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Oxytocin differentially modulates the early neural responses to faces and non-social stimuli

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Abstract

Oxytocin (OT) alters social cognition partly through effects on the processing and appraisal of faces. It is debated whether the hormone also impacts the processing of other, non-social, visual stimuli. To this end, we conducted a randomized, counter-balanced, double-blind, placebo (PL)-controlled within-subjects' electro-encephalography (EEG) study with cismale participants (to control for gender dimorphic hormonal effects; $n = 37$). Participants received intranasal OT (24IU) and completed a one-back task viewing emotional (fearful/ happy) and neutral faces, and threat (snakes/spiders) and non-threat (mushrooms/flowers) non-social stimuli. OT differentially impacted event-related potentials (ERP)s to faces and non-social stimuli. For faces regardless of emotion, OT evoked greater occipital N1 and anterior P1 amplitudes at ~155 ms than after PL, and lead to sustained differences over anterior, bilateral parietal and occipital sites from 205 ms onwards. For all non-social stimuli, OT evoked greater right parietal N1 amplitudes, and later only impacted threat stimuli over right parietal and occipital sites. None of these OT-induced modulations was related to individual anxiety levels. This pattern of results indicates that OT differentially modulates the processing of faces and non-social stimuli, and that the hormone's effect on visual processing and cognition does not occur as a function of non-clinical levels of anxiety.

Keywords: EEG; intranasal oxytocin; face processing; ERP; threat; emotion

Oxytocin (OT) is a neuropeptide that facilitates prosocial behaviour and social bonding (Carter *et al.*, 2008; Walum *et al.*, 2009; MacDonald and MacDonald, 2010), in part, through its modulatory effect on the perception and appraisal of social stimuli like faces (Domes *et al.*, 2007). OT alters social perception and processing through many varied mechanisms, and has been linked to changes in attention, memory and perception (for comprehensive reviews, see Carter *et al.*, 2008; MacDonald and MacDonald, 2010; Veening and Olivier, 2013; Brambilla *et al.*, 2016; Grace *et al.*, 2018). While the hormone impacts many cognitive and physiological systems (Veening and Olivier, 2013), understanding and isolating the hormones influence on the early neural processing of social stimuli like faces can provide insight into the hormonal impact on social processing.

Research with intranasal OT indicates the hormone alters expression recognition (Di Simplicio *et al.*, 2009; Quintana *et al.*, 2015; Taubert *et al.*, 2019) and attentional biases to faces (Dal Monte *et al.*, 2014; Domes *et al.*, 2016). There is no evidence that OT produces overt emotional changes in human participants (Domes *et al.*, 2007; Petrovic *et al.*, 2008), but neuroimaging has shed light on its implicit effect on activity in the brain. Research has demonstrated that OT alters activity in brain regions related to social and affective processing, including the fusiform gyrus, superior temporal gyrus, anterior cingulate cortex and a key structure in the threat and emotion-sensitive limbic system—the amygdala (Grace *et al.*, 2018; Tully *et al.*, 2018). Changes in both amygdala activity and connectivity are associated with intranasal-OT (Liu *et al.*, 2015; Wang *et al.*, 2017; Grace *et al.*, 2018; Tully *et al.*, 2018), with marked reductions in the activity elicited by fearful faces (Kirsch *et al.*, 2005; Dodhia *et al.*, 2014; Grace *et al.*, 2018) and marked increases in the activity elicited by happy faces (Gamer *et al.*, 2010). These OT-induced modulations occur as a function of clinical anxiety (Labuschagne *et al.*, 2010), yet it remains unclear whether the hormone uniquely impacts social processing or produces a blanket anxiolytic effect that impacts all visual stimuli.

While OT is thought to modulate activity in several neural regions, the time course of these effects is less established. This is unfortunate because understanding how OT changes the speed of face processing will help contextualize the underlying mechanisms. Research with female participants has found OT alters face processing as early as 150 ms at the N170 over occipitoparietal regions (Peltola *et al.*, 2018), and the vertex positive potential over anterior regions (VPP; Huffmeijer *et al.*, 2013); both of which

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are well documented face-sensitive markers that fluctuate as a function of facial emotion (Joyce and Rossion, 2005; Hinojosa *et al.*, 2015). Other face-sensitive ERP markers that have not been investigated with respect to OT but are of interest include the occipital P100 which reflects early visual processing and attention (Itier and Taylor, 2002), the occipital N1 which is linked to attentional allocation to emotional stimuli (Carretié *et al.*, 2004) and the P2 which reflects later stage face processing such as contextual decision-making (Itier and Taylor, 2002). Crucially, the present ERP-OT face findings cannot be extended to men because OT's effects are sexually dimorphic (Domes *et al.*, 2010; Lischke *et al.*, 2012; Gao *et al.*, 2016). Consequently, the impact of OT on the temporal dynamics of face processing in cismales remains unknown.

In this problem space, the inclusion of social and non-social stimuli in the experimental design is important because of the debate surrounding the specificity of OT's effects. Some researchers have reported that OT has no impact on ERPs or behavioural responses to non-social stimuli (Rimmele *et al.*, 2009; Althaus *et al.*, 2015), whereas others have reported OT attenuated amygdala activation to non-social scenes, though the magnitude of this reduction was markedly less than to faces (Kirsch *et al.*, 2005). It is important to highlight that it has proven difficult to compare the neural correlates of faces and non-social stimuli because these different classes of stimuli evoke different patterns of neural activity (Schindler and Bartels, 2016). We circumvent this issue by matching social and non-social stimuli by threat-relevance.

The current study had three goals addressing three questions in the temporal domain. Firstly, we intended to determine the temporal dynamics of intranasal-OT's impact on face processing, and to assess whether this varies across facial emotion. As OT attenuates the fear-selective amygdala and increases prosociality, we predicted that OT would differentially impact electrophysiological markers of face processing dependant on facial emotion. Given the OTs prosocial influence and anxiolytic effects, we predict the threat-related N170 would be reduced to fearful faces and that attention markers would be reduced (such as N1 and P2) after OT. For happy faces, we expected such markers of attention (N1/P2) to increase after OT. Secondly, we investigated whether OT alters neural activity to non-social threats. Considering the conflicting finding non-social OT effects, we expect that if OT impacts behaviour via social-cognition specific mechanisms, OT modulations should not extend to non-social stimuli. Lastly, we sought to assess whether anxiety modulates OT's effect on ERPs. We expected that individual anxiety would predict the magnitude of OT-induced modulations, as OT-induced neural attenuations occur as a function of clinical anxiety (Labuschagne *et al.*, 2010). Importantly, this study will control for established OT-sex based differences (Gao *et al.*, 2016) and correct the asymmetry in the OT-ERP literature by recruiting cismale participants.

Methods

Participants

Participants were 40 right-handed cisgender men, who were tested on two occasions, once with a placebo (PL) and once with OT. One participant was excluded for failing to return for the second session and two were excluded due to numerous muscle artefacts, leaving a total of 37 (mean age = 23.27 years, SD = 3.87). They were a combination of volunteers and students who participated in exchange for course credit at the University of Queensland. The eligibility criteria was that participants were cisgender men, were on no mood altering or neurologically active prescribed medication, had no diagnosed neurological disorders and had normal or corrected-to-normal vision. The study was approved by the Human Ethics Committee at the University of Queensland, Australia (#2019/HE002182).

Materials, stimuli and apparatus

Treatment consisted of 24IU of synthetic OT (40.32 μg, Syntocinon) or PL. The Beck Anxiety Inventory (BAI; Beck *et al.*, 1988), Liebowitz Social Anxiety Scale (LSAS; Liebowitz, 1987) and State-Trait Anxiety Inventory (STAI; Spielberger *et al.*, 1983) were used. Seven types of grayscale stimuli were included to create three conditions: faces (neutral, fearful and happy emotions), non-social threatening images (snakes, spiders) and non-social non-threatening images (mushrooms, flowers). All stimuli were presented against a black background. For faces, 44 images (22 male, 22 female) from the Karolinska Directed Emotional Faces database (Lundqvist *et al.*, 1998) were used. Faces were neutral (18), fearful (18) and happy (18) emotions, with equal representations of male and female faces for each emotion. For non-social stimuli, 36 images (9 each of flowers, mushrooms, spiders and snakes) were used (Lipp *et al.*, 2004). All stimuli were of equiluminance, corrected using ImageJ (Rasband, 2018). Stimuli were 236 × 195 pixels (3.97 × 3.28° of visual angle) and were presented centrally from a fixed distance of 90 cm.

Apparatus

Stimulus presentation was coded in E-Prime 3.0 software (Psychology Software Tools, I., 2016). The experimental computer contained an Intel® Core™ i7-4790 CPU with a NVIDIA GeForce GTX 745 graphics card, and stimuli were displayed on a 28-inch colour LCD monitor with 1920 × 1080 resolution and 144 Hz refresh rate. Continuous EEG was recorded at 1024 Hz using an AD-Box BioSemi ActiveTwo amplifier (BioSemi, Amsterdam, the Netherlands), with 64 electrodes placed in accordance with the international 10–20 system, and 2 external electrodes placed vertically below (EXG2) and at the lateral canthus of the right eye (EXG1).

Procedure

Participants attended two sessions, approximately 1 week apart in a counter-balanced, double-blind, PL-controlled within-subjects design. At each session, participants self-administered an intranasal dose of OT (24IU) or PL in accordance with recommendations for intranasal OT administration (Guastella *et al.*, 2013)—3 sprays into each nostril, alternating sides and waiting 45 s between each spray. Participants completed the BAI and LSAS at the first session before drug administration, and the STAI at both sessions. Experimental testing (including the state portion of the STAI) began approximately 50 min post-administration around the peak of OT's effect (Spengler *et al.*, 2017).

Participants completed a 1-Back task, and responded with a key-press using their right index finger when an image was repeated. On each trial, subjects attended to a white central fixation cross (500–750 ms), then were presented with an image from one of the seven stimuli conditions (500 ms), which was followed by a black screen (for an interstimulus interval (ISI) of 1000 ms). Repetition trials were followed by a repetition of the same image, and standard trials were followed by a different image. See Figure 1 for example trials. Each group (fearful/happy/neutral/non-social threat/non-social non-threat) of 18 images were presented 6 times in random order over two blocks resulting in 108 usable trials per condition. There were 558 trials in total, 18 of which were one-back repetition trials (which were excluded from analysis), leaving 540 trials total per participant.

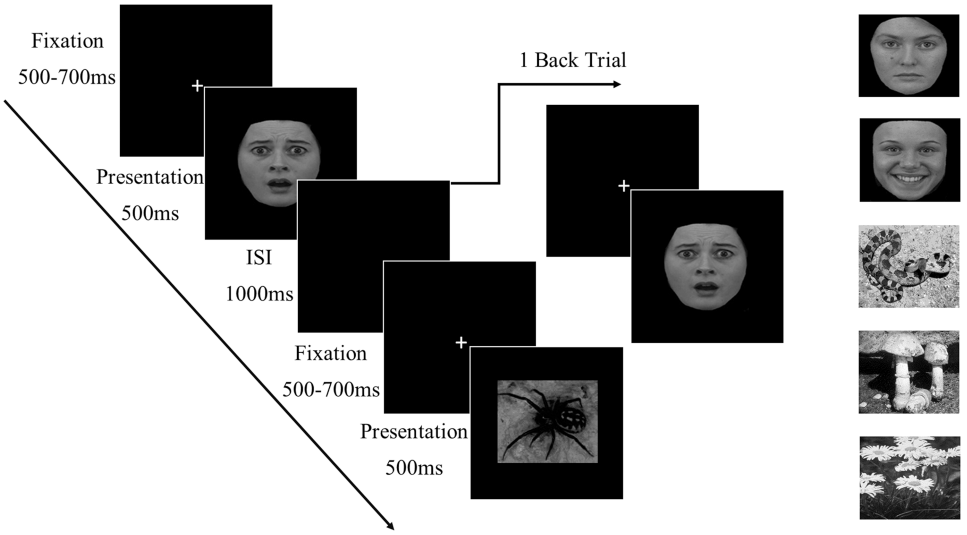

Fig. 1. Schematic illustrating a 1-Back trial and stimuli conditions.

Note. (Left) Examples of a 0-Back (no repetition) and a 1-Back trial, with fearful facial stimuli and non-social threat stimuli (spider). (Right) Examples of other stimuli conditions, from top to bottom: neutral face, happy face, non-social threat (snake) and non-social non-threat (mushrooms/flowers).

The one-back task was approximately 18 min, and each of the two sessions (OT and PL) lasted approximately 2 h.

EEG pre-processing

Pre-processing was conducted using BrainVision Analyzer, Version 2.20 (BrainVision Analyzer (Version 2.2.0) [Software], 2019). EEG data were downsampled from 1024 to 512 Hz, and re-referenced offline against the average of all 64 electrodes. Data were filtered with a high-pass filter of 0.18 Hz and a low-pass filter of 40 Hz with a notch filter at 50 Hz to account for electrical mains. Any bad electrodes were topographically interpolated by the method of spherical splines, with a cut-off of 3 interpolated electrodes before the participant was excluded from analysis (0 excluded). An independent component analysis was conducted to extract the 'eyeblink' component. Trials were segmented to −100 ms before and 800 ms after time-locked triggers, and a 100 ms baseline correction was applied. Trials where excessive muscle movements on any channel exceeded ±100 μV were removed using semi-automatic inspection, and there was a cut-off of 10% of trials before a participant was excluded from analysis (two excluded).

Experimental design and statistical analyses

Design

This experiment was a counter-balanced, double-blind, placebo-controlled within-subjects design. The design was 2 (Treatment: OT or PL) × 7 (Stimuli: Happy Face, Fearful face, Neutral Face, Mushroom [Non-Social Non-Threat], Flower [Non-Social Non-Threat], Spider [Non-Social Threat], Snake [Non-Social Threat]).

Analyses

To control for visual attention, one-back trials were assessed and an exclusion criteria implemented whereby if participants had average reaction times of over 1 s they would be excluded, or average accuracy of less than 75%.

Anxiety levels were examined with a two-way ANOVA as a function of session order (first, second), and treatment (OT, PL).

For face-ERPs, all epochs were analysed using 2 (Treatment: OT or PL) × 3 (Emotion: Fearful, Neutral or Happy) repeated measures ANOVAs. Multiple comparisons were corrected for with the use of Bonferroni corrected *P*-values for follow-up comparisons of main effects and interactions. For non-face ERPs, epochs were analysed separately for threat and non-threat using paired *t*-tests (Treatment: OT or PL).

The relationship between OT-induced impacts on ERPs was investigated for any epoch that showed an effect of OT. For each such epoch, difference scores were calculated for each participant by subtracting the average OT amplitude to all faces from the average PL amplitude to all faces (OT-PL). These scores were then normalized by dividing the difference score by the sum of the two scores. Each normalized OT difference epoch was compared in a correlation matrix to STAI, LSAS and BAI scores, and multiple comparisons were corrected for with Bonferroni *P*-values.

Results

Anxiety measures

On average, participants reported low levels of anxiety on the BAI ($M = 12.43$, $SD = 10.22$, range = 0–36 out of a total 63), low levels of social anxiety on the LSAS ($M = 39.67$, $SD = 19.68$, range = 4–113 out of a total 144) and moderate levels of trait anxiety on the STAI ($M = 39.70$, $SD = 11.98$, range = 13–66 out of a total 80). Participants reported low levels of state anxiety at both OT ($M = 34.89$, $SD = 9.85$, range = 21–70 out of a total 80) and PL ($M = 33.76$, $SD = 10.38$, range = 20–60 out of a total 80) sessions. A two-way ANOVA revealed that participants' state anxiety did not differ significantly between the two sessions as a product of the OT treatment, $F(1, 15) = 0.46$, $P = 0.505$, as a result of session order, $F(1, 15) = 0.015$, $P = 0.905$ or as an interaction between the two, $F(1, 15) = 1.32$, $P = 0.268$.

ERP results

ERP waveforms were computed as the average of all trials for each participant for fearful faces, happy faces, neutral faces, threatening non-social stimuli (snakes/spiders) and non-threatening non-social stimuli (flowers/mushrooms).

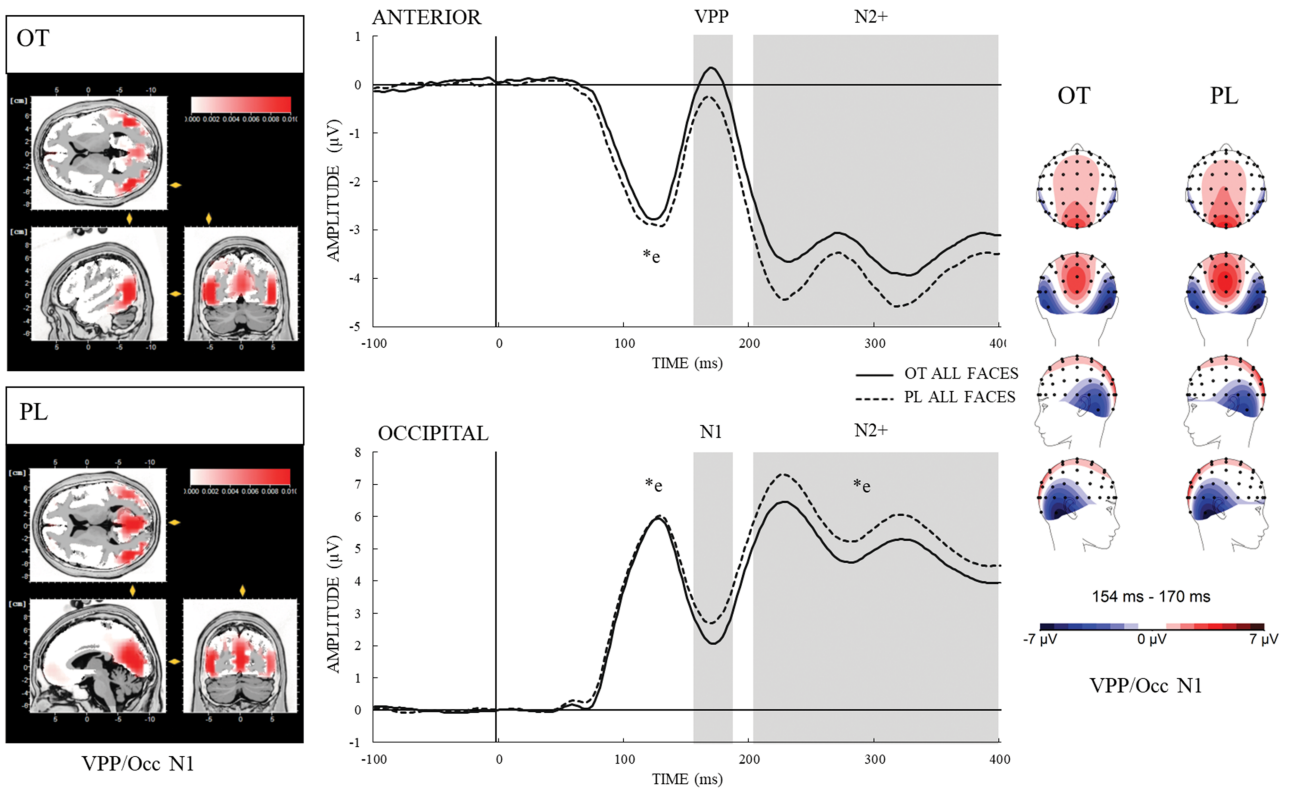

Fig. 2. Anterior and occipital ERPs to all faces after PL or OT.

Note. (Left) Source localization at 155–170 ms (the first time-point that revealed an OT-effect) after OT or PL to all faces. (Middle) ERPs to faces after OT or PL over anterior or occipital electrodes. ERPs have been collapsed across all faces (all faces represent the average ERP to happy, fearful and neutral faces) as there was no emotion × OT interaction (see Figure 4). Grey regions represent epochs where PL amplitudes significantly differ from OT amplitudes. *e refers to ERP peaks where facial emotion significantly modulated peak amplitude. ERPs represent the grand average of all participants' data. (Right) Topographical maps of activity at 155–170 ms after OT or PL to all faces.

Electrode clusters were pooled (anterior electrodes: Fp1, Fpz, Fp2, AF3, AFz, AF4, centroparietal electrodes: CP1/CP2/CPz/P1/P2/Pz, left and right parietal electrodes: P7/P9/PO7, P8/P10/PO8, occipital electrodes: O1/O2/Oz/PO3/PO4/POz) and relevant time epochs were exported for analysis. Epochs were based on previous studies of face and object processing and visual assessment of the data (Neumann *et al.*, 2011; Schindler *et al.*, 2021). ERP analyses have been presented in temporal stage-wise presentation for clarity, whereby early components are those occurring over the first peak at all respective regions of interest, mid-components occurring over the second peak and mid-late components occurring thereafter.

Face ERP results

See Figures 2 and 3 for significant treatment effects.

Early components (first peak)

Occipital P100 (110–125 ms). There was a main effect of emotion, $F(2, 72) = 14.34$, $P < 0.001$, $\eta_p^2 = 0.285$, but no effect of treatment, $F(2, 72) = 0.06$, $P = 0.800$ and no interaction, $F(2,72) = 0.26$, $P = 0.771$. Post-hoc comparisons revealed no significant differences between fearful, happy and neutral faces, all $p_{bonf} = 0.800$.

Mid-stage components (second peak)

Anterior P1 (155–170 ms). There was no main effect of emotion, $F(2, 72) = 0.78$, $P = 0.463$, but there was a main effect of treatment, $F(2, 72) = 5.77$, $P = 0.022$, $\eta_p^2 = 0.138$, such that OT ($M = 0.25$, $SE = 0.44$) enhanced the P1 amplitude compared to PL ($M = -0.33$, $SE = 0.44$).

Occipital N1 (155–170 ms). There was no effect of emotion, $F(2, 72) = 0.55$, $P = 0.579$. There was a main effect of treatment, $F(2, 72) = 4.65$, $P = 0.239$, $\eta_p^2 = 0.114$, such that OT ($M = 2.11$, $SE = 0.52$) evoked a larger negative deflection at N1 than PL ($M = 2.78$, $SE = 0.52$). There was no interaction between emotion and treatment, $F(2, 72) = 0.52$, $P = 0.599$.

Parietal N170 (155–170 ms). Over the left hemisphere, there was a main effect of emotion, $F(2, 72) = 8.93$, $P < 0.001$, $\eta_p^2 = 0.199$. Post-hoc comparisons revealed no significant difference between fearful, happy and neutral faces, all $p_{bonf} = 0.439$ (see Figure 4). There was no main effect of treatment, $F(2, 72) = 0.61$, $P = 0.439$, and no interaction, $F(2, 72) = 0.08$, $P = 0.921$.

Over the right hemisphere, there was a main effect of emotion, $F(2, 72) = 3.25$, $P = 0.045$, $\eta_p^2 = 0.083$. Post-hoc comparisons revealed no significant difference between fearful, happy and neutral faces, all $p_{bonf} = 0.461$. There was no main effect of treatment, $F(2, 72) = 0.55$, $P = 0.461$, and no interaction, $F(2, 72) = 1.00$, $P = 0.372$.

CentroParietal VPP (150–165 ms). There was an effect of emotion $F(2, 72) = 6.63$, $P = 0.002$, but no effect of treatment, $F(2, 72) = 2.69$, $P = 0.109$, and no interaction, $F(2, 72) = 1.28$, $P = 0.28$. Post-hoc comparisons revealed no significant differences between fearful, happy and neutral faces, all $p_{bonf} = 0.109$.

Mid-late components (post second peak)

Anterior Sustained N2 (205–400 ms). There was no effect of emotion, $F(2, 72) = 2.51$, $P = 0.089$, but there was an effect of treatment, $F(2, 72) = 5.05$, $P = 0.031$, $\eta_p^2 = 0.123$, such that OT ($M =$

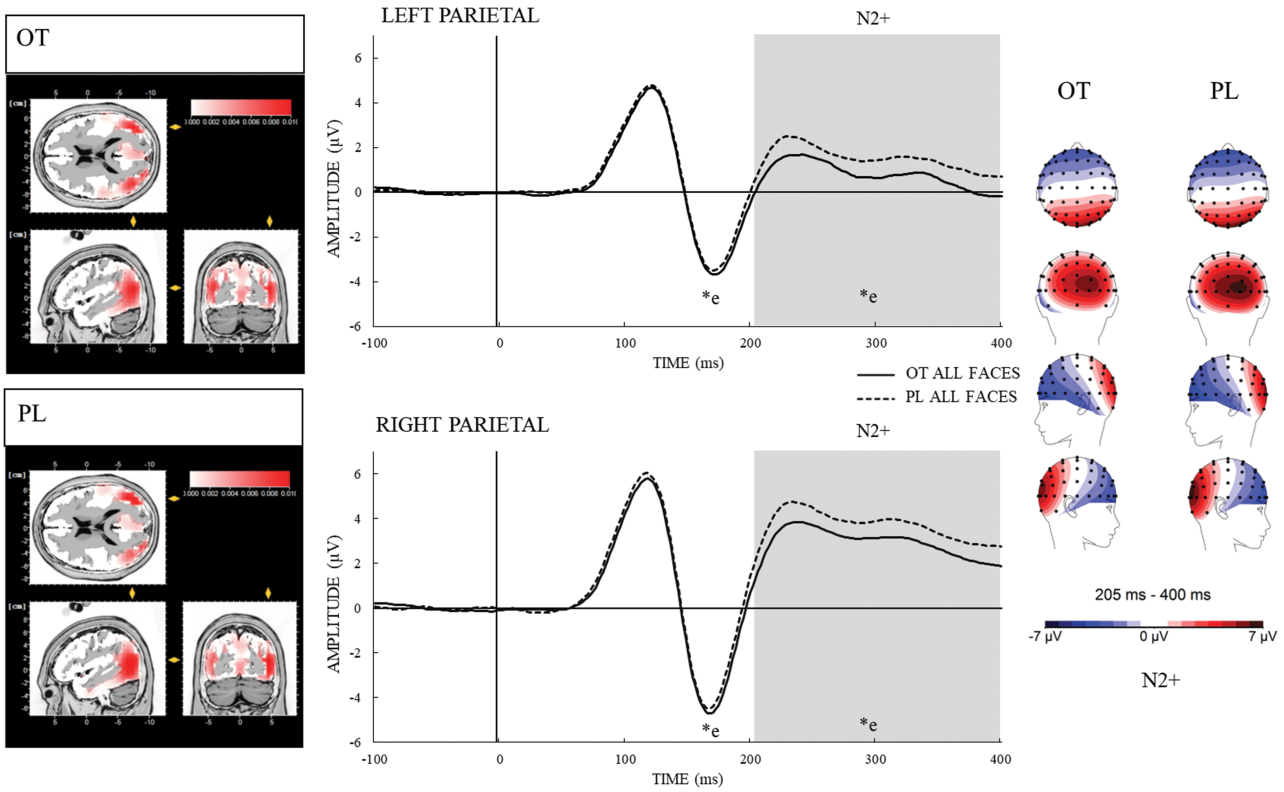

Fig. 3. Left and right parietal ERPs to all faces after PL or OT.

Note. (Left) Source localization at 205–400 ms (the second time-point that revealed an OT-effect) after OT or PL to all faces. (Middle) ERPs to faces after OT or PL over anterior or occipital electrodes. ERPs have been collapsed across all faces (all faces represents the average ERP to happy, fearful and neutral faces) as there was no emotion × OT interaction. Grey regions represent epochs where PL amplitudes significantly differ from OT amplitudes. *e refers to ERP peaks where facial emotion significantly modulated peak amplitude. ERPs represent the grand average of all participants' data. (Right) Topographical maps of activity at 205–400 ms after OT or PL to all faces.

–3.42, SE = 0.31) attenuated the sustained N2 compared to PL (M = –3.96, SE = 0.31). There was no interaction, $F(2, 72) = 2.45$, $P = 0.093$.

Occipital sustained P2 (205–400 ms). There was a main effect of emotion, $F(2, 72) = 15.55$, $P < 0.001$, $\eta_p^2 = 0.302$, and a significant effect of treatment, $F(2, 72) = 7.53$, $P = 0.009$, $\eta_p^2 = 0.173$, such that OT (M = 4.97, SE = 0.46) attenuated the P2 amplitude compared to PL (M = 5.63, SE = 0.46). There was no interaction, $F(2,72) = 1.69$, $P = 0.190$. Post-hoc comparisons revealed significant differences between all emotional faces. Neutral faces (M = 5.62, SE = 0.45) evoked the largest P2 amplitude (fearful: t = –2.75, $p_{bonf} = 0.009$, happy: t = –2.75, $p_{bonf} = 0.009$), followed by fearful faces (M = 5.28, SE = 0.45), then happy (M = 5.01, SE = 0.45, fearful: t = –2.75, $p_{bonf} = 0.009$).

Parietal sustained P2 (205–400 ms). Over the left hemisphere, there was a main effect of emotion $F(2, 72) = 12.01$, $P < 0.001$, $\eta_p^2 = 0.250$. Post-hoc comparisons revealed that fearful (M = 1.01, SE = 0.38) and happy faces (M = 0.88, SE = 0.38) did not differ ($p_{bonf} = 1.00$), but both evoked a smaller P2 amplitude than neutral faces (M = 1.45, SE = 0.38; t = –3.83 $p_{bonf} = 0.001$, and t = –4.94, $p_{bonf} < 0.001$, respectively). There was a main effect of treatment, $F(2, 72) = 6.58$, $P = 0.015$, $\eta_p^2 = 0.155$, such that OT (M = 0.81, SE = 0.39) attenuated P2 amplitudes compared to PL (M = 1.44, SE = 0.39). There was no interaction, $F(2, 72) = 0.35$, $P = 0.708$.

Over the right hemisphere, there was a main effect of emotion, $F(2, 72) = 15.64$, $P < 0.011$, $\eta_p^2 = 0.303$. Post-hoc comparisons revealed that neutral faces (M = 3.62, SE = 0.40) evoked the largest P2, which were significantly larger than fearful (M = 3.24, SE = 0.40; $p_{bonf} = 0.017$) and happy faces (M = 2.89, SE = 0.40; $p_{bonf} < 0.011$). In addition, fearful faces were larger than happy faces (t = 2.63, $p_{bonf} = 0.037$). There was a significant main effect of treatment, $F(2, 72) = 8.17$, $P = 0.007$, $\eta_p^2 = 0.185$, such that OT (M = 2.88, SE = 0.42) evoked smaller P2 amplitudes than PL (M = 3.62, SE = 0.42). There was no interaction, $F(2, 72) = 1.135$, $P = 0.327$.

Non-face ERP results

Next, we examined responses to the threatening and non-threatening stimuli. Due to the different pattern of non-threat and threat ERPs, analysis was performed separately on threat and non-threat ERPs. Epochs of interest were selected based on previous literature and through visual analysis. Due to the large number of non-significant results, for clarity these are grouped by significant *vs* non-significant epochs. See Figure 5 for significant treatment effects.

Threat significant epochs

Right parietal N1 (150–165 ms). There was a significant difference between N1 amplitude for OT compared to PL sessions, $t(36) = -2.37$, $P = 0.023$, Cohen's d = –0.39, such that the N1 over right parietal electrodes was amplified after OT (M = 3.99, SE = 0.69) compared to PL (M = 4.52, SE = 0.72).

Occipital sustained P2 (195–400 ms). There was a significant difference between P2 amplitude for OT compared to PL sessions, $t(36) = -2.07$, $P = 0.046$, Cohen's d = –0.34, such that the P2 was

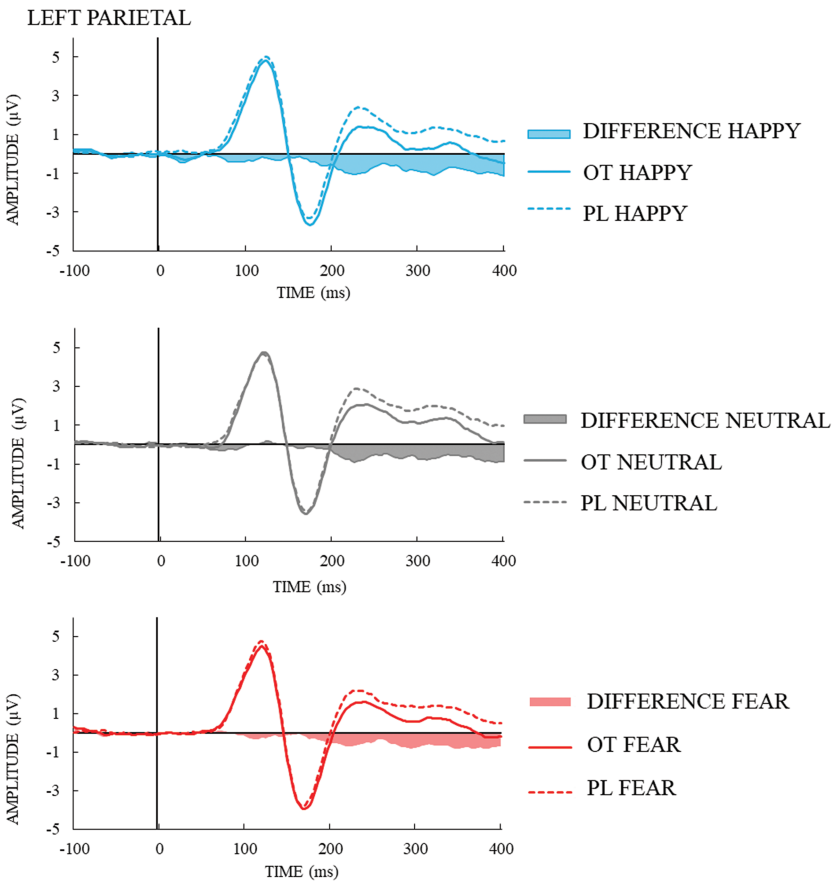

Fig. 4. Left parietal ERPs to happy, fearful and neutral faces after OT and PL, and difference waveforms.
Note. Solid lines represent ERPs to faces after OT and dotted lines after PL. Shaded regions indicate difference waveforms (OT ERP—PL ERP). (Top) Happy faces. (Middle) Neutral Faces. (Bottom) Fearful faces.

attenuated after OT (M = 8.41, SE = 0.70) compared to PL (M = 9.11, SE = 0.75).

Right parietal sustained P2 (253-400 ms). There was a significant difference between P2 amplitude for OT compared to PL sessions, t (36) = –2.68, $P = 0.011$, Cohen's d = –0.44, such that the P2 over right parietal electrodes was amplified after OT (M = 8.81, SE = 0.64) compared to PL (M = 9.74, SE = 0.71).

Threat non-significant epochs

Occipital P100 (90–100 ms) t = –0.72, $P = 0.478$; N1 (130–150 ms) t = –0.98, $P = 0.330$. Anterior P1 (150–170 ms) t = 1.34, $P = 0.190$; N2 (200–350 ms) t = 1.35, $P = 0.185$. Parietal P1 (110–130 ms) left t = –0.18, $P = 0.855$, right t = 2.22, $P = 0.333$; N1 (150–160 ms) left t = –1.02, $P = 0.314$; sustained P2 (253–400 ms) left t = –1.86, $P = 0.071$. Centroparietal CP2 (210–235 ms) t = –0.48, $P = 0.632$, CN2 (250–270 ms) t = –0.12, $P = 0.905$, CP3 (300–400 ms) t = –0.147, $P = 0.884$.

Non-threat significant epochs

Parietal N1 (150-165 ms). There was a significant difference between N1 amplitude for OT compared to PL sessions, t (36) = –2.10, $P = 0.043$, Cohen's d = –0.35, over right parietal electrodes such that the N1 was amplified after OT (M = 5.16, SD = 3.88) compared to PL (M = 5.76, SD = 4.53).

Non-threat non-significant epochs

Occipital P100 (90–100 ms) t = 0.87, $P = 0.392$; N1 (130–150 ms) t = –1.16, $P = 0.252$; P2 (195–230 ms) t = –1.68, $P = 0.101$; P3 (300–400 ms) t = –1.60, $P = 0.117$. Anterior P1 (150–170 ms) t = –0.93, $P = 0.358$; N2 (200–230 ms) t = 0.61, $P = 0.542$; Sustained P2 (205–400 ms) left t = –0.84, $P = 0.405$, right t = –1.94, $P = 0.060$. CentroParietal CP2 (210–235 ms) t = –0.31, $P = 0.759$; CN2 (250–270 ms) t = 0.19, $P = 0.852$; CP3 (300–400 ms) t = –0.03, $P = 0.974$. Parietal P1 (110–130 ms), N1 (150–165 ms) left t = –0.49, $P = 0.621$; sustained P2 (205–340 ms) left t = –1.30, $P = 0.201$, right t = –1.71, $P = 0.096$.

Anxiety results

Face ERPs

No normalized OT difference scores (occipital N1, anterior P1, anterior, occipital and bilateral parietal sustained P2) were significantly correlated with any anxiety measure (BAI/LSAS/STAI) after Bonferroni correction for multiple comparisons.

Non-face ERPs

No normalized OT difference scores (right parietal N1 for threat and non-threat, and occipital and right parietal sustained P2 for threat stimuli) were significantly correlated with any anxiety scores Bonferroni correction for multiple comparisons.

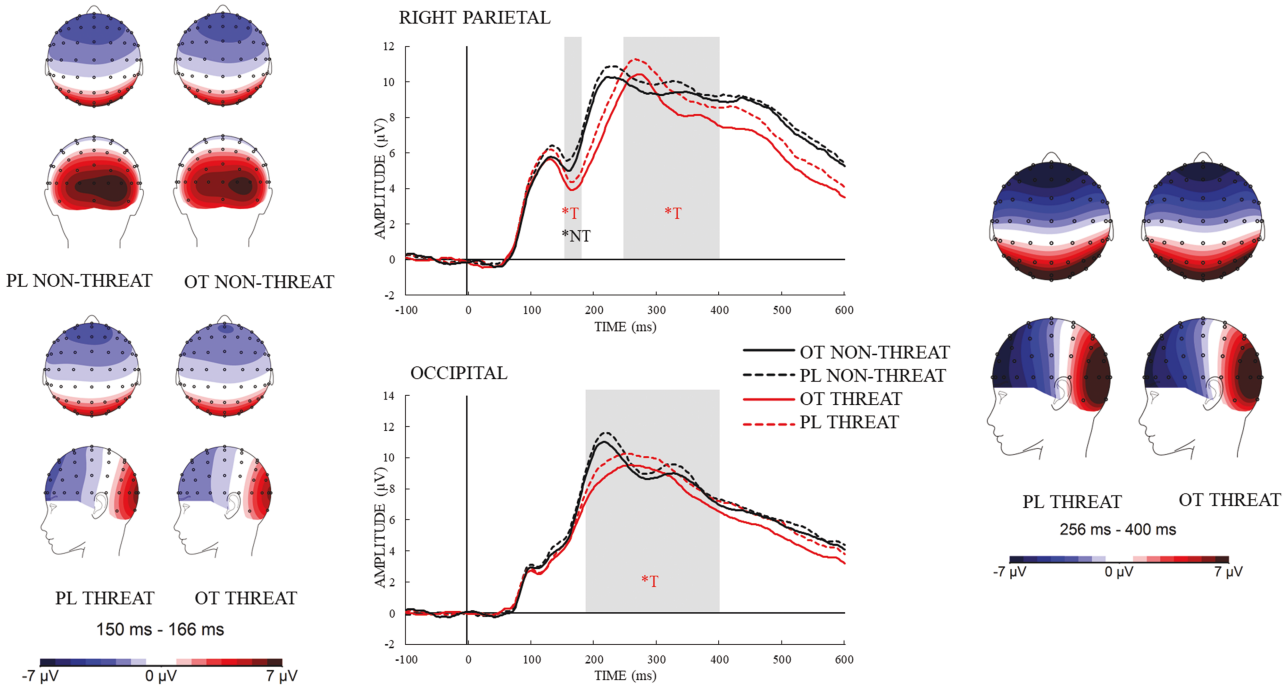

Fig. 5. ERPs to non-social stimuli.

Note. (Left) Topographical maps at 150–166 ms (the first time-point that revealed an OT-effect) after OT or PL to non-social stimuli, top are non-threat, bottom are threat. (Middle) ERPs to non-social stimuli after OT or PL over right parietal or occipital electrodes. ERPs have been collapsed across threat (snakes/spiders) and non-threat (flowers/mushrooms). Grey regions represent epochs where PL amplitudes significantly differ from OT amplitudes non-threat or threat ERPs. *T refers to regions where OT amplitude differed from PL to threat stimuli, *NT indicates regions where OT amplitude differed from PL for non-threat stimuli. ERPs represent the grand average of all participants' data. (Right) Topographical maps of activity at 256–400 ms after OT or PL to all faces.

Discussion

Our results yielded a number of key electrical differences in the human male brain that were dependent on OT. We found that OT administration affected both face and non-face stimuli, though the pattern of the hormone's influence differed based on stimuli type, suggesting that this was not solely a non-specific effect. In relation to facial stimuli, this study revealed an enhancement of early ERP markers at the anterior P1 and occipital N1 starting at 155 ms, followed by a global attenuation of later neural components, specifically the sustained P2 over anterior, parietal and occipital electrodes. These findings indicate that OT modulates the early stages of face processing and that this modulation is sustained throughout the course of activation. However, we found no interaction between OT administration and the emotional valence of face stimuli on any ERP epoch.

Contrary to our expectations, we found that OT altered ERPs to non-social stimuli. After OT administration, both threat and non-threat relevant stimuli evoked larger N1 amplitudes over right parietal electrodes. OT altered the later amplitudes of threat-relevant stimuli, with an attenuated occipital and right parietal sustained P2, suggesting some interaction with threat-relevance. Unlike facial ERPs where OT did not interact with expression, OT did seem to produce different effects for non-social stimuli, and the attenuated of the P2 after OT to threats was not seen for non-threat non-social stimuli. Finally, regarding anxiety, contrary to our predictions, we found no relationship between individual's level of anxiety and the magnitude of any OT-induced neural change. This helps to rule out individual differences in anxiety as a contributing factor to these results and other previous results. Collectively, these findings indicate that the impacts of OT administration on the neural correlates of visual processing are multiplexed.

Social stimuli

As with previous work (Tillman *et al.*, 2019), we found no impact of OT on N170 amplitude. The N170 reflects face categorization and configural processing, and these findings support that this marker is an index of automatic face processing (Heisz *et al.*, 2006), insensitive to trait-modulations in anxiety (Chronaki *et al.*, 2018). This aligns with the absence of any OT effect on the VPP as both components are hypothesised to have the same neural origin (Itier and Taylor, 2002; Joyce and Rossion, 2005; Luo *et al.*, 2010). Previous ERP research with cisfemales found OT-induced effects at these markers (Huffmeijer *et al.*, 2013; Peltola *et al.*, 2018), but the sexually dimorphic effect of OT explains this inconsistency in findings. A mechanism for this dimorphism is the interaction between OT and estradiol. Females have endogenously higher OT plasma levels, and the gonadal steroid estradiol occurs in higher levels in females than males (Kramer *et al.*, 2004). Estradiol has been found to interact antagonistically with intranasal OT's effects, neutralizing any neural impact that each hormone would produce when delivered independently (Coenjaerts *et al.*, 2022).

OT's earliest impact was an enhancement of the occipital N1, another face-sensitive marker (Mitsudo *et al.*, 2011). The visual N1 is reflective of attention (Mangun and Hillyard, 1987; Luck *et al.*, 2000) and related discriminative processes (Vogel and Luck, 2000). The one-back task is an active discriminative similarity assessment task; this N1 enhancement could reflect an improved attentional and discriminatory processing of face stimuli as a product of OT. An attenuated anterior P1 at the same epoch was also found, but source localization revealed the focal origin of this activity is occipital in nature for both OT and PL conditions (see Figure 2, Left). Therefore, the OT-induced modulation to activity at this early stage reflects enhanced processing over posterior visual areas, indexed by both the P1 and N1 changes.

From ~200 ms onwards OT attenuated amplitudes at anterior, occipital and parietal sites, indicating that OT prompts sustained, continuous activation and that the hormone does not alter processing of a singular electrophysiological component or stage of a cognitive process. This diffuse activation aligns with findings that OT increases functional connectivity with extended regions involved in the evaluation and appraisal of stimuli (Dodhia *et al.*, 2014; Gorka *et al.*, 2015). Reduced amplitudes at this stage of face-processing can reflect reduced attentional resources (Luo *et al.*, 2010). Models of face processing suggest that these later stages of processing post-structural encoding reflect cognitive processes like judgements, identity retrieval and the processing of related semantic information (Vanderploeg *et al.*, 1987; Bentin and Deouell, 2000). Therefore, these results indicate that OT does not affect the earliest stages of general visual processing (occipital P1), but instead alters the earliest stages of face-specific processing (occipital N1/anterior P1) and this effect then propagates through later stages of perceptual and cognitive processing.

Non-social stimuli

Our second aim was to elucidate how OT modulates ERPs to non-social stimuli. Compared to socially relevant faces, activity to non-social stimuli was first modulated by OT at approximately the same time (~150 ms); however, the hormone modulated the later neural response over fewer topographical locations. At the early stage, OT-induced differences to faces were observed over anterior and occipital sites, but for non-social stimuli this effect was restricted to occipital only. Regardless of emotion, OT attenuated the P2 over anterior, bilateral parietal and occipital sites. Meanwhile, OT was related to an attenuated P2 over right parietal and occipital electrodes for threat-related stimuli alone. This demonstrates that OT does impact the processing of non-social stimuli in a dissociable pattern from social stimuli. This dissociable but evident effect of OT is in line with findings that OT attenuates amygdala activity to non-social stimuli, but with a less pronounced effect than for social stimuli (Kirsch *et al.*, 2005). These different OT-induced patterns observed for faces and non-social stimuli indicate that there may be independent neural circuits underscoring the evaluation of threat for social and non-social stimuli (Prather *et al.*, 2001; Meyer-Lindenberg *et al.*, 2005). Intranasal OT impacts multiple brain structures (Grace *et al.*, 2018; Tully *et al.*, 2018), and the present findings indicate that the hormone affects both the networks governing early face processing and others involved in the slower assessment of visual stimuli more generally. Further, since these differences were not related to individual levels of anxiety, we conclude that OT does not act on visual processing through a generalized anxiolytic effect.

While our results indicate that OT alters stimuli processing through a more complex route than mere anxiety reduction, the hormone does appear to interact with threat-relevance when considering the processing of non-social stimuli. OT differentially impacted the ERPs to threat and non-threat relevant stimuli, altering the processing of threat-related stimuli over more epochs and topographical locations. This could reflect that OT reduces unconscious threat response to such stimuli, as OT decreases coupling to brainstem regions involved in autonomic threat responses (Kirsch *et al.*, 2005). However, it must be noted that threat and non-threat stimuli are confounded by object animacy; therefore, these differential effects can only be tentatively related to threat relevance.

General discussion

The regions altered by OT have been established through neuroimaging, but the present study establishes that OT impacts the processing of faces relatively early and over a sustained period. The mechanism through which OT facilitates this is still revealing itself. OT appears to increase the salience of social stimuli (Averbeck, 2010; Bartz *et al.*, 2011; Cardoso *et al.*, 2014), potentially by reducing its perceived ambiguity (Zheng *et al.*, 2021). Greater amygdala activation is proposed to determine the ambiguity, intent and threat value of emotional faces (Morris *et al.*, 1998; Davis and Whalen, 2001), and the reduction of this activity after OT may reflect a reduction of perceived ambiguity and the related attentional resources required to assess subtle cues when judging valence (Domes *et al.*, 2007). Our early attenuation and later diffuse global modulation of activity could reflect that OT enhances the attention to and early discrimination of faces, reducing ambiguity and increasing salience.

As high anxiety individuals have hyperactive amygdala activity which is normalised after OT (Labuschagne *et al.*, 2010), we had expected to see a reduction in electrophysiological markers as a function of individual anxiety levels. Our findings did not reveal such a relationship; however, this may be due to the non-clinical nature of the sample (Labuschagne *et al.*, 2010; Dodhia *et al.*, 2014; Gorka *et al.*, 2015), and could suggest that the effect of OT on social processing does not vary with non-pathological levels of state or trait anxiety. Explicit anxiety levels did not change significantly after OT, supporting the implicit nature of OTs effect. However, although we found no evidence of a relationship between individual anxiety levels and the effect of OT in this experimental context, we cannot rule it out. More research is needed to understand how other factors such as perceived gender of stimuli mediate this relationship.

Intranasal OT has been linked to both an attenuation of amygdala activity and importantly increased connectivity between the amygdala and medial prefrontal (Dodhia *et al.*, 2014) and anterior cingulate cortices (Gorka *et al.*, 2015). These connections are key bodies of the neural emotion regulation (Etkin *et al.*, 2011) and salience networks, respectively (Seeley, 2019). It is clear that OT does not alter social processing through one mechanism, but by altering the activation and connection of a host of interconnecting neural networks. OT increases prosocial behaviour and social bonding by decreasing amygdala activation, leading to a reduction in perceived ambiguity and threat appraisals of stimuli at early processing stages. The increased coupling with cortical areas involved in the regulation of emotion and evaluation of stimuli may lead to accurate assessments of stimuli and increased trust, leading to global changes in neural activity at mid to later stages of processing.

Some limitations must be considered when considering the current findings and related implications. Firstly, the present experiment was designed to examine the effect of OT on the processing of a range of facial emotions, and due to the attenuating relationship between clinical anxiety and the hormone to examine the effect of OT on threat and non-threat relevant non-social stimuli. As such, a full comparison of social to non-social stimuli cannot be made, as the social stimuli include stimuli with positive, negative and neutral valences, whereas the non-social stimuli are comprised of positive and negatively valanced stimuli. Regarding stimuli selection, the non-social set is confounded by object animacy, where the non-threat group is made up of inanimate objects and the threat related is comprised of inanimate objects. Another consideration is that as the hormone impacts social processing, its application may also impact the neural processing of facial stimulus gender. This presents an important area for future research as perception of own *vs* other gender modulates mid-stage ERP components (Ito and Urland, 2003).

In sum, our findings reveal a pronounced differential pattern of activation of OT on ERPs evoked by faces compared to ERPs evoked by non-social stimuli. We found an enhanced occipital N1 and anterior P1 response to all faces after OT followed by a global topographical attenuation of activity at the P2, indicating that OT alters face processing at an early stage seemingly regardless of emotion. Conversely, we found that the impact of OT on processing of non-social stimuli was not as global (restricted to occipital and right parietal regions) and varied by threat relevance. These findings contribute to our understanding of the interplay between the complex, composite brain mechanisms underlying visual processing and cognition.

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Data availability

The data underlying this article will be made available upon request to the corresponding authors. Conceptualization: EM, NN, JT and AJP; Methodology: EM & AJP; Investigation: EM; resources: AJP; Data curation, EM & AJP; Writing—original draft preparation; EM & AJP; writing—review and editing: EM, NN, JT & AJP; Supervision, AJP; Project administration: EM & AJP.

Conflict of interest

The authors declared that they had no conflict of interest with respect to their authorship or the publication of this article.

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