Journal Club

Editor's Note: These short, critical reviews of recent papers in the *Journal*, written exclusively by graduate students or postdoctoral fellows, are intended to summarize the important findings of the paper and provide additional insight and commentary. For more information on the format and purpose of the Journal Club, please see http://www.jneurosci.org/misc/ifa_features.shtml.

Does the Amygdala Mediate Oxytocin Effects on Socially Reinforced Learning?

Matthias Gamer

Department of Systems Neuroscience, University Medical Center Hamburg-Eppendorf, D-20246 Hamburg, Germany
Review of Hurlemann et al.

The neuropeptide oxytocin is crucially involved in modulating affiliative behavior in nonhuman mammals. It has an essential role in coordinating birth and maternal care, it modulates alloparental behavior and pair bonding, and it facilitates social recognition. Many of these functions seem to rely on an oxytocin-dependent enhancement of social information processing either by increasing the saliency of social signals or by altering the valence of social cues (Ross and Young, 2009).

An involvement of this neuropeptide in initiating parturition as well as milk ejection during lactation is also well known in humans. Psychosocial effects of oxytocin in humans, however, are less well established and an important topic of ongoing research. Recent studies have shown that intranasal application of oxytocin facilitates emotion recognition from facial cues, it enhances trust in human interactions, and it dampens behavioral and endocrine stress responses (for review, see Heinrichs et al., 2009). However, an important aspect of social behavior that has been largely neglected until now is social learning. Early studies in experimental psychology have revealed that social rein-

forcement is effective in enhancing learning (e.g., Buss et al., 1958). However, the neural underpinnings of these effects are largely unclear and it is currently unknown whether oxytocin influences such learning processes in humans.

A recent report by Hurlemann et al. (2010) that appeared in *The Journal of Neuroscience* addressed these issues and provided first evidence for an enhancing effect of oxytocin on socially reinforced learning in humans which seems to depend on amygdala function.

The authors used a between-subject, double-blind design with participants either receiving an intranasal dose of oxytocin or a placebo spray. After substance administration, participants performed a reinforcement associative learning task which required classifying the category membership (A or B) of sequentially presented three-digit items. Importantly, the reinforcing feedback that was presented after each response was either shown using social or nonsocial cues. In the former condition, human faces changed from neutral to happy or angry expressions depending on whether the preceding response was correct. In the nonsocial condition, comparable feedback was provided by a black circle changing to green for correct and to red for incorrect responses. Learning was examined by calculating the percentage of correct responses as a function of repeated item presentations (cycles).

In line with previous research, the authors found enhanced learning when so-

cial feedback was provided (Buss et al., 1958). Interestingly, oxytocin further and selectively boosted the advantage of social reinforcers. To gain insights into the neural underpinnings of this effect, the task performance of a second unmedicated group of controls was compared to two patients with Urbach–Wiethe (UW) disease who suffered from selective bilateral amygdala calcification. These patients showed only minor performance deficits in the nonsocial condition but were considerably impaired when social reinforcers were used. These data thus suggest that socially reinforced learning depends on amygdala function and can be enhanced by oxytocin. It remains an open question, however, whether the modulatory effect of oxytocin on these learning processes in healthy individuals is also mediated by the amygdala.

Previous neuroimaging studies on the influence of oxytocin on neural activation indicated that oxytocin primarily reduces amygdala activity (e.g., Domes et al., 2007). Such unspecific suppressive effects do not provide a viable explanation for the selective enhancement of learning rates in social conditions. However, a recent study now indicates that oxytocin does not only reduce amygdala activity to unpleasant social stimuli but additionally increases amygdala activation for pleasant stimuli (Gamer et al., 2010). In line with data from animal research, these results indicate that oxytocin is capable of shifting the processing focus toward positive social information. It seems possible that a similar

Received June 4, 2010; accepted June 9, 2010.

I thank Christian Büchel for helpful comments on this manuscript.

Correspondence should be addressed to Matthias Gamer, Department of Systems Neuroscience, University Medical Center Hamburg-Eppendorf, Martinistrasse 52, Building W34, D-20246 Hamburg, Germany. E-mail: m.gamer@uke.uni-hamburg.de.

DOI:10.1523/JNEUROSCI.2847-10.2010

Copyright © 2010 the authors 0270-6474/10/309347-02\$15.00/0

mechanism is responsible for the enhancement of saliency and the rewarding aspect of positive social feedback. The amygdala might thus be a key structure mediating not only the positive influence of social feedback in general but also the specific modulatory influence of oxytocin on socially reinforced learning.

An important limitation of the study by Hurlemann et al. (2010), however, is related to the neuropsychological profiles of the UW patients. Similar to previous studies, these patients were severely impaired in discriminating between emotional facial expressions. The failure of effectively using social feedback could thus be a result of difficulties in differentiating positive and negative facial expressions during the relatively short feedback period (1 s). Such an explanation could also account for differences in the response time profile between healthy controls and UW patients. In the first cycle, all participants had to guess because category membership of all items was unknown. Correspondingly, healthy controls and UW patients showed similar response times. In subsequent cycles, however, items were repeatedly presented and previously provided feedback could be used to improve classification accuracy. At that time, UW patients showed a substantial enhancement of response times that remained stable until the end of the experiment [see Hurlemann et al. (2010), their Fig. 2Civ]. This response profile might indicate that UW patients recognized previously presented items but at the same time realized that they could not make use of previously presented feedback. It remains an open question whether this was due to an inability of recognizing negative and positive feedback per se or a failure of ascribing motivational value to different social reinforcers.

Hurlemann et al. (2010) argued that UW patients did not spontaneously report difficulties in distinguishing positive and negative social feedback. Furthermore, the same patients showed normal performance in inferring the mental state of others in the so-called “Multifaceted Empathy Test” (MET) (Dziobek et al., 2008). It has to be mentioned, however, that pictures in the MET are presented

much longer and also provide nonfacial information about the mental state of the depicted person. It thus seems possible that preserved amygdala function is primarily important for quickly interpreting facial expressions. The use of such information in guiding socially reinforced learning, however, might depend on other brain circuits and UW patients might in fact show comparable performance as healthy controls when sufficient time is given to elaborate facial expressions in more detail.

Taken together, the precise role of the amygdala in socially reinforced learning remains to be elucidated. Does this also apply to oxytocin effects on such learning processes? As discussed above, there is some evidence that oxytocin increases amygdala activity to positive social cues which might reflect prioritized processing of social signals. Such processing advantages might lead to a better use of such information in social learning situations. However, further studies are necessary to investigate whether other brain structures also contribute to these effects. Most importantly, animal research indicates that a number of oxytocin effects on social cognition and affiliative behavior are not exclusively mediated by the amygdala but result from modulatory effects of the neuropeptide on the ventral striatum (Keverne and Curley, 2004). For example, the density of oxytocin receptors in the nucleus accumbens of female voles is positively correlated with the probability of alloparental care. Injections of selective oxytocin receptor antagonists in the nucleus accumbens inhibit this alloparental behavior and also block partner-preference formation in female prairie voles (for review, see Ross and Young, 2009).

These modulatory effects of oxytocin on the ventral striatum are especially interesting since this brain region is also well known to be involved in reinforcement learning (O'Doherty et al., 2004). Activity in the ventral striatum is modulated by phasic activity of dopamine neurons which is essential for reward-based learning. It thus seems possible that dopamine and oxytocin interact in the ventral striatum to enhance learning in social situations. Interestingly, such interaction has already been described for the regulation of pair

bond formation in voles (Liu and Wang, 2003). It is currently unknown, however, whether similar interactions are involved in human social learning.

To sum up, Hurlemann et al. (2010) provided important evidence for the role of oxytocin in modulating social learning. It remains an interesting challenge for future research to elucidate the precise functional role of the amygdala and the ventral striatum in this process. Especially neuroimaging studies using pharmacological manipulations seem to be well suited for examining brain regions mediating the effects of oxytocin on human social behavior.

References

- Buss AH, Gerjuoy IR, Zusman J (1958) Verbal conditioning and extinction with verbal and nonverbal reinforcers. *J Exp Psychol* 56:139–145.
- Domes G, Heinrichs M, Gläscher J, Büchel C, Braus DF, Herpertz SC (2007) Oxytocin attenuates amygdala responses to emotional faces regardless of valence. *Biol Psychiatry* 62:1187–1190.
- Dziobek I, Rogers K, Fleck S, Bahnemann M, Heekeren HR, Wolf OT, Convit A (2008) Dissociation of cognitive and emotional empathy in adults with Asperger syndrome using the Multifaceted Empathy Test (MET). *J Autism Dev Disord* 38:464–473.
- Gamer M, Zurovski 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.
- Heinrichs M, von Dawans B, Domes G (2009) Oxytocin, vasopressin, and human social behavior. *Front Neuroendocrinol* 30:548–557.
- Hurlemann R, Patin A, Onur OA, Cohen MX, Baumgartner T, Metzler S, Dziobek I, Gallinat J, Wagner M, Maier W, Kendrick KM (2010) Oxytocin enhances amygdala-dependent, socially reinforced learning and emotional empathy in humans. *J Neurosci* 30:4999–5007.
- Keverne EB, Curley JP (2004) Vasopressin, oxytocin and social behaviour. *Curr Opin Neurobiol* 14:777–783.
- Liu Y, Wang ZX (2003) Nucleus accumbens oxytocin and dopamine interact to regulate pair bond formation in female prairie voles. *Neuroscience* 121:537–544.
- O'Doherty J, Dayan P, Schultz J, Deichmann R, Friston K, Dolan RJ (2004) Dissociable roles of ventral and dorsal striatum in instrumental conditioning. *Science* 304:452–454.
- Ross HE, Young LJ (2009) Oxytocin and the neural mechanisms regulating social cognition and affiliative behavior. *Front Neuroendocrinol* 30:534–547.