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Review article

The many faces of oxytocin: Implications for psychiatry

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ABSTRACT

Oxytocin is known as the 'love hormone' due its role in promoting mother–child and pair bonding. More recent research indicates that oxytocin may have broader pro-social effects on behavior and cognition, which points towards oxytocin's potential as an agent to help improve social cognition and functioning in psychiatric disorders such as schizophrenia and autism. However, new research on oxytocin has also uncovered a 'darker side', including oxytocin's possible role in social out-grouping and envy. Instead of a simple view of oxytocin as 'good' or 'bad', a more accurate depiction of oxytocin's role in social processing likely involves the presence of moderating factors. We review moderation effects in oxytocin and their implications for psychiatry. One implication is that, across diagnostic categories, oxytocin administration may have positive effects for patients with social cognitive deficits but negative effects for patients with social cognitive bias. We conclude that future intervention studies should use methods such as signal detection to measure both deficit and bias parameters of social cognition and to evaluate potential individual and contextual moderators both within and between psychiatric diagnoses in order to determine for whom oxytocin treatment may be beneficial and for whom it may actually be harmful.
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Contents

1. Introduction

Oxytocin (OT) is a small nonapeptide synthesized in the hypothalamus that acts both as a hormone in the peripheral bloodstream and as a neurotransmitter in the brain (Churchland and Winkielman, 2012). The relationship between central and peripheral OT levels is not well characterized (Ludwig and Leng, 2006; Neumann, 2007), and research on variation in OT levels across patient and healthy groups remains equivocal. Nonetheless, OT has developed a reputation as the 'love hormone' due to a robust literature supporting its role in pair bonding and motherhood. More recently, OT has been linked to broader pro-social effects, including the potential to improve social cognition, the ability to infer the thoughts and feelings of others. This evidence of broad pro-social effects has created interest in the possibility of using OT as a treatment to attenuate the social dysfunction prominent in some psychiatric disorders, including schizophrenia and autism.

However, evidence has also emerged that OT has a "darker side," such as prompting social out-grouping and envy. These seemingly contradictory findings suggest the presence of factors moderating OT's social effects in both healthy and psychiatric populations (Bartz et al., 2011). Thus, although OT holds potential as a treatment to improve social cognition, in the context of certain moderators it may actually exacerbate social dysfunction.

In this paper, we first summarize the research that supports the view of OT as a 'love hormone,' including promising early treatment trials in psychiatry. We then describe the emerging literature on what has been called the "dark side" of OT—studies showing

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that under some circumstances OT may promote socially dysfunctional behavior. To integrate the positive and negative OT findings, we draw on behavioral and biological research to suggest a novel theoretical model that posits OT administration may benefit patients who have social cognitive deficits but may be detrimental to patients who exhibit social cognitive biases.

2. OT: the love hormone

OT has been heralded as 'the love hormone' due to its association with attachment and affiliation in mammals. In humans, OT is released in mothers following childbirth, and has been shown to enhance bonding between mother and child and to facilitate milk ejection during nursing (Insel and Young, 2001). OT also has been associated with higher-level attachment behaviors, such as affectionate verbalizations to infants, behavioral mirroring in fathers and mothers (Feldman et al., 2011; Gordon et al., 2010), and positive communication in male–female pair bonding (Ditzen et al., 2009). Affiliative processes, such as trust (Kosfeld et al., 2005), generosity (Zak et al., 2007), cooperation (Ditzen et al., 2009), social hugging (Light et al., 2005) and emotional empathy (Hurlemann et al., 2010) have also been linked with OT.

In addition to OT's role in attachment and affiliation, recent research indicates that OT action may improve social cognition, defined as "the mental operations underlying social interaction, which include the human ability and capacity to perceive the intentions and dispositions of others" (Brothers, 1990). OT administration has been found to improve face emotion perception (Di Simplicio et al., 2009; Leknes et al., 2012) and mental state inference (Domes et al., 2007b). Behavioral evidence suggests that OT regulates perceptual engagement in social cues (Guastella et al., 2008), for example by increasing ability to interpret mental state from the eye region of the face during emotion perception tasks (Domes et al., 2007b). On a neural level, OT may increase the salience of social cues through interactions with the amygdalar and dopaminergic systems (Rosenfeld et al., 2011). In addition to OT's short-term effects on social perception, it has also been shown to improve longer-term social memory, specifically the ability to identify previously seen faces (Marsh et al., 2010; Savaskan et al., 2008; Guastella et al., 2008).

This evidence regarding OT's effects on social cognition has led to hopes that it may be used as a treatment to reduce social cognitive dysfunction in individuals with disorders like schizophrenia, autism, and borderline personality disorder (Feifel et al., 2010; Bartz et al., 2011).

In schizophrenia, social cognitive impairment, including diminished ability to interpret social cues, is one of the greatest contributors to social dysfunction (Couture et al., 2006; Fett et al., 2011). fMRI studies suggest that social cognitive dysfunction in schizophrenia may be due in part to dysregulation of amygdalar dopaminergic/OT processing, leading to aberrant salience signaling to the frontal cortex (Rosenfeld et al., 2011). Functionally, this may lead to biasing of attention and attribution of self-relevant meaning to non-significant social cues. Over time, this may result in social withdrawal due to increased negative sensitivity to social stimuli (Brunet-Gouet and Decety, 2006).

A small number of studies suggest that acute OT administration may improve social cognition in schizophrenia. In a randomized, placebo controlled, double-blind trial, male veterans with schizophrenia who received a single dose of intranasal OT ($n=11$) showed significant improvement in higher-level social cognitive tasks relative to those who received placebo ($n=12$; Davis et al., 2013). In a randomized, double-blind study ($n=30$), males with schizophrenia who received a single dose of intranasal OT exhibited significant improvement in emotion perception relative to those who received saline placebo.

Positive OT effects have also been found in longer outpatient trials. In a 3-week study of OT administration in schizophrenia using a randomized, double-blind crossover design, Feifel et al. (2010) found OT-related improvements in PANSS total and positive symptoms and in Clinical Global Impression Scale scores with no adverse side effects. Pedersen et al. (2011) conducted a randomized, double blind, placebo-controlled trial in which 20 schizophrenia patients were either given bi-daily intranasal OT (11) or placebo (9) for 2 weeks. At post-test, OT recipients showed significant decreases in positive and general schizophrenia symptoms and improvements on several social cognition measures. There is some evidence that OT's beneficial effects may increase with longer-term treatment (Arletti and Bertolini, 1987). These pilot trials must be viewed with caution due to their small sample sizes, but they suggest that OT has potential as an outpatient treatment for schizophrenia.

Oxytocin administration also has shown therapeutic potential for individuals with Autism Spectrum Disorders (ASD), with minimal side effects (Anagnostou et al., 2012, 2014; Andari et al., 2010; Preti et al., 2014). Positive findings include increased trust and cooperation, increased gaze to the eye region of the face while interpreting emotion in pictures of faces (Andari et al., 2010, Alvares et al., 2010), increased empathic accuracy (Bartz, 2010), and increased skin conductance in response to human sounds, which is correlated with increased social functioning (Lin et al., 2014). In addition, positive social effects have been found to last for 3 months after OT discontinuation (Anagnostou et al., 2014). As in schizophrenia, these ASD studies must be viewed with caution as they generally have small sample sizes and are heavily male dominated. Also, it is possible that future larger studies may reveal side effects associated with OT treatment (Bales et al., 2013).

Not all ASD studies have found positive social effects (e.g., Dadds et al., 2014). Overall, studies looking specifically at individuals with Asperger's or high functioning Autism have found more positive findings than those in lower functioning individuals with Autism (Domes et al., 2014, 2013; Gordon et al., 2013). Thus, OT's beneficial effects may be moderated by the severity of Autism.

In sum, a growing number of studies suggest that OT administration may have beneficial social effects in schizophrenia and autism. However, this literature remains very tentative due to methodological constraints.

3. The dark side of OT and moderator effects

In this section, we review the growing evidence that in some instances OT administration has negative social effects. One way of understanding the positive and negative effects of OT is to conceptualize OT as playing a social self-regulatory function in which it mediates both affiliative and defensive social processes. OT may have evolved from ancient nonapeptides that served self-regulatory functions in invertebrate organisms to maintain the boundary between the organism and its environment (Archer, 1974; Gainer and Wray, 1994). Boundary maintenance requires both defenses against harm as well as receptivity to positive cues such that entry is allowed for nourishment and sexual reproduction. As humans' cognitive and social complexity evolved, it is possible that OT's role in physical boundary maintenance evolved to include social boundary regulation functions that both protect against harm and facilitate positive exchange.

In mammals, this dual role may be partially mediated by the amygdala. For example, OT may be involved in cueing both affiliative social processing via dopamine controlled, protein kinase A dependent OT receptors in the central nucleus of the amgydala (Bale et al., 2001) and also in orienting attention toward negatively-valenced social cues by affecting dopaminergic action in the amygdala (Adolphs, 2010). Although the amygdala is often thought of specifically in relation to

threat detection and fear, it has been found to be more broadly associated with detection of social salience and triggering attention to social cues, particularly those with incentive value to the subject. The amygdala has extensive connections with dopaminergic nuclei in the ventral tegmental area and the nucleus accumbens, which are involved in encoding memories of emotional images and incentivization, as well as several cortical areas implicated in higher-order social cognition (Laviolette, 2007). These links provide a neural basis suitable for OT to play a key role in both positive and negative social processing. In the remainder of this section, we review specific factors that may moderate whether OT action promotes adaptive or dysfunctional social cognition and behavior.

Gender is a well-known moderator of OT effects. In healthy individuals, OT has most often been associated with female gender, such as its role in milk-letdown (Insel and Young, 2001). However, studies have also shown lack of gender moderation where it might have been expected. For example, Feldman et al., 2011 found that OT's association with higher-level attachment behaviors applied to fathers as well as mothers. Other research has found evidence of reverse gender effects. Kubzansky et al. (2012) found that males given exogenous OT reported less distress when exposed to stress, whereas females report more distress and anger. Other studies have produced gender-moderated effects that are difficult to interpret and may depend on situational factors. For example, Domes et al. (2010) found increased amygdala activity in women and a reduction of activity in men following OT administration (Domes et al., 2007a). Although the sample sizes of these studies are low (13 in the male study and 16 in the female study), they suggest a complex pattern of gender moderation effects from OT treatment.

In psychiatry, evidence is beginning to emerge regarding gender moderation of OT effects. Plasma levels of OT have been found to correlate negatively with positive symptoms and overall psychopathology in females with schizophrenia (Rubin et al., 2010). Also in schizophrenia, OT plasma levels correlated with the perception of faces as happy in women, but not in men (Rubin et al., 2011). Finally, Ozsoy et al. (2009) found that females with unipolar and bipolar depression had lower OT blood levels than healthy females, while males with these disorders had more normal levels of OT. Of note, interpretation of these studies is limited by their measurement of plasma OT levels rather than OT effects in the brain.

A second potential moderator of the social effects of OT is individual variation in genotype. Chen et al. (2011) found that variation in the gene coding for the OT receptor moderates the protective function of positive social interaction in regards to stressful events. Specifically, they singled out rs53576, a single nucleotide polymorphism (SNP) in the third intron of the OT receptor gene as the main correlate for this effect such that individuals homozygous for the A allele were found to be less likely to benefit from social interaction when coping with stress than individuals with at least one G allele. This means the authors have linked OT's actions to a nucleotide difference within individuals.

Different SNPs within the third intron of the OT receptor gene have also been linked to social behaviors including increased empathic concern in healthy subjects as well as those with schizophrenia (Montag et al., 2012), aggressive behavior in adolescents (Malik et al., 2012), and ability to imitate in children with autism spectrum disorder (Insel et al., 1999; Egawa et al., 2013). Because these alleles are found within an intron and are therefore not expressed, they are likely markers and not the direct cause of altered OT receptor effects. An MRI study with a large sample size found both that, within males only, the rs53576 A allele is associated with decreased activation of limbic structures, such as the amygdala and hippocampus, and that activation of these limbic structures correlated with pro-social processing as exhibited by fMRI in response to emotional face processing tasks and a separate pro-social personality questionnaire (Tost, et al., 2010). These findings should be viewed with caution because the allele being studied is a portion of an intron, which is considered to be inactive.

There is also evidence that environmental factors moderate the social effects of OT, in some cases leading to cross-over interactions in which OT has a positive effect in one group and a negative effect in another group. These factors include the subject's trauma history and relationship to the person with whom she/he is interacting. Regarding the latter, OT's affiliative effects may be limited to situations in which the subject already feels a sense of social inclusion (De Dreu et al., 2010; Alvares et al., 2010; Declerck et al., 2010). In the presence of out-group members and strangers, OT administration may strengthen subjects' desire to exclude others (De Dreu et al., 2010). In the absence of prior contact, OT administration significantly decreases cooperation between partners (Declerck et al., 2010). In fact, OT has been found to globally increase the expression of envy in the face of losses and gloating in the face of gains (Shamay-Tsoory et al., 2009). These in-group/out-group effects are in line with the hypothesis that OT functions as a social boundary regulator.

Also in line with this idea, OT's effects appear to be moderated by the presence of early life trauma. In one study, the administration of intranasal OT to individuals with Borderline Personality Disorder who had experienced early life trauma decreased cooperation and trust despite the fact that OT administration in healthy individuals increased these prosocial effects (Bartz et al., 2010). It has been proposed that early life trauma and neglect permanently modify the OT system, which, in turn, alters expression and regulation of social behavior throughout life (Benarroch, 2013; Veeneema, 2012). Again, this falls in line with the theory of OT as a social boundary regulator. In this case, early life trauma may trigger a heightened wariness for and response to negative social stimuli via OT modulation. This process may be mediated in part by epigenetic mechanisms (Veenema, 2012; Curley et al., 2011), as suggested by the finding that OT concentration in CSF was significantly higher in adults who reported having experienced no or mild childhood abuse on the Childhood Trauma Questionnaire (Bernstein et al., 2003) compared to those who reported moderate to severe exposure to abuse or neglect (Heim et al., 2009). Similarly, in studies of peripheral OT, lower blood plasma levels of OT in animals and humans with disruption of normal social attachment processes have been associated with lasting impairment in attachment and affiliative functioning (Bowlby, 1969; Heim and Nemeroff, 2001; Winslow et al., 2003). Again, the relationship between plasma and CSF OT levels is unclear (Ludwig and Leng, 2006; Neumann, 2007). Nonetheless, convergent findings across both levels suggest links between disrupted early social experience and OT function.

Polydipsia may be another moderator of OT's effects, specifically in patients with schizophrenia. Approximately 20% of schizophrenia patients have primary polydipsia (De Leon et al., 1994). There is evidence of a link between OT and polydipsia via the neurohormone vasopressin. Vasopressin and OT are strongly linked as they are both created in the hypothalamus and released from the posterior pituitary. Although OT administration has not been found to affect vasopressin levels, increased vasopressin has been found to exert negative feedback effects on OT (Cheng and North, 1992). Patients with schizophrenia have been reported to have high levels of plasma vasopressin in relation to serum sodium concentration, pointing towards Syndrome of Inappropriate Secretion of Antidiuretic Hormone (SIADH) (Raskind et al., 1975; Vieweg and Godleski, 1998; Delva et al., 1990). In fact, polydipsic patients have been found to have particularly prominent social and cognitive dysfunction (Bralet et al., 2007; Goldman, 2009), which is correlated with plasma levels of OT particularly in patients with

hyponatremia (Goldman et al., 2008). The findings from this study are tempered by the uncertain relationship between plasma and CSF OT levels. Another study found that OT administered to schizophrenia patients in a 10 IU dose worsened emotion recognition, while a 20 IU dose improved emotion recognition in polydipsic patients compared to non-polydipsic patients (Goldman et al., 2011). These studies highlight the need for both sub-group and dose-response analyses, as well as possible therapeutic-window studies in future OT treatment research.

A final potential moderator of OT effects is baseline social competence. Several studies have found that healthy individuals with lower baseline social and emotional competence obtain a greater positive social cognitive effect from the administration of OT than do individuals with high social competence (Luminet et al., 2011; Leknes et al., 2012). In contrast, the studies reviewed above in ASD suggest that higher functioning individuals respond more favorably to OT administration. Although these two bodies of research at first appear contradictory, it may be the case that individuals at the low end of average healthy social competence and individuals at the high end of Autistic social competence benefit more from OT administration. If an individual already has optimal social functioning or, on the other hand, is too socially dysfunctional, OT may not be as effective.

4. Bias versus deficit: an integrative approach to OT moderation effects

The moderation literature reviewed above signals the need for theory and methods that accommodate the varied nature of OT's social effects. One promising approach suggests that OT effects may depend on the type of baseline social dysfunction. Whereas some individuals exhibit deficient social processing, others exhibit biased processing. Deficit may result from insufficient signaling of social salience while bias may be due to excessive or aberrant salience signaling.

The relative contributions of deficit and bias to task performance can be quantified using signal detection methodology (Green and Swets, 1966). In this approach, responses are scored on the dual parameters of sensitivity and bias. Poor sensitivity refers to an unpredictable pattern of inaccurate responses, whereas elevated bias refers to systematic over- or under-endorsement of a certain response. For example, on a test of face emotion perception, a poor performance of, say, 40% accuracy may be due to random responding, which would indicate poor sensitivity. On the other hand, it may be due to the subject having a bias toward over-endorsing a specific emotion, such as happiness. A deficit profile suggests diminished capacity to process facial cues, whereas a bias profile suggests the influence of motivational states or the purposeful use of a biased response strategy (e.g., over-endorsing happiness in an effort to appear friendly to the test administrator).

Signal detection theory provides a framework for examining the relationship between the three findings on OT's social effects, namely: (1) it promotes pro-social bias, (2) it sometimes promotes anti-social bias, and (3) it may improve social processing accuracy.

Applying this approach to schizophrenia, one leading hypothesis is that OT administration increases the salience of social cues (Averbeck, 2010). In schizophrenia, this may boost deficient social cognitive processing, and thereby increase accuracy. This view fits with evidence that some individuals with schizophrenia have deficient capacity to process social information, but it does not account for evidence that other individuals have more prominent social cognitive biases, including hostile attributional bias (Combs et al., 2007), jumping-to-conclusions bias (Garety and Freeman, 1999) and self-referential bias (Green and Phillips, 2004). These social cognitive biases generally correlate with the severity of delusional status and are treated as distinct from social cognitive deficits in treatment programs (e.g., Moritz et al., 2013; Roberts et al., In press).

Using a signal detection framework, several studies suggest a broader view that incorporates OT's effects on both accuracy and bias in schizophrenia. Walss-Bass et al. (2013) divided schizophrenia subjects into delusional and non-delusional groups and administered the Waiting Room Task, a measure of eye gaze perception and Theory of Mind that records both accuracy and self-referential bias. They found that all schizophrenia subjects exhibited diminished accuracy, but in the delusional group this was attributable to self-referential bias whereas in the non-delusional group it was due to deficient sensitivity to social cues. Interestingly, in both delusional patients and healthy controls, bias was positively correlated with OT blood level, although OT blood level did not differ across groups. These findings are consistent with the hypothesis that OT increases salience of social cues, but they suggest that the primary effect of this increased sensitivity may be to increase subjects' tendency to perceive social cues as self-relevant rather than to boost accuracy. This self-referential bias may be beneficial to healthy adults and some patients—for example, by increasing empathic attunement and accuracy—but detrimental to delusional individuals who already have pathologically elevated self-referential bias.

To further explore whether OT administration is detrimental to individuals with delusional biases, we conducted a post-hoc subgroup analysis of the Pedersen OT trial summarized above (Pedersen et al., 2011). We found that although the group who received OT showed significant overall mean improvement in social cognitive performance from baseline to post-treatment, four of the five participants who had prominent delusions did not show mean improvements (Cort Pedersen, personal communication).

In a separate study, we examined whether increasing the self-relevance of social cues increased social cognitive bias in schizophrenia. We allocated schizophrenia patients to receive either a standard social cognitive training intervention or an intervention including self-referential stimuli, such as video of people looking at and speaking to the patient about the patient (e.g., "You always do this!"). Data were analyzed using signal detection methodology. Whereas patients receiving the standard intervention showed improved social cognitive accuracy and decreased bias, those receiving the self-referential intervention showed statistically significant increases in bias and decreases in accuracy (Roberts and Hillner, 2014). These findings suggest that if OT does increase the perceived self-relevance of social cues (via increased salience of cues) this may have negative social cognitive effects among delusional individuals.

Delusionality in schizophrenia has been linked to aberrant salience experiences related to dopamine dysregulation (Kapur, 2003). The deficit/bias approach to social cognition in schizophrenia coheres with this view, further bolstered by the evidence (Rosenfeld et al., 2011) that dopamine antagonist medications may have the beneficial effect of decreasing social cognitive biases among delusional individuals by blunting salience, but at the expense of exacerbating social cognitive deficit in non-delusional patients. In future research, it may be fruitful to study whether OT administration is useful in counteracting this negative effect of medication on social sensitivity.

Contrasting with the deficit/bias model above, Macdonald and Feifel (2012) have suggested that OT administration may be particularly beneficial for the subgroup of schizophrenia patients with prominent positive symptoms due to OT's modulatory effects on the mesolimbic dopamine pathway (Macdonald and Feifel, 2012). This view is supported by studies linking OT administration with decreased positive schizophrenia symptoms (Feifel et al., 2010; Pedersen et al., 2011). Moving forward, to clarify OT's effects

in schizophrenia, future studies will benefit from the use of larger samples that allow for symptom-based stratification, and from signal detection-type measurement that distinguishes social cognitive bias from deficit.

The deficit/bias approach has implications for psychiatric disorders other than schizophrenia. For example, a substantial literature suggests that OT may have pro-social biasing effects via anxiolytic properties (e.g., de Oliveira et al., 2012), and one study found OT administration to bias responding toward trust and cooperativeness among people who have anxiety-based attachment avoidance more than in people who do not (De Dreu et al., 2011). The neural mechanism for this OT effect on attachment avoidance may relate to OT action in portions of the amygdala and hippocampus (Andari et al., 2012; Kirsch et al., 2005; Gamer et al., 2010). OT receptors have been found within brain regions associated with emotion regulation, including the substantia nigra, the nucleus of the solitary tract, the central nucleus of the amygdala, the lateral septal nucleus, and parts of the basal ganglia (Macdonald and Feifel, 2012). Some evidence suggests that plasma levels of OT correlate inversely with volume in brain regions associated with negative emotion, such as fear and negative memory (portions of the amygdala and hippocampus) (Andari et al., 2012). MRI research indicates that OT administration typically reduces activation of portions of the amygdala and associated brainstem regions associated with fear, and increases activation of the portions associated with happiness (Kirsch et al., 2005; Gamer et al., 2010). Thus, for some individuals, OT may induce bias away from fear-based responding and the creation of memories associated with fear. It is plausible that for individuals with anxiety-based social dysfunction these effects may lower social stress and increase prosocial responding. There is some evidence that OT's anxiolytic effects may be moderated by gender (Zink and Meyer-Lindenberg, 2012; Domes et al., 2007a, 2010).

5. Further implications for psychiatry

Research on the use of OT as a treatment in psychiatry is young and growing. The studies conducted to date have been promising but methodologically limited and difficult to integrate with the growing literature on moderator effects in OT administration. We have suggested a deficit/bias model in an effort to advance conceptual integration of research methods. In this section we suggest future directions for research based on this model and the evidence reviewed above.

The literature on in-group/out-group moderation effects suggests that OT administration may enhance patients' interactions with familiar individuals, such as family, co-workers, or roommates, but may be counter-productive in helping patients to make new friends or otherwise interact with strangers. This has implications for existing work on the use of OT to augment the effects of behavioral social cognitive skills training in schizophrenia (Davis et al., 2013). Specifically, waiting to administer OT until after several skill-training sessions have been completed may foster prosocial instead of antisocial OT effects by leveraging patients' familiarity with care providers and peers in the treatment setting.

In regards to the research described above about gene polymorphisms linked with the OT receptor, it would be beneficial for future research to examine whether these gene polymorphisms that have been linked to both social behavior and differences in limbic activation fit with the deficit/bias model. Namely, this model would suggest that individuals with socially antagonistic biases would have genetics predisposing them to be less receptive to social aid in stressful situations whereas those with social cognitive deficits would have genetics predisposing them to be more receptive to social aid in stressful situations. If a treatment arm were added to this correlational study, the deficit/bias model would predict that OT administration would further diminish the already lower receptivity to social support among subjects with social cognitive biases, and further enhance the ability to benefit from support among subjects with prominent deficits.

Stratifying patients based on the prominence of social cognitive deficit vs. bias may clarify for whom OT administration is potentially beneficial or harmful. Measures of social cognitive bias in schizophrenia are in the early stages of development and have inconsistent psychometric properties (Green et al., 2009). There is currently work underway to improve measurement of this domain (Pinkham et al., 2014). In our initial work linking social cognitive bias and OT, bias was operationalized self-referential bias using facial video stimuli (Roberts and Hillner, 2014; Walss-Bass et al., 2013). The consistent effects in this work suggest that future research on OT-related bias may do well to use measures that include self-relevant stimuli.

The OT research on early life trauma and baseline social competence point toward the need for larger treatment trials that can accommodate multiple moderator variables. Regarding early life trauma, one study among women with Borderline Personality Disorder (BPD) found that OT had the beneficial effect of reducing the tendency to over-estimate negative and threatening aspects of facial expressions (Bertsch et al., 2013). However, BPD is also associated with an elevated rate of early life trauma, which has been associated with negative social outcomes from OT administration (Bartz et al., 2011). As in the schizophrenia literature, this suggests that within diagnostic categories, OT's effects may hinge upon patient-level factors. Future research should focus on determining in which subgroups of individuals with BPD OT administration may be beneficial or contraindicated.

Research on OT administration in other diagnoses is sparse, but is sufficiently equivocal to suggest that moderators may affect these groups as well. Regarding Major Depressive Disorder, research in rats suggests that OT may reduce depression symptoms (Arletti and Bertolini, 1987), however administration studies in humans have been less promising. A recent study found that OT had no effect on social aspects of low-severity depression (Ellenbogen et al., 2013). In more severe depression, OT seemed to aggravate depressive social tendencies, as indicated by increased time spent processing sad faces (Ellenbogen et al., 2013). One interpretation of these results is that in patients with severe depression, OT further increases the salience of depressive cues that are already the focus of surplus attention. That is, OT may exacerbate a socially detrimental bias in depressive patients. This interpretation is consistent with theories of the role of cognitive bias in depression (Mathews and MacLeod, 2005) and is analogous to the mechanism proposed above regarding individuals with delusions. Delusional schizophrenia and severe depression both may be characterized by social cognitive bias rather than deficiency, and this may be aggravated rather than ameliorated by OT administration.

Research on OT and anxiety also is equivocal. Symptom severity in individuals with generalized social anxiety disorder (GSAD) positively correlates with OT blood levels (Hoge et al., 2008). Although this again is a peripheral measurement rather than a central measurement of OT, this finding is compatible with the hypothesis that OT can promote social processing across valence types, and that this could be detrimental in individuals with baseline social cognitive bias (for whom more social processing may increase stress and dysfunction). On the other hand, some research indicates that exogenous OT administration leads to a more positive evaluation of self in individuals with social anxiety, although it does not improve overall treatment outcome in exposure therapy (Guastella et al., 2009). Another study found that individuals with GSAD showed greater activity in the bilateral amygdala to fearful faces than did healthy individuals, and OT

administration lowered this hyperactivity to normal levels (Labuschagne et al., 2010). This suggests that OT may decrease social threat reactivity in this disorder. Clearly, more research is needed. As in schizophrenia and depression, it appears that the identification of person- and/or context-level moderators may help to resolve the equivocal literature on OT and social anxiety.

Looking forward, OT treatment trials in psychiatry should use larger sample sizes with stratification designed to detect moderator effects across diagnoses, subgroups within diagnoses, and characteristics of individual patients. Larger sample sizes will also facilitate detection of potential side effects from OT administration. With the growing evidence of cross-over moderator effects in OT administration trials, it is incumbent on researchers to design trials that will efficiently identify those patients at highest risk for negative outcomes. Due to the promising potential of OT as a treatment for social cognitive dysfunction, which is a devastating aspect of many psychiatric disorders, it is imperative to determine for whom OT administration may be beneficial or detrimental.

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