

COMPARATIVE EMOTION

Evolutionarily conserved role of oxytocin in social fear contagion in zebrafish

Ibukun Akinrinade^{1††}, Kyriacos Kareklas^{1†}, Magda C. Teles¹, Thais K. Reis¹, Michael Gliksberg², Giovanni Petri^{3,4}, Gil Levkowitz^{2,5}, Rui F. Oliveira^{1,6,7*}

Emotional contagion is the most ancestral form of empathy. We tested to what extent the proximate mechanisms of emotional contagion are evolutionarily conserved by assessing the role of oxytocin, known to regulate empathic behaviors in mammals, in social fear contagion in zebrafish. Using oxytocin and oxytocin receptor mutants, we show that oxytocin is both necessary and sufficient for observer zebrafish to imitate the distressed behavior of conspecific demonstrators. The brain regions associated with emotional contagion in zebrafish are homologous to those involved in the same process in rodents (e.g., striatum, lateral septum), receiving direct projections from oxytocinergic neurons located in the pre-optic area. Together, our results support an evolutionary conserved role for oxytocin as a key regulator of basic empathic behaviors across vertebrates.

Emotional contagion, described as the ability to match the emotional state of another individual, has been considered the most ancestral form of empathy, on top of which more complex forms of empathic behaviors, such as consolation and helping, have evolved (e.g., rodents, elephants, dolphins, and primates) (1–3). Emotional contagion relies on simple perception-action mechanisms and provides important adaptive advantages to social living species (1). It enhances social cohesion and the establishment of social bonds, as well as promoting the rapid spread of fear among group members once a threat (e.g., predators) is detected, which allows individuals to survive potential dangers without directly experiencing them (3). Therefore, emotional contagion is expected to be phylogenetically ancient, being present even in species with less elaborate social cognition. Indeed, social contagion of fear has been recently described in zebrafish (*Danio rerio*), consisting of transmission of the alarm response (i.e., distress behavior consisting in erratic movement and freezing) to observers and increases in observer cortisol levels similar to those of target individuals (4–6). Moreover, behavioral responses are influenced by familiarity, with familiar distressed target fish eliciting stronger alarm responses in observers (5). The extent to which the distress behavior observed in zebrafish in response to alarmed conspecifics are phenomenologically similar

to emotional contagion, can also be argued through comparison with mammalian models of emotional contagion, such as facial expressions in orangutans (7) and freezing in rodents (8). We investigated whether social transmission of the alarm response in zebrafish shares the same proximate mechanisms that have been described for social fear contagion in mammals. We focused on the oxytocin signaling system because nonapeptides of the oxytocin family are evolutionarily conserved across vertebrates (9) and have been implicated in the regulation of emotional contagion in rodents (10, 11) and fear recognition in humans (12, 13).

Oxytocin signaling is necessary and sufficient for social fear contagion

We used zebrafish mutant lines for the ligand (*oxt*) and the two receptors (*oxtr* and *oxtrl*) of the zebrafish oxytocin nonapeptide CYISNCPG-NH₂ (isotocin) (9) to assess the role of oxytocin in social fear contagion. In zebrafish, as in other Ostariophysi fish species, injured individuals release an alarm substance from their skin into the water, originally termed Schreckstoff (fear substance), which is detected through olfaction eliciting a distress response consisting of erratic movement followed by freezing behavior (14). The sight of conspecifics in distress also elicits the expression of this response in observers, indicating the occurrence of social fear contagion in zebrafish (4–6) (Fig. 1). Therefore, we have used an experimental paradigm in which a naïve observer fish watches an unfamiliar conspecific shoal in a neighboring tank (i.e., without chemical communication), to which we have administered either water (control) or the alarm substance (Fig. 1A). Given that freezing behavior was a more consistent distress response in wild types than erratic movement (Fig. 1, B to K), we have used it as a read-out for fear contagion. Observer individuals of all wild-type (WT) control lines (i.e., *oxt*^{+/+}, *oxtr*^{+/+}, and *oxtrl*^{+/+}) significantly increased their freezing behavior when exposed to a distressed

shoal. By contrast, observer individuals of mutant lines (i.e., *oxt*^{-/-}, *oxtr*^{-/-}, and *oxtrl*^{-/-}) failed to significantly increase their freezing behavior when exposed to a distressed shoal (Fig. 1, C, E, and G). This indicates that oxytocin signaling is necessary for social fear contagion in zebrafish. Moreover, we administered exogenous oxytocin to the ligand mutants and their controls to assess whether it could rescue the social fear contagion phenotype. We also injected another group of ligand mutants and their respective control with the vehicle solution to control for putative stressful effects of the injection. Mutants injected with oxytocin also significantly increased their freezing behavior when exposed to distressed conspecifics, indicating that oxytocin is both necessary and sufficient for social fear contagion (Fig. 1, E and G). These results also suggest the lack of compensatory actions by the vasotocin system, which is known to crosstalk with the oxytocinergic system.

Oxytocin modulates the activity of ventral forebrain regions associated with social fear contagion

To characterize the neural circuits associated with emotional contagion in zebrafish we examined the expression of a neuronal activity marker, phospho-S6 ribosomal protein (pS6), in a set of forebrain and midbrain areas involved in social decision-making across vertebrates [i.e., social decision-making network (15)]. Significant changes were identified in two of these areas, the ventral (Vv) and central nucleus (Vc) of the ventral telencephalic area (Fig. 2A). The Vv is a putative homolog of the mammalian lateral septum and the Vc of the mammalian striatum (15). Notably, the expression, recognition, and sharing of emotions in humans also relies on the regulation of activity in these forebrain areas by oxytocin, even if higher order empathic functions are dependent on neocortical circuits (16–19). In zebrafish, we find that both areas exhibit a decrease in activity associated with the expression of freezing behavior in observer wild types and an increase in activity with the lack of response in *oxtr* mutants (Fig. 2B). This suggests that zebrafish distress behavior during contagion is mediated by decreases in inhibitory cell activity and that overactivation of these cells in mutants prevents the expression of this behavior. To test this hypothesis, we used a double reporter line for both excitatory (glutamate: *vglut2/dsRed*) and inhibitory (γ -aminobutyric acid, GABA: *gad1b/GFP*) neurotransmission (Fig. 2C). Compared with controls, during contagion the Vv indeed exhibits greater activity in inhibitory cells ($\chi^2_{1,13} = 5.09$, $p = 0.024$), but the Vc instead exhibits increased activity in excitatory cells ($\chi^2_{1,13} = 9.90$, $p = 0.002$). Notably, the oxytocinergic modulation of GABAergic inhibition is also

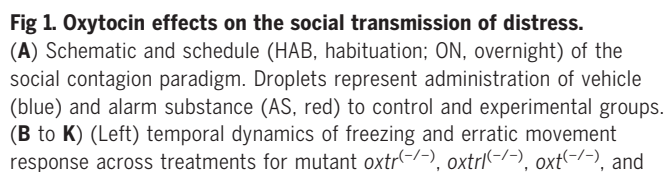
¹Integrative Behavioral Biology Lab, Instituto Gulbenkian de Ciência, Oeiras 2780-156, Portugal. ²Department of Molecular Cell Biology, Weizmann Institute of Science, Rehovot 7610001, Israel. ³ISI Foundation and ISI Global Science Foundation, Torino 10126, Italy. ⁴CENTA Institute, Torino 10138, Italy. ⁵Department of Molecular Neuroscience, Weizmann Institute of Science, Rehovot 7610001, Israel. ⁶ISPA-Instituto Universitário, Lisboa 1149-041, Portugal. ⁷Champalimaud Neuroscience Program, Champalimaud Centre for the Unknown, Lisbon 1400-038, Portugal.

*Corresponding author. Email: ruiol@ispa.pt

†These authors contributed equally to this work.

‡Present address: Department of Physiology and Pharmacology, Cumming School of Medicine, University of Calgary, 2500 University Drive NW, Calgary Alberta T2N 1N4, Canada.



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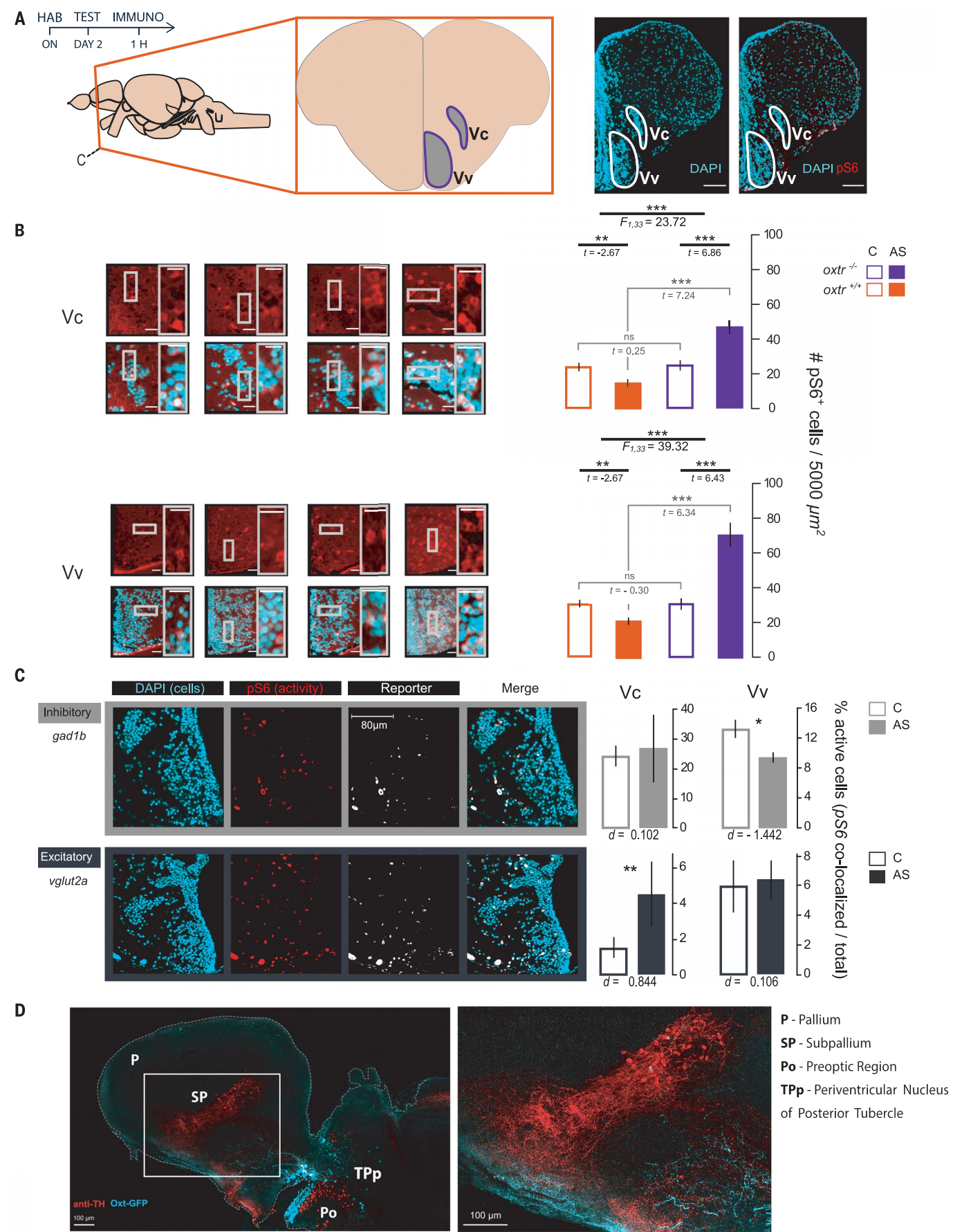


Fig 2. Oxytocin receptor deletion alters nodal neuronal activation.

(A) Schedule of behavioral assay and immuno-staining; anatomical localization of the two brain areas responding to fear contagion: the central nucleus (Vc) and the ventral nucleus of the ventral telencephalon (Vv), with representative hemispherical sections identified by DAPI (cyan) and patterns of neuronal activity shown by pS6 (magenta) through immunostaining. (B) Quantification of the density (cells per 5000 μm^2) of pS6 positive cells in each brain area, Vc and Vv; panels show representative examples (left to right: WT control, WT alarm, mutant control, mutant alarm; scale = 20 μm). (C) Quantified activity in cells

(pS6 and DAPI) identified as either excitatory (glutamatergic: *vglut2a*) or inhibitory (GABAergic: *gad1b*) in double reporter lines (*vglut2a:dsRed* / *gad1b:GFP*) compared between the observation of control (C) or alarm-response (AS) in demonstrators (linear mixed model, with pS6 as covariate; Cohen's *d* quantifies effect size), with representative microscopy examples shown in panels. [Results are shown as mean \pm SEM; * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$.] (D) Representative example of sagittal brain slice (confocal maximum intensity z-stack) showing immunostained *oxtr* positive neuronal fibers (yellow) projecting to the Vv in the subpallium of adult zebrafish with TH cell groups (pink) also projecting to the Vv.

exhibited in the lateral septum of mice during social fear transmission (17).

The zebrafish Vv conserves the role of the mammalian lateral septum as a functional connectivity area between the social behavior and mesolimbic system (15). Thus, the decreasing inhibition when distress is observed enables otherwise suppressed signals during control conditions to be relayed between areas of the network. By contrast, the Vc conserves the role of the striatum as part of the mesolimbic reward pathway for downstream other-oriented motor and motivational controls (16, 18), which explains the excitatory increases similar to those noted in parts of the striatum in mice (19). Because the proportion of active cells during social fear contagion that were either inhibitory or excitatory was a minority (Vc 31.26% and Vv 15.86%), the overall decreased activity may relate to other oxytocin-induced changes in local cells, likely due to shifts in connectivity across the network. Oxytocin regulation of these ventral forebrain areas relies on projections from oxytocin neurons in the pre-optic area (Fig. 2D), and is confirmed by the expression of both zebrafish oxytocin receptors in these areas (*oxtr*, *oxtrl*; fig. S1), which is also in agreement with the pattern of brain distribution of *oxtr* in other teleost fish (20). Notably, both receptors are also expressed across most nodes of the social decision-making network, but the expression of the primary receptor (*oxtr*) is distinctly greater and more widespread (fig. S1). Thus, we examined the effect of *oxtr* expression on patterns of functional connectivity across the social decision-making network.

Oxytocin modulates functional connectivity across brain regions in response to social contagion

To study functional connectivity, we constructed networks representing coactivation patterns during social fear contagion and control treatments, for both wild types and *oxtr* mutants, with positive and negative correlations between nodes indicating excitatory and inhibitory patterns respectively. Although functional distributions differ between wild types and mutants under both control and treatment conditions, average inhibition and excitation notably differ only under the fear contagion treatment (fig. S2). Networks were tested for both excitatory and inhibitory dis-

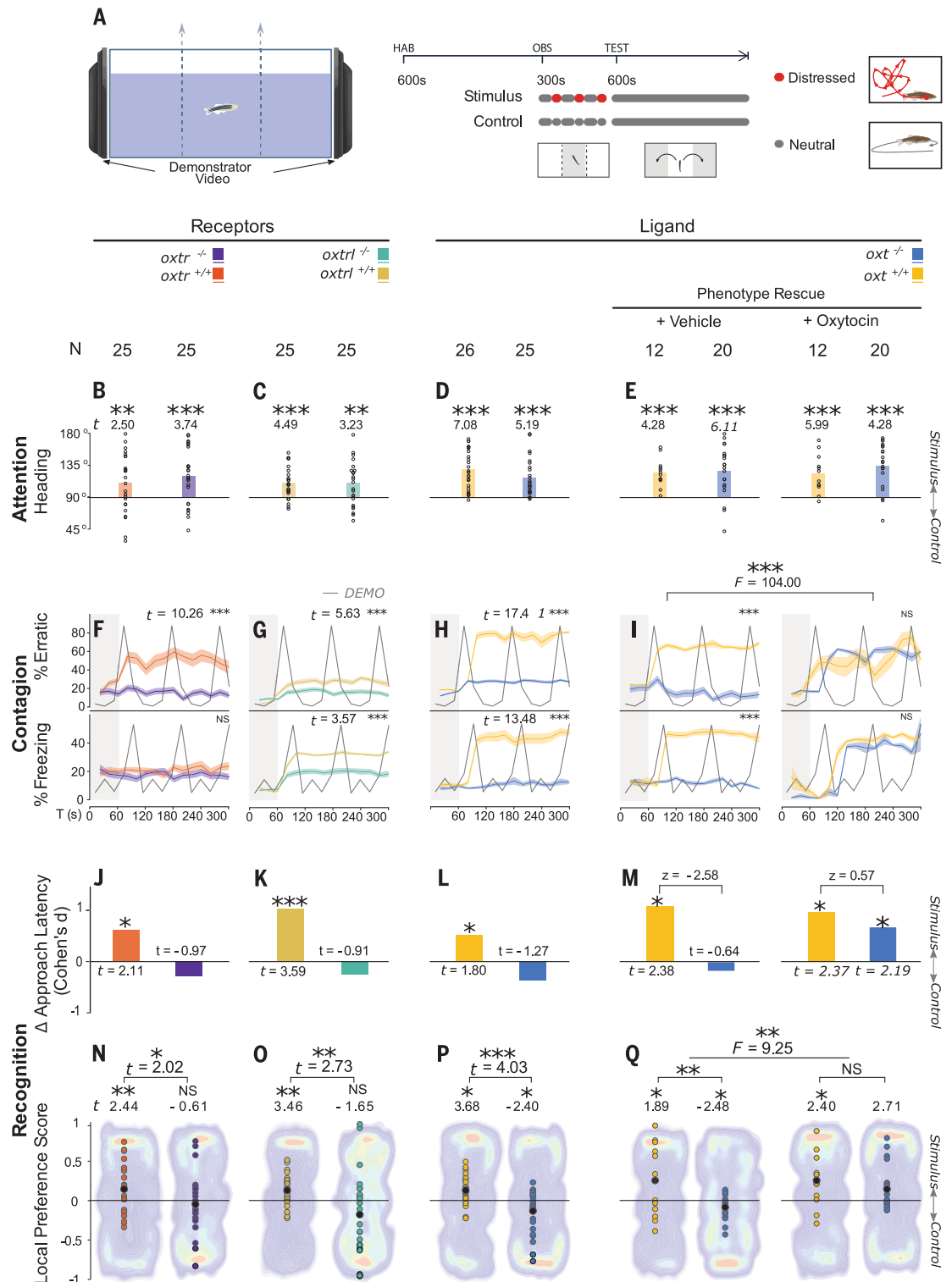
tributions across genotypes and treatments, and for computed average levels of each [probability in sample space, $p(\omega)$]. Under control conditions wild types and mutants show differences in the network distribution (excitation: $KS = 0.23$, $P < 10^{-4}$; inhibition: $KS = 0.55$, $P < 10^{-6}$), but negligible differences in average signals (only inhibition: $U = 3492$, $P < 10^{-5}$, Cohen's $d = 0.18$). Under treatment, *oxtr* mutants exhibited both higher average excitation ($U = 5744$, $P < 10^{-6}$, Cohen's $d = 0.67$) and inhibition ($U = 1972$, $P < 10^{-6}$, Cohen's $d = 0.68$), as well as greater differences in distribution (excitation: $KS = 0.49$, $P < 10^{-6}$; inhibition: $KS = 0.73$, $P < 10^{-6}$). Overall, the absence of emotional contagion in *oxtr* mutants was paralleled by a segregated pattern of functional connectivity (excitatory: $KS = 0.38$, $P < 10^{-6}$; inhibitory: $KS = 0.50$, $P < 10^{-4}$) with significantly greater average excitation in their brain network ($U = 5680$, $P < 10^{-6}$, Cohen's $d = 0.49$) than wild types displaying the socially transmitted distress behavior. In line with our findings in the reporter line, the Vv of the wild type loses all its inhibitory connectivity during treatment compared with the control, but in mutants inhibitory connectivity is partially retained—namely to the anterior tuberal nucleus. By contrast, the Vc of wild types maintains inhibitory connectivity during contagion, shifting only in target nodes and reducing strong neighboring connections, which may explain the overall reduced activity. We also confirm that it exhibits excitatory links, most of which are to non-neighboring nodes and which do not appear in *oxtr* mutants. These include the habenula (HAV), the lateral hypothalamic nucleus, and the posterior dorsal telencephalic area, which are involved in fear and alarm responses (6, 21). Node centrality also radically shifted in ranking between the brain networks of wild types and *oxtr* mutants, and with fear contagion compared with the control (fig. S3 and table S1). In turn, only a single preserved submodule (at $z > 3$, $P < 0.01$) was shared between wild types and *oxtr* mutants under the fear contagion treatment, and it constitutes the dorsal and ventral habenula, the posterior pre-optic area and the magnocellular preoptic nucleus. Considering the implications of the habenular nuclei in zebrafish fear responses and that the pre-optic area responds to the alarm substance (6, 21), this submodule is

likely involved in processing fear stimulation in both groups. Notably, although the submodule is isolated in *oxtr* mutants, in wild types it is integrated in a larger module together with ventral and dorsal areas of the telencephalon, and the ventral zone of the periventricular nucleus. This indicates that oxytocin drives greater functional integration when animals are exposed to distressed conspecifics.

Oxytocin regulates the recognition of emotion-like states needed for social fear contagion

The observed social transmission of fear in zebrafish can be regarded simply as behavior contagion based on motor imitation or as emotional contagion, which requires recognition of the demonstrator's state (i.e., emotion) and which triggers an automatic representation of the same state in the observer, causing an equivalent expression of behavior (22). Although zebrafish match both the behavior and cortisol levels of distressed individuals (4), this may be due to either recognizing and sharing the internal state of others or because the behavior of others signals local danger (e.g., predators) (14), which triggers proportional physiological and behavioral changes. Therefore, we decided to test state recognition explicitly by separating (in time) the moment the observer sees the distressed conspecific (observation phase) from a second moment (test phase), when the observer must discriminate between the demonstrator previously observed in distress and the individual that was relaxed (i.e., only swimming). If observers can make this discrimination, it means that when they expressed alarm behavior in response to the observed distress behavior of conspecifics (observation phase), they were not merely responding with motor imitation but were able to encode information on the behavioral state of demonstrators, which they subsequently used to discriminate between the two demonstrators when they are in a similar behavioral state (test phase). To this end, observers of *oxtr*, *oxtr*, and *oxtrl* mutants and their respective WT controls were first exposed to two simultaneous prerecorded video playbacks of the same demonstrator in conflicting states: neutral (swimming) and periodic distress (three bouts of erratic movement and freezing). Observers were then exposed to two videos both showing the demonstrator in the neutral state,

Fig. 3. Content validity of fear transmission by state recognition. (A) Video playback tests enabled the controlled assessment of stimulus versus state recognition across two experimental phases: a 5-min observation of two conflicting videos presenting the same demonstrator in either a neutral state (control) or periodically distressed (stimulus) and a 10-min local preference test while both videos displayed the demonstrator in a neutral state. During observation attention was measured by (B to E) the absolute heading toward the stimulus video (0 to 180°; one-sample *t*-tests, $\mu \neq 90^\circ$) and (F to I) temporal changes in the proportion time erratic and freezing following analogous behavior in the stimulus video, which were compared between genotype and treatment (linear mixed models, full factorial). During tests (J to M) differences in latency to first approach the stimulus compared with the control location were tested (Welch's two-sample *t*-tests; effect-size comparisons: *z* tests, $d_1 \neq d_2$, $|z| \geq 1.96$ at $\alpha = 0.05$ two-sided) and (N to Q) local preference scores, calculated from cumulative durations, were also compared (one-sample *t*-tests, $\mu \neq 0$; genotypic comparisons: Welch's two-sample *t*-tests; genotype times treatment: two-way ANOVA with post hoc Fisher's LSD). Heat maps are representative examples with the least deviation from the mean. [^{NS}*P* > 0.05, **P* < 0.05, ***P* < 0.01, ****P* < 0.001.]



in which recognition was tested through local preferences based on the previously observed conflicting states (Fig. 3A).

During observation, fish oriented toward erratic movement and freezing and thus attention shifted to the distressed behavior and not the level of movement (fig. S4). Notably, orientation preferences were not different be-

tween any of the oxytocin mutants and WT controls (Fig. 3, B to E). By contrast, the wild types replicated the distress behavior of the demonstrators whereas the oxytocin mutants failed to do so. However, the administration of oxytocin to the ligand mutant (*oxtr*) rescued the distress contagion (Fig. 3, F to I, and fig. S5). This replicated the results of the live demon-

strator experiment regarding the necessary and sufficient role of oxytocin and further shows that attention is not moderating these effects. Notably, during the test phase wild type observers were motivated to approach and preferred being near the previously distressed demonstrator, whereas oxytocin mutants did not express a motivation to approach

the previously distressed demonstrator (Fig. 3, J to M) and preferred being near the demonstrator that remained in a neutral state (Fig. 3, N to Q). This indicates that oxytocin is necessary and sufficient for zebrafish to recognize the distress from the neutral behavior in the same conspecific, suggesting the occurrence of an oxytocin-dependent emotion recognition in zebrafish (23, 24). This is in line with responses in humans and mammals that implicate the recognition of a fearful state in others and not simply their behavior (25, 26). Moreover, because distressed behavior in zebrafish signals local predation risk (14), our findings also show that oxytocin promotes interaction with distressed others despite heightened local risk. Such other-oriented acts that involve individual costs and benefits for others are typically referred to as prosociality, which is well-defined in mammals where it is also regulated by oxytocin (2, 21–23). In this case the benefit for the receiver can be due to the buffering of distress in the presence of others, which has been also described in zebrafish (21). Thus, approaching and interacting with a distressed individual may prove to be a prosocial behavior in zebrafish, but further evidence is needed.

Discussion

The oxytocin regulation of social transmission of fear in zebrafish described here supports its evolutionary conserved role in emotional contagion, given its similar effects in mammals, where exogenous administration of oxytocin increases observational fear responses (10, 11). Furthermore, in both zebrafish and rodents, oxytocin also regulates emotion recognition (25, 27), which is the cognitive basis for emotional contagion. Therefore, it is plausible that oxytocin has been recruited early in the evolution of nonapeptides to regulate ancestral empathic behaviors in group living species, and that it has been evolutionarily coopted to regulate more complex empathic

behaviors, such as consolation and helping (26, 28–30), in species with more complex cognitive abilities. However, to what extent the social contagion of fear observed in zebrafish and in mammals is homologous, or represents a case of convergent evolution, remains an open question. Although at this stage the homology hypothesis is more parsimonious as it requires fewer evolutionary transitions for the observed similarities, more comparative research across different relevant species is needed to disentangle these two hypotheses. From a human translational research perspective our results contribute to the validation of a phylogenetically distant model of emotional contagion.

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SUPPLEMENTARY MATERIALS

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Materials and Methods
Figs. S1 to S6
Tables S1 and S2
Data S1
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Fundamentals of empathy

Emotional contagion, in which individuals display fear or distress behaviors in response to observations of the same in another, is considered a basal form of empathy and is known to occur in fishes. Akinrinade *et al.* have shown that the neuropeptide oxytocin is responsible for these behaviors in zebrafish, as it is in mammals (see the Perspective by DeAngelis and Hofmann). They also found that the same regions of the brain are involved in zebrafish and in mammals. Such homologies in emotional response mechanisms across fishes and mammals suggest that this most basal form of empathy could have evolved many, many millions of years ago. —SNV

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