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Intranasal oxytocin attenuates attentional bias for eating and fat shape stimuli in patients with anorexia nervosa

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Summary We examined the impact of oxytocin on attentional processes for eating, shape, and weight stimuli in patients with anorexia nervosa (AN). A double-blind, placebo-controlled within-subject crossover design was used. Intranasal oxytocin or placebo followed by a visual probe detection task with food, weight, and shape images was administered to 64 female subjects: 31 patients with AN and 33 control students. The AN group showed significant reductions in the attentional biases toward eating-related stimuli ($p = 0.030$, $d = 0.516$) and toward negative shape stimuli ($p = 0.015$, $d = 0.498$) under the influence of intranasal oxytocin. The effect of oxytocin was correlated with autistic spectrum traits in the AN group. Oxytocin had no effect on the amount of juice consumed in either group. The results of this study suggest that oxytocin attenuates the attentional vigilance to eating and fat shape stimuli in patients with AN. Further studies using oxytocin as a form of intervention for patients with AN are needed.
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Anorexia nervosa (AN) is characterized by avoidance of eating, which causes weight loss and is associated with concerns about weight and shape. The National Institute of Health suggested using a method of classification that characterizes disorders according to their underlying neurobiology to facilitate translational work and an understanding of the basic mechanisms underpinning psychiatric disorders (Cuthbert and Insel, 2013). The psychopathology of AN is not thought to be a lack of appetite, but rather a fear of appetite associated with possible anomalies in systems related to fear and defense of appetitive behaviors, particularly in relationship to food, shape and weight. Anomalies in these systems can impact attention.

Attention is part of the process of selectively processing information. The allocation of attention is influenced by top-down information (representations of goals and their relevance). These goals are merged with bottom-up priority signals. A balance and synthesis of these inputs determines the allocation of attention. Certain bottom-up signals such as threats have high salience. Additionally, motivational drives such as hunger can also change attentional processing (Mogg et al., 1994). Anxiety disorders are thought to be underpinned by maladaptive attentional biases toward threats. In a meta-analysis of 172 studies, patients with a wide variety of anxiety disorders had a small to moderate attentional bias to threat cues [effect size (ES) = 0.45] (Bar-Haim et al., 2007). ''Fear of fat'' is central to the diagnosis of AN as it relates to body shape or weight with a fear of ingesting fats. Patients with AN usually report anxiety in anticipation of a meal, concern about the content of the foods consumed, and fear of the effects of food on shape and weight (Sunday et al., 1995; Steinglass et al., 2011). Thus, both food and fatness are feared in AN. Cognitive models of eating disorders suggest that selective attention to shape-, weight- and food-related information may lead to the maintenance of eating disorder symptoms (Vitousek and Hollon, 1990).

Attentional biases to food, weight, and shape cues have been documented in systematic reviews of the eating disorder literature (Faunce, 2002; Dobson and Dozois, 2004; Johansson et al., 2005; Brooks et al., 2011; Aspen et al., 2013). Most studies measuring this construct have used the Stroop paradigm and found small to moderate interference effects in AN and bulimia nervosa with an effect sizes of 0.38 (n = 13) and 0.43 (n = 11), respectively (Brooks et al., 2011). However, the Stroop task is not a simple measure of attention. The dot probe task is more specific, but it has been less frequently used in this population. A meta-analysis of a small number of studies (n = 3, some with overlapping populations) measuring attention using the dot-probe task in women with eating disorders (predominantly bulimia nervosa) found vigilance to binge food (ES = 0.8) and a small vigilance bias toward shapes depicting fatness (ES = 0.24) (Aspen et al., 2013). The interpretation of studies using the dot probe task is difficult, as this task does not distinguish emotional valence. For example, increased attention may be due to threat processing, as has been found using angry faces, for example in people with anxiety disorders (Mogg and Bradley, 1998), or it may be due to reward processing, as has been found in the case of addictions (Friederich et al., 2006). The startle paradigm is sensitive to valence and has shown that the mechanism of an increased attentional bias may differ between AN and bulimia nervosa. For example, food stimuli accentuated the startle response in AN which contrasted with the attenuated startle in people with bulimia nervosa, suggesting that food is associated with fear in AN but reward in bulimia nervosa. In AN, changes in attention to both food and fatness may be caused by increased threat sensitivity. Many of the neural circuits that are relevant to AN, including problems with social processing, fear, anxiety, and stress, are moderated by oxytocin (Kirsch et al., 2005). One of the mechanisms by which oxytocin produces its effect is through its influence on attentional processing. For example, intranasal oxytocin given to rhesus monkeys specifically decreases the attention paid to threatening facial expressions (Parr et al., 2013). Thus, oxytocin might be expected to reduce attention vigilance to the specific food, weight and shape stimuli that are threatening to people with AN.

A recent review synthesized evidence for abnormal oxytocin functioning in patients with AN (Maguire et al., 2013). The cerebrospinal fluid levels levels of oxytocin decrease during the starvation phase of AN (Demitrack et al., 1990; Chiodera et al., 1991). The nocturnal serum oxytocin levels in patients with AN are also reduced (Lawson et al., 2011). Lawson et al. (2012) reported that oxytocin release increases in response to a meal in the acute state of AN and decreases after recovery. This observation suggests that there are both state and trait anomalies in oxytocin function in patients with AN. Anomalies in oxytocin secretion are correlated with the severity of the eating disorder psychopathology and with the level of activation in the brain circuitry in response to images of food (Lawson et al., 2012). Finally, in a proof-of-concept study, intranasal oxytocin given to patients with AN over 6 weeks during nutritional rehabilitation reduced their eating and weight concerns (Russell et al., 2012). A possible mechanism to explain this finding is the effect of oxytocin on attentional responses and the threat of eating disorder-related stimuli.

Over the past decade, oxytocin has been diversely tested as a form of treatment for many psychiatric disorders. Clinical trials of patients with autism, social anxiety, postnatal depression, obsessive-compulsive problems, schizophrenia, borderline personality disorder, and post-traumatic stress (n = 19) were included in a recent comprehensive review by Bakermans-Kranenburg and van Ijzendoom (Bakermans-Kranenburg and van Ijzendoorn, 2013). Overall, a moderate effect was seen (d = 0.32) and, in particular, a large ES was observed in studies on autism spectrum disorder (d = 0.57). This result is of interest for research into the effect of oxytocin on patients with eating disorders, as Gillberg (1992) suggested a strong association between eating disorders and autism, connected by low levels of empathy. Several lines of evidence summarized in recent reviews support this hypothesis. First, there is frequently co-morbidity within cases and families. Second, there are similar patterns of neuropsychological functioning (Zucker et al., 2007; Oldershaw et al., 2011; Treasure et al., 2012). Third, there are shared traits such as those measured by the Autism Spectrum Questionnaire (Hambrook et al., 2008; Baron-Cohen et al., 2013). It is possible that oxytocin may have a greater effect in the subgroup of patients with eating disorders with higher levels of autistic spectrum traits.

In addition to its effects on fear and reward circuits, oxytocin has an effect on appetite in animals. For example, oxytocin selectively suppresses sugar intake, perhaps by

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