Neurochemical Contributions to Interpersonal Emotion Dynamics

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A central theme of this book is that psychology's traditional focus on emotion as an intrapersonal process overlooks the rich, dynamic nature of emotion. Studying an isolated person sitting in a laboratory watching an emotion inducing film doesn't capture the full palette of human emotional experience. Humans are fundamentally social animals and our emotional states ebb and flow primarily based on interactions with others.

In many ways the fields studying the chemical components of neurotransmission – neuropharmacology, neurochemistry, and psychiatry -- have followed the same trajectory as the psychological study of emotions. Experimental studies on the psychological effects of pharmacological agents have largely examined individuals performing tasks in the laboratory by themselves. The standard paradigm involves participants reporting to the laboratory, being administered a drug, and then after the drug has entered the brain completing a battery of tasks on the computer. As described below, only recently has there begun to be an examination of how receiving a drug might impact an individual's interactions with others and also how these interactions might impact the other person's neurochemistry.

There is much less data on interpersonal neurochemistry than there is on interpersonal emotions. Accordingly, the theoretical framework for interpersonal emotion is much better delineated. In the study of interpersonal emotions, specific dynamic processes such as emotion contagion, coregulation, coupling, and time-lagged synchrony have been clearly defined (Butler, 2011). In spite of the important

role of neurochemical signaling in these processes, data from neurochemical studies can't be fit easily into this framework.

There are several methodological impediments preventing the ability to seamlessly integrate neurochemistry into this psychological framework. First, most changes in neurochemicals cannot be measured noninvasively in humans with current technology. This is because most neurotransmitters do not cross the blood-brain barrier so peripheral measures such as blood levels are not related to levels in the brain. However, for some systems, particularly the oxytocin system, in which the neurochemical can act as both a hormone as well as a neurotransmitter the neurochemical can be assayed in the blood. But, the relationship between these blood measurements and central levels of the neurochemical is often unclear. Positron Emission Tomography (PET) allows measurement of neurotransmitter release, but this is only possible for a few neurochemical systems (e.g. Dopamine, Endogenous Opioids). The second methodological impediment is that although most neurochemical signaling occurs on the order of milliseconds, methods for noninvasively measuring it, such as blood assays or PET, require much larger time scales. At best, minutes are required to obtain reliable measurement and more often even longer time scales. Thus, the psychological processes that can be studied with these methodologies need to occur over protracted periods of time, which changes the nature of the psychological experience that can be studied and the ability to following the temporal patterns of change. Finally, most of these methods require measurement in the laboratory, which precludes experience sampling or daily diary designs.

Because most current neurochemical data can't be fit within the current psychological models of interpersonal emotion dynamics, we unfortunately can't strictly adhere to these definitions. For example, in our discussion of susceptibility to partner affect we provide a few examples of neurochemical influences on this susceptibility that are consistent with the time-lagged nature of this measure as operationalized in relationships studies (e.g. Schoebi, 2008), but also supplement this work with studies on neurochemical effects on sensitivity to the environment in general that don't adhere precisely to the temporal characteristics used in studies of close relationships.

In terms of a roadmap to the chapter, we first clarify our theoretical perspective on emotion because that frames our discussion of how neurochemistry can impact interpersonal emotion dynamics. We then discuss the potential role of the serotonin and immune systems in contributing to susceptibility to partner affect. Finally, because oxytocin has become the cause celebre of neurochemicals impacting social processes, we will conclude our discussion with intriguing evidence that oxytocin levels are influenced by interpersonal interactions. These effects may be reciprocal. In other words, person A's oxytocin levels impact person B's oxytocin levels, which feedback to affect person A's oxytocin levels. This could be the potential building blocks of interpersonal neurochemical coregulation. We then conclude with suggestions for how these interpersonally driven shifts in oxytocin might impact interpersonal emotion dynamics.

Emotion, Psychological Constructivism, and Neurochemistry

Because emotion and its exchange between individuals is the focus of this chapter, we feel it is important to briefly address our perspective on emotion. Defining emotion has been a contentious issue for over a hundred years and we certainly don't intend to resolve this issue here. However, it is important for conceptualizing how neurochemicals might impact interpersonal emotion dynamics.

One way of characterizing the study of emotion is to crudely divide the field into two frameworks. One would be the basic emotions perspective (Ekman, 1992) where there are specific emotions such as fear or happiness that elicit associated subjective experiences, patterns of autonomic activity, and behavioral tendencies. For example, fear is associated with elevation of autonomic arousal, avoidant behaviors, and a psychological experience of being afraid. Consistent with this perspective would be that there are neurochemicals that are particularly associated with specific emotional states. For example, cortisol is often conceived of as the "stress hormone" and oxytocin as the "cuddle chemical." This basic emotions perspective is inherent in the names we give to the drugs that are routinely used in psychiatry to reduce pathological affective states such as depression or anxiety. Thus, selective serotonin reuptake inhibitors (e.g. Prozac) are called "anti-depressants" because they are purported to reduce the emotional state of depression. Similarly, anxiolytics (e.g. Valium) are so named because they reduce the emotional state of anxiety.

An alternative framework is constructivist in nature where the words we used to describe an emotional state (e.g. fear) are actually an emergent property arising from activity in different component systems (Barrett, 2013; Coan, 2010). To

build on William James (James, 1884) classic example of being afraid because we are running from a bear, according to a constructivist perspective this running reflects core affect that is negative in valence and high in arousal, which is categorized as fear due to the accessibility of fear as a category in this situation. According to this framework the relative activation of the autonomic nervous system, behavioral tendencies, and psychological experience we associate with fear are highly dependent on the situation. Thus, there are few paradigmatic examples of fear. Many situations that are labeled as fearful will only activate one or two of these components of emotion and not necessarily all in concert. In other words, a particular situation may only activate the psychological experience and elicit particular behavioral tendencies, but not have measurable effects on the autonomic nervous system. According to this perspective, neuorochemicals would be expected to affect the different components of emotion that lead to the state we call fear. Importantly, because these different components of emotion --- behavioral, autonomic, and psychological --- are reliant on different neural pathways we should expect that they are under different neurochemical influences. In other words, a particular neurotransmitter may have a greater signaling role in producing one component of emotion than another and would therefore have greater influence over that component than another. This suggests that rather than neurochemicals affecting specific emotions, they are more likely to affect specific component processes of emotion. This is the theoretical perspective that is adopted here and we will focus on the component processes of interpersonal emotion dynamics that are likely to be impacted by neurochemicals rather than focusing on specific emotions.

Since the activation of these different components of emotion are highly situationally dependent, we should also expect that neurotransmitter activation is then going to be highly situationally dependent. In other words, if a particular situation activates one neural circuit that is involved in one component of emotion more than another we should expect that the predominant neurotransmitter in the activated circuit will be more involved in the process than a neurotransmitter in a different circuit that is not activated. It follows then that the effects of drugs activating these neurotransmitter systems might also have different behavioral effects depending on the current state of activation of these circuits. Thus, drug effects might be contextually dependent; a drug could have greater or even qualitatively different effects in one situation than another.

Serotonin and Susceptibility to Partner Affect

Susceptibility to a partner's affect is a form affect exchange between romantic partners where an individual's affect at one time point is influenced by his or her partner's affect at a prior time point. For example, in a study of multiple structured interactions between couples over the first eight years of marriage, a participant's positive affect after the discussions was influenced by his or her partner's positive affect prior to the discussion (Schoebi, Way, Karney, & Bradbury, 2012). This susceptibility to a partner's positive affect is important because it appears to be associated with mental health. In a study of couples who reported their affect multiple times per day for a period of 10 days, the degree to which an

individual was susceptible to the partner's positive affect predicted lower levels of depressive symptomatology twelve months later (Randall & Schoebi, 2015).

There are multiple individual differences at the psychological level that can influence the degree of susceptibility to partner affect. One example of susceptibility to partner affect comes from an experience sampling study of couples transitioning from individual activities to being together. For husbands who were high in perspective taking proclivity (e.g. the cognitive or mentalizing form of empathy), their affect after reunion on a dimension from sad to upbeat was influenced by their partner's affect on this same sad to upbeat dimension (Schoebi, 2008). In another example, having a more collectivistic value orientation (e.g. valuing the regard of one's extended family) led to greater transmission of anger between members of the couple (Schoebi, Wang, Ababkov, & Perrez, 2010).

In terms of neurochemical modulators of susceptibility to partner affect, the most pertinent evidence has come from studies on the serotonin system using a genetic approach. One of the better studied genetic variants in psychiatry is a genetic polymorphism (5-HTTLPR) in the promoter region of the serotonin transporter gene (SCL6A4). The reason the serotonin transporter gene has been the focus of so much research is that serotonin reuptake inhibitors act on the serotonin transporter to exert their clinical effect (Owens, Knight, & Nemeroff, 2001). Due to the location of this polymorphism within the serotonin transporter gene, it would be expected to affect expression of the serotonin transporter. In peripheral cells, it does indeed appear that the 5-HTTLPR impacts the amount of serotonin transporter produced by the gene (Lesch et al., 1996). At this site there are two primary alleles,

one is called the short allele and the other is called the long allele. Every individual has two alleles in one of three different possible combinations (e.g. short/short; short/long; or long/long).

In the study of couples during the first eight years of their marriage described above, variation in the 5-HTTLPR was associated with the degree of susceptibility to partner affect (Schoebi et al., 2012). Two findings are of note. First, based on reports of positive affect after the interaction, spouses with the short allele were more responsive to their partner's positive affect over the course of the interaction than individuals with two copies of the long allele (i.e. long/long individuals). This suggests that the short allele facilitates detection of positive emotional signals or heightens the reaction to them. Second, individuals with the short allele were also more responsive to the partner's negative affect. When one spouse was anxious prior to the interaction, spouses with the short allele were more positively responsive. They showed greater reductions in negative affect, specifically aggressive or dominant affect.

The combination of these findings highlight two points that facilitate understanding of how neurochemistry is likely to impact interpersonal emotion dynamics. First is that the 5-HTTLPR doesn't appear to impact responses to just negative affective signals, but also to positive affective signals. In other words, rather than affecting reactivity to a particular valence of stimuli, it appears to affect general reactivity to both positive and negative stimuli. Those with the short allele appear to be more sensitive to affective stimuli in general. This is reflective of a larger process known as differential susceptibility that was first noted in the

developmental literature (Belsky, 1997) and has now been extended to the genetics literature (Belsky & Pluess, 2009). Many other examples have been documented. For example, a recent meta-analysis of developmental studies showed that individuals with the short allele were more impacted by both negative and positive environments than individuals with the two copies of the long allele (van Ijzendoorn, Belsky, & Bakermans-Kranenburg, 2012). This model also fits with the constructivist view of emotion described previously where neurochemicals are less likely to impact a specific affective state or even valence, but rather appear to impact responsivity to situational factors in the environment.

Second, this 5-HTTLPR based sensitivity to environmental variables involves more than just a simple reproduction of the affective state of the target in the receiver. This could be a result of serotoninergic influence in one or several different ways. On the one hand, it could suggest that the 5-HTTLPR is influencing more than just sensitivity to emotion transmission through a process such as emotion contagion. Such processes would presumably lead to reproduction of the same affective state in the perceiver rather than the different state seen here. The opposite valence response in the receiver would be more consistent with complementarity from interpersonal theory (Kiesler, 1983) or a social-functional view of emotion (Keltner & Haidt, 1999). There are several different ways that this opposite valence response in the receiver could be influenced by the 5-HTTLPR and the serotonin system more generally. One is that serotonin amplifies the signal being processed in a complementary way. In other words, serotonin doesn't affect the qualitative nature of the complementary response, it just amplifies its output.

Alternatively, serotonin could generate this complementary response, which would not have been active otherwise. Thus, serotonin directly contributes to this opposite valence response. Finally, serotonin could affect basic sensory sensitivity to a emotion transmission process at an initial state of processing that would be the same valence as the sender and then the valence of the perceiver's affective state reverses as a result of subsequent stages of iterative processing of situational factors such as the importance of the person who is sending the emotional signal (Cunningham, Dunfield, & Stillman, 2013), consistent with the constructivist view of emotion described above. In other words, serotonin and the 5-HTTLPR could still be influencing the degree of responsivity to the transmission of the sender's affective state but the nature of the perceiver's emotion changes with further processing. Future research will be needed to delineate between these mechanisms.

These effects of the 5-HTTLPR on susceptibility to partner affect do appear to carryover to important relationship outcomes such as marital satisfaction. In a longitudinal study of middle aged and older married couples, the 5-HTTLPR moderated the relationship between behavior during a conflict discussion and marital satisfaction 12 to 13 years later (Haase et al., 2013). Critically, the 5-HTTLPR behaved in a differentially susceptible manner. For individuals with two copies of the short allele, observer coded negative behaviors of the partner(e.g. anger, contempt, defensiveness) during the conflict discussion at baseline predicted marital satisfaction 13 years later. There was no relationship between these behaviors and marital satisfaction for those with one or two copies of the long allele, which indicates they were less impacted by their partner's behavior. Similarly for

positive behaviors during the conflict discussion, for those with two copies of the short allele greater positive behaviors were associated with greater marital satisfaction 13 years later. There was no relationship between these variables for those with at least one copy of the long allele. Thus, for those with the short allele the emotion conveyed in these discussions appears to have greater effects upon relationship satisfaction, suggesting that their relationship satisfaction is differentially susceptible to the effects of these emotional behaviors.

This genetic evidence provides an intriguing window into neurochemical processes that might be involved in influencing susceptibility to partner affect. However, because such genetic effects are fundamentally correlational in nature and small in effect size, they need to be validated with experimental pharmacology approaches. We are not aware of a study that has examined the effects of serotonin reuptake inhibitors on susceptibility to partner affect in a romantic relationship context or other dyadic context. However, the aforementioned effects of the 5-HTTLPR are consistent with other research and clinical observations on sensitivity to the environment. Most of the following studies are not time-lagged like in studies of susceptibility to partner affect, so may involve slightly different processes but nonetheless are informative. For example, clinicians have long noted that one side effect of selective serotonin reuptake inhibitors is that they lead to a blunting of affect. Obviously, one of the main reasons these drugs are prescribed and have achieved such a high rate of use is that they reduce negative affect. Hence the common name “anti-depressant.” But, the impact of these drugs appears to extend to positive affect as well. In a qualitative study of interviews of individuals

chronically using serotonin reuptake inhibitors, the authors noted, “Most participants reported that the intensity of positive emotions was ‘dampened down’ or ‘toned down’, such that participants did not experience the same emotional ‘lift’ or ‘high’.” (Price, Cole, & Goodwin, 2009, p. 213). With respect to social situations, the authors also noted “many participants described reduced enjoyment of, for example, social situations, …. [and] felt reduced love or affection towards others and, in particular, reduced attraction towards their partner or reduced feelings of love or pride towards their family.” This blunting of positivity in a social context along with the better documented blunting of negativity is consistent with the 5-HTTLPR data reported previously where it affected susceptibility to partner affect in a differentially susceptible manner.

There also is experimental evidence to support the serotoninergic blunting of positive affect. Subchronic (7 days) SSRI administration blunted the neural response to eating chocolate in regions involved in reward processing (McCabe, Mishor, Cowen, & Harmer, 2010) and acute SSRI administration blunted the heart rate response to looking at positive, arousing images (A. H. Kemp & Nathan, 2004). In a meta-analysis of neuroimaging studies of anti-depressants, these drugs were found to reduce activity in reward circuits (i.e. nucleus accumbens, medial prefrontal cortex) in healthy subjects (Ma, 2015). There is some evidence that antidepressants may have the opposite effect and enhance responses to positive emotions, though this may happen in patients more than healthy subjects (Harmer, 2008; Ma, 2015) potentially due to the psychological or neurochemical differences associated with clinical conditions. As an aside, we don’t mean to imply that serotonin will always

affect susceptibility to both positive and negative emotions. Situational or personal factors may influence whether or not the serotonin system acts in a differentially susceptible manner or a more valence consistent manner. Our goal here is just to emphasize that serotonin seems to be associated with a general sensitivity or attunement that can impact the degree of emotion exchange for both valences of emotion.

At this point, the specific psychological mechanisms for this differential susceptibility are not clear. Because most of the evidence is derived from epidemiological genetic studies, there has been less focus on experimental laboratory methodologies that would provide insight into mechanism. Much of the reason for this is that the effect sizes of genetic studies require sample sizes that are larger than most experimental psychologists can reasonably study. Therefore, our lab has taken a pharmacological approach to trying to identify mechanisms that might contribute to differential susceptibility due to the larger effect sizes of drugs. In particular, our lab has focused on using acetaminophen to model this process. In animal models, an acute dose of acetaminophen increases brain levels of serotonin within an hour to a level comparable to those seen after a serotonin reuptake inhibitor (Pini, Sandrini, & Vitale, 1996). Acetaminophen also has effects on other neurochemical systems, in particular the immune system, so it is not as clean a manipulation as the administration of a serotonin reuptake inhibitor. Though, as an aside, it should be noted that although the drugs are called “selective” serotonin reuptake inhibitors, they have clear effects on other neurochemical pathways as well (Owens et al., 2001). The advantage of acetaminophen is that it reduces the

logistical hurdles to conducting a study and thus provides the opportunity for larger samples, as well as replication samples, which is generally not done in experimental psychopharmacology studies because it can take multiple years to recruit a sample.

In two separate samples of healthy young adults, we found that an acute dose of acetaminophen (1000mg; the dose for a headache) acted in a differentially susceptible manner. Participants rated how much emotion they saw in a set of both positive (e.g. babies, erotic images) and negative (e.g. feces, mutilations) emotional images. Acetaminophen reduced the extremity of ratings for both positive and negative images, having a slightly greater effect on blunting responses to positive images (Durso, Luttrell, & Way, 2015). The drug did not impact judgments of the extremity of non-emotional stimuli. Thus, ratings of the amount of the color blue in the slides was not different between the placebo and drug groups. Generalizing broadly from this model of differential susceptibility, it suggests that differential susceptibility may be impacting the salience given to an emotional stimulus more than the amplification of its perceptual attributes.

We have also studied the effects of acetaminophen on empathy. In two separate double-blind, placebo-controlled studies, an acute dose of acetaminophen (1000mg) reduced the personal distress and empathic concern over reading about another suffering a physically painful or socially painful experience (Mischkowski, Crocker, & Way, 2016). Across the studies, the effect sizes for acetaminophen were greater for the personal distress and empathic concern (Hedge's g = .47 and .45, respectively) than for the perception of the target's suffering (g = .23). This may

indicate that acetaminophen is impacting the affective component of empathy more than cognitive empathy.

In the second study, acetaminophen also blunted personal distress and empathic concern for an individual undergoing an actual experience of rejection so the effects were not just limited to narrative descriptions. Furthermore, acetaminophen also blunted affective empathy for positive events such as reading about another's wedding proposal. Additionally, participants rated the positive and negative scenarios using the same ratings as were used to rate the emotional images in the previously discussed acetaminophen study. The effects of acetaminophen on the empathy responses were independent of these ratings of extremity, suggesting that acetaminophen may be reducing empathy by means other than just blunting of affect. However, the degree to which these would generalize to the interpersonal context and the emotional transmission that would be occurring in that context is a question that will need to be addressed in future research.

The neurochemical pathway(s) that is impacting this reduction in empathy by acetaminophen is unclear. One obvious candidate is the serotonin system. In a study of moral dilemmas where those high in trait empathy were less likely to endorse hypothetical actions that involved personal harm to others acute administration of a serotonin reuptake inhibitor seemed to amplify the aversiveness of harming others, presumably because the other is represented with greater saliency and this signal is amplified by serotonin (Crockett, Clark, Hauser, & Robbins, 2010). This is consistent with genetic data that found two copies of the 5-HTTLPR short allele are associated with greater psychological distress to watching

empathy inducing video's and also greater physiological reactivity on an index reflecting primarily sympathetic nervous system activation (Gyurak et al., 2013). These studies suggest that the serotonin system is indeed involved in empathy, but don't clearly delineate whether it is higher or lower levels of serotonin that increase empathy due to the unspecified relationship between genetic variation and neurochemical data.

Another approach to answering this question is to study the effects of the "hug drug" methylenedioxymethamphetamine (MDMA), which goes by the street name ecstasy. MDMA leads to elevation of serotonin levels one or two orders of magnitude greater than a selective serotonin reuptake inhibitor (Mechan et al., 2002). MDMA increased affective empathy, particularly for positive situations, but had no effect on cognitive empathy (Hysek et al., 2014; Schmid et al., 2014). In a different study, MDMA again raised affective empathy, but did not impact performance on the reading the mind in the eyes test, a measure of cognitive empathy. Furthermore, these effects were unrelated to changes in oxytocin levels (Kuypers et al., 2014), suggesting that MDMA's effects on empathy are independent of its effects on oxytocin. Thus, according to multiple methods, the serotonin system appears to be involved in affective empathy and thus may impact interpersonal affect dynamics by affecting the degree to which one partner feels the distress or joys of the other partner. More speculatively, serotonin may even be involved in perceived partner responsiveness, as MDMA increased the degree to which one felt understood and regarded by the research assistant after a structured social interaction (Wardle & de Wit, 2014).

Overall, it seems clear that the serotonin system is impacting responses to others that are relevant to susceptibility to partner affect. What is less clear is the mechanism by which it is doing so. On the one hand, the data from selective serotonin reuptake inhibitors and acetaminophen (in so far as it is increasing central serotonin levels) suggest serotonin is blunting the components of the affective response that leads to empathy. On the other hand, the evidence from the MDMA studies indicates that serotonin is amplifying affiliative signals from others. Perhaps, there is a dose dependence of the effect, with the extremely high levels of serotonin release following MDMA leading to an amplification of the emotional signal that is transmitted and the more moderate increase in serotonin associated with serotonin reuptake inhibitors and acetaminophen leading to a blunting of the emotional single that is transmitted.

With respect to acetaminophen, an alternative possibility is that its effects on empathy are mediated more by the immune system than the serotonin system. Acetaminophen is not traditionally viewed as an anti-inflammatory like ibuprofen or aspirin due to it's lack of effects on inflammation in the periphery (Graham, Davies, Day, Mohamudally, & Scott, 2013). However, it has been known since the 1970's that acetaminophen acts in the brain like aspirin and ibuprofen to inhibit the production of prostaglandins (Vane, 1971), which are inflammatory molecules.

Inflammation as a Potential Moderator of Interpersonal Emotion Dynamics

Inflammation reflects activation of the immune system and can be triggered not only by pathogens such as bacteria or viruses, but also by psychological stress.

For example, there is a robust increase in inflammation after a couples conflict discussion (Janice K. Kiecolt-Glaser et al., 2005). While there has been attention to how inflammation triggered by marital conflict is likely to be a critical factor in how marriage can impact health (J. K. Kiecolt-Glaser & Newton, 2001), there has been less attention to the role inflammation can play in contributing to affective dynamics in couples. Yet this is likely to contribute to the transmission of affect between partners because peripheral activation of the immune system can signal the brain either via the vagus nerve or via entry of inmune signaling molecules (e.g. pro-inflammatory cytokines such as IL-6 and TNF-alpha) into the brain itself (Dantzer, O'Connor, Freund, Johnson, & Kelley, 2008). Again, as with the data from the serotonin system we initially borrow from studies of intrapersonal emotion that are likely to be relevant to the interpersonal context as well.

Inflammation's Effect on Intrapersonal Emotion

In human samples, research has primarily focused on the effects of inflammation on intrapersonal mood, emotional processing, and reactivity. Multiple theorists have proposed a causal role for pro-inflammatory cytokines in depression (Dantzer et al., 2008; Raison, Capuron, & Miller, 2006). Pharmacological therapies that increase inflammatory cytokines trigger clinical depressive episodes in half of patients (Lucile Capuron & Miller, 2004). In correlational designs, baseline levels of interleukin-6 (IL-6) and C-Reactive Protein (CRP), markers of inflammation, have been associated with both anxiety and depression (e.g. L. Capuron et al., 2011). The correlation of higher levels of inflammation with depression has been validated in

meta-analysis (Howren, Lamkin, & Suls, 2009). These findings would suggest that cytokines can augment negative reactions to stimuli.

Experimentally manipulated inflammation also reliably affects mood and reactivity. One way to experimentally induce inflammation is to inject participants with endotoxin, which mimics a bacterial infection and leads to robust increases in pro-inflammatory cytokines. As would be expected based on the correlational data, endotoxin induced depressed mood (Eisenberger, Inagaki, Mashal, & Irwin, 2010; Moieni, Irwin, Jevtic, Breen, & Eisenberger, 2015). Additionally, endotoxin reduced reactivity in the ventral striatum, an area associated with reward processing, to monetary reward cues (Eisenberger, Berkman, et al., 2010). Low-dose endotoxin injections induce anxiety and depressed mood, as well as selectively impair memory for emotional stimuli (Grigoleit et al., 2011). In this study, participants injected with low-dose endotoxin showed reduced memory for emotional images presented 24-hours earlier, but there was no effect on memory for non-emotional images. These effects are not limited to endotoxin. Typhoid vaccination is another methodology to acutely increase inflammation. Typhoid vaccination lowered mood, which was associated with increased neural reactivity in brain areas implicated in depression (subgenual anterior cingulate) and decreased connectivity between this area and other emotionally relevant areas (e.g. nucleus accumbens and amygdala) (Harrison et al., 2009). Overall, the work in humans suggests inflammation can affect mood, emotional processing, and reactivity to one's environment.

Inflammation's Effect in Interpersonal Situations

Finally, recent work has begun to examine the effects of inflammation on emotion and mood within more interpersonal contexts. For instance, experimentally-induced inflammation increases feelings of social disconnection (Eisenberger, Inagaki, Mashal, & Irwin, 2010). For women, endotoxin also increases neural reactivity in the dorsal anterior cingulate cortex and anterior insula to experiences of social rejection (Eisenberger, Inagaki, Rameson, Mashal, & Irwin, 2009), suggesting the inflammation makes this a more aversive experience for them. Measured cytokines in bereaved women are also associated with increased neural reactivity during a grief elicitation task (O'Connor, Irwin, & Wellisch, 2009), suggesting inflammation increases how responsive one is to emotionally-evocative tasks. With respect to threat, those injected with endotoxin showed increased amygdala reactivity to social threat (Inagaki, Muscatell, Irwin, Cole, & Eisenberger, 2012). This effect was specific to images of social threat (fear faces), with no effect of inflammation on reactivity to non-social threat (gun images).

Experimentally induced inflammation via endotoxin reduces performance on a measure of cognitive empathy (Moieni et al., 2015), even when controlling for self-reported confusion. Though, there was no control task to determine effects of endotoxin on motivation and cognitive ability, which could be potential confounds. Nonetheless, these findings do suggest that reductions in the ability to mentalize about others could impact interpersonal emotion dynamics in close relationships.

Based on the above evidence, inflammation would seem to be heightening responses to negative stimuli and decreasing it to positive stimuli. This would suggest it is having a valence-consistent effect. However, this may be due to

insufficient attention to the social context. If one has high levels of inflammation due to an illness (e.g. the flu), it could potentially be adaptive to seek out support from close others. Thus, the emotional salience of such individuals might be heightened. Accordingly, endotoxin increased the self-reported desire to be around a highly supportive other and increased ventral striatum reactivity in response to viewing images of a supportive other (Inagaki et al., 2015). This suggests that inflammation could potentially moderate both negative as well as positive emotions in an interpersonal interaction.

Altogether then, there is considerable evidence to suggest inflammation plays a role in emotion in interpersonal contexts. One intriguing aspect of inflammation for interpersonal emotional dynamics is that it could contribute to reciprocal effects on each partner. As mentioned earlier, conflictual discussions between couples can lead to elevated inflammation. This elevated inflammation can then heighten reactivity to this social threat (Inagaki et al., 2012), which could then perpetuate the conflict and then further increase inflammation in both members of the couple. This might be one way that couples can get into a morphogenic pattern (Butler & Randall, 2013) of emotional reactivity. Although such reciprocal neurochemical influences have not been documented for the immune system, they have been for the oxytocin system, to which we turn next.

Interpersonal Oxytocin Dynamics

One of the reasons that oxytocin research is well suited for the study of reciprocal neurochemical influences between dyads is due to its unique anatomical

structure , which will be briefly reviewed here to orient the reader. The neurons producing oxytocin reside in the hypothalamus (paraventricular and supraoptic nuclei). As established over 50 years ago (Bargmann & Scharrer, 1951), these neurons have axonal projections that release oxytocin into the bloodstream via the pituitary. Within the last several years, it has become clear that these oxytocin neurons in the hypothalamus also project to many forebrain regions including the ventral striatum and amygdala as well as the cingulate, insular, and association cortices (Knobloch et al., 2012). All of these are areas that are important for emotion as well as social behavior. The degree to which there is coordinated release between these forebrain and pituitary projections is unclear even in animal models where both can be measured. Although there is evidence of coincident release into the brain and bloodstream in response to some stressors, there is also evidence of a lack of correspondence, suggesting that the coordination is dependent on the nature of the stimulus (Neumann, 2007). In other words, in response to some social stimuli there will be coincident release of oxytocin into the brain and the blood and in response to other stimuli there will be only release into the blood or into the brain. Therefore, it should be noted that when peripheral oxytocin is measured in the blood it may or may not correlate with oxytocin release within the brain.

The first step in identifying a role for oxytocin in interpersonal neurochemical regulation is demonstrating that social interactions influence oxytocin signaling. This evidence is based on inferences from peripheral measures of oxytocin. For example, the duration of gaze at an infant by a mother during a

structured laboratory interaction is related to her increase in extracted[1] plasma oxytocin levels (Kim, Fonagy, Koos, Dorsett, & Strathearn, 2014). During a structured interaction with their infant, the more affectionate touch the mother displayed or the more stimulatory touch (e.g. prodding to induce play) the father showed, the greater the increase in unextracted plasma and salivary oxytocin in the parent (Feldman, Gordon, Schneiderman, Weisman, & Zagoory-Sharon, 2010). These effects can also be seen at the neural level. A mother's increase in plasma oxytocin (extracted) when interacting with her infant is correlated with neural activation in the ventral striatum and hypothalamus when looking at images of her infant relative to other infants (Strathearn, Fonagy, Amico, & Montague, 2009). The ventral striatum is a critical region for reward and these results suggest that gazing at their infant is more rewarding for mothers whose oxytocin levels show the largest response to gazing at their infant. Furthermore, hearing comforting and reassuring words from one's mother by phone after a stressor increases urinary oxytocin relative to a comforting conversation via instant message (Seltzer, Prososki, Ziegler, & Pollak, 2012) or no interaction (Seltzer, Ziegler, & Pollak, 2010).

A second element of oxytocin's effects that facilitates coregulation is that oxytocin appears to increase behaviors facilitating social engagement. When receiving intranasal oxytocin, fathers show greater stimulation of their toddler's

[1] The optimal methodology for measuring the concentration of oxytocin in the blood is controversial. The prevailing view is that blood samples should be run through an extraction procedure before measurement in order to remove blood-borne factors that potentially give a false signal (Nave, Camerer, & McCullough, 2015). In contrast, there is a counter-argument that this extraction procedure eliminates factors that sequester oxytocin and therefore under-measures the available oxytocin (Carter, 2014). This debate is still ongoing and awaits future work in the area to reach a resolution. Here, we simply specify whether the measurements used an extraction procedure or not.

exploration during a play session in the laboratory than when they receive placebo (Naber, van Ijzendoorn, Deschamps, van Engeland, & Bakermans-Kranenburg, 2010). Similarly, when fathers receive intranasal oxytocin they show greater touching behavior (index combining affectionate and stimulatory touch) than when they receive placebo (Weisman, Zagoory-Sharon, & Feldman, 2012).

Especially intriguing is that these oxytocin induced behavioral changes can influence oxytocin levels in the interaction partner, suggesting that neurochemical signaling is an interdependent process. In the aforementioned study, when the father receives intranasal oxytocin the interaction with his infant triggers a larger increase in the infant's unextracted salivary oxytocin than when the father receives placebo. This mutual coordination of peripheral oxytocin (extracted) has even been seen between humans and their pet when intranasal oxytocin was given to the dog (Nagasawa et al., 2015; Romero, Nagasawa, Mogi, Hasegawa, & Kikusui, 2014). The intranasal oxytocin facilitated the dog's gaze with his owner, which lead to corresponding increases in urinary oxytocin in the owner as well as the dog. These intriguing findings demonstrate how two bonded individuals can mutually influence each other's neurochemistry in a potentially salubrious manner. It should be remembered that this evidence comes from studies of closely bonded individuals for whom affiliation is a likely goal. As alluded to previously, the effects of oxytocin may be very different in other contexts (e.g. J. A. Bartz, Zaki, Bolger, & Ochsner, 2011).

Although there is some concern about the methodological details of specific studies (Leng & Ludwig, in press; Nave, Camerer, & McCullough, 2015), we believe that taken together these findings suggest that human oxytocin levels shift and

move in response to the give and take of social interactions. If this is the case, what might the effects of such shifts in oxytocin be upon interpersonal emotion dynamics?

Potential Mechanisms by which the Oxytocin System can Impact Interpersonal Emotion Dynamics

There have been a plethora of theories as to the psychological roles of oxytocin. It has been suggested that elevated oxytocin can facilitate general approach behavior (Andrew H. Kemp & Guastella, 2011), context-dependent affiliation (Jennifer A. Bartz, 2016), and social salience (Shamay-Tsoory & Abu-Akel, 2016). We follow the latter most closely here, not because we believe the other theories are incorrect, but because it helps to best understand potential mechanisms that could influence susceptibility to partner affect. We discuss here oxytocin's facilitation of the recognition of emotional expressions, the facilitation of multiple components of empathy, and the increased value given to social information. Each of these mechanisms could potentially explain the transmission of affect from one person to another.

Oxytocin, Emotion Recognition and Empathy

A key component of interpersonal emotion dynamics is the decoding of emotional expressions, particularly facial expressions by one's interaction partner. As was recognized by Darwin (Darwin, 1965), such expressions provide insights into how another is feeling and reacting to one's presence and communication. Not surprisingly, the ability to better identify another's emotional expressions is

associated with relational well-being (Carton, Kessler, & Pape, 1999). In a meta-analysis of intranasal oxytocin administration studies (Shahrestani, Kemp, & Guastella, 2013), oxytocin was found to facilitate the recognition of emotional expressions of both positive and negative valence. Specifically, oxytocin facilitated the recognition of happy faces and angry faces, particularly when presented for shorter latencies, as well as fear faces at longer durations. This suggests that a social interaction that raises one's oxytocin may facilitate greater exchange of affect due to better detection of the expressions sent by another. Due to improved recognition of both positive and negative expressions this could be a mechanism to increase the exchange of both positive and negative emotion between couples (e.g. Schoebi, 2008). Thus, oxytocin would not necessarily be expected to have only valence specific effects.

One mechanism likely to account for these effects on improved processing of facial expressions is increased allocation of attention to the eye region of the face. For example, in an eye-tracking study, intranasal administration of oxytocin increased attention to the eye region of static facial images (Guastella, Mitchell, & Dadds, 2008). This effect is not limited to humans, but also occurs in monkeys (Dal Monte, Noble, Costa, & Averbeck, 2014). These effects have recently been replicated in an interpersonal interaction within a naturalistic setting (Auyeung et al., 2015).

Consistent with these effects on facial emotion processing, oxytocin also appears to improve cognitive empathy. Intranasal oxytocin administration led to improvements on the Reading the Mind in the Eyes task (Domes, Heinrichs, Michel, Berger, & Herpertz, 2007). In replication studies, this effect appeared to be driven

by those who were low in empathy (Feeser et al., 2015; Radke & de Bruijn, 2015). That oxytocin has the largest effect on those who are low in empathic abilities, suggests that these individuals may have low levels of baseline oxytocinergic activity that the treatment is supplementing. Similar results were seen for oxytocin in an empathic accuracy task where participants provided ratings of the emotions of an individual undergoing a particular emotional experience (Jennifer A. Bartz et al., 2010). In this case, it was those who were high on a self-report measure of autism symptoms that were most benefited by oxytocin. Intranasal oxytocin administration also increases affective empathy (Hurlemann et al., 2010). Thus, oxytocin appears to affect multiple components of empathy, indicating oxytocin is likely to robustly influence interpersonal emotion transmission.

Social Specificity of Oxytocin

Increasing evidence from both human and animal data suggest that oxytocin has the potential to specifically heighten the signal-to-noise ratio of social information. For example, in rodent mothers oxytocin acts on the oxytocin receptor to alter the firing pattern in the auditory cortex in a manner that heightens the ability to detect vocalizations from pups, but does not impact the ability to discriminate non-social auditory stimuli (Marlin, Mitre, D'amour, Chao, & Froemke, 2015). Similarly, oxytocin acts in the olfactory cortex to enhance responses to social odors, but not general odors (Choe et al., 2015).

Oxytocin appears to be necessary for the recognition and memory of others as mice with the oxytocin gene deleted fail to recognize other mice (Ferguson et al., 2000). Similar effects were seen with the deletion of *CD38* (Jin et al., 2007), a gene

necessary for the release of oxytocin. These findings suggest that there is dedicated circuitry for processing social memory that is not used for other memory processes (Maroun & Wagner, 2016).

Turning to human studies, the effect of oxytocin on amplifying social information may be even more selective and increase the salience not just of others, but of valued others. In an initial study of male subjects and a replication, participants rated their partners as more attractive when receiving intranasal oxytocin than when receiving placebo. In both studies, oxytocin increased activity in the ventral striatum to viewing their partner's face relative to an unfamiliar woman's face, suggesting that oxytocin enhanced the reward value of their partner (Scheele et al., 2013).

Taken together, these findings highlight multiple ways that oxytocin could impact interpersonal emotion dynamics. Oxytocin seems to impact the attention and the ability to decode emotional expressions of others, which could lead to greater transmission of affect that is communicated by these expressions. In addition, oxytocin appears to enhance the ability to understand and interpret these signals based on the improvements in mentalizing abilities. This is likely to enhance the situational appropriateness of the eventual emotional response. Finally, oxytocin appears to heighten the salience of social cues, which could amplify response to the affect that is transmitted. Although only responses to positive cues were discussed here, there is accumulating evidence that oxytocin also enhances responses in aggressive contexts (Alcorn, Green, Schmitz, & Lane, 2015; Ne'eman, Perach-Barzilay, Fischer-Shofty, Atias, & Shamay-Tsoory, 2016), suggesting that oxytocin is

not specific for a particular emotion, but that it affects the components of information processing that lead to an emotion.

The apparent socially selective effects of oxytocin have interesting implications for interpersonal emotion dynamics. If increases in oxytocin either due to a drug or a social interaction tune neural circuits to more effectively process social stimuli, then this might suggest that interpersonal emotions are processed differently than emotional reactions to other stimuli. Hence, there may be unique properties to interpersonal emotion transmission that are different from other forms of emotional reactivity. This is entirely consistent with the constructivist model we have been proposing here. It will be the task of future research to determine if this is the case and if these effects are of a quantitative nature or a qualitative nature.

Conclusion

Although neurochemistry and emotion have largely been examined from an intrapersonal perspective, adopting an interpersonal perspective is likely to advance both fields. As described above, oxytocin studies suggest that social information processing can be selectively amplified, meaning that social information may be processed differently than nonsocial information. This evidence from neurochemical studies would suggest that a comprehensive psychological theory of interpersonal emotion dynamics may be fundamentally different from that of intrapersonal emotion. Similarly, the interpersonal perspective is also likely to affect psychiatry. If interacting with others impacts one's own neurochemistry, then this

could fundamentally change responses to a drug and may explain the sometimes paradoxical and idiosyncratic reactions individuals have to drugs used by psychiatrists. For example, anti-depressants, which are prescribed to reduce the risk of suicide, can increase suicidal ideation in some people.

In addition to these methodological and theoretical contributions to each field, better understanding of interpersonal affect dynamics is likely to aid studies of social influences on health. Social relationships are one of the most powerful influences on our health (Holt-Lunstad, Smith, & Layton, 2010), yet the processes by which this is occurring are poorly specified and have not been empirically demonstrated. Interpersonal affect transmission is likely to be a key component of these health effects and neurochemicals are likely to be the key means by which these social influences are transduced into the physiological processes that cause disease.

We think the study of neurochemical contributions to interpersonal emotion dynamics has a rich future and we look forward to watching the field develop.

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