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Oxytocin-Augmented Psychotherapy: Beware of Context

The hypothalamic peptide oxytocin modulates a wide range of social and cognitive functions in humans and nonhuman primates. As a result, much effort is currently being devoted to developing oxytocin into an adjunct treatment for mental illness, with a particular focus on anxiety, autism, and schizophrenia spectrum disorders.

In the field of imaging neuroscience, one of the most consistent findings with oxytocin is an inhibition of human amygdala responses to fearful facial expressions following exogenous administration of a single nasal dose—an effect recently replicated in macaques (Liu *et al*, 2015). An oxytocin-induced modulation of neural activity in the amygdala and other regions is in line with observations that intranasal administration yields increased cerebrospinal fluid concentrations of the peptide in humans (Striepens *et al*, 2013) as well as macaques (Freeman *et al*, 2016), although much controversy still exists regarding the exact route of brain penetration.

We recently reported that oxytocin may facilitate fear extinction by down-regulating the amygdala and concomitantly upregulating medial prefrontal cortex activity in healthy volunteers (Eckstein *et al*, 2015), implicating the peptide as a potential adjunct treatment during extinction-based psychotherapy to reduce fear renewal. Interestingly, in a follow-up imaging study, oxytocin produced the opposite effect by promoting fear-conditioned responses (Eckstein *et al*, 2016). Thus, depending on the timing of administration, i.e., prior to versus after conditioning, the peptide can enhance the acquisition or extinction of fear, leading to contrary behavioral outcomes. Another intriguing example in this vein is a social economics experiment, in which volunteers could donate money for a charity project located in the Kongo delta. Subjects treated with placebo devoted more money to saving the rainforest rather than supporting the indigenous population living in that reserve. Under oxytocin treatment, participants showed the opposite behavioral pattern, suggesting that administration of the peptide can transiently alter altruistic attitudes and reward values, thereby shaping decisions towards social priorities (Marsh *et al*, 2015). These results are in accord with current concepts that the contextual framing of an experimental scenario interacts with oxytocin and determines its effects in a top-down regulatory manner (Quattrocki and Friston, 2014). The latter is substantiated by our observation that oxytocin increased the hedonic pleasure associated with social touch when heterosexual male volunteers were made believe that a female experimenter performed the touch as opposed to a male (Scheele *et al*, 2014).

Contextual framing not only matters to 'message makers' in journalism, advertising, or politics—it is also of crucial relevance to psychotherapy, especially when interventions are trialled with oxytocin. Converging evidence from a series of imaging experiments carried out in our laboratory suggests that nasal oxytocin evokes a shift in the neural activity away from the amygdala to the anterior insula, pregenual anterior cingulate cortex, and precuneus—areas that orchestrate the conscious monitoring of what happens in and around us. Current attempts to translate oxytocin neuroscience to psychotherapy thus face the crucial caveat that therapeutic context should be strictly controlled to avoid the risk of unfavorable outcomes.

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A Self-Generated Environmental Factor as a Potential Contributor to Atypical Early Social Communication in Autism

Autism spectrum disorder (ASD) is defined by deficits in reciprocal social communication and interactions, as well as deficits in cognitive and behavioral flexibility. In the United States, the mean age for diagnosis of ASD is 4; diagnosis can be made as early as age 2. There is an intense interest in identifying much earlier signs of ASD because of the proven effectiveness of early intervention. Many infant behaviors, such as atypical cries (Esposito and Venuti, 2010), are being explored as such signs. However, the manner in which such early signs of ASD are causally involved in the developmental trajectory of cardinal symptoms of ASD remains unclear.

This picture is about to change, thanks to the development of mouse models of highly reliable genetic risk factors. Many cases of duplications or hemizygous deletions of kilo- to megabase chromosomal segments, termed copy number variants (CNVs), are robustly and reproducibly associated with high rates of ASD. For example, it has been known since 2001 that ASD is seen at high rates among carriers of 22q11.2 hemizygosity (Hiroi *et al,* 2013). Since 2007, other human CNVs have been similarly found to be associated with high rates of ASD.

Our group has altered copy numbers of small chromosomal segments within the 22q11.2 CNV and identified *Tbx1* as one of the 22q11.2 genes critical for various signs of ASD (Hiramoto *et al*, 2011; Hiroi *et al,* 2013). Moreover, we have developed and tested an experimental procedure to reliably assess the effects of typical and atypical vocal call sequences on maternal behavior. Our data showed that *Tbx1* heterozygosity caused atypical pup vocal call sequences, which then evoked less than optimal maternal care (Takahashi *et al*, 2016).

Less than optimal maternal care can be considered a 'self-generated environmental factor' of ASD, as it is induced, through atypical vocal sequences, by a genetic ASD risk carrier. Such an environmental factor clearly differs from those that unilaterally impact—and are passively perceived by—risk carriers, such as accidental environmental insults (eg, fetal and infant exposures to pesticides, viruses, and chemicals). The negative phenotypic loop between a risk carrier and its mother is likely to affect the developmental trajectory of ASD symptoms. Certainly, such a hypothesis is consistent with empirical evidence that parent-mediated interventions are effective in alleviating the ultimate degree of some ASD symptoms in humans (Green *et al*, 2010; Wetherby *et al,* 2014).

The Refrigerator Mother theory of autism claimed that autism was caused by a lack of maternal warmth. Our view does not attribute the causative event of ASD to mothers.

We submit that less than optimal maternal care is caused by atypical vocal signals of carriers of genetic risk factors and has a modulatory–not causative–impact on the developmental trajectory of severity of ASD symptoms. Our mouse-based hypothesis provides a novel potential mechanistic basis to improve our understanding of the developmental trajectory of ASD and innovative theoretical grounds to develop effective therapeutic interventions.

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