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Kinetics and Dose Dependency of Intranasal Oxytocin Effects on Amygdala Reactivity

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ABSTRACT

BACKGROUND: Current neuroimaging perspectives on a variety of mental disorders emphasize dysfunction of the amygdala. The neuropeptide oxytocin (OXT), a key mediator in the regulation of social cognition and behavior, accumulates in cerebrospinal fluid after intranasal administration in macaques and humans and modulates amygdala reactivity in both species. However, the translation of neuromodulatory OXT effects to novel treatment approaches is hampered by the absence of studies defining the most effective dose and dose–response latency for targeting the amygdala.

METHODS: To address this highly relevant issue, a total of 116 healthy men underwent functional magnetic resonance imaging using a randomized, double-blind, placebo-controlled crossover study design. The experimental rationale was to systematically vary dose–test latencies (15–40, 45–70, and 75–100 minutes) and doses of OXT (12, 24, and 48 international units) in order to identify the most robust effects on amygdala reactivity. During functional magnetic resonance imaging, subjects completed an emotional face recognition task including stimuli with varying intensities ranging from low (highly ambiguous) to high (less ambiguous).

RESULTS: Our results indicate that the OXT-induced inhibition of amygdala responses to fear was most effective in a time window between 45 and 70 minutes after administration of a dose of 24 international units. Furthermore, the observed effect was most evident in subjects scoring high on measures of autistic-like traits. Behavioral response patterns suggest that OXT specifically reduced an emotional bias in the perception of ambiguous faces.

CONCLUSIONS: These findings provide initial evidence of the most effective dose and dose–test interval for future experimental or therapeutic regimens aimed at targeting amygdala functioning using intranasal OXT administration.

Keywords: Amygdala, Autistic-like traits, Dose, Emotion recognition, fMRI, Oxytocin

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The neuropeptide oxytocin (OXT) is a key modulator of numerous social processes ranging from emotion recognition to stress coping and fear learning (1–4). Both human and animal studies have consistently shown that intranasal OXT administration affects the processing of emotional stimuli and exerts anxiolytic effects, most likely by modulating activity of the amygdala (5–12).

In light of the peptide's prosocial and anxiolytic effect profile and the low side effects (13–15), OXT has recently evolved into a promising candidate compound for treating various mental disorders (16,17). Two avenues for clinical applications have been proposed: First, OXT could restore impaired social interaction abilities that constitute common core symptoms of clinically heterogeneous disease phenotypes in the anxiety, borderline, schizophrenia, or autism spectrum, with the latter showing the greatest improvements in a recent meta-analysis of potential clinical applications of OXT (18). Second, OXT may also augment psychotherapy efficacy by improving both the therapeutic alliance and the readiness to interact socially, thereby facilitating successful engagement in feared social situations outside of therapy sessions (16,19–21).

However, translational progress is hampered by the lack of comprehensive studies probing dose–response relationships and the temporal dynamics of intranasal OXT administration. The vast majority of studies administered 24 international units (IU) of OXT intranasally and measured its effects around 45 minutes later, following pioneering behavioral studies in the field (2,22,23). Clear empirical evidence supporting the superiority of this administration protocol is still scarce, though.

The utility of the intranasal route of peptide administration was originally demonstrated with numerous neuropeptides, including the OXT-related nonapeptide arginine vasopressin (AVP) (24). Heightened OXT levels in cerebrospinal fluid (CSF) following intranasal OXT administration have since been well documented in both humans (25) and macaques (26) and underline OXT's central mode of action (27). Specifically, Striepens *et al.* (25) detected an increased OXT signal in human CSF 75 minutes after intranasal delivery of 24 IU, while comparable studies in macaques have shown heightened OXT levels in

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CSF 35, 40, and 60 minutes after aerosolized or intranasal OXT administration [25 IU (28), 48 IU (29), and 24 IU (30), respectively]. Only one study examined OXT's spatiotemporal effects on the cerebral blood flow at rest, identifying peak response changes between 39 and 51 minutes after OXT administration (31). The few studies directly comparing different doses of OXT treatment have yielded divergent results (15,32–36), yet these findings were gained either in clinical samples or by using special administration devices or different outcome measures. Thus, clear recommendations for standard OXT administration procedures are still lacking, and calls for sufficiently powered, well-controlled target engagement studies have grown louder (18,37–40). (For a detailed discussion on the intranasal administration route, see Supplemental Discussion.)

Moreover, it is increasingly acknowledged that the partially heterogeneous and not exclusively prosocial effects of OXT might result from context- and person-dependent effect patterns (21,41,42). In this respect, alterations in amygdala activation (43,44) and variance of OXT effects as a function of autistic-like traits seem particularly informative (45).

In the current randomized, double-blind, placebo-controlled crossover study involving 116 healthy subjects, we had an a priori focus on the amygdala as a central hub of social perception and emotion processing. Our experiment was designed to systematically compare the effects of three different intranasal OXT doses (12, 24, and 48 IU) and dose–test latencies (15, 45, and 75 minutes) on behavioral and neural indices of amygdala function. We hypothesized that OXT would decrease the amygdala response to fearful faces differently as a function of dose and latency. In particular, we expected the highest effects on fear-specific amygdala function after the established dose–test latency of 45 minutes. Moreover, based on the previous finding of weaker OXT effects after administration of 48 IU compared with 24 IU (32), we assumed that the dampening effects on amygdala function might follow an inversed U-shaped curve with the highest effects after administration of 24 IU OXT. We further investigated the influence of autistic-like traits on our readouts in exploratory post hoc analyses.

METHODS AND MATERIALS

Experimental Design

The current study followed a randomized, double-blind, placebo-controlled crossover design. A total of 116 male participants (mean age ± SD = 24.7 ± 4.4 years) were allocated to one of five groups differing in their treatment protocol: 12 IU scanned after 45 minutes (n = 21), 24 IU scanned after 45 minutes (n = 25), 48 IU scanned after 45 minutes (n = 22), 24 IU scanned after 15 minutes (n = 24), and 24 IU scanned after 75 minutes (n = 24) (see Figure 1). Participants underwent a screening session (see Supplemental Methods) followed by two identical testing sessions on separate days (one session after placebo [PLC] and the other after OXT administration, scheduled at least 24 hours apart, with substance order randomized across participants). Among other psychometric measures, each subject's autistic-like traits were assessed using the Autism-Spectrum Quotient (AQ) (46).

Testing Sessions

Testing sessions included a functional magnetic resonance imaging (fMRI) scan and questionnaires on mood and anxiety completed at the start and end of the session [the Positive and Negative Affect Schedule (47) and the State-Trait Anxiety Inventory (48)]. Blood and saliva were sampled before substance administration (baseline) and immediately after fMRI scanning. To obtain time course measurements, additional saliva samples were taken immediately before scanning and at approximately 15, 40, 80, and (for some groups) 105 minutes after substance administration.

fMRI Task

Based on a recent meta-analysis (49), we decided to employ a facial emotion recognition task in this study. Stimuli comprised morphed face pictures displaying neutral mood and high- and low-intensity fear and happiness (see Figure 1 and Supplemental Methods). The fMRI scan consisted of an event-related facial emotion recognition paradigm. In each trial, a

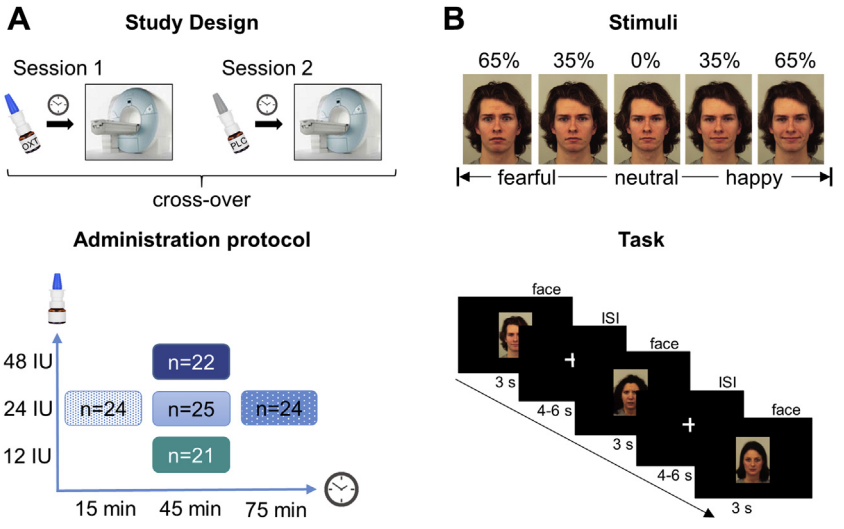

Figure 1. **(A)** Study design and administration protocol. Treatment conditions varied as a function of oxytocin (OXT) dose and dose–test latency. **(B)** Stimuli and functional magnetic resonance imaging task. During the functional magnetic resonance imaging task, participants viewed face pictures displaying fear (low or high intensity), happiness (low or high intensity), or no emotion. The depicted neutral faces are exemplary stimuli taken from the Karolinska Directed Emotional Faces stimuli set (79), image identifier: AF01NES, AF02NES, AM14NES. ISI, interstimulus interval; IU, international units; PLC, placebo.

stimulus was presented for 3 seconds, followed by a jittered interstimulus interval (4–6 seconds, mean = 5 seconds) during which a fixation cross was presented. Participants were instructed to identify the emotion depicted by the face in the picture (neutral mood, happiness, or fear) as quickly and accurately as possible by pressing one of three response buttons. No feedback was given after the responses. The total task duration was 23 minutes per session.

Intranasal Treatment

Participants self-administered 12, 24, or 48 IU of synthetic OXT (depending on the treatment group) or PLC via nasal spray at the beginning of each testing session under the supervision of a trained research assistant and in accordance with the latest standardization guidelines (50). The PLC solution contained identical ingredients except for the peptide itself (for details, see Supplemental Methods). The substances were provided by Sigma-Tau Pharmaceuticals Inc. (Pomezia, Italy).

Neuroendocrine Parameter Extraction

OXT concentrations in plasma and saliva were extracted and quantified using a highly sensitive and specific radioimmunoassay. The area under the curve describing the increase of salivary OXT 0 to 70 minutes after substance administration (51) constituted a time-independent outcome measure comparable across participant groups. Sampling procedure and analysis details are described in Supplemental Methods.

Acquisition of fMRI Data and Data Analysis

Imaging data were collected on a 1.5T Siemens Avanto MRI system (Siemens AG, Erlangen, Germany). Data were then preprocessed and analyzed using standard procedures in SPM8 software (Wellcome Trust Centre for Neuroimaging, London, UK; http://www.fil.ion.ucl.ac.uk/spm) implemented in MATLAB 7.10.0 (The MathWorks, Inc., Natick, MA). Voxelwise p values were familywise error (FWE) corrected for multiple comparisons (p_{FWE}), with a corrected threshold of $p < .05$ considered significant (for details, see Supplemental Methods). To disentangle dose- and latency-dependent effects, we analyzed parameter estimates extracted from the amygdala using two separate analyses of variance (ANOVAs) (one for dose and one for latency; effects in post hoc comparisons remain significant at a Bonferroni-corrected alpha level of .05/3 = .016).

Demographical, behavioral, and neuroendocrine data were analyzed using standard procedures in SPSS 22 (IBM Corp., Armonk, NY), including repeated-measures ANOVAs, Pearson's product-moment correlation, and paired t tests. Two-tailed p values of $< .05$ were considered significant (for details, see Supplemental Methods).

RESULTS

OXT Concentrations in Plasma and Saliva

A mixed ANOVA with the within-subject factor treatment (OXT or PLC), the between-subject factor dose (12, 24, or 48 IU), and the area under the curve describing the increase of the saliva OXT level as dependent variable yielded a main effect of treatment ($F_{1,109} = 106.05$, $p < .01$, $\eta_p^2 = .54$) and an interaction between dose and treatment ($F_{2,109} = 3.09$, $p = .05$, $\eta_p^2 = .05$). Post hoc comparisons revealed significantly lower OXT effects after 12 IU of OXT as compared with 24 IU ($t_{77.47} = 3.68$, $p < .01$, $d = 0.72$) or 48 IU ($t_{30.72} = 2.63$, $p = .01$, $d = 0.81$), whereas there was no difference in OXT treatment effects between the 24- and 48-IU groups ($t_{90} = 0.20$, $p = .84$, $d = 0.05$; see Figure 2A). For plasma OXT increase, we observed a main effect of treatment ($F_{1,60} = 40.56$, $p < .01$, $\eta_p^2 = .40$), but no main or interaction effect of dose ($F_{2,60} = 1.87$, $p = .16$, $\eta_p^2 = .06$). However, explorative post hoc tests revealed a trend-to-significant difference between OXT increase after 12 IU as compared with 24 IU ($t_{42} = 1.81$, $p = .08$, $d = 0.55$), while there was no difference between the 24- and 48-IU groups ($t_{44} = 1.30$, $p = .21$, $d = 0.39$; see Figure 2B and Supplemental Results). Treatment-induced increases in plasma and saliva concentrations of OXT were positively correlated with each other ($r_{102} = .24$, $p = .02$; see Figure 2C; correlation across all subjects, measures taken at the end of the fMRI experiment).

fMRI Results

As expected from previous findings, OXT (24 IU, 45 minutes latency) significantly reduced the response to fearful faces [($Fear_{PLC} > Neutral_{PLC}$) > ($Fear_{OXT} > Neutral_{OXT}$)] in the left amygdala (Montreal Neurological Institute peak coordinates x, y, z: −26, −6, −16 and −18, 2, −16, $t_{1,808} = 3.47$, $k = 90$, $p_{FWE} = .046$). This cluster was cytoarchitectonically mapped to the basolateral and superficial subregions of the amygdala using the SPM Anatomy toolbox version 1.8 [see Eickhoff *et al.* (52)] (for details, see Supplemental Results). Activation in the right amygdala was not significantly affected (30, −6, −16, $t_{1,808} = 1.97$, $k = 1$, $p_{FWE} = .79$).

To examine whether this inhibitory effect was moderated by fear intensity, we extracted parameter estimates averaged across all left amygdala voxels (PE_{AMY}) and submitted them to an ANOVA with the within-subject factors treatment (OXT or PLC) and fear intensity (neutral, low, or high). The ANOVA yielded a main effect of fear intensity ($F_{1,44} = 5.26$, $p = .01$, $\eta_p^2 = .19$) and a trend-to-significant interaction between treatment and fear intensity ($F_{2,44} = 3.40$, $p = .055$, $\eta_p^2 = .12$). Post hoc tests revealed a graded effect of OXT on the response to fearful faces (high fear: $t_{22} = -2.65$, $p = .01$, $d = 0.68$; low fear: $t_{22} = -1.37$, $p = .18$, $d = 0.42$; neutral: $t_{22} = -0.675$, $p = .51$, $d = 0.18$; see Figure 3A). In a next step, we used PE_{Amy} to assess dose and latency effects. More comprehensive data can be found in the Supplemental Results.

Dose-Dependent Effects. An ANOVA with the amygdala response (fearful > neutral) as dependent variable and the within-subject factors treatment (OXT or PLC), dose (12, 24, or 48 IU), and intensity (low or high) revealed a trend-to-significant main effect of fear intensity ($F_{1,59} = 3.75$, $p = .06$, $\eta_p^2 = .06$) and an interaction between treatment and dose ($F_{2,59} = 3.15$, $p = .05$, $\eta_p^2 = .10$). To disentangle this interaction, separate ANOVAs for the low and high intensities were conducted. In the high-intensity condition, no main effect, but a significant interaction of treatment and dose, was evident ($F_{2,59} = 4.10$, $p = .02$, $\eta_p^2 = .12$) such that amygdala responses decreased after 24 IU ($t_{22} = -2.67$, $p = .01$, $d = 0.80$;

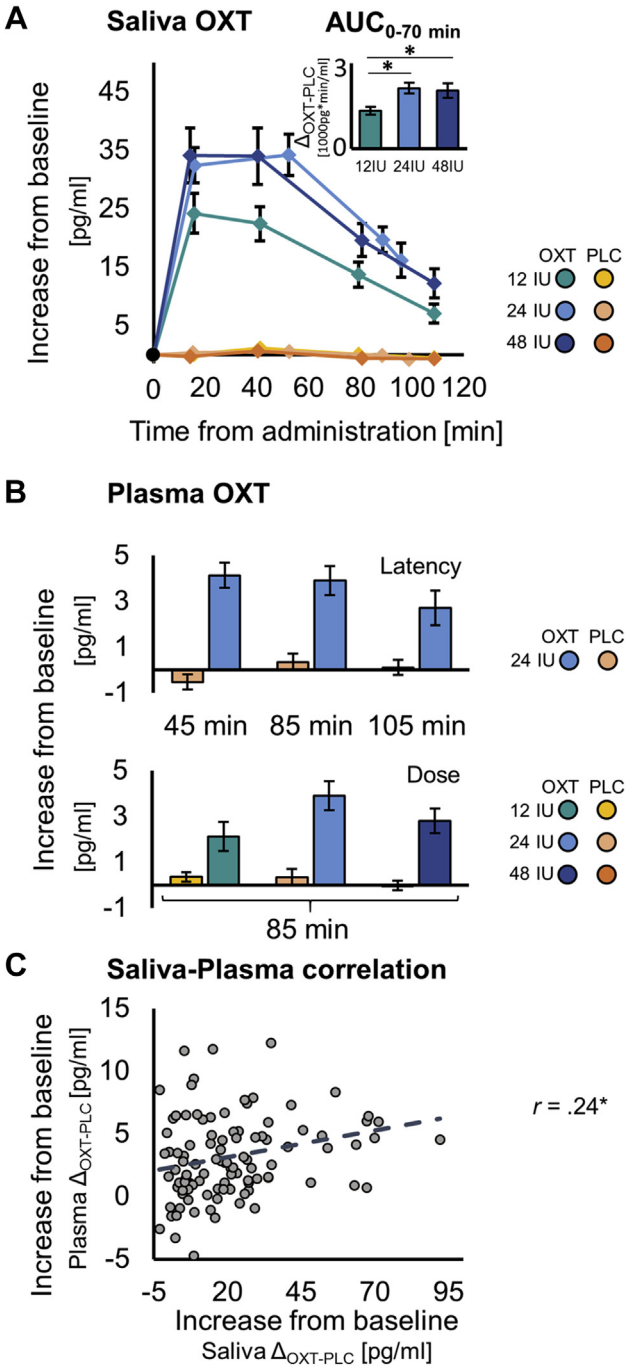

Figure 2. **(A, B)** Changes in saliva **(A)** and plasma **(B)** oxytocin (OXT) concentrations following OXT and placebo (PLC) treatment. OXT level increases after 12 international units (IU) of oxytocin were lower compared with 24 IU (saliva: $t_{77.47} = 3.68$, $p < .01$, $d = 0.72$; plasma: $t_{42} = 1.81$, $p = .08$, $d = 0.55$), while increases after 24- and 48-IU doses of OXT were comparable (saliva: $p > .20$; plasma: $p > .80$). **(C)** Treatment-induced increases in plasma and saliva OXT levels correlated ($r_{102} = .24$, $p = .02$). AUC, area under the curve. *$p < .05$.

planned post hoc tests) but not after 12 IU ($t_{18} = -0.90$, $p = .38$, $d = 0.32$; see Figure 3B). Interestingly, 48 IU induced a trend-to-significant increase in amygdala activation ($t_{19} = 1.81$, $p = .09$, $d = 0.49$) and effects differed significantly from those in the 24-IU condition ($t_{41} = 3.16$, $p = .003$, $d = 0.96$). No main or interaction effects were found in the low-intensity fear condition.

Latency-Dependent Effects. An additional ANOVA with the amygdala response (fearful > neutral) as dependent variable and the within-subject factors treatment (OXT or PLC), latency (15, 45, or 75 minutes), and intensity (low or high) yielded a trend-to-significant main effect of treatment ($F_{1,59} = 3.36$, $p = .07$, $\eta_p^2 = .05$) and a main effect of fear intensity ($F_{1,59} = 18.58$, $p < .01$, $\eta_p^2 = .23$). In the high-intensity condition, we observed a main effect of treatment ($F_{1,64} = 4.88$, $p = .03$, $\eta_p^2 = .07$), but no significant interaction effect of treatment and latency ($F_{2,64} = 0.87$, $p = .42$, $\eta_p^2 = .03$; see Figure 3B). However, amygdala activity significantly decreased 45 minutes after OXT administration ($t_{22} = -2.67$, $p = .01$, $d = 0.80$), but not after 15 minutes ($t_{23} = -0.33$, $p = .75$, $d = 0.10$) or 75 minutes ($t_{19} = -1.10$, $p = .25$, $d = 0.37$). No main or interaction effects were found in the low-intensity condition.

Behavior

OXT increased the tendency to perceive ambiguous faces as neutral (trend-to-significant main effect of treatment in total sample, $F_{1,103} = 3.00$, $p = .09$, $\eta_p^2 = .03$; significant treatment effect in subsample with dose–task latency of 45 minutes, $F_{1,59} = 5.21$, $p = .03$, $\eta_p^2 = .08$). We did not detect any dose- or latency-dependent effects (interaction effects, all $ps > .05$; for details, see Figure 4A and Supplemental Results).

Across subjects, the OXT effect on low fearful face perception correlated with OXT's dampening effect on the neural left amygdala response to low fearful faces ($r_{99} = -.22$, $p = .03$ for neutral ratings and $r_{99} = .22$, $p = .03$ for fearful ratings). The more OXT attenuated the amygdala response, the less fearful and the more neutral subjects rated low fearful faces as compared with the PLC session. Importantly, this effect was driven by a very high correlation in the subsample tested on the 24-IU dose of OXT 45 minutes prior to the fMRI scan ($r_{18} = -.60$, $p = .01$ for neutral ratings and $r_{18} = .60$, $p = .01$ for fearful ratings; see Figure 4B; correlations in the other treatment condition groups did not reach significance, all $ps > .05$). There was no correlation between ratings and neural responses to low happy faces across groups ($r_{99} = -.06$, $p = .51$ for neutral ratings and $r_{99} = .15$, $p = .15$ for happy ratings).

Autism-Spectrum Quotient

Each subject's autistic-like traits were assessed using the AQ (43). Mean AQ was 14.14 (SD = 4.97); no subject exceeded the clinical cutoff value of 32 points, indicating a low-to-moderate penetrance of autistic-like traits in our sample (see Supplemental Table S1 and Supplemental Results).

fMRI Results. A whole-brain regression analysis revealed that the AQ score significantly predicted the neural responses to highly fearful faces ($FearHigh_{PLC}$ > baseline) in the right inferior frontal gyrus (58, 18, 8, $t_{100} = 5.41$ $k = 44$, $p_{FWE} < .01$) and the left amygdala (−18, 0, −12, $t_{100} = 5.34$, $k = 55$, $p_{FWE} = .035$) in the PLC session. In line with these findings, AQ also

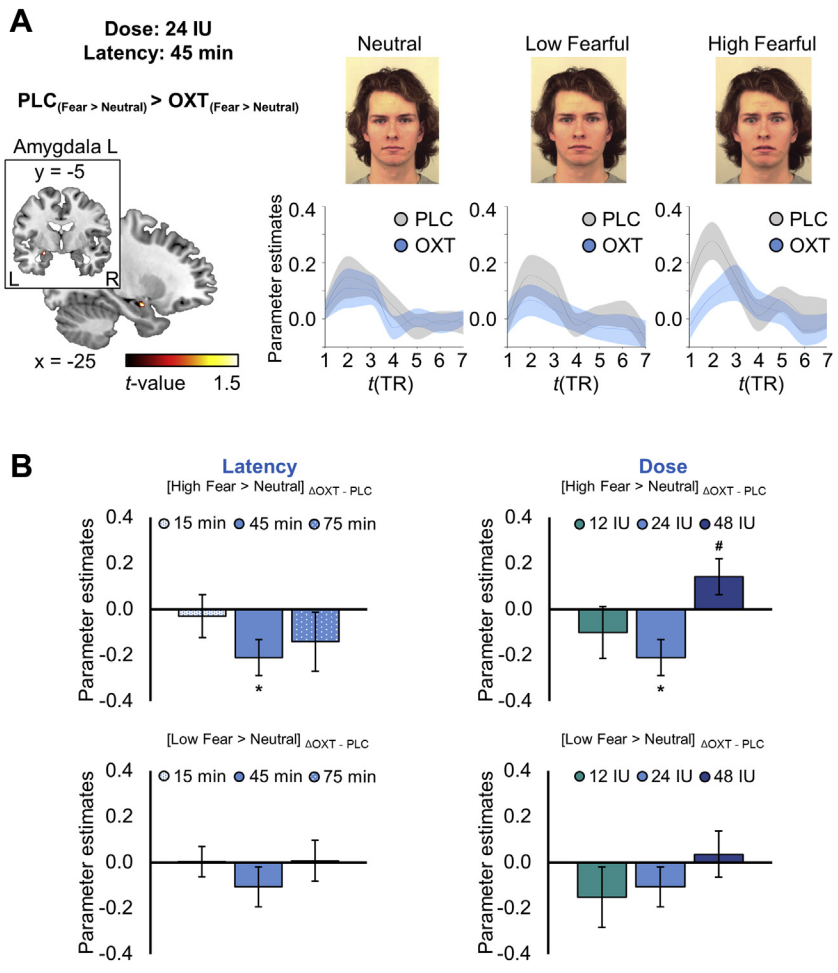

Figure 3. Left amygdala response change after treatment with intranasal oxytocin (OXT). **(A)** The amygdala response to fearful faces decreases after 24 international units (IU) administered 45 minutes prior to the task onset (Montreal Neurological Institute peak coordinates: −26, −6, −16, $t_{1,808}$ = 3.47, k = 90, p_{FWE} = .046). Time courses show a stronger OXT effect for high-intensity fearful faces. **(B)** OXT effect on amygdala response to low- and high-intensity fearful faces as a function of treatment dose and dose–test latency. The largest decrease in amygdala activation was observed following 24 IU administered 45 minutes prior to the task. The depicted neutral face is taken from the Karolinska Directed Emotional Faces stimuli set (79), image identifier: AM14NES. FWE, familywise error corrected; L, left; PLC, placebo; R, right; TR, repetition time. *$p < .05$; #$p < .10$.

predicted the PE_{AMY} under PLC (R = .30, p = .002) but not under OXT (R = −.02, p = .86; see Figure 5A).

Importantly, the OXT effect ($FearHigh_{OXT} > FearHigh_{PLC}$) on amygdala activation was moderated by the AQ. Participants with higher autistic-like traits showed larger OXT effects than participants with lower AQ scores (R = .23, $F_{1,99}$ = 5.26, p = .02; regression analysis over all subjects). When looking at the different treatment groups, the moderation was significant only in subjects receiving 24 IU and scanned after 45 minutes (R = .51, $F_{1,19}$ = 6.49, p = .02). A median dichotomization (at AQ = 13.5) revealed higher effects 45 minutes after administration of 24 IU of OXT in high-AQ subjects compared with low-AQ subjects (t_{16} = 2.13, p = .049, d = 1.07; see Figure 5B for within-group comparisons; no other significant differences between AQ subgroups in any other treatment condition).

Behavior. AQ influenced neither the tendency to judge ambiguous faces as neutral (all $ps > .15$) nor the OXT effect on these judgments ($PerceivedNeutral_{OXT} - PerceivedNeutral_{PLC}$) when tested across all subjects (R = .12, $F_{1,102}$ = 1.60, p = .21). However, a median dichotomization (at AQ = 13.5) revealed higher OXT effects on emotion recognition 45 minutes after administration of 24 IU of OXT only in the high-AQ subjects compared with the low-AQ subjects (t_{16} = −2.21, p = .041, d = 1.12; no other significant differences between AQ subgroups).

DISCUSSION

Building on a comprehensive PLC-controlled crossover design, this study sought to determine the kinetics and dose dependency of intranasal OXT effects on amygdala reactivity using task-based fMRI. By comparing five different treatment conditions, our findings provide evidence indicating that OXT effects on fear processing in the amygdala are dose dependent and most pronounced 45 minutes after intranasal delivery of a 24-IU dose of OXT. While behavioral response patterns were not sensitive enough to detect dose- or latency-dependent effects, they at least suggest that OXT reduces an emotional bias in the perception of ambiguous faces. Strikingly, both neural and behavioral effects of the optimal OXT dose/latency combination were most evident in subjects exhibiting high autistic-like traits.

Importantly, our data reveal a significant decrease in amygdala activation following 24 IU doses, but not lower (12 IU) or higher (48 IU) doses, of intranasal OXT. This finding is in line with a multitude of previous reports of reduced

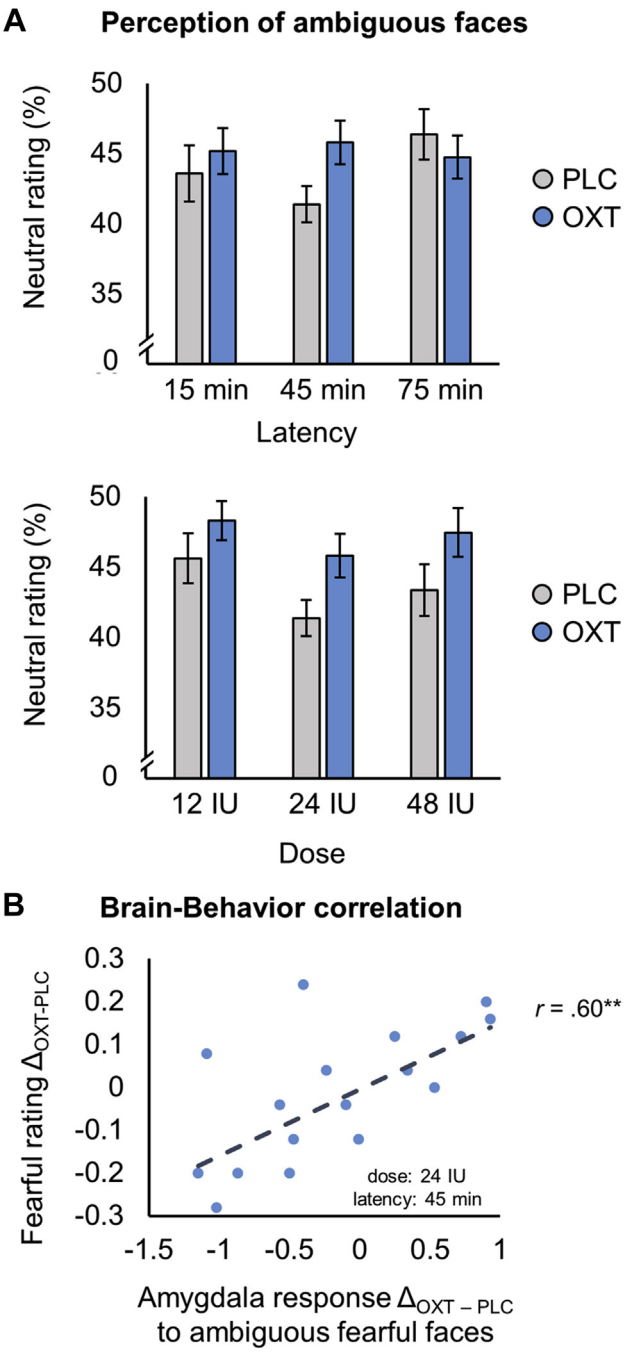

Figure 4. **(A)** Behavioral changes in the perception of ambiguous (i.e., low-intensity) emotional faces after oxytocin (OXT) separated by treatment condition. Oxytocin increased the tendency to perceive ambiguous faces as neutral. **(B)** Oxytocin-induced amygdala response changes to low fearful faces positively correlated with the OXT-induced changes in the fearfulness rating of low fearful faces after 24 IU administered 45 minutes prior to the task. IU, international units; PLC, placebo. $^{**}p < .01$.

amygdala reactivity with this particular dose [e.g., (3,7,12,53)]. Our findings partially corroborate the only two studies that systematically compared different intranasal OXT doses in healthy volunteers. Specifically, it was found that 24 IU, but not 48 IU, attenuated a stress-induced cortisol increase (32) and that 8 IU, but not 24 IU, administered with a bidirectional breath-powered nasal spray device reduced anger ratings of ambiguous faces (34) and amygdala response to angry faces (34). Our results with 24 IU closely resemble both the behavioral and neural effects of 8 IU administered via the breath-powered device, suggesting equivalent central availability in both administration conditions.

Interestingly, after administration of 48 IU of OXT, we observed an increase, rather than a decrease, of amygdala response to fearful faces. There is evidence for receptor cross-affinity between OXT and AVP; however, OXT binds to AVP receptors with much lower affinity compared with the OXT receptor (54). At higher doses, OXT may occupy AVP receptors and produce AVP-like effects (55), consistent with a nonlinear, inverted-U-shaped dose–response curve. In this context, we note that the OXT concentrations we measured in saliva after intranasal delivery of the peptide peaked fivefold higher than those occurring in response to natural triggers of endogenous release (56), which underlines the possibility of supra-physiological processes in the high-dose range.

Surprisingly, the opposite neural findings for 24 and 48 IU were not mirrored by significant differences in plasma and saliva concentrations of OXT between these doses. While uptake of the nasal spray from the richly vascularized nasal mucosa into the blood stream may be saturated at doses exceeding 24 IU, direct OXT transport into the brain via the transnasal route may rely on divergent absorption processes, perhaps yielding higher central bioavailability but less specific receptor activity of OXT following high-dose treatment. Our data thus question assumptions that neural effects of intranasal OXT primarily result from indirect blood-to-brain transport (57). It rather appears that the dose-dependent response profile we observed in the amygdala could reflect direct nose-to-brain transport, with the amygdala potentially being a privileged locus of OXT action due to its close anatomical vicinity to the putative transnasal entry points.

Given OXT's short plasma half-life of just 3 to 9 minutes (58), one would expect plasma and saliva levels to substantially drop within a 20-minute period. Interestingly, our data show relatively constant saliva levels of OXT at 20 and 40 minutes postadministration, which closely resembles the plateau observed in plasma at 15, 30, 45, and 60 minutes post-administration (25). This plateau may reflect OXT's initially continuous nose-to-blood transfer from reservoirs within the nasal cavity at approximately the same pace as concentrations decrease in plasma and saliva, which would be compatible with a gradient-dependent diffusion process.

Remarkably, the observed inhibition of amygdala responses to fear was significant only in a time window between 45 and 70 minutes after administration of a 24-IU dose of OXT. This result is relatively consistent with findings of heightened OXT signals in CSF between 35 and 60 minutes after OXT administration in animals (26,29,30) and 75 minutes after OXT administration in humans (25). The longer response lag observed in the human study may be due to CSF sampling via lumbar puncture. Furthermore, our findings are well in line with a study measuring the spatiotemporal dynamics of OXT effects on the neural activation of the brain at rest, which identified neural network changes after 40 IU of OXT peaking 39 to 51

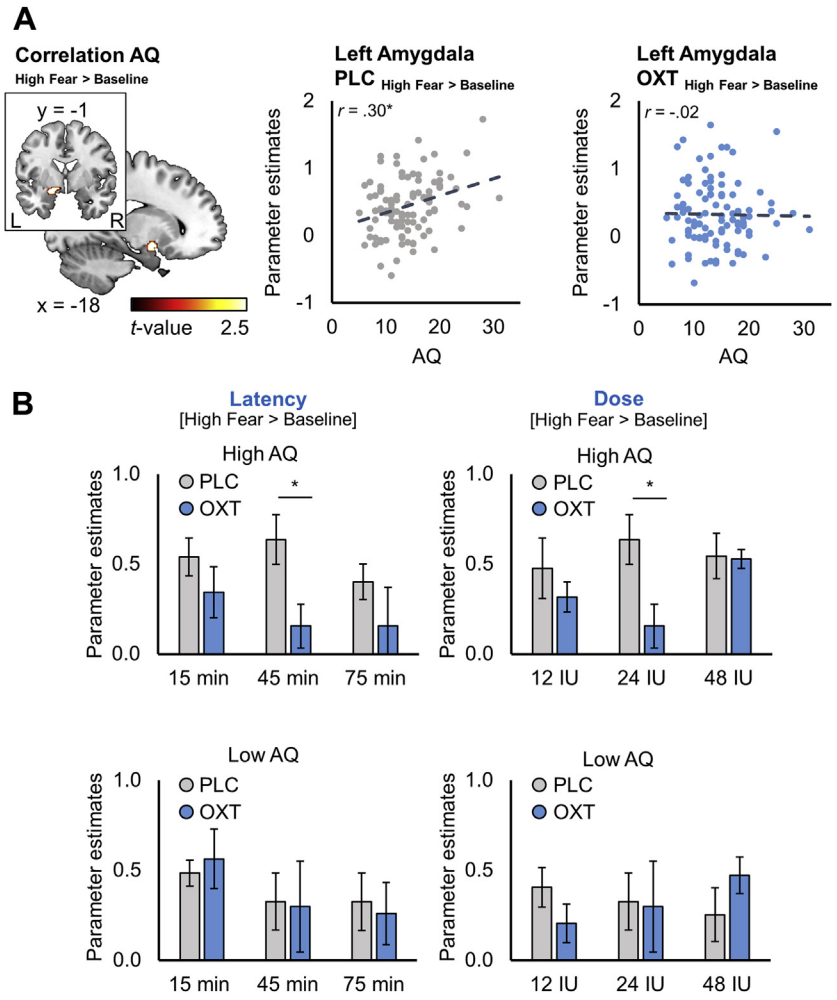

Figure 5. The effects of oxytocin (OXT) vary as a function of the autism-spectrum quotient (AQ). **(A)** A whole-brain regression analysis showed a significant correlation between AQ and left amygdala response to high-intensity fearful faces under placebo (PLC) (Montreal Neurological Institute: −18, 0, −12, t_{100} = 5.34, k = 55, p_{FWE} = .035). **(B)** The OXT effect was more pronounced in participants with high autistic-like traits, applying a median split at AQ = 13.5. FWE, familywise error corrected; IU, international units; L, left; R, right. *$p < .05$.

minutes after nasal spray administration. Together with previous findings, our results thus suggest an optimal time point of OXT administration approximately 45 minutes prior to the desired effect time window. This finding may help to maximize the effects of OXT administration on amygdala reactivity in experimental or therapeutic contexts.

Our behavioral data reveal an increased tendency to perceive ambiguous (i.e., low-intensity) emotional faces as neutral after OXT administration. Given that these ambiguous stimuli were predominantly neutral (only 35% emotional intensity), this finding is in agreement with previous observations of improved emotion recognition abilities [e.g., (1,59,60)] and reduced anger ratings of ambiguous faces after OXT administration (35). The absence of an OXT effect on recognition of highly salient emotional expressions is probably due to a ceiling effect (recognition rates were > 90%). The OXT-induced changes in the perception of ambiguous fearful faces correlated with OXT's amygdala dampening effects. This reduced tendency to perceive ambiguous faces as threatening is in line with the hypothesis of a reduced defensive behavior pattern following amygdala inhibition (61). While we did not detect dose- and latency-dependent OXT effects in the categorical behavioral responses [using continuous rating scales may have allowed revealing subtle effects (62)], our behavioral findings are of high clinical relevance; reducing the tendency to perceive ambiguous faces as threatening is believed to be one of the mechanisms underlying the beneficial long-term effects of antidepressant and anxiolytic medication (63). More generally, such behavioral effects may indicate the way in which OXT could be used to treat amygdala-mediated physiological hyperreactivity to social threat signals, a symptom at the core of social anxiety (64) but also associated with other mental disorders involving severe social deficits such as borderline personality (65) and somatoform disorders (66).

Interestingly, the optimal dose/latency combination of OXT treatment had the strongest effects in subjects with higher autistic-like traits, hinting at a therapeutic potential of OXT in the treatment of patients on the autism spectrum. This is consistent with the recent report by Kosaka *et al.* (15) of significant improvements in patients on the autistic spectrum after long-term administration of a high dose (> 21 IU), but not a low dose (≤ 21 IU), of OXT. Our results thus advocate the idea of a personalized OXT dosing regimen guided by individual autistic characteristics and might encourage further clinical trials to

disentangle OXT's impact on behavioral and neural correlates of social interaction in several psychiatric disorders. Indeed, OXT treatment for autism has been considered in various studies (14,15,59) and is being discussed for schizophrenia as well (67,68).

More generally, the person-dependent OXT effects reported here are well in line with previous studies (41,60,62), although the direction of the moderation effect may be domain specific and may vary with baseline responses. For instance, in the current study, we observed elevated amygdala response to fearful faces under PLC and the most robust OXT effect in participants with high autistic-like traits. By contrast, individuals exhibiting high AQ scores show a diminished neural response to affective touch at baseline (69,70) and a reduced OXT effect (45). We also found larger OXT effects for the highly fearful faces that are associated with stronger amygdala activation under PLC, indicating that conditions with heightened basic activity may facilitate the detection of inhibitory action of OXT. It is noteworthy that neither the baseline plasma and saliva OXT concentrations nor the treatment-induced increases were predictive of autistic-like traits. Therefore, the moderation effect could be driven by different OXT receptor distributions or the interplay with other hormonal systems. Notably, the individual body mass index did not moderate OXT's effect on the neural or behavioral level. Thus, our findings suggest no need for a weight-dependent dose titration.

One limitation of this study is a potential sexually dimorphic effect of intranasal OXT on amygdala activation (71,72). Therefore, future studies are warranted to replicate the current findings in women and explore possible interactions with gonadal steroids. It is noteworthy that the modulatory effect of OXT on responses to fearful faces in the left amygdala found here is consistent with observations in previous studies (8,12), while other studies (7) pinpointed the OXT effect in the right amygdala. These functional asymmetries might be related to methodological differences between the studies and demand further elucidation. In addition, the relationship between peripheral and central OXT measures is still unclear, and there is no consensus regarding the best protocol to determine OXT concentrations (73). In view of emerging evidence suggesting OXT receptor downregulation following chronic dosing in rodent models (74), further clinical trials using long-term treatment are needed. While we consider studies of single-dose effects valid and informative tools for designing treatment protocols entailing intermittent dosing (e.g., once weekly for augmentation of psychotherapeutic interventions), the effects of continuous administration need to be assessed in further studies. Various studies have provided evidence that amygdala activation during emotion processing is affected by the OXT receptor genotype and its epigenetic modification [e.g., (75,76)]. Future studies using neuropharmacogenetic study designs thus should consider genetic modulation of brain reactivity and sensitivity to different doses of intranasal oxytocin, with direct implications for the development of innovative personalized treatment perspectives (77). Finally, in light of studies showing altered OXT receptor expression in patient populations [e.g., (78)], the modulatory influence of OXT receptor expression in the amygdala demands further investigation.

Collectively, the current study may help to define the most effective dose (24 IU) and dose–test interval (45 minutes) for future experimental or therapeutic regimens aimed at targeting amygdala functioning with OXT administration.

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FBS, DS, and RH designed the experiments; FBS and ME conducted the experiments; FBS, JS, DS, and RH analyzed the data; and FBS, JS, DS, ME, WM, MH, and RH wrote the manuscript.

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ClinicalTrials.gov: Temporal Dynamics and Pharmacokinetics of Intranasally Administered Oxytocin; https://clinicaltrials.gov/ct2/show/NCT03011970?term=Pharmacokinetics+Oxytocin&rank=4; NCT03011970.

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