be very interesting to further investigate the neuronal dynamics, connectivity and transcriptional profiles of PVN CRF neurons using techniques with single-neuron resolution[8–10].

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Competing interests

The authors declare no competing interests.

SOCIAL NEUROSCIENCE

Oxytocin and the altruistic 'Goldilocks zone'

When choosing whether to act altruistically, people may compare the current option to an idiosyncratic ideal. Prosocial individuals seem to represent deviations from that ideal in the amygdala, but selfish individuals do not. Oxytocin administration makes selfish individuals look more like prosocial individuals, behaviorally and neurally.

Ian D. Roberts, Yi Yang Teoh and Cendri A. Hutcherson

Imagine that you and a friend receive a windfall inheritance from a rich acquaintance (lucky you!). The deceased was a bit peculiar and made a very specific bequest. Of $10,000, you get $5,532 and your friend gets $4,468. How would you feel? What if instead you received $9,999, and your friend got only $1? Or your friend got $9,999 and you got $1? $5,000 and $5,000? If you felt best about that first option, you wouldn't be alone. It's just a bit better for you, but not so much so that you feel too guilty to enjoy it. In other words, it's hit the 'Goldilocks zone' for balancing what you'd like for yourself and what you'd want for your friend. Of course, not everyone would feel the same way. Some would be much happier with $9,999 for themselves. What explains such stark individual differences? New research from Liu et al.[1] suggests that the amygdala, a region of the brain important for emotion and arousal[2], might be key. In people who are relatively prosocial, but not in people who are relatively selfish, this area encodes outcomes in reference to that Goldilocks zone split. Moreover, administering oxytocin, a neuropeptide widely thought to be important for social bonding, moves the Goldilocks zone for selfish individuals closer to that of prosocial people and amps up the amygdala response when proposed outcomes deviate from it. This research has important implications for a number of important outstanding questions about human sociality.

In the experiments, people rated how much they liked different proposed distributions of money to themselves and their assigned partner. To capture the pattern of preferences, the authors propose a model in which people calculate a ratio of their partner's outcomes to their own and are sensitive to the difference between this ratio and an 'ideal' or reference ratio. Importantly,

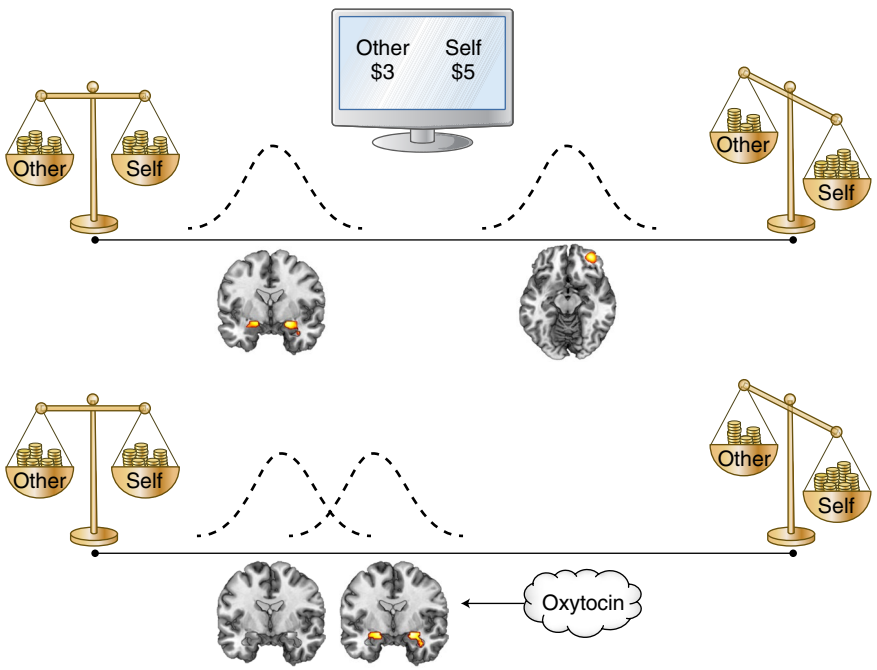

Fig. 1 | Alteration of prosocial reference points by oxytocin. Participants rated various possible monetary divisions between themselves and a partner. Liu and colleagues calculated each participant's reference point based on these ratings. On placebo, prosocial participants exhibited a reference point that was closer to equality while individualist participants had a more selfish reference point. The degree to which each proposal deviated from a given person's reference point was encoded in the amygdala among prosocial participants and in lOFC among individualist subjects. On OT, the reference points of individualist subjects became more like those of the prosocial participants and the amygdala encoded deviations from this shifted reference point. Brain images reproduced from ref. [1], Nature Publishing Group.

Liu and colleagues also find that individuals vary widely in what that ideal ratio is. For someone generous, it might be close to 1:1, while for someone selfish, it might be skewed 5:1 or even 500:1 in favor of the self. They succinctly describe this ratio as the angle φ of a line drawn from the origin to the point representing the ideal combination of self and other. Deviations from φ reduced liking for an outcome. Remarkably, this 'reference point' account provided a more parsimonious fit to the data than many other popular accounts of altruistic choice, including models based on inequality[3].

The impact of reference points on choice has a long history of study[4]. In the social domain, researchers often assume that reference dependence is expressed as a concern for equality: outcomes for one party in reference to the other should be the same, and deviations from inequality are disliked. Importantly, inequality can be computed objectively as the difference in outcomes for self and other. Liu et al. give a new perspective by arguing that social preferences about resource distributions may also be processed in relation to subjectively-defined reference points. The deviation from that reference point was represented neurally across multiple structures, including the posterior cingulate cortex and the middle frontal gyrus, regions recently associated with context-sensitive representations of others[5] and moral preferences[6].

However, other brain regions encoding deviations from this reference point depended on whether people tend toward selfish or prosocial choices. In individualist participants (who favored distributions skewed toward the self), deviations from the reference were more strongly represented in lateral orbitofrontal cortex (lOFC). In prosocial subjects (who favored more equal ratios) these deviations appeared more strongly in the amygdala. The researchers also found that in prosocial individuals, trial-by-trial fluctuations in amygdala response were associated with decreases in liking, even after controlling for model predictions. Moreover, the amygdala was functionally connected with an area of the ventromedial prefrontal cortex (vmPFC) thought to be important in constructing preferences. This suggests that the amygdala provides an important altruism-promoting input to the valuation process.

Liu and colleagues then went a step further. Some research suggests that individual differences in prosocial disposition result in part from differences in the action of the neuropeptide oxytocin (OT) and its receptor expression in the amygdala[7]. The authors thus hypothesized that administering OT might shift individualist participants' ideal reference point. Remarkably, this was exactly what they found. In the between-subjects functional MRI study and then again in a larger, within-subjects replication study, OT shifted the reference points of a priori individualist participants toward more equitable monetary divisions, but had no effect on prosocial people (Fig. 1). The same pattern was observed in a modified version of the task that evoked competitive motives. Moreover, OT increased individualist subjects' amygdala representations of reference point deviance and functional connectivity with the vmPFC.

These striking results expand our understanding of how contextual and dispositional factors can modulate the behavioral effects of OT administration[8]. Previous findings regarding OT's effect on social behavior have been decidedly mixed, and the literature has been the target of deeply-worrying statistical[9] and physiological[10] criticisms. Liu and colleagues' work features larger-than-typical sample sizes and includes a separate well-powered replication experiment. This adds considerably to the strength of their conclusions. Thus, the work by Liu and colleagues exemplifies how concerns over the replicability of OT results should be met. Of course, questions of exactly how intranasal OT influences choice remain, and the results pose several interesting questions for how social preferences are expressed during decision-making.

For example, this new 'social referencing' model suggests that choices arise from a comparison process that evaluates potential outcomes relative to a ratio of self and other outcomes rather than their absolute magnitude. This implies that the size of outcomes may be less consequential than their relative distribution. Individuals may similarly like receiving $3 while their partner receives $2 and receiving $6 when their partner receives $4. This also makes the counterintuitive prediction that people may sometimes prefer that both parties receive less money, as long as the ratio is more even. Future work will need to more directly test the idea that social preferences are scale-independent.

These results also raise important questions about how to conceptualize the amygdala's computational role in prosocial decision making. This area is strongly implicated in the production of emotional, autonomic and visceral responses, and prior work also points to its importance in prosocial choice[11]. The current findings conceptualize it as a type of comparator that, in conjunction with the vmPFC, integrates multiple factors relative to a holistic social reference point. Such a role is consistent with research suggesting that the amygdala influences attentional deployment after unexpected events[12], which here might be represented by deviations from a social reference.

Considering the influence of OT raises more intriguing possibilities. Some theories[13] argue that OT attenuates the precision or salience of interoceptive signals, permitting attention to turn outward, away from the self. This outward deployment of attention then enables incoming social signals to be incorporated into predictions about desired outcomes. In the studies presented here, OT may have attenuated interoceptive signals in individualist subjects that otherwise lead to an overly self-focused reference point. Shifting reference point 'predictions' from egocentric to more egalitarian appears to also alter brain regions that encode deviations, from lOFC to amygdala, respectively. This raises the intriguing possibility that a more prosocial reference might be a default[14] that is released when interoceptive inputs to the lOFC are attenuated. Future studies measuring physiological arousal and linking those responses to choice could test such currently speculative hypotheses and provide support for the social predictive-coding interpretation suggested by Liu and colleagues.

Future work should also be targeted at integrating these findings with previous results. For example, whereas OT increased the prosociality of individualist participants in the current study, it has decreased trusting behavior in people with borderline personality disorder[15]. This suggests that a fruitful avenue for exploration might be to compare social reference points and effects of oxytocin in individualist people and in people with borderline personality disorder, as well as in people with other disorders that have sometimes been tied to oxytocin, such as autism[13].

A final key set of questions concerns how the amygdala computes social reference signals, which require considerations of self and other to construct. Previous work suggests that computations related to these quantities may be partially dissociable, with others' outcomes being represented in the temporoparietal junction and posterior cingulate cortex or precuneus[5]. Is there a functional connection between these regions and the amygdala? Does this connection depend on OT? Future research answering these questions would provide a clearer map of the computations carried out by different components of a distributed brain network during prosocial choice.

How people make social decisions, and what produces changes in prosocial behavior, has occupied philosophers, economists and psychologists for decades. More recently, interest has also grown in understanding how the brain is implicated in these complex

social decisions. Liu and colleagues' work points to the important idea that people's social behavior depends on their reference point, which can be manipulated by oxytocin. In making this case, we suspect their work will itself serve as a reference point in the field of social neuroscience. ❐

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HISTORICAL NEWS AND VIEWS: ASTROCYTES

Astrocytes usurp neurons as a disease focus

Astrocytes are emerging as causal or modulating factors in diverse neurological disorders. Two papers published in *Nature Neuroscience* in 2007 revealed astrocytes as causally contributing to motor neuron loss in amyotrophic lateral sclerosis, thereby challenging the longstanding neuron-centric view of neurodegenerative disease.

Shane A. Liddelow and Michael V. Sofroniew

For many decades neurons were the focus of studies seeking to unravel the mechanisms that underlie dysfunction and disease in the CNS. In what appeared as a stark challenge to this long-standing status quo, two key papers published in *Nature Neuroscience* in 2007 by the Eggan and Przedborski labs highlighted astrocytes as a causally contributing cell type in the neurodegenerative disease amyotrophic lateral sclerosis (ALS)[1,2].

Astrocytes are a type of glial cell that tile the entire CNS and provide essential physiological support for neurons. Indeed, neurons would be unable to function without the critical functions provided by astrocytes in the healthy CNS. In addition, astrocytes respond to all forms of injury and disease with changes commonly termed 'astrogliosis' or 'astrocyte reactivity'. The diverse functions and consequences of these disorder-associated changes are gradually being identified, and astrocytes are emerging as likely initiators of and contributors to disease through both gain-of-function and loss-of-function mechanisms (Fig. 1).

The two papers from 2007 contributed substantively to changing the neuron-centric view of degenerative disease of the CNS. Both groups began their investigations by focusing on mouse models of ALS (largely the *hSOD1*^{G93A} mouse: a mouse expressing a mutated form of human *SOD1* (*hSOD1*), although other mutations were also investigated). Cu–Zn superoxide dismutase, encoded by *SOD1*, was the first gene associated with ALS[3]. Both studies used cells from mice carrying mutant or wild-type *hSOD1*, with Nagai et al. focusing on cultures of primary neurons and astrocytes[2] and Di Giorgio et al. using embryonic stem cell-derived motor neurons[1].

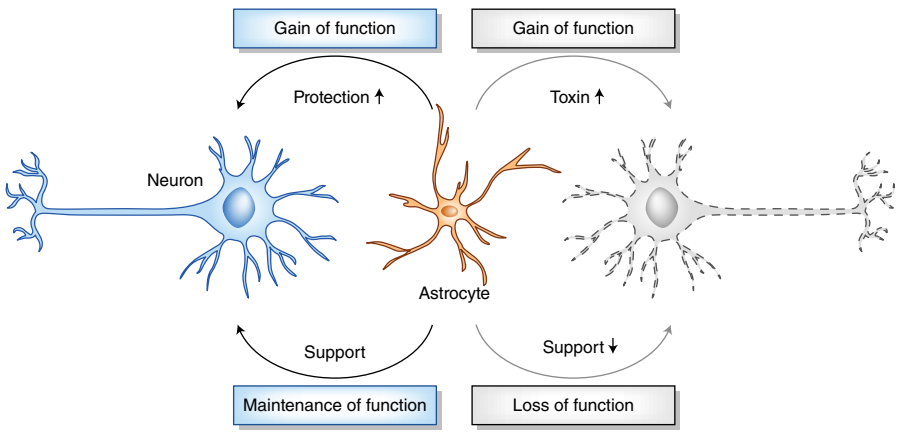

Fig. 1 | Astrocytes can play diverse roles in CNS disorders in different contexts. They can provide essential support or protection (for example, in stroke or trauma) or they can cause or contribute to neurodegeneration via gain- and loss-of-function mechanisms (for example, in ALS).

Di Giorgio et al. showed that motor neurons carrying either the nonpathological *hSOD1* transgene or the mutant *hSOD1*^{G93A} allele were not susceptible to degeneration when cultured alone; however, when the motor neurons were co-cultured with astroglial cells expressing *hSOD1*^{G93A}, they rapidly degenerated[1]. In equally elegant experiments, the authors showed that mixed neuron–glial cultures (neuron cultures with around 30% contaminating glia) from *hSOD1*^{G93A} stem-cell derived precursors were more likely to die than those prepared from nonpathological *hSOD1* transgene mice. Further investigation showed that this SOD1-mediated neurotoxicity derived from mutant astrocytes prepared from *hSOD1*^{G93A} animals. These findings demonstrated for the first time that astroglial cells carrying a *hSOD1*^{G93A} mutation have a direct, non-cell-autonomous effect on motor neuron survival[1].

Nagai and colleagues expanded on this idea and showed that the motor neuron death was triggered by soluble toxic factor(s)