & McCloskey, M. S. (2009). Attributional and emotional responses to socially ambiguous cues: Validation of a new assessment of social/emotional information processing in healthy adults and impulsive aggressive patients. *Journal of Psychiatric Research*, *43*(10), 915–925.

Cools, R., Calder, A. J., Lawrence, A. D., Clark, L., Bullmore, E., & Robinson, T. W. (2005). Individual differences in threat sensitivity predict serotonergic modulation of amygdala response to fearful faces. *Psychopharmacology*, *180*(4), 670–679.
Corlett, P. R., Honey, G. D., & Fletcher, P. C. (2016). Prediction error, ketamine and psychosis: An updated model. *Journal of Psychopharmacology*, *30*(11), 1145–1155.
Cowdry, R. W., & Gardner, D. L. (1988). Pharmacotherapy of borderline personality disorder. Alprazolam, carbamazepine, trifluoperazine, and tranylcypromine. *Archives of General Psychiatry*, *45*(2), 111–119.
Cremers, H., Lee, R., Keedy, S., Phan, K. L., & Coccaro, E. F. (2015). Effects of escitalopram administration on face processing in intermittent explosive disorder: An fMRI Study. *Neuropsychopharmacology*, *41*(2), 590–597.
Crick, N. R., & Dodge, K. A. (1994). A review and reformulation of social information-processing mechanisms in children's social adjustment. *Psychological Bulletin*, *115*(1), 74–101.
De Boer, S. F., & Koolhaas, J. M. (2005). 5-HT1A and 5-HT1B receptor agonists and aggression: A pharmacological challenge of the serotonin deficiency hypothesis. *European Journal of Pharmacology*, *526*(1), 125–139.
Dodge, K. A. (1993). Social-cognitive mechanisms in the development of conduct disorder and depression. *Annual Review of Psychology*, *44*, 559–584.
Dougherty, D. M., Richard, D. M., James, L. M., & Mathias, C. W. (2010). Effects of acute tryptophan depletion on three different types of behavioral impulsivity. *International Journal of Tryptophan Research*, *3*, 99–111.
Doya, K. (2002). Metalearning and neuromodulation. *Neural Networks*, *15*(4–6), 495–506.
Duke, A. A., Bègue, L., Bell, R., & Eisenlohr-Moul, T. (2013). Revisiting the serotonin-aggression relation in humans: A meta-analysis. *Psychological Bulletin*, *139*(5), 1148–1172.
Endrass, T., Schuermann, B., Roepke, S., Kessler-Scheil, S., & Kathmann, N. (2016). Reduced risk avoidance and altered neural correlates of feedback processing in patients with borderline personality disorder. *Psychiatry Research*, *243*, 14–22.
Fava, M., Rosenbaum, J. F., Pava, J. A., McCarthy, M. K., Steingard, R. J., & Bouffides, E. (1993). Anger attacks in unipolar depression, Part 1: Clinical correlates and response to fluoxetine treatment. *American Journal of Psychiatry*, *150*(8), 1158–1163.
Friston, K. J., Stephan, K. E., Montague, R., & Rolan, R. J. (2014). Computational psychiatry: The brain as a phantastic organ. *The Lancet Psychiatry*, *1*(2), 148–158.
Gerra, G., Zaimovic, A., Avanzini, P., Chittolini, B., Giucastro, G., Caccavari, R., et al. (1997). Neurotransmitter-neuroendocrine responses to experimentally induced aggression in humans: Influence of personality variable. *Psychiatry Research*, *66*(1), 33–43.
Grzyb, B., Boedecker, J., Asada, M., Pobil, A. P., & Smith, L. B. (2011). Between frustration and elation: Sense of control regulates the lntrinsic motivation for motor learning. In *Workshops at the twenty-fifth AAAI conference on artificial intelligence* (pp. 10–15): AAAI Publications.
Guzmán, Y. F., Tronson, N. C., Jovasevic, V., Sato, K., Guedea, A. L., Mizukami, H., et al. (2013). Fear-enhancing effects of septal oxytocin receptors. *Nature Neuroscience*, *16*(9), 1185–1187.
Hall, J. R., Bernat, E. M., & Patrick, C. J. (2007). Externalizing psychopathology and the error-related negativity. *Psychological Science*, *18*(4), 326–333.
Han, Y., Shaikh, M. B., & Siegel, A. (1996). Medial amygdaloid suppression of predatory attack behavior in the cat: II. Role of a GABAergic pathway from the medial to the lateral hypothalamus. *Brain Research*, *716*(1–2), 72–83.
Harmer, C. J., Rogers, R. D., Tunbridge, E., Cowen, P. J., & Goodwin, G. M. (2003). Tryptophan depletion decreases the recognition of fear in female volunteers. *Psychopharmacology*, *167*(4), 411–417.

Hassanain, M., Zalcman, S., Bhatt, S., & Siegel, A. (2003). Interleukin-1 beta in the hypothalamus potentiates feline defensive rage: role of serotonin-2 receptors. *Neuroscience*, *120*, 227–233.

Heritage, A. J., & Benning, S. D. (2012). Impulsivity and response modulation deficits in psychopathy: Evidence from the ERN and N1. *Journal of Abnormal Psychology*, *122*(1), 215–222.

Herkenham, M., Lynn, A. B., Little, M. D., Johnson, M. R., Melvin, L. S., de Costa, B. R., et al. (1990). Cannabinoid receptor localization in brain. *Neurobiology*, *87*(5), 1932–1936.

Jakab, R. L., & Goldman-Rakic, P. S. (1998). 5-Hydroxytryptamine2A serotonin receptors in the primate cerebral cortex: Possible site of action of hallucinogenic and antipsychotic drugs in pyramidal cell apical dendrites. *Proceedings of the National Academy of Sciences of the United States of America*, *95*(2), 735–740.

Jørgensen, L. M., Weikop, P., Villadsen, J., Visnapuu, T., Ettrup, A., Hansen, H. D., et al. (2016). Cerebral 5-HT release correlates with [11C]Cimbi36 PET measures of 5-HT2A receptor occupancy in the pig brain. *Journal of Cerebral Blood Flow & Metabolism*, *37*(2), 425–434.

Karl, T., Lin, S., Schwarzer, C., Sainsbury, A., Couzens, M., Wittmann, W., et al. (2004). Y1 receptors regulate aggressive behavior by modulating serotonin pathways. *Proceedings of the National Academy of Sciences of the United States of America*, *101*(34), 12742–12747.

Kask, A., & Harro, J. (2000). Inhibition of amphetamine- and apomorphine-induced behavioural effects by neuropeptide Y Y1 receptor antagonist BIBO 3304. *Neuropharmacology*, *39*(7), 1292–1302.

Kogo, N., & Trengove, C. (2015). Is predictive coding theory articulated enough to be testable? *Frontiers in Computational Neuroscience*, *9*, 111.

Kolla, N. J., & Mishra, A. (2018). The endocannabinoid system, aggression, and the violence of synthetic cannabinoid use, borderline personality disorder, antisocial personality disorder, and other psychiatric disorders. *Frontiers in Behavioral Neuroscience*, *12*, 41.

Lee, R. (2014). The psychopharmacology of criminality and oxytocin modulation of social behavior in aggressive individuals. In M. DeLisi & M. G. Vaughn (Eds.), *The Routledge International Handbook of Biosocial Criminology* (pp. 236–250). London and New York: Routledge/Taylor & Francis Group.

Lee, R., Arfanakis, K., Evia, A. M., Fanning, J., Keedy, S., & Coccaro, E. F. (2016). White matter integrity reductions in intermittent explosive disorder. *Neuropsychopharmacology*, *41*(11).

Lee, R., Ferris, C., Van der Kar, L. D., & Coccaro, E. F. (2009). Cerebrospinal fluid oxytocin, life history of aggression, and personality disorder. *Psychoneuroendocrinology*, *34*(10), 1567–1573.

Lee, R. J., Coccaro, E. F., Cremers, H., McCarron, R., Lu, S. F., Brownstein, M. J., et al. (2013). A novel V1a receptor antagonist blocks vasopressin-induced changes in the CNS response to emotional stimuli: An fMRI study. *Frontiers in Systems Neuroscience*, *7*, 100.

Lee, R. J., Gill, A., Chen, B., McCloskey, M., & Coccaro, E. F. (2012). Modulation of central serotonin affects emotional information processing in impulsive aggressive personality disorder. *Journal of Clinical Psychopharmacology*, *32*(3), 329–335.

Leyton, M., Okazawa, H., Diksic, M., Paris, J., Rosa, P., Mzengeza, S., et al. (2001). Brain Regional alpha-[11C]methyl-L-tryptophan trapping in impulsive subjects with borderline personality disorder. *The American Journal of Psychiatry*, *158*(5), 775–782.

Linnoila, M., Virkkunen, M., Scheinin, M., Nuutila, A., Rimon, R., & Goodwin, F. K. (1983). Low cerebrospinal fluid 5-hydroxyindoleacetic acid concentration differentiates impulsive from nonimpulsive violent behavior. *Life Sciences*, *33*(26), 2609–2614.

Loup, F., Tribollet, E., Dubois-Dauphin, M., & Dreifuss, J. J. (1991). Localization of high-affinity binding sites for oxytocin and vasopressin in the human brain. An autoradiographic study. *Brain Research*, *555*(2), 220–232.

Lozano-Soldevilla, D. (2018). On the physiological modulation and potential mechanisms underlying parieto-occipital alpha oscillations. *Frontiers in Computational Neuroscience*, *12*(20), 1.

Mann, E. O., & Mody, I. (2010). Control of hippocampal gamma oscillation frequency by tonic inhibition and excitation of interneurons. *Nature Neuroscience*, *13*(2), 205–212.

Marsh, D. M., Dougherty, D. M., Moeller, F. G., Swann, A. C., & Spiga, R. (2002). Laboratory-measured aggressive behavior of women: Acute tryptophan depletion and augmentation. *Neuropsychopharmacology*, *26*(5), 660–671.

McCloskey, M. S., Phan, K. L., Angstadt, M., Fettich, K. C., Keedy, S., & Coccaro, E. F. (2016). Amygdala hyperactivation to angry faces in intermittent explosive disorder. *Journal of Psychiatric Research*, *79*, 34–41.

Meyer, J. H., Kapur, S., Eisfeld, B., Brown, G. M., Houle, S., DaSilva, J., et al. (2001). The effect of paroxetine on 5-HT2A receptors in depression: An [18F]setoperone PET imaging study. *American Journal of Psychiatry*, *158*(1), 78–85.

Meyer-Lindenberg, A., Kolachana, B., Gold, B., Olsh, A., Nicodemus, K. K., Mattay, V., et al. (2009). Genetic variants in AVPR1A linked to autism predict amygdala activation and personality traits in healthy humans. *Molecular Psychiatry*, *14*, 968–975.

Mobini, S., Chiang, T. J., Ho, M. Y., Bradshaw, C. M., & Szabadi, E. (2000). Effects of central 5-hydroxytryptamine depletion on sensitivity to delayed and probabilistic reinforcement. *Psychopharmacology*, *152*(4), 390–397.

Moskowitz, D. S., Pinard, G., Zuroff, D. C., Annable, L., & Young, S. N. (2003). Tryptophan, serotonin and human social behavior. *Advances in Experimental Medicine and Biology*, *527*, 215–224.

Mottahedin, A., Ardalan, M., Chumak, T., Riebe, I., Ek, J., & Mallard, C. (2017). Effect of neuroinflammation on synaptic organization and function in the developing brain: Implications for neurodevelopmental and neurodegenerative disorders. *Frontiers in Cellular Neuroscience*, *11*, 190.

Ne'eman, R., Perach-Barzilay, N., Fischer-Shofty, M., Atias, A., & Shamay-Tsoory, S. G. (2016). Intranasal administration of oxytocin increases human aggressive behavior. *Hormones and Behavior*, *80*, 125–131.

New, A. S., Buchsbaum, M. S., Hazlett, E. A., Goodman, M., Koenigsber, H. W., Lo, J., et al. (2004). Fluoxetine increases relative metabolic rate in prefrontal cortex in impulsive aggression. *Psychopharmacology*, *176*(3–4), 451–458.

New, A. S., Hazlett, E. A., Buchsbaum, M. S., Goodman, M., Reynolds, D., Mitropoulou, V., et al. (2002). Blunted prefrontal cortical 18Fluorodeoxyglucose positron emission tomography response to meta-chlorophenylpiperazine in impulsive aggression. *Archives of General Psychiatry*, *59*(7), 621–629.

Newman, E. L., Smith, K. S., Takahashi, A., Chu, A., Hwa, L. S., Chen, Y., et al. (2015). α2-containing GABA(A) receptors: A requirement for midazolam-escalated aggression and social approach in mice. *Psychopharmacology*.

Ng, N. -K., Lee, H. -S., & Wong, P. T. -H. (1999). Regulation of striatal dopamine release through 5-HT1 and 5-HT2 receptors. *Journal of Neuroscience Research*, *55*(5), 600–607.

Parsey, R. V., Oquendo, M. A., Simpson, N. R., Ogden, R. T., Van Heertum, R., Arango, V., et al. (2002). Effects of sex, age, and aggressive traits in man on brain serotonin 5-HT1A receptor binding potential measured by PET using [C-11]WAY-100635. *Brain Research*, *954*(2), 173–182.

Passamonti, L., Crockett, M. J., Apergis-Schoute, A. M., Clark, L., Rowe, J. B., Calder, A. J., et al. (2012). Effects of acute tryptophan depletion on prefrontal-amygdala connectivity while viewing facial signals of aggression. *Biological Psychiatry*, *71*(1), 36–43.

Pelletier, M., & Siegel, R. M. (2009). Wishing away inflammation? New links between serotonin and TNF signaling. *Molecular Interventions*, *9*(6), 299–301.

Peremans, K., Audenaert, K., Hoysbergs, Y., Otte, A., Goethals, I., Gielen, I., et al. (2005). The effect of citalopram hydrobromide on 5-HT2A receptors in the impulsive-

aggressive dog, as measured with 123I-5-I-R91150 SPECT. *European Journal of Nuclear Medicine and Molecular Imaging*, *32*, 708–716.
Perez-Rodriguez, M. M., Hazlett, E. A., Rich, E. L., Ripoll, L. H., Weiner, D. M., Spence, N., et al. (2012). Striatal activity in borderline personality disorder with comorbid intermittent explosive disorder: Sex differences. *Journal of Psychiatric Research*, *46*(6), 797–804.
Piñeyro, G., & Blier, P. (1999). Autoregulation of serotonin neurons: Role in antidepressant drug action. *Pharmacological Reviews*, *51*(3), 533–591.
Placidi, G. P., Oquendo, M. A., Malone, K. M., Huang, Y. Y., Ellis, S. P., & Mann, J. J. (2001). Aggressivity, suicide attempts, and depression: Relationship to cerebrospinal fluid monoamine metabolite levels. *Biological Psychiatry*, *50*(10), 783–791.
Prochazka, H., & Ågren, H. (2003). Self-rated aggression and cerebral monoaminergic turnover: Sex differences in patients with persistent depressive disorder. *European Archives of Psychiatry and Clinical Neuroscience*, *253*(4), 185–192.
Reichmann, F., & Holzer, P. (2016). Neuropeptide Y: A stressful review. *Neuropeptides*, *55*, 99–109.
Richell, R. A., Deakin, J. F. W., & Anderson, I. M. (2005). Effect of acute tryptophan depletion on the response to controllable and uncontrollable noise stress. *Biological Psychiatry*, *57*(3), 295–300.
Ring, R. (2005). The central vasopressinergic system: Examining the opportunities for psychiatric drug development. *Current Pharmaceutical Design*, *11*(2), 205–225.
Robinson, S., & Thiele, T. (2017). Chapter seven—The role of neuropeptide Y (NPY) in alcohol and drug abuse disorders. *International Review of Neurobiology*, *136*, 177–197.
Rogers, C. N., Ross, A. P., Sahu, S. P., Siegel, E. R., Dooyeman, J. M., Cree, M. A., et al. (2018). Oxytocin- and arginine vasopressin-containing fibers in the cortex of humans, chimpanzees, and rhesus macaques. *American Journal of Primatology*, *80*, e22875.
Romney, C., Hahn-Holbrook, J., Norman, G. J., Moore, A., & Holt-Lunstad, J. (2018). Where is the love? A double-blind, randomized study of the effects of intranasal oxytocin on stress regulation and aggression. *International Journal of Psychophysiology*. epub ahead of print.
Rosas-Ballina, M., & Tracey, K. J. (2009). The neurology of the immune system: Neural reflexes regulate immunity. *Neuron*, *64*(1), 28–32.
Rosell, D. R., Tjompson, J. L., Slifstein, M., Xu, X., Frankle, W. G., New, A. S., et al. (2010). Increased serotonin 2A receptor availability in the orbitofrontal cortex of physically aggressive personality disordered patients. *Biological Psychiatry*, *67*(12), 1154–1162.
Rubia, K., Lee, F., Cleare, A. J., Tunstall, N., Fu, C. H., Brammer, M., et al. (2005). Tryptophan depletion reduces right inferior prefrontal activation during response inhibition in fast, event-related fMRI. *Psychopharmacology*, *179*(4), 791–803.
Rutkoski, N. J., Lerant, A. A., Nolte, C. M., Westberry, J., & Levenson, C. W. (2002). Regulation of neuropeptide Y in the rat amygdala following unilateral olfactory bulbectomy. *Brain Research*, *951*(1), 69–76.
Samuels, B. A., Anacker, C., Levinstein, M. R., Pickenhagen, A., Tsetsenis, T., Madronal, N., et al. (2015). 5-HT1A receptors on mature dentate gyrus granule cells are critical for the antidepressant response. *Nature Neuroscience*, *18*(11), 1606–1616.
Schlüter, T., Winz, O., Henkel, K., Prinz, S., Rademacher, L., Schmaljohann, J., et al. (2013). The impact of dopamine on aggression: An [18F]-FDOPA PET Study in healthy males. *The Journal of Neuroscience*, *33*(43), 16889–16896.
Schweighofer, N., Bertin, M., Shishida, K., Okamoto, Y., Tanaka, S. C., Yamawaki, S., et al. (2008). Low-serotonin levels increase delayed reward discounting in humans. *Journal of Neuroscience*, *28*(17), 4528–4532.
Seo, D., Patrick, C. J., & Kennealy, P. J. (2008). Role of serotonin and dopamine system interactions in the neurobiology of impulsive aggression and its comorbidity with other clinical disorders. *Aggression and Violent Behavior*, *13*(5), 383–395.

Shaikh, M. B., & Siegel, A. (1994). Neuroanatomical and neurochemical mechanisms underlying amygdaloid control of defensive rage behavior in the cat. *Brazilian Journal of Medical and Biological Research*, *27*(12), 2759–2779.

Siever, L. J., Buchsbaum, M., New, A. S., Spiegel-Cohen, J., Wei, T., Hazlett, E. A., et al. (1999). d,l-Fenfluramine response in impulsive personality disorder assessed with [18F] fluorodeoxyglucose positron emission tomography. *Neuropsychopharmacology*, *20*(5), 413–423.

Soloff, P. H., George, A., Nathan, R. S., Schulz, P. M., & Perel, J. M. (1986). Paradoxical effects of amitriptyline on borderline patients. *American Journal of Psychiatry*, *143*(12), 1603–1605.

Soloff, P. H., Meltzer, C. C., Greer, P. J., Constantine, D., & Kelly, T. M. (1999). A fenfluramine-activated FDG-PET study of borderline personality disorder. *Biological Psychiatry*, *47*(6), 540–547.

Sterzer, P., Adams, R. A., Fletcher, P., Frith, C., Lawrie, S. M., Muckli, L., et al. (2018). The predictive coding account of psychosis. *Biological Psychiatry*, *84*, 634–643.

Tanaka, S. C., Schweighofer, N., Asahi, S., Shishida, K., Okamoto, Y., Yamawaki, S., et al. (2007). Serotonin differentially regulates short- and long-term prediction of rewards in the ventral and dorsal striatum. *PLoS One*, *2*(12).

Tononi, G., & Cirelli, C. (2014). Sleep and the price of plasticity: From synaptic and cellular homeostasis to memory consolidation and integration. *Neuron*, *81*(1), 12–34.

Vekovischeva, O. Y., Aitta-Aho, T., Kankaanpaa, S., Seppala, T., Honkanen, A., Sprengel, R., et al. (2004). Reduced aggression in AMPA-type glutamate receptor GluR-A subunit-deficient mice. *Genes, Brain and Behavior*, *3*(5), 253–654.

Vila-Ballo, A., Hdez-Lafuente, P., Rostan, C., Cunillera, T., & Rodriguez-Fornells, A. (2014). Neurophysiological correlates of error monitoring and inhibitory processing in juvenile violent offenders. *Biological Psychology*, *102*(1), 141–152.

Virkkunen, M., Nuutila, A., Goodwin, F. K., & Linnoila, M. (1987). Cerebrospinal fluid monoamine metabolite levels in male arsonists. *Archives of General Psychiatry*, *44*(3), 241–247.

Walter, L., & Stella, N. (2004). Cannabinoids and neuroinflammation. *British Journal of Pharmacology*, *141*(5), 775–785.

Wang, G. J., Volkow, N. D., Fowler, J. S., Hitzemann, R. J., Pappas, N. R., & Netusil, N. (1998). Evaluation of gender difference in regional brain metabolic responses to lorazepam. *Psychiatry Research*, *82*(1), 37–46.

Weber, E. T., & Andrade, R. (2010). Htr2a gene and 5-HT2A receptor expression in the cerebral cortex studied using genetically modified mice. *Frontiers in Neuroscience*, *4*(36), 1.

Wolpert, D. M., Doya, K., & Kawato, M. (2003). A unifying computational framework for motor control and social interaction. *Philosophical Transactions of the Royal Society, B: Biological Sciences*, *358*(1431), 593–602.

Yanowitch, R., & Coccaro, E. F. (2011). The neurochemistry of human aggression. *Advances in Genetics*, *75*, 151–169.

Yip, J., & Chahl, L. (2001). Localization of NK1 and NK3 receptors in guinea-pig brain. *Regulatory Peptides*, *98*, 55–62.

Young, E. J., & Williams, C. L. (2010). Valence dependent asymmetric release of norepinephrine in the basolateral amygdala. *Behavioral Neuroscience*, *124*(5), 633–644.

Zanarini, M. C., Frankenburg, F. R., & Parachini, E. A. (2004). A preliminary, randomized trial of fluoxetine, olanzapine, and the olanzapine-fluoxetine combination in women with borderline personality disorder. *Journal of Clinical Psychiatry*, *65*(7), 903–907.