OXFORD

Social Cognitive and Affective Neuroscience, 2017, 1668–1677

doi: 10.1093/scan/nsx094
Advance Access Publication Date: 25 July 2017
Original article

Electrophysiological correlates of oxytocin-induced enhancement of social performance monitoring

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Abstract

Altered performance monitoring has been demonstrated after administration of different pharmacological compounds and in various clinical populations, such as excessive neurophysiological responses to mistakes in anxiety disorders. Here, a novel social pharmacological approach was applied to investigate whether oxytocin administration (24 IU) enhances performance monitoring for errors that have negative consequences for another individual, so-called social mistakes. Healthy male volunteers ($N = 24$) participated in a placebo-controlled crossover design. EEG measures were obtained while pairs of participants performed a speeded choice reaction-time task in an individual and social context. Following oxytocin administration, error-related negativity amplitudes were increased for social compared with individual mistakes. This increase was not found in the placebo condition. No effects of oxytocin were present in the individual context. The current study shows that oxytocin enhances performance monitoring specifically for social mistakes. This outcome is in line with a presumed role for oxytocin in salience attribution to social cues and underlines its context-dependency. Combining these processes may thus open up new research avenues and advance our understanding of individual differences in performance monitoring and oxytocin responses from a social neurocognitive, pharmacological and clinical perspective.

Key words: oxytocin; error-related negativity (ERN); performance monitoring; event-related potential (ERP); social mistakes

Introduction

Humans are usually quite efficient in detecting their errors and generating adequate behavioral adjustments in response to them. To accomplish this, people monitor their performance continuously for errors and possible deviations from their goals (de Bruijn *et al.*, 2009). The cognitive and neural mechanisms of performance monitoring have been studied extensively since the discovery of an event-related potential (ERP) related to error detection. This so-called error-related negativity (ERN) or error negativity (Ne) is elicited immediately after an erroneous response and is followed by positive deflections specific to error trials collectively known as the error positivity (Pe; Falkenstein *et al.*, 1990; Gehring *et al.*, 1993). The Pe consists of two subcomponents: (i) the 'early' Pe that immediately follows the ERN and shares the same neural generators and (ii) the 'late' Pe—also referred to as the classical Pe –, which is a slow positive wave at more parietal electrodes observed between 300 and 500 ms post-response (Ullsperger *et al.*, 2014b). The exact function of the Pe is still under debate, but it is thought to be involved in more conscious affective processing of the error (Ullsperger *et al.*, 2014a). Functional magnetic resonance imaging (fMRI) studies have revealed a central role for an emotional and

Received: 4 January 2017; **Revised:** 15 July 2017; **Accepted:** 20 July 2017

cognitive control network involving anterior cingulate cortex and bilateral insular cortex, with increased activations in this cingulate-insula network for erroneous compared with correct actions (de Bruijn *et al.*, 2009; Ridderinkhof *et al.*, 2004). Here, we employ a psychopharmacological approach to study the effects of oxytocin administration on the electrophysiological correlates of performance monitoring in a social context.

The ERN is assumed to trigger short-term behavioral adjustments or long-term learning, and thus ensures efficient, safe and flexible behavior (Falkenstein *et al.*, 1990; Gehring *et al.*, 1993). However, the distress associated with making mistakes is usually something we prefer to avoid, and the level of distress may also be reflected in the neural response to errors. Hajcak *et al.* (2005), for example, showed that ERN amplitudes were larger when another person evaluated subjects' performance online, inducing increased error significance. This finding is in line with an abundance of clinically oriented research showing that heightened levels of trait anxiety are related to increased error-related activations (de Bruijn and Ullsperger, 2011), such as enhanced ERN amplitudes in healthy volunteers with high levels of trait anxiety (e.g. Aarts and Pourtois, 2010; Hajcak *et al.*, 2003; Moser *et al.*, 2013) or in individuals suffering from obsessive–compulsive disorder (OCD; e.g. Endrass *et al.*, 2008, 2010; Endrass and Ullsperger, 2014; Gehring *et al.*, 2000; Stern *et al.*, 2010).

Modulations of performance-monitoring processes may thus be related to changes in affective distress associated with errors, but the exact underlying mechanisms remain unclear. Errors made in a social context are often even more upsetting as they may be linked to increased responsibility for others or elicit feelings of embarrassment. However, performance-monitoring research has mainly focused on individual behavior and has only more recently ventured into the domain of social performance monitoring (e.g. de Bruijn *et al.*, 2011; de Bruijn and von Rhein, 2012; Koban and Pourtois, 2014; Koban *et al.*, 2012). This is surprising, because the social nature of human behavior implies that our actions often also affect the people around us. Mistakes are of specific interest as they usually have negative consequences not only for ourselves, but also for the persons around us.

Using fMRI, we previously showed that these so-called 'social mistakes', i.e. errors that additionally affected a co-actor, increased activations in mentalizing areas, such as dorsal medial pre-frontal cortex (dMPFC; Radke *et al.*, 2011). This finding supports the notion that participants are thinking more about their co-actor's thoughts and feelings (Mitchell, 2009; Van Overwalle, 2011) and take their perspective (Shamay-Tsoory *et al.*, 2009a) when their actions also have consequences for the other person compared with when errors only affect themselves. Another study showed that for errors that caused pain in others, fMRI revealed increased activations in the (left) anterior insula (Koban *et al.*, 2013). Taken together, these fMRI studies suggest that increased error significance associated with social mistakes may result in enhanced activations in areas known to be involved in social cognitive processes and performance monitoring. Importantly however, performance monitoring usually takes place within milliseconds, and methods with a high temporal resolution such as ERPs are thus more suited to capture the entire process.

Previous ERP studies have shown that activations of the performance-monitoring network are highly susceptible to modulations induced by psychopharmacological compounds and that especially the neurotransmitter dopamine seems to play a crucial role (see e.g. de Bruijn *et al.*, 2004, 2006; Jocham and Ullsperger, 2009; Zirnheld *et al.*, 2006). Interestingly, dopaminergic activity appears to be affected by the hormone oxytocin (Love, 2014) and a recently proposed model highlights the overlap in performance-monitoring structures targeted by oxytocin and dopamine, specifically anterior cingulate, insula and striatum (Quattrocki and Friston, 2014). From a social and therapeutic perspective, the role of oxytocin in human behavior has been the topic of a growing number of investigations over the past years. Oxytocin is a non-apeptide synthesized in the hypothalamus and has been suggested to facilitate prosocial behavior in healthy volunteers (e.g. Domes et al., 2007; Heinrichs *et al.*, 2009; Kosfeld *et al.*, 2005) and clinical populations (e.g. Yatawara *et al.*, 2016; Guastella *et al.*, 2015).

Indeed, initial studies mainly reported positive effects of oxytocin administration on a wide range of socio-emotional behaviors, e.g. improved trust or emotion recognition abilities (see e.g. Kosfeld *et al.*, 2005; but see Nave and McCullough, 2015; Radke and de Bruijn, 2013). This view, however, has been challenged with recent studies emphasizing the context dependency of such effects (see e.g. Bartz *et al.*, 2011; Tabak *et al.*, 2016). In an attempt to explain the influence of context and personality characteristics as well as oxytocin-induced antisocial behaviors, such as envy and unfairness (see e.g. de Dreu *et al.*, 2011; Radke and de Bruijn, 2012; Shamay-Tsoory *et al.*, 2009b), Shamay-Tsoory and Abu-Akel (2016) have recently proposed the social salience hypothesis of oxytocin. The central idea of this framework is that the salience effect of oxytocin modulates attention-orienting responses to external contextual social cues, but is dependent on baseline individual differences such as gender and personality traits. Importantly, Quattrocki and Friston (2014) also point out that oxytocin receptor activation facilitates neuronal communication on several time scales, both short-term and in a more enduring manner. This is important, as oxytocin-induced modulations of immediate neural transmission seem required for alterations of fast processes such as attention-orienting and error detection. To the best of our knowledge, no studies have yet investigated possible effects of oxytocin on (social) performance monitoring.

Using a cross-over placebo-controlled design and a social choice-reaction time task, we investigated whether oxytocin modulates the electrophysiological correlates of social performance monitoring. In the placebo condition, we expected ERN and Pe amplitudes to be enhanced for social compared with individual mistakes due to increased error significance. Following the social salience hypothesis, the effect of social mistakes on ERN and Pe amplitudes should be even further increased after oxytocin administration.

Materials and methods

Participants

Healthy male volunteers ($N = 24$; mean age = 21.5 years; SD = 1.9) performed two versions of a social flanker task. All participants received financial compensation for participation. None of the participants reported current or past neurological or endocrine diseases, medication use, or drug or alcohol abuse, and participants had to be between 18 and 30 years of age (see Supplementary Material for further exclusion criteria). All participants gave their written informed consent. Procedures were in accordance with the Declaration of Helsinki and approved by the Medical Ethics Committee of the University Medical Centre in Nijmegen, the Netherlands.

Experimental procedure

We used a double-blind placebo-controlled within-subjects design. Two participants—who did not know each other

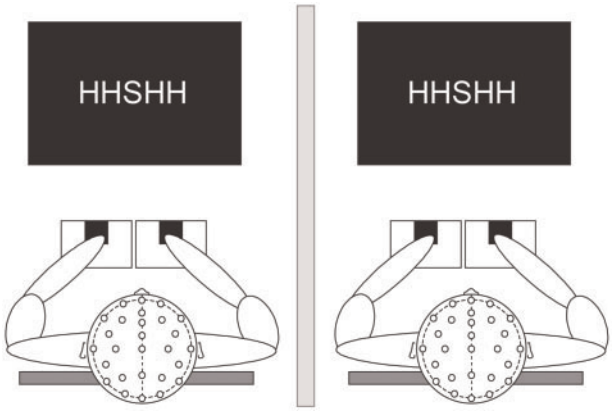

Fig. 1. Experimental setup with two participants seated next to each other behind their own individual computer screens. Both participants performed the task simultaneously while EEG was recorded.

beforehand—were invited to come to the lab at the same time. Upon arrival they self-administered six puffs (three per nostril) resulting in a total of 24 intranasal units (IU) of placebo (a solution of sodium chloride or NaCl) or oxytocin (synthesized by Defiante Farmaceutica, sigma-Tau, the Netherlands). An independent research assistant who was blind to the experimental hypotheses and who left immediately after administration supervised the procedure. The experimenter was not present during the administration. Randomization was performed and controlled by the pharmacy of the University Medical Centre in Nijmegen. The two experimental sessions were separated by 14 days scheduled for weekdays starting at 10 AM.

Following administration, preparations for EEG measurements were taken and participants received written and verbal task instructions. Participants were then seated next to one another behind individual computer screens (see Figure 1) and started task performance ~40 min after substance administration. Throughout, participants wore earplugs to ensure that button clicks from the co-actors could not be heard. A screen was placed between the participants so that they could not see the buttons or computer screen of their co-actor.

Social flanker task

Participants performed a social version of the Flanker task (Eriksen and Eriksen, 1974) in two different contexts (see Figure 1). The goal of the Flanker task is to give a left or right button press depending on the central letter (H or S) in a string of five letters. The central letter can either be the same to the surrounding (i.e. flanking) letters (congruent trial: e.g. HHHHH) or different (incongruent trial: e.g. SSHSS). The two contexts (individual, social) were identical, except for the consequences of errors. On top of the standard financial compensation, participants could win two additional money prizes. The winners would be determined after completion of the entire study based on their individual and joint performance, respectively. For the individual prize, participants were split into two groups based on their seating position, i.e. on the left or on the right. The best performing participant of each group would win an additional bonus meaning that members of a pair would never compete against each other. For the joint prize, the best performing pair of all pairs that participated would win. Ranking was based on a combination of reaction times (RTs) and accuracy. Participants were informed that the number of errors would be added to the average RT and that the lowest scoring individual or pair would be ranked highest. Importantly, this meant that in the individual context, any errors they made would only affect their own chances of winning an additional bonus, while in the social context errors would also negatively affect their co-actor's chances of winning additional money. Participants always performed the tasks simultaneously and independently. Each context consisted of 400 trials (50% congruent, 50% incongruent) and speed and accuracy were equally emphasized in the general task instructions (see Supplementary Material for further task details).

Electrophysiological recordings and pre-processing of the data

EEG data were recorded from both participants simultaneously using 27 active electrodes per participant (ActiCap, Brain Products, Munich, Germany) arranged according to an extended version of the 10-20 system. Vertical eye movements were recorded by placing electrodes above and below the left eye and horizontal eye movements were registered at the outer canthi of the eyes. Electrophysiological data were acquired at 1000 Hz without filtering with the QuickAmp amplifier (Brain Products) and the electrodes were referenced to the left ear during signal acquisition.

EEG data were further analyzed offline using Brain Vision Analyzer 2.0 (Brain Products, Munich, Germany). All signals were re-referenced to the average of the left and right mastoids. All EEG signals were filtered with a band-pass filter between .02 Hz and 20 Hz (24 dB/oct) and a notch filter of 50 Hz. Eye movements were corrected using the Gratton, Coles and Donchin method (Gratton *et al.*, 1983) followed by artifact rejection. Artifact rejection was done on the four electrodes of interest (Fz, FCz, Cz and Pz) with the following settings: maximal allowed voltage step: 50 μV/ms, maximal amplitude difference of 100 μV in 200 ms intervals, minimal allowed amplitude: –50 μV, maximal allowed amplitude: 50 μV, lowest allowed activity in intervals: 0.5 μV in 100 ms intervals. Response- and stimulus-locked ERPs were baseline corrected relative to a 200 ms pre-response or stimulus baseline. For both contexts and drug conditions, epochs associated with correct and incorrect responses to incongruent stimuli were averaged separately and time-locked to response onset, starting 200 ms before and ending 600 ms after response onset. The ERN was determined on correct and error trials in separate subject averages by subtracting the most negative peak in the 0–200 ms time window after response onset from the most positive peak in the time window starting 80 ms before and ending 80 ms after response onset at electrodes Fz, FCz and Cz, covering the typical frontocentral distribution of the ERN (Falkenstein *et al.*, 1990; Gehring *et al.*, 1993). The Pe is a slowly developing ERP component with a more distributed topography and known to consist of an early and a late component (Ullsperger *et al.*, 2014). Therefore, Pe amplitude was determined on electrodes Fz, FCz, Cz and Pz on correct and error trials in separate subject averages in two ways: (i) the early Pe was defined as the most positive peak in the 150–250 ms post-response time window and (ii) the late Pe was determined as the mean amplitude in the 300–500 ms post-response time window.

Statistical analyses

For all dependent variables, linear mixed modeling (LMM) was applied with Subject as a random factor using SPSS version 23. LMM was chosen in order to keep subjects in the analysis for

whom all conditions were not available on the assumption that incomplete data were missing at random (Spronk *et al.*, 2016). Twelve cases (out of 96: 24 subjects × 2 contexts × 2 drug conditions) were missing because of equipment failure (four cases) or too few error trials (<6 errors). The averages of all included cases were based on at least 11 trials.

The behavioral measures of interest were RT, the percentage of erroneous responses, post-error slowing (PES; Rabbitt, 1966) and post-error accuracy. PES was defined in a so-called robust way that has been shown to be less sensitive to global performance fluctuations (Dutilh *et al.*, 2012). PES robust is quantified as a single-trial value of PES by comparing correct trials preceding (pre-error) and following an error (post-error). Only error trials that were both preceded and followed by at least one correct response were included.

For the behavioral analyses, the possible fixed factors were Substance (placebo, oxytocin), Context (individual, social), Congruency (congruent, incongruent), Correctness (correct, error) and PES (pre-error, post-error). The possible fixed factors for the ERP analyses were the same, with the exception of PES and the additional factor of Electrode (Fz, FCz, Cz for ERN, and Fz, FCz, Cz, Pz for Pe). Significant interactions were further investigated with follow-up analyses, which were adjusted for multiple comparisons using Bonferroni corrections. Finally, bivariate correlation analyses were conducted to investigate relationships between ERN amplitude on the one hand and post-error adjustments (PES and post-error accuracy) on the other.

Results

RTs and error rates

Mean RTs can be found in Table 1. The RT patterns were analyzed using two main analyses (cf. de Bruijn *et al.*, 2004, 2006). First, to investigate the effects of congruency, an analysis was conducted on correct responses only. The main effect of Substance was not significant ($F < 1$). As expected, the main effect of Congruency was significant with slower RTs for incongruent (332 ms) compared with congruent trials (392 ms), $F(1,136.743) = 434.54$, $P < .001$. The main effect of Context was also significant, with overall slower RTs for the individual (365 ms) than the social context (358 ms), $F(1,136.988) = 7.12$, $P = .009$. None of the remaining two- or three-way interactions were significant (all Fs < 1).

Second, to investigate the effect of correctness on RTs, an analysis was conducted using incongruent trials only. Neither the main effect of Substance ($F < 1$) nor the main effect of Context, $F(1,137.161) = 3.42$, $P = .066$, reached significance. The main effect of Correctness was significant, with faster RTs for erroneous responses (289 ms) compared with correct ones (392 ms), $F(1,136.857) = 966.98$, $P < .001$. The two-way interactions (all Fs < 1) and three-way interaction, $F(1,136.857) = 1.55$, $P = .216$, were not significant.

Mean error rates are given in Table 2. The error rate analyses revealed a main effect of Congruency, with more errors made on incongruent trials (26.6%) compared with congruent ones (6.8%), $F(1,136.134) = 322.32$, $P < .001$. The main effect of Context was near significant, $F(1,137.143) = 3.69$, $P = .057$, with numerically more errors made in the social (17.8%) compared with the individual context (15.6%). The main effect of Substance was not significant, $F(1,140.718) = 2.13$, $P = .147$) and neither were any of the remaining two- or three-way interactions (all Fs < 1).

Adaptive behavior following errors

The main effect of PES was significant, $F(1,136.59) = 25.49$, $P < .001$, with increased RTs for post-error responses (361 ms) compared with pre-error responses (342 ms). None of the other main effects or interactions was significant (all Fs < 1).

Bivariate correlations across all cases showed that PES did not correlate significantly with ERN amplitude ($r = .161$, $P = .148$), but that it did correlate significantly with post-error accuracy ($r = .22$, $P = .046$), suggesting that PES provided time for more task specific adjustments (cf. Danielmeier and Ullsperger, 2011; Fischer *et al.*, 2015). In line with this, a significant positive correlation between ERN amplitude and post-error accuracy was also present, $r = .472$, $P < .001$.

To summarize, the behavioral analyses showed that RTs were overall slower for the individual *vs* the social context, while oxytocin did neither affect RTs nor error rates. Post-error adjustment analyses showed that PES was present, but unaffected by context or substance. Finally, larger ERN amplitudes were overall associated with improved post-error accuracy.

Response-locked ERN analyses

Figure 2 depicts the mean ERN amplitudes for the different conditions and the grand average waveforms are shown in Figures 3A and 4A. As expected, the analyses on ERN amplitude demonstrated a main effect for Correctness, $F(1,459.803) = 778.39$, $P < .001$, with increased amplitudes for erroneous (11.97 μV) compared with

Table 2. Mean error percentages for all conditions in both the individual and social context. Standard deviations are given in parentheses

	Placebo		Oxytocin	
	Congruent	Incongruent	Congruent	Incongruent
Individual	5.4 (3.7)	25.4 (13.2)	5.2 (3.9)	25.5 (12.0)
Social	6.3 (5.4)	25.7 (12.1)	7.7 (6.6)	27.1 (14.3)

Table 1. Mean reaction times in milliseconds for all conditions in both the individual and social context. Standard deviations are given in parentheses

	Placebo				Oxytocin			
	Congruent		Incongruent		Congruent		Incongruent	
	Correct	Error	Correct	Error	Correct	Error	Correct	Error
Individual	334 (39)	324 (57)	394 (44)	286 (42)	339 (36)	317 (59)	399 (33)	300 (54)
Social	333 (41)	322 (72)	391 (48)	295 (50)	334 (45)	318 (75)	396 (45)	291 (39)

correct responses (1.38 μV). The main effect for Electrode was also significant, $F(2,459.688) = 6.87$, $P = .001$. Neither the main effect of Substance, $F(1,472.361) = 1.52$, $P = .218$), nor the main effect of Context, $F(1,462.336) = 1.27$, $P = .260$) was significant. The interaction between Electrode and Correctness was significant, $F(2,459.688) = 7.91$, $P < .001$, showing that the effect of Electrode was significant for erroneous responses, $F(2,459.688) = 14.73$, $P < .001$, but not for correct ones ($F < 1$). For errors, the amplitude was maximal for FCz (13.76 μV) compared with Fz (11.94 μV, $F(1,138.508) = 6.78$, $P = .010$) and Cz (10.21 μV, $F(1,139.156) = 25.06$, $P < .001$), reflecting the frontocentral distribution as depicted in Figures 3B and 4B.

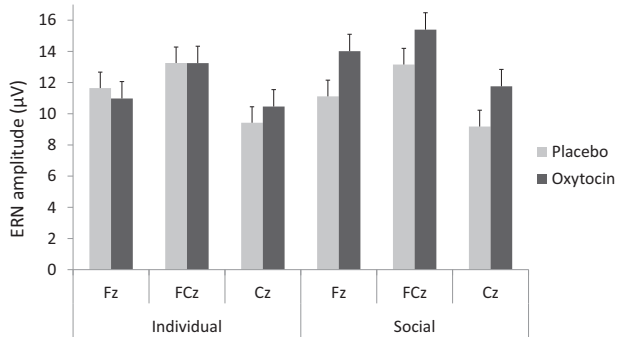

Fig. 2. Mean ERN amplitudes (in μV) of error trials for the placebo and oxytocin condition in the individual and social context for electrodes Fz, FCz and Cz. Error bars represent standard errors of the mean.

Importantly, the interactions between Substance and Context, $F(1,462.270) = 4.51$, $P = .034$, and between Substance and Correctness, $F(1,459.803) = 5.14$, $P = .024$, were significant. These interactions were explained by the finding that the effect of Substance was significant for the social context, $F(1,468.391) = 5.56$, $P = .019$, but not for the individual one ($F < 1$) and only for erroneous responses, $F(1,466.775) = 6.11$, $P = .014$, not correct ones ($F < 1$). None of the remaining interactions were significant (All Fs < 1.75, all Ps > .18).

To investigate the specificity of the effects of Substance and Context on monitoring of errors further, we focused our analyses on erroneous responses only. The main effect of Electrode remained significant, $F(2,219.932) = 12.37$, $P < .001$. Neither the main effect of Substance, $F(1,225.185) = 3.55$, $P = .061$, nor the main effect of Context was significant, $F(1,220.854) = 1.62$, $P = .205$). Importantly, however, the interaction between Substance and Context was significant, $F(1,220.854) = 4.43$, $P = .036$, revealing increased ERN amplitudes in the social context only after oxytocin (13.38 μV) compared with placebo

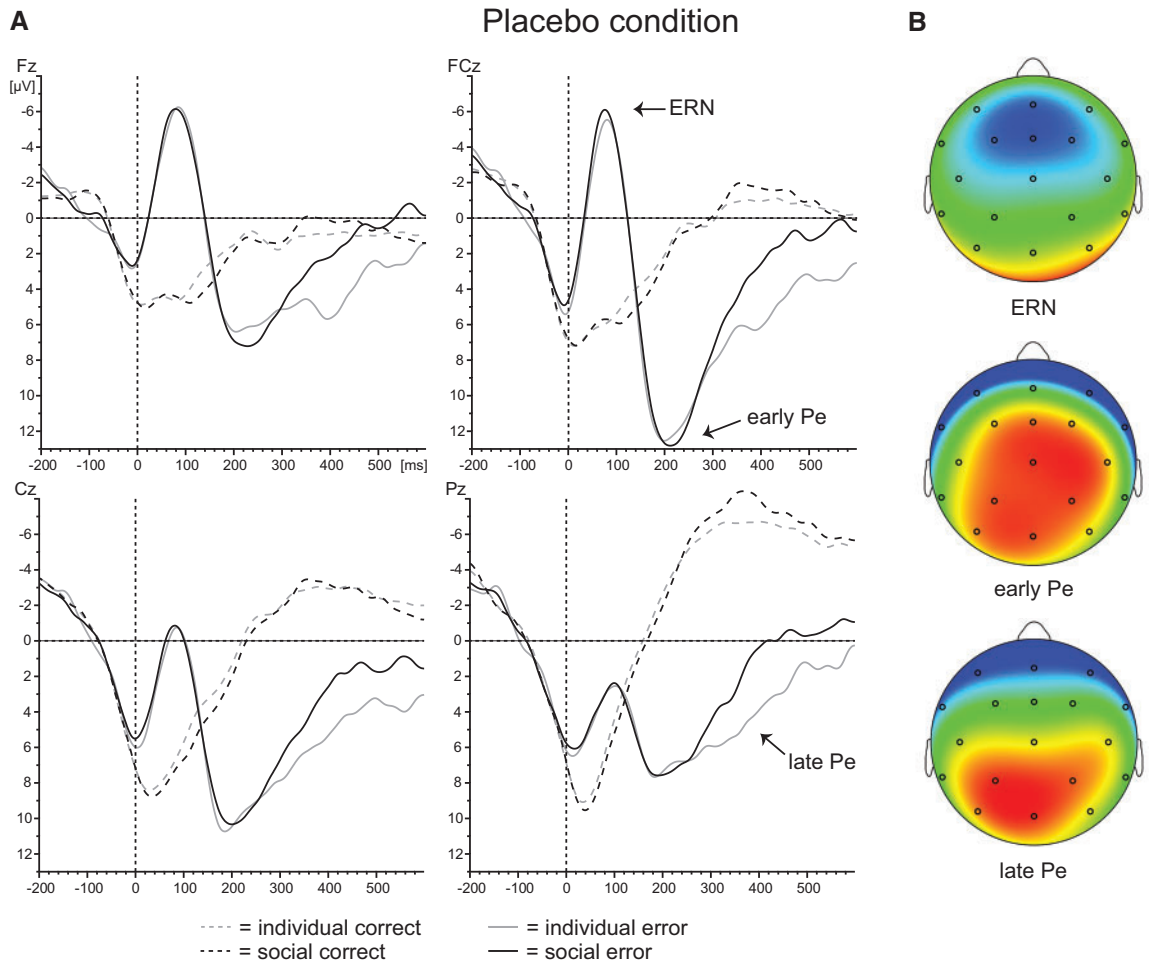

Fig. 3. (A) Response-locked grand average waveforms for correct and incorrect responses in the individual and social context in the placebo condition for electrodes Fz, FCz, Cz and Pz. (B) Topographical distributions of the difference waves (incorrect minus correct responses) collapsed over context for the ERN (peak onset at 78 ms, top), the early Pe (peak onset at 229 ms, middle) and for the late Pe (mean amplitude in 300–500 ms time window, bottom).

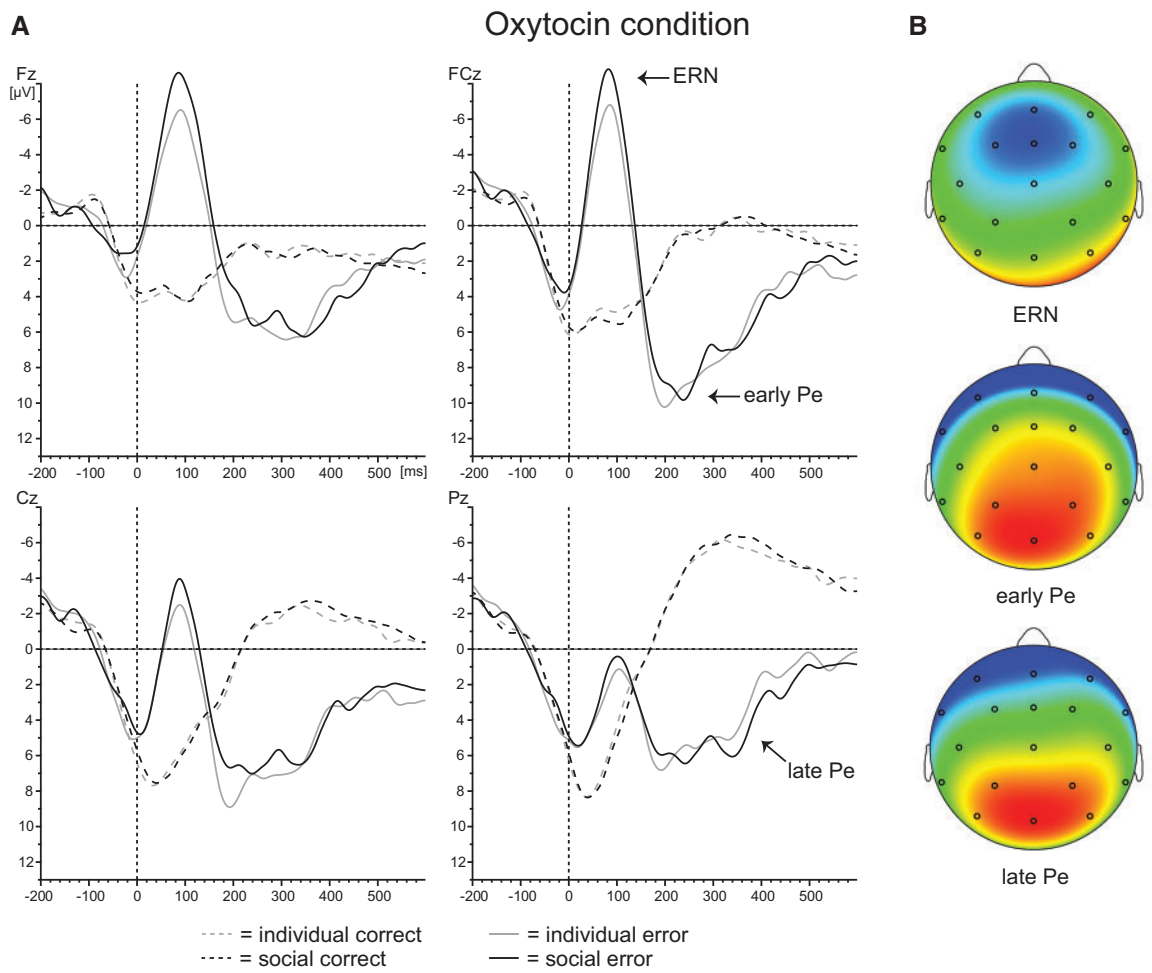

Fig. 4. (A) Response-locked grand average waveforms for correct and incorrect responses in the individual and social context in the oxytocin condition for electrodes Fz, FCz, Cz and Pz. (B) Topographical distributions of the difference waves (incorrect minus correct responses) collapsed over context for the ERN (peak onset at 85 ms, top), the early Pe (peak onset at 236 ms, middle) and for the late Pe (mean amplitude in 300–500 ms time window, bottom).

administration (10.99 μV, $F(1,223.395) = 7.83$, $P = .006$). ERN amplitudes did not differ significantly between the oxytocin (11.39 μV) and placebo (11.48 μV) condition for the individual context ($F < 1$). Please note that similar patterns and outcomes were observed when including order of the sessions as an additional factor and when not the peak-to-peak measure of the ERN, but only the most negative peak in the 0–150 ms time window following response onset was taken as a measure of ERN amplitude (see Supplementary Material for details).

Response-locked Pe analyses

The analyses on early Pe amplitudes showed a main effect of Correctness, $F(1,617.18) = 319.94$, $P < .001$, with increased amplitudes for incorrect (12.29 μV) compared with correct responses (6.04 μV). The main effect of Electrode, $F(1,617.18) = 13.78$, $P < .001$, and the significant interaction between Correctness and Electrode, $F(3,617.18) = 4.26$, $P = .005$, revealed the frontocentral topographical distribution of the component (see Figures 3B and 4B). Amplitudes were maximal for erroneous responses at FCz (14.71 μV) and Cz (12.94 μV) compared with Fz (10.55 μV; $Ps < .005$) and Pz (10.94 μV; $Ps < .027$). None of the remaining main effects or interactions was significant (all $Fs < 2.35$, all $Ps > .125$).

The analyses on late Pe amplitudes demonstrated a main effect of Correctness, $F(1,617.495) = 331.14$, $P < .001$, with increased amplitudes for incorrect (3.84 μV) compared with correct responses (−2.06 μV). Significant effects were also present for Electrode, $F(3,617.495) = 34.20$, $P < .001$, and Substance, $F(1,630.281) = 3.96$, $P = .047$. The interactions between Substance and Context, $F(1,620.415) = 5.81$, $P = .016$, and between Correctness and Electrode, $F(3,617.495) = 17.03$, $P < .001$, were significant. Pairwise comparisons for the first interaction demonstrated that the effect of Context was not significant for the oxytocin condition ($F < 1$), but limited to placebo administration, $F(1,620.280) = 8.71$, $P = .003$, with decreased amplitudes in the social context (−.10 μV) compared with the individual one (1.22 μV). The three-way interaction between Substance, Context and Correctness was not significant, $F(1,617.495) = 3.47$, $P = .063$.

Discussion

The aim of the current study was to investigate the effects of oxytocin on individual *vs* social mistakes by analyzing performance-related ERP components. With the exception of slower correct response times in the individual compared with the social context, behavior was neither modulated by oxytocin

nor by the social context. At the electrophysiological level, following oxytocin administration, ERN amplitudes were increased for social compared with individual mistakes. After placebo, reduced (late) Pe amplitudes were present for the social compared with the individual context, but ERN amplitudes did not differ between individual or social mistakes.

As participants were seated next to each other both in the individual and the social context, the overall slower RTs in the individual context cannot be simply explained by social facilitation, i.e. the idea that people in general perform better or faster on simple tasks in the presence of other people (Zajonc, 1965). The slower responses may, however, result from an absence of direct performance feedback. Consequently, participants were unsure how well their co-actor was performing and this may have resulted in a tendency to speed up compared with the individual setting. The numerically higher error rate in the social context may also be seen as indicative of the presence of a speed-accuracy tradeoff of in the social compared with the individual setting. Previous studies have shown that performance differences, such as dissimilar error rates, may affect the amplitude of the ERN (see e.g. Fischer *et al.*, in press; Gehring *et al.*, 1993). The currently observed absence of behavioral drug effects thus ensures that the present ERP findings are not confounded by such differences in performance.

In line with our hypotheses, oxytocin increased ERN amplitudes specifically for social compared with individual mistakes. This outcome shows that, under the influence of oxytocin, knowing that one's actions may negatively affect another person results in stronger error-related activations in the brain. Enhancements in performance monitoring have previously been associated with increased error significance or affective distress in an online evaluation task (Hajcak *et al.*, 2005). It is plausible that similar mechanisms are at work for mistakes that additionally affect a co-actor in a negative manner, for example through enhanced feelings of responsibility in the social context. In line with this, there is an abundance of clinical work on (non-social) performance monitoring, showing that OCD is related to excessive error-related brain responses (Endrass and Ullsperger, 2014). Interestingly, one of the major symptoms of patients suffering from OCD is inflated responsibility and a fear of making mistakes that will negatively affect other people (Hezel and McNally, 2016). Hence, the current outcomes may have important clinical implications. Although studies using animal models have suggested a close link between oxytocin and compulsive behavior such as hypergrooming in rats (Marroni *et al.*, 2007), the few studies that investigated effects of intranasal oxytocin in patients with OCD did not demonstrate clear effects on obsessive–compulsive symptoms (see e.g. den Boer and Westenberg, 1992; Epperson *et al.*, 1996). On the contrary, one case study that did demonstrate improvement during 4 weeks of treatment (Ansseau *et al.*, 1987) also reported unexpected but serious side effects such as the development of psychotic symptoms. The latter supports the idea that caution in using oxytocin in OCD treatment is warranted and that more research is needed. Future studies should therefore focus on whether OCD patients show a similar excessive response to social mistakes and whether oxytocin administration may thus even result in adverse effects on social performance-monitoring processes in these patients.

The finding of enhanced performance monitoring of social mistakes after oxytocin administration is in line with the idea that oxytocin may increase the salience of social cues (see e.g. Nave, Camerer and McCullough, 2015; Burkett and Young, 2012; Gordon *et al.*, 2011; Quattrocki and Friston, 2014) and that some social-behavioral effects may result from its impact on motivational networks (Love, 2014). The central idea of the recently proposed social salience theory of oxytocin (Shamay-Tsoory and Abu-Akel, 2016) is that the hormone facilitates attention-orienting to external contextual social cues, but that effects may be baseline dependent. Our data therefore suggest that oxytocin may increase the salience of mistakes, specifically in a social context. The current outcomes also show that this is not simply the result of a general increase in attention, as there were no substance or context effects on relevant attentional stimulus-locked ERP components (see Supplementary Material).

The neurotransmitter dopamine is known to play a primary role in salience attribution and has therefore been thought to be involved in oxytocin-induced effects of social salience (Shamay-Tsoory and Abu-Akel, 2016). This assumption is based on the fact that oxytocin's receptors are located throughout the mesocorticolimbic dopamine system (Love, 2014). Also, animal studies have demonstrated a direct influence of oxytocin on dopamine release (Sanna *et al.*, 2012; Shahrokh *et al.*, 2010). Notably, dopamine has also been proposed to play a central role in performance monitoring. The reinforcement-learning theory of performance monitoring (Holroyd and Coles, 2002) posits that whenever an outcome is worse than expected (i.e. an error) a temporarily decrease in dopamine release occurs. This prediction error signal (see e.g. Schultz, 2016a,b) may importantly generate the ERN and subsequent behavioral changes. Support for the involvement of dopamine in performance monitoring in non-social contexts comes from studies from our own and other labs showing that increasing levels of dopamine through administering compounds that act as indirect dopamine agonists results in increased ERN amplitudes (see e.g. de Bruijn *et al.*, 2004), while the reverse occurs for indirect dopamine antagonists (see e.g. de Bruijn *et al.*, 2006; Zirnheld *et al.*, 2006).

More recently, Quattrocki and Friston (2014) have highlighted that both dopamine and oxytocin have specific and targeted effects on the cingulate-insula network. In their review, the authors propose a central role for the oxytocin system in interoception, i.e. the process of sensing the internal state of the body. Crucially, they postulate that the cingulate-insula network not only modulates proprioceptive signals allowing for flexible motor control, but that it also controls autonomic processes through updating of expectations about our emotional and embodied self through interoceptive predictions. While the first process is assumed to rely on dopamine function and may thus explain the effects dopamine has on performance monitoring, oxytocin may be similarly involved by regulating homeostasis through minimizing interoceptive prediction errors. We propose that, during performance monitoring, such prediction errors may result from the distress and averseness associated with social mistakes. The current findings seem thus to be more in line with a relative direct effect of oxytocin on performance monitoring rather than an indirect effect through oxytocin-induced dopamine release. On the basis of the outcomes of existing pharmacological performance-monitoring studies, one would actually expect such indirect effect of dopamine release to affect performance monitoring in a more general manner, i.e. increases in both the individual and social context. The present study therefore suggests that the effects of oxytocin on performance monitoring are context

dependent with specific enhancements in the social context only. Future studies should aim at unraveling the complex interplay of these fundamental processes and oxytocin-dopamine interactions further.

The finding that ERN amplitudes were not increased for social compared with individual mistakes in the placebo condition was unexpected, but may be related to the indirect nature of the manipulation. To keep the comparisons as clean as possible, the two contexts were identical and only the instructions varied between the individual and the social setting. As a result, the manipulation of error consequences remained subtle and might thus not have had the required impact to affect performance monitoring in the placebo condition. In contrast to previous fMRI studies (Radke *et al.*, 2011; Koban *et al.*, 2013), for example, committed errors in the current study were not visible to the co-actor and also the consequences of an error were delayed until after the study ended.

Interestingly, however, an effect of context did occur in the placebo condition for the (late) Pe, with *decreased* amplitudes in the social setting. The Pe has often been associated with conscious error awareness (Overbeek *et al.*, 2005) and the motivational salience of errors (Ridderinkhof *et al.*, 2009). The reduced Pe in the social context may thus reflect a diminished emotional response to possible errors. Accordingly, this outcome reveals a reversed pattern of the one seen in the oxytocin condition, with a *reduced* impact on performance monitoring in the *social* rather than the individual context. Although we remain cautious in interpreting this unexpected finding in a post-hoc manner, possible explanations may be found in theories of social psychology focusing on diffusion of responsibility and social loafing (see e.g. Gilovich *et al.*, 2005; Karau and Williams, 1993; Latané *et al.*, 1979). Both participants performed the task simultaneously and were aware that the other person is likely to make mistakes as well and will thus also negatively affect the chance of winning a joint prize. Unlike the oxytocin condition, following placebo this knowledge seems to result in a decrease of personal accountability in the social compared with the individual context. It would be interesting to see whether future studies could shed more light on this by focusing on (i) a possible relationship between decreased personal accountability and later—more conscious and emotional—performance-monitoring processes as reflected in the Pe and (ii) the possible role of oxytocin in responsibility alterations in social performance monitoring.

Although there are many practical reasons for not including female participants in an oxytocin administration study, such as issues related to menstrual cycle, the inclusion of only male participants can be considered a limitation and may prevent generalizations across genders. Compared with other pharmacological performance-monitoring studies (see e.g. de Bruijn *et al.*, 2004, 2006; Riba *et al.*, 2005; Spronk *et al.*, 2014), the current sample size of 24 participants in a within-subjects design with repeated measures is relatively large. However, we would like to emphasize that the present findings are in need of replication preferably in a larger sample size that also includes female participants (see Walum *et al.*, 2016). Another limitation of the current study is the use of delayed feedback. Although this had the major advantage of keeping the two contexts as similar as possible, this may have reduced the impact of the social mistakes, especially in the placebo setting. Future studies should therefore increase the immediate impact of errors in the social context.

The current study did not reveal a behavioral equivalent of increased social performance monitoring after oxytocin administration. However, the finding of a drug-induced ERN effect in the absence of an effect on PES is quite common. Almost all previous pharmacological performance-monitoring studies have demonstrated this pattern, thus ERN effects in the absence of effects on PES (e.g. de Bruijn *et al.*, 2004, 2006; Riba *et al.*, 2005; Spronk *et al.*, 2014; Zirnheld *et al.*, 2006). Even in studies with larger sample sizes, e.g. because of an additional focus on individual differences, no drug effects on post-error behavior were found (Barnes *et al.*, 2014; Spronk *et al.*, 2016). The current method may thus not be sensitive enough to investigate this specific issue also because several factors are known to modulate PES. Specifically, although behavioral measures such as overall performance, general RTs, and PES can be derived from the Flankers paradigm, a fine balance between instructions, task details, and these measures exists. For example, the general instruction that equally emphasizes speed and accuracy may limit the occurrence of PES (Danielmeier and Ullsperger, 2011) and a recent study in a large sample size showed that males display less PES than females (Fischer *et al.*, 2016). Also, in pharmacological ERP studies one general aim is to keep performance as similar as possible between the different conditions. This enables drawing conclusions about the ERP findings without possible confounds of behavioral effects. A side effect of this may be that it limits the occurrence and variance of behavioral measures of interest.

The only support for a relationship between performance monitoring and post-error adjustments was reflected in the positive correlation between post-error accuracy and ERN amplitude across all cases. This finding, which was previously shown by Carp and Compton (2009), suggests that independent of context and substance enhanced performance monitoring was associated with increased performance following errors. We would like to emphasize, however, that the current data did not provide direct evidence that this finding is indicative of improved task-specific adjustments following social mistakes after oxytocin administration. On the contrary, one might also argue that increased responsiveness to social mistakes may actually lead to worse performance resulting from a lapse of attention due to the distress associated with the error and resulting re-orienting process. Dedicated studies that, for example additionally examine the coupling between ERN amplitude and post-error adjustments (see e.g. Fischer *et al.*, 2015, 2016) may be able to shed more light on the question if and how enhanced social performance monitoring following oxytocin is reflected in behavior.

To summarize, the present study is the first to demonstrate acute effects of oxytocin on performance monitoring. This central process enables humans to perform in a flexible and safe manner, not only in individual but also in social contexts. The results showed an oxytocin-induced enhancement of performance monitoring specifically for social mistakes, which was not present in the placebo condition. These outcomes are in line with recent theories that propose a central role for oxytocin in salience attribution to social cues. Moreover, dopamine has been argued to play a crucial role in both oxytocin-induced salience attribution and performance monitoring, which additionally emphasizes the clinical relevance of the combined research topics. Performance monitoring deficits have been reported in many psychiatric disorders and especially anxiety disorders are associated with excessive responses to mistakes. Bringing together these two relevant research domains may thus importantly open up new research avenues and improve our understanding of individual differences in performance monitoring and oxytocin responses from a social neurocognitive, a pharmacological, as well as a clinical perspective.

Funding

This work was supported by a personal grant from the Netherlands Organization for Scientific Research to E.D.B. (NWO; VIDI grant nr. 452-12-005).

Author contributions

E.D.B. and S.R. designed the experiment. S.R. collected the data. E.D.B., M.I.R. and S.R. analyzed and interpreted the data. E.D.B. wrote the first version of the manuscript. E.D.B., M.I.R. and S.R. provided feedback and revised the manuscript. All authors approved of the final version.

Supplementary data

Supplementary data are available at *SCAN* online.

Conflict of interest. None declared.

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