The Journal of Neuroscience
Journal Club

Response to Matthias Gamer

Does the Amygdala Mediate Oxytocin Effects on Socially Reinforced Learning?

René Hurlemann[1] and Keith M. Kendrick[2]

[1] Department of Psychiatry, University of Bonn, 53105 Bonn, Germany; renehurlemann@me.com
[2] Laboratory of Molecular Signalling, The Babraham Institute, CB22 3AT Babraham, Cambridge, United Kingdom; keith.kendrick@bbsrc.ac.uk

In his review of our paper (Hurlemann et al., 2010a) Matthias Gamer raises several important issues, particularly regarding our proposal that oxytocin might facilitate socially reinforced learning via the amygdala. He suggests that instead, or additionally, effects are mediated via oxytocin modulation of rewarding properties of social stimuli through increased dopamine release acting upon D_2 receptors in the ventral striatum.

The main point Gamer raises regarding our contention that the amygdala is critical to the social facilitation of learning concerns whether the two Urbach-Wiethe (UW) patients, with complete bilateral amygdala calcification damage, were simply impaired on their ability to discriminate between smiling and angry facial expressions, and therefore did not benefit optimally from the social feedback condition. In support of this possibility, he cites the fact that the patients show impaired face-emotion discrimination in our neuropsychological tests, and that their response times are consistently longer than controls after the first cycle of trials. As we state in our paper, however, neither of the UW patients reported any subjective problems in distinguishing smiling from angry faces during the task. Also, in the supplementary information, we report performance of the UW patients on the Florida Affect Battery (FAB) showing that

although they have trouble deciding whether pairs of facial expressions are the same or different, they perform normally when required to identify facial expressions *per se*, to identify named expressions, or to match faces showing similar expressions. Thus our neuropsychological test data supports the patients' subjective claim that they had no problems identifying whether faces were smiling or angry. We therefore believe that in the absence of a functional amygdala, only a weak association between specific stimuli and their reinforcement outcome is formed, and that therefore more extensive processing by other, less effective, brain regions is required for implementing a decision.

We have further investigated the amygdala dependence of this socially reinforced learning effect in normal healthy human subjects given a single dose of the β-noradrenergic antagonist propranolol. Propranolol treatment reduced amygdala activation in response to both neutral and emotional faces (Hurlemann et al., 2010b) and prevented facilitation of learning with social feedback without affecting learning performance with non-social feedback (Mihov et al., 2010). Subjects also did not report problems in recognising smiling and angry faces. We did not find increased response times during the social feedback condition in the propranolol treatment group. This might simply reflect the fact that the UW patients were more impaired by extensive amygdala damage and/or that they had adapted over many years to recruit other slower and less effective compensatory brain mechanisms for learning in the context of social reinforcement. Subjects given short-term propranolol treatment would have been unlikely to adapt in the same way.

In animal models, olfactory social recognition memory enhancing effects of oxytocin require amygdalar stimulation of noradrenaline release acting on either α- or β-noradrenergic receptors (Sanchez-Andrade and Kendrick, 2009). Our finding that

propranolol prevents oxytocin-sensitive social facilitation of learning therefore supports the hypothesis that the peptide acts via the noradrenergic system within the amygdala, or elsewhere. However, this requires further experiments to show that noradrenergic receptor antagonists can prevent the facilitatory actions of oxytocin. As Gamer rightly points out, several functional imaging studies have reported reduced amygdala activation in response to emotional faces following oxytocin treatment (Domes et al., 2007; Kirsch et al., 2005), whereas our results would predict an increased activation in response to the positive effects of social feedback faces. Our propranolol studies show that reduced activation of the amygdala in response to faces is associated with an impaired social feedback facilitation. In line with our prediction, a recent study confirms that positive affect stimuli enhance amygdala activity while negative affect ones inhibit it (Gamer et al., 2010). Although we used angry as well as smiling faces in our study, subjects were exposed to significantly more smiling ones as they successfully learned. Therefore, a our working hypothesis remains that oxytocin reduces amygdala activity in response to aversive or threatening social stimuli and promotes forgetting of them, whereas with positive social stimuli, it does the opposite.

We believe that these findings taken together make a strong case for the amygdala playing a key role in social facilitation of learning. Of course this does not necessarily imply that oxytocin produces its observed effects via the amygdala. Oxytocin could indeed be enhancing the rewarding effects of positive smiling faces downstream of the amygdala by acting on its receptors in the ventral striatum to enhance dopamine release and D_2 receptor activation. In animals, oxytocin modulates dopamine release (da Costa et al., 1996) and the peptide's facilitation of social bonding in monogamous voles is D_2 receptor dependent (Liu and Wang, 2003). In humans, attractive faces with direct gaze increase ventral striatal activity (Kampe et al., 2001) and recent studies have

shown that oxytocin enhances recognition of smiling, but not angry faces (Marsh et al., 2010) and memory for positive social experiences (Guastella et al., 2008). Again, however, a direct test of this hypothesis depends upon carrying out experiments where oxytocin treatment is given in conjunction with D_2 receptor antagonists.

References

Da Costa AP, Guevara-Guzman RG, Ohkura S, Goode JA, Kendrick KM (1996) The role of oxytocin release in the paraventricular nucleus in the control of maternal behaviour in the sheep. J Neuroendocrinol 8:163–177.

Domes G, Heinrichs M, Glascher J, Buchel C, Braus DF (2007) Oxytocin attenuates amygdala responses to emotional faces regardless of valence. Biol Psychiatry 62:1187–1190.

Gamer M, Zurowski B, Büchel C (2010) Different amygdala subregions mediate valence related and attentional effects of oxytocin in humans. Proc Natl Acad Sci U S A 107:9400–9405.

Guastella AJ, Mitchell PB, Mathews F (2008) Oxytocin enhances the encoding of positive social memories in humans. Biol Psychiatry 64:256–258.

Hurlemann R, Patin A, Oezguer P, Onur OA, Cohen MX, Baumgartner T, Metzler S, Dziobek I, Gallinat J, Wagner M, Maier W, Kendrick KM (2010a) Oxytocin enhances amygdala-dependent, socially reinforced learning and emotional empathy in humans. J Neurosci 30:4999–5007.

Hurlemann R, Walter H, Rehme AK, Kukolja J, Santoro SC, Schmidt C, Schnell K, Musshoff F, Keysers C, Maier W, Kendrick KM, Onur OA (2010b) Human amygdala reactivity is diminished by the beta-noradrenergic antagonist propranolol. Psychol Med 27:1–10.

Kampe KKW, Frith, CD, Dolan, RJ, Frith U (2001) Reward value of attractiveness and gaze. Nature 413:589

Kirsch P, Esslinger C, Chen Q, Mier D, Lis S, Siddhanti S, Gruppe H, Mattay VS, Gallhofer B, Meyer-Lindenberg A (2005) Oxytocin modulates neural circuitry for social cognition and fear in humans. J Neurosci 25:11489–11493.

Liu Y, Wang ZX (2003) Nucleus accumbens oxytocin and dopamine interact to regulate pair bond formation in female prairie voles. Neuroscience 121:537–544.

Marsh AA, Yu HH, Pine DS, Blair RJR (2010) Oxytocin improves specific recognition of positive facial expressions. Psychopharmacology (Berl) 209:225–232.

Mihov Y, Mayer S, Musshoff F, Maier W, Kendrick KM, Hurlemann R (2010) Socially reinforced learning in humans is beta-noradrenergic-dependent. Neuropsychologia, in press (doi:10.1016/j.neuropsychologia.2010.04.035)

Sanchez-Andrade G, Kendrick KM (2009) The main olfactory system and social learning in mammals. Behav Brain Res 200: 323–335.