LETTER TO THE EDITOR

Reply: Does imitation act as an oxytocin nebulizer in autism spectrum disorder?

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Sir,

We thank Dr Delaveau and colleagues for their thoughtful comments demonstrating similarities between intranasally administered oxytocin and imitation by others at the behavioural and neural levels among individuals with autism spectrum disorder (ASD). In our recent study, individuals with ASD demonstrated lower accuracy in inferring others’ social emotions, and lower brain activity in the right anterior insula during the inferring, compared with matched-individuals with typical development. Intranasally administered oxytocin increased accuracy in inferring others’ social emotions, and enhanced originally-diminished brain activity in the right anterior insula among individuals with ASD (Aoki et al., 2014). Delaveau and colleagues recruited six adult males with ASD and demonstrated that after exposure to being imitated, the individuals with ASD display increased activity in the right anterior insula during the condition ‘being imitated’ compared to ‘observation’. Delaveau et al. suggest that brain activation in the anterior insula during the act of being imitated by others may reflect increased salience of the social signal.

A number of behavioural studies show an association between oxytocin administration and social affiliation (Young and Wang, 2004; Bakermans-Kranenburg and van, 2013), as well as studies suggesting that being imitated by others fosters social affiliation (Thelen et al., 1975; van Baaren et al., 2004; Bailenson and Yee, 2005; Sclafani et al., 2015). These two associations suggest a possible link between being imitated by others and administration of oxytocin at the behavioural level. Delaveau et al. suggest that being imitated by others may have similar effects to an administration of oxytocin at the neural level. Indeed, the authors demonstrate that being imitated by others enhances brain activity in the right anterior insula, similar to the response of the brain to the administration of oxytocin (Aoki et al., 2014). Although Delaveau et al. do not elaborate further on the relationship between being imitated by others and the administration of oxytocin; it is intuitively acceptable that being imitated by others may have similar effects to oxytocin administration. Does being imitated by others increase oxytocin secretion?

We would like to provide one possible example that may support the salience network hypothesis posited by Delaveau and colleagues and support our speculation that being imitated by others may increase oxytocin secretion. Previous studies have shown that perception of pain, which can be associated with strong salience, induces secretion of cortisol, and increases in cortisol induce oxytocin secretion (Tops et al., 2012). Such serial reactions may be a physiological response that underlies the well-known effect of oxytocin in decreasing pain (Rash et al., 2014). Moreover, experiencing pain enhances anterior insula activity (Lamm et al., 2011), which is also associated with sharing others’ emotions such as empathy (Singer et al., 2004). As it is reported that externally administered oxytocin does not enhance brain activity in the anterior insula during
observation of pain in others compared with experiencing pain (Singer et al., 2008), the enhancement of anterior insula activity is not simply promoted by an increased level of oxytocin associated with feeling the pain of others. However, this may provide an example in which externally administered oxytocin and internally secreted oxytocin in response to behaviour/perception (i.e. imitation by others/pain) share common target brain regions, particularly the anterior insula.

With regard to localization, the anterior insula is a critical brain region involved in ASD and responses to oxytocin. Indeed, a recent meta-analysis, which included placebo-controlled studies, showed that oxytocin administration enhances left anterior insula activity (Wigton et al., 2015). Furthermore, we have shown previously that the risk allele of the oxytocin receptor gene for ASD in the Asian population is associated with grey matter volume in the right anterior insula (Saito et al., 2014). Moreover, in a recent functional MRI study, we detected oxytocin-induced brain activation in the right anterior insula during a social communication task in individuals with ASD (P < 0.01), although the significance level was marginal after adjusting for multiple comparisons (Watanabe et al., 2014). Finally, both our group and Delaveau and colleagues have identified brain activation in the right anterior insula after pharmacological and behavioural interventions among individuals with ASD. Thus, these results suggest that oxytocin may act predominantly on the left anterior insula in typically developed individuals, but predominantly on the right anterior insula in individuals with ASD.

Although the precise mechanisms of how and where oxytocin acts in the brain remain undetermined, Von Economo neurons may partially explain such inconsistency in laterality across diagnoses. Abnormal development of Von Economo neurons is a potential pathophysiology of ASD (Allman et al., 2005). Von Economo neurons are located in the anterior insula and express the vasopressin 1a receptor (Allman et al., 2005; Uddin and Menon, 2009). As the balance between oxytocin and vasopressin may have an influence on social behaviour (Meyer-Lindenberg et al., 2011; Neumann and Landgraf, 2012), von Economo neurons are potential targets for oxytocin in influencing this behaviour. Furthermore, von Economo neurons are concentrated more in the right hemisphere compared with the left (Allman et al., 2005; Uddin and Menon, 2009). Interestingly, von Economo neurons are also located in the anterior cingulate cortex, where we identified an effect of oxytocin among individuals with ASD (Aoki et al., 2015; Watanabe et al., 2014). The relationship between von Economo neurons and oxytocin is also partially supported by results from Guionnet and colleagues who have reported enhanced activation of the left anterior insula in typically developed individuals (Guionnet et al., 2012).

Again, we would like to emphasize the importance of the result that being imitated by others has similar effects to oxytocin administration at the neural level, and the fascinating hypothesis that being imitated by others may act similarly to oxytocin administration through enhanced secretion of endogenous oxytocin. To address this hypothesis, future studies are needed to measure the change in endogenous oxytocin levels before and after being imitated in a large sample of individuals with ASD, setting appropriate control conditions. This will be required to assess the potential effect of the intervention on anterior insula activity and oxytocin levels.

References


