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Oxytocin effects on neural correlates of self-referential processing

Yi Liu[a,b], Feng Sheng[a,b], Kate A. Woodcock[a,c], Shihui Han[a,b,*]

[a] Department of Psychology, Peking University, Beijing, China
[b] PKU-IDG/McGovern Institute for Brain Research, Peking University, Beijing, China
[c] School of Psychology, University of Birmingham, Edgbaston, Birmingham, UK

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ABSTRACT

Oxytocin (OT) influences how humans process information about others. Whether OT affects the processing of information about oneself remains unknown. Using a double-blind, placebo-controlled within-subject design, we recorded event-related potentials (ERPs) from adults during trait judgments about oneself and a celebrity and during judgments on word valence, after intranasal OT or placebo administration. We found that OT vs. placebo treatment reduced the differential amplitudes of a fronto-central positivity at 220–280 ms (P2) during self- vs. valence-judgments. OT vs. placebo treatment tended to reduce the differential amplitude of a late positive potential at 520–1000 ms (LPP) during self-judgments but to increase the differential LPP amplitude during other-judgments. OT effects on the differential P2 and LPP amplitudes to self- vs. celebrity-judgments were positively correlated with a measure of interdependence of self-construals. Thus OT modulates the neural correlates of self-referential processing and this effect varies as a function of interdependence.

1. Introduction

Oxytocin (OT) is a peptide hormone produced in the hypothalamus and plays an important role in social cognition and social behavior. Animal studies have shown that OT contributes to the development of prosocial behavior such as mother–infant attachment, grooming, and approach behavior (see Lim & Young, 2006 for review). In humans, OT promotes social trust and cooperation such that individuals receiving intranasal sprays of OT compared to a placebo are more inclined to invest money in others even when there is no guarantee of reciprocation (Kosfeld, Heinrichs, Zak, Fischbacher, & Fehr, 2005). To account for the enhanced prosociality induced by OT, previous studies focused on how OT treatment affects the processing of information about conspecific others. It has been shown that, relative to placebo administration, intranasal OT results in increased sensitivity to others' facial expressions (Marsh, Yu, Pine, & Blair, 2010; Schulze et al., 2011), better understanding of others' thoughts and intentions (Domes, Heinrichs, Michel, Berger, & Herpertz, 2007), and enhanced perception of trustworthy and attractiveness of others' faces (Theodoridou, Rowe, Penton-Voak, & Rogers, 2009, see Campbell, 2010 for review).

There is also increasing evidence that OT modulates neural activities involved in the processing of social cues (see Zink & Meyer-Lindenberg, 2012 for review). Functional magnetic resonance imaging (fMRI) studies found that intranasal OT administration decreased neural responses in the amygdala during implicit (Domes, Heinrichs, Glascher, et al., 2007) and explicit (Gamer, Zurowski, & Buchel, 2010) processing of fearful facial expressions in males but increased amygdala activity during explicit processing of fearful faces in females (Domes et al., 2010). An electroencephalograph (EEG) study showed that, while perception of social stimuli (e.g., a point-light display of human biological motion) was associated with suppression of EEG activity in the mu/alpha and beta bands (Perry, Troje, & Bentin, 2010; Ulloa & Pineda, 2007), this suppression was significantly enhanced following intranasal OT versus placebo treatment (Perry, Bentin, et al., 2010). OT also modulated the amplitudes of event-related potentials (ERPs) elicited by facial stimuli such that OT, compared to a placebo, increased the amplitude of a frontal positivity at 140–180 ms and the amplitude of a late positive potential (LPP) at 400–800 ms over the parietal region in response to emotional faces (Huffmeijer et al., 2013). Moreover, OT interacts with social factors to modulate neural activities to emotional cues. Sheng, Liu, Zhou, Zhou, and Han (2013) recorded ERPs from Chinese adults while they perceived pain or neutral facial expressions of Asian and Caucasian models. They first showed that, in the placebo condition, pain compared to neutral expressions increased the amplitude of a fronto-central positive activity at 128–188 ms (P2) and this effect was evident for Asian but not for Caucasian models. This replicates the racial bias in empathic neural responses (Sheng & Han, 2012). Moreover, Sheng et al. (2013) found that OT compared to a placebo increased the P2 empathic neural responses to pain vs. neutral

* Corresponding author at: Department of Psychology, Peking University, 5 Yiheyuan Road, Beijing 100871, China. Tel.: +86 10 6275 9138; fax: +86 10 6276 1081.
E-mail address: shan@pku.edu.cn (S. Han).

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expressions of Asian but not Caucasian models, suggesting that OT may selectively enhanced the neural activity to facial expressions of racial in-group (but not out-group) members.

The reciprocally interconnected role of self related and other related processing in social cognition has been widely discussed. How one thinks of the self and the relationship between the self and others significantly influence social interaction. For example, a person may expend self-concept to include close others in order to acquire resources, perspectives, and identities from others and to enhance one's own ability to accomplish goals (Aron et al., 2004). Self-other merging facilitates cooperation in social dilemmas (Cremer & Stouten, 2003) and perceived "oneness" (i.e., one comes to incorporate the self within the boundaries of the other) or perceptions of self in relation to others links to emotional empathy (Burris & Rempel, 2012; Cialdini, Brown, Lewis, Luce, & Neuberg, 1997). Previous studies of OT effects on neural correlates of social cognition have focused exclusively on other-related processing. There has been no existing data so far on how OT affects neural correlates of self-related processing.

Consistent with the idea that the processes of the self and others are the two sides of social cognition (Iacoboni, 2006; Sedikides & Skowronski, 2009), it has been shown that priming independent vs. interdependent self-construals in Chinese participants speeded their responses to their own faces but slowed their responses to others' faces (Sui & Han, 2007). Moreover, while fMRI studies suggest that the medial prefrontal cortex and anterior cingulate cortex are engaged in self-referential processing of personality traits (Heatherton, 2011;

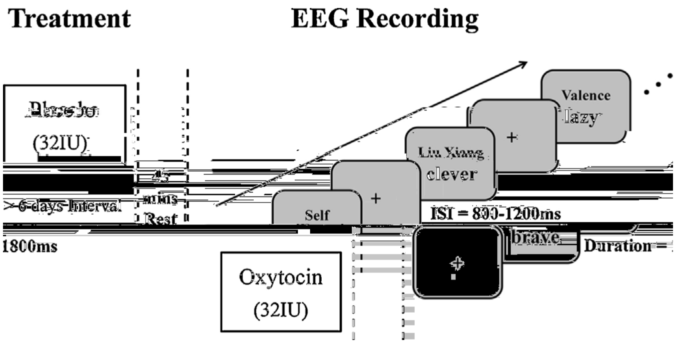

Fig. 1. Illustration of the procedure and stimuli used in the current study. Both the cue and stimuli words were in Chinese.

adjective can describe the self on 24 trials, whether a trait adjective can describe Liu Xiang (a well-known Chinese athlete) on 24 trials, and the valence (positive vs. negative) of a trait adjective on 24 trials. Half positive and half negative trait adjectives were used for each type of judgments within each block.

We used an event-related design with the target person and the adjective were presented in a random order within each block. On each trial, a trait adjective were presented at the center of the screen with a cue word (self, Liu Xiang, valence) above it for 1800 ms, which were followed by a fixation with a duration that varied randomly between 800 and 1200 ms. Each character of a trait word subtended a visual angle of $0.7^\circ \times 0.7^\circ$ and each character of the cue word subtended a visual angle of $0.51^\circ \times 0.51^\circ$ at a viewing distance of 120 cm. Participants responded to each trait adjective by pressing one of the two buttons using the left or right thumb. The relation between responding hands and yes/no response for trait judgments and positive/negative response for valence judgments were counterbalanced across participants.

Participants completed the Self-Construal Scale (Singelis, 1994) after the second session of EEG recording. The Self-Construal Scale consists of 24-items that assess one's independent and interdependent self-construals on a 7-point Likert scale (1 = strongly disagree, 7 = strongly agree). Interdependence was defined by the difference between the sum score of the12 interdependent self-construal items and the sum score of the 12 independent self-construal items. Higher difference scores indicate greater interdependent cultural values, similar to the previous research (Ma et al., 2013).

2.3. EEG data recoding and analysis

EEG was recorded during the judgment tasks from 62 scalp electrodes that were mounted on an elastic cap according to the extended 10–20 system. EEG was referenced to the algebraic average of the electrodes at the left and right mastoids. The electrode impedance of each electrode was kept less than 5 kΩ. Eye blinks and vertical eye movement were monitored with electrodes located above and below the left eye. The horizontal electrooculogram was recorded from electrodes placed 1.5 cm lateral to the left and right external canthi. The EEG was amplified (band pass 0.01–100 Hz), digitized at a sampling rate of 250 Hz and stored for off-line analysis. Trials contaminated by eye blinks, eye movements, or muscle potentials exceeding $\pm 50\,\mu V$ at vertical electrode and trials containing behavioral errors (in valence-judgment task) were excluded from further analysis. ERPs were calculated separately in each condition (self-judgment, celebrity-judgment and valence-judgment after OT or placebo treatment). The ERPs in each condition were averaged separately off-line with an epoch beginning 200 ms before stimulus onset and continuing for 1800 ms. Similar numbers of trials remained in the analysis after the artifacts rejection (ranged between 40 and 94 across all participants, mean number of trials included were self/other/valence = 75.5/75.5/72.3 in the OT condition, and self/other/valence = 74.0/74.1/72.0 in the placebo condition, $Ps > 0.05$). Preliminary repeated measures analyses of variance (ANOVAs) of ERP data at bilateral electrodes included Hemisphere (electrode over the left vs. right hemispheres) as a within-subjects variable. The effect of Hemisphere and its interaction with other variables was not significant and thus was not reported in Section 3.

Both voltage topography and the standardized Low Resolution Brain Electromagnetic Tomography (sLORETA, Pascual-Marqui, 2002) were used to estimate potential sources of the OT effects on the neural activity related to self- vs. other-referential processing. sLORETA is a linear method of computing statistical maps from EEG data that reveal locations of the underlying source processes and does not require a priori hypotheses regarding the field distribution of the active sources. We performed analysis using sLORETA to assess the 3D current source of neural activity that showed an effect of OT on differential ERPs between self- and other-reference. A boundary element model was first created with about 5000 nodes from a realistic head model. Statistical nonparametric mapping was calculated in specific time windows to estimate potential sources of OT effects on the neural activity related to self- vs. other-referential processing. The log of the F ratio of averages was used and considered with a 0.95 level of significance.

3. Results

3.1. Behavioral results

Reaction times to trait and valence-judgments were subjected to an ANOVA with Treatment (OT vs. placebo) and Task (Self, Other vs. Valence) as independent within-subjects variables. There was a significant main effect of Task ($F(2, 38) = 7.59$, $P < 0.01$) due to faster responses to self-judgments than to celebrity-judgments ($P < 0.01$) or valence-judgments ($P < 0.01$). However, these effects did not differ between OT and Placebo conditions ($F < 1$). Questionnaire measurement of independent and of interdependent self-construal showed that each was above the midpoint and the interdependence score was significantly higher than the independence score (62.68 ± 7.41 vs.55.89 ± 6.59, $t(18) = 3.27$, $P = 0.004$). Rating scores of interdependence and independence were not correlated with each other ($r(19) = 0.17$, $P = 0.49$)

3.2. ERP results

Fig. 2 illustrates the ERPs to trait and valence judgments after placebo and OT treatment, respectively. Trait adjectives during both trait and valence judgments elicited a frontal negativity at 80–120 ms (N1), a positivity at 220–280 ms (P2) widely distributed over the frontal/central/parietal electrodes, and a late positive potential (LPP) at 520–1000 ms over the frontal/central/parietal regions.

Mean amplitudes of the N1, P2 and LPP were measured in the time window around the peak latency of each component (i.e., N1: 80–120 ms; P2: 220–280

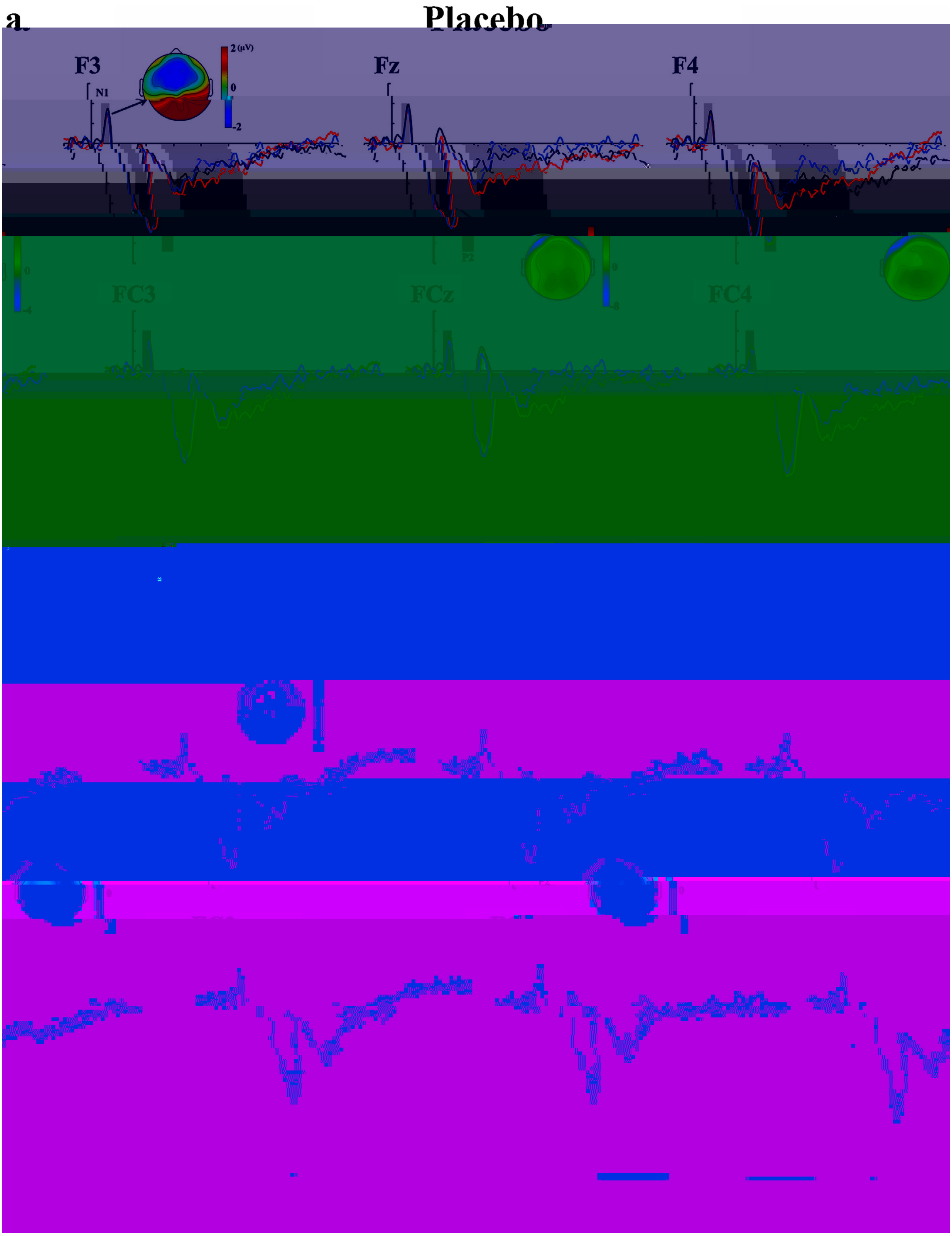

Fig. 2. Illustration of ERPs recorded at F3, F4, Fz, FC3, FC4, FCz to self-, celebrity-, and valence-judgment and the topographies of N1, P2 and LPP after (a) placebo and (b)

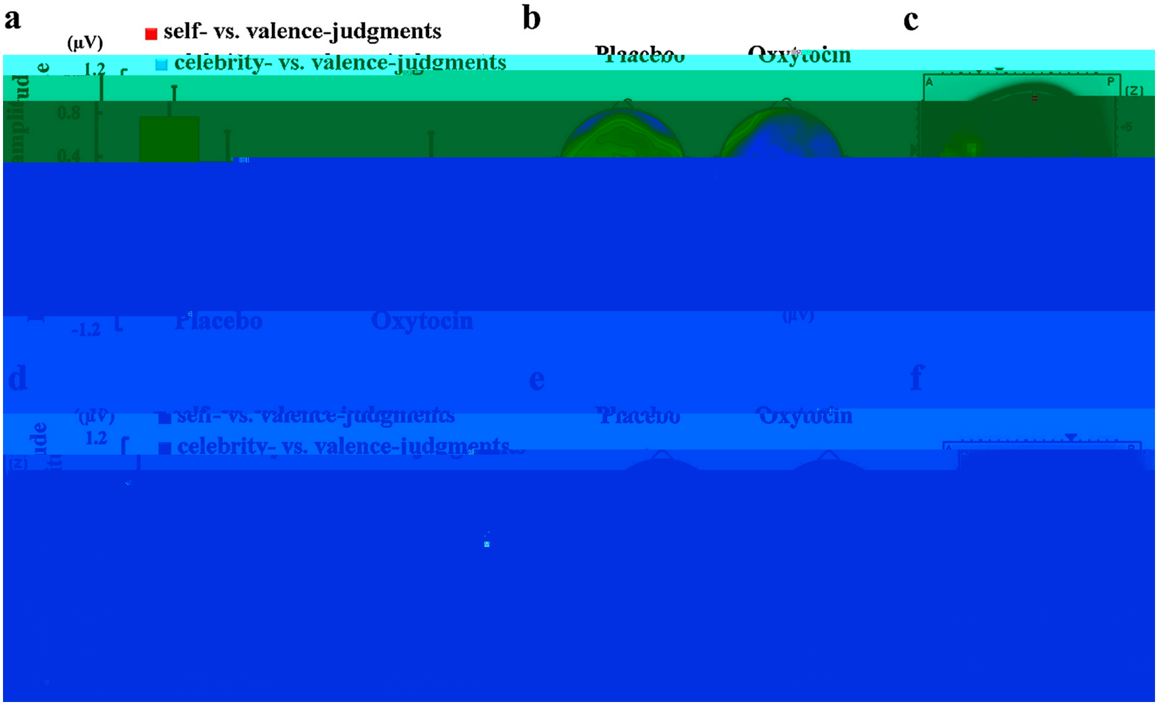

Fig. 3. (a) The mean amplitude of the difference wave at 220–280 ms obtained by subtracting the ERPs to valence-judgment from those to self- or celebrity-judgment at fronto-central electrodes. (b) Topographies of the difference wave of self- vs. celebrity-judgments in the P2 time window in OT and placebo conditions, respectively. The difference wave showed a positivity over the fronto-central region in the placebo condition but a negative over the same region in the OT condition. (c) Source estimation of the OT effect in the P2 time window on self- and other-referential processing. The maximum OT effect was observed over the anterior cingulated and medial prefrontal cortex. (d) The mean amplitude of the difference wave at 520–1000 ms obtained by subtracting ERPs to valence-judgment from those to self- or celebrity-judgment at fronto-central electrodes. (e) Topographies of the difference wave of self- vs. celebrity-judgment in the LPP time window in OT and placebo conditions, respectively. The difference wave showed a positivity over the fronto-central region in the placebo condition but not in the OT condition. (f) Source estimation of the differential OT effect in the LPP time window on self- and other-referential processing. The maximum OT effect was observed over the right inferior parietal lobule.

show any significant main effects or interactions ($Fs < 3$, $Ps > 0.05$). The ANOVAs of the mean differential amplitude in the P2 time window did not show significant main effects of Task or Treatment either ($Fs < 3$, $Ps > 0.05$). However, there

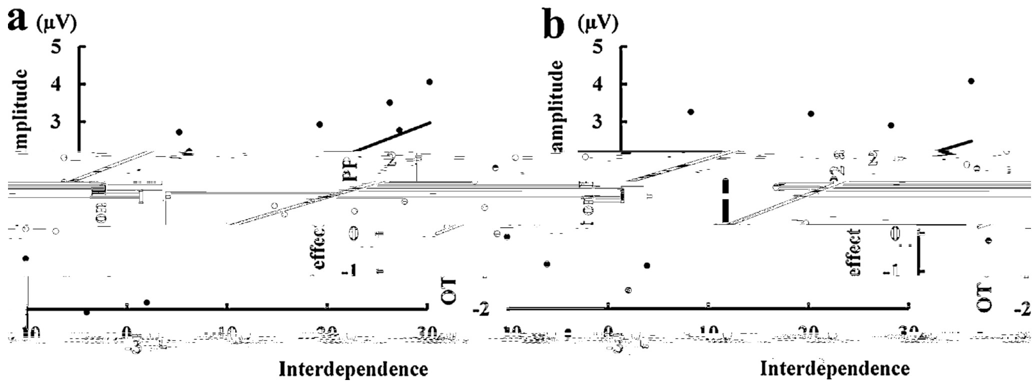

Fig. 4. (a) The correlation between the OT effect on the P2 amplitude at F5 to self- vs. celebrity-judgments (i.e., $(\text{Self-Other})_{placebo}$ minus $(\text{Self-Other})_{OT}$) and the rating score of interdependence. (b) The correlation between the OT effect on LPP amplitude at F5 to self- vs. celebrity-judgment (i.e., $(\text{Self-Other})_{placebo}$ minus $(\text{Self-Other})_{OT}$) and the rating score of interdependence.

celebrity-judgments were significantly positively correlated with the measurement of interdependence over the frontal/central/parietal electrodes (rs = 0.81–0.51; Ps < 0.05 at F4, F5, FC1, FC4, FC5, C3, C5, CP3, CP5; Fig. 4a). Similarly, the differential OT effects on the LPP amplitudes were positively correlated with the measurement of interdependence (rs = 0.48–0.59; Ps < 0.05 at F2, F5, FC1; Fig. 4b). Participants who self-reported greater interdependence showed greater OT effects on the neural activity related to self- vs. other-referential processing in P2 and LPP time windows.

4. Discussion

The present research examined the OT effects on the neural activity involved in self-referential processing. We recorded ERPs elicited by trait judgments about oneself and a celebrity and valence judgments of trait adjectives after placebo and OT treatment. Behavioral measurements showed faster responses during self-judgments compared to celebrity-judgments and valence-judgments. The ERP results in the placebo condition showed that self-referential processing was associated with increased ERP amplitudes over the fronto-central region in the LPP time window, whereas the N1 and P2 amplitudes failed to show evidence for modulations by self-referential processing. Several previous ERP studies have shown that the increased fronto-central positivity in the P2 and LPP time windows was associated with the processing of self-relevant vs. other-relevant stimuli such as personality trait words (Mu & Han, 2010), name/date of birth (Hu, Wu, & Fu, 2011), and sentences about life events (Fields & Kuperberg, 2012). The P2 self-referential effect may be sensitive to the paradigms used in these studies as an event-related designed was employed in the current work and a block design was used in the previous research (Mu & Han, 2010). The LPP findings suggest that the increased fronto-central positivity in the LPP time window related to self-relevant stimuli may be independent of stimuli and tasks and play an important functional role in self-referential processing. Most interestingly, the present work showed evidence that intranasal OT tended to decrease the neural activity related to self-referential processing in the P2 and LPP time window and these effects were not observed during other-referential processing. These findings uncovered the OT effects on neural activities specifically involved in self-referential processing.

Source estimation suggested that the OT effect on self- vs. other-referential processing in the P2 time window may be linked to the modulation of neural activity in the medial prefrontal cortex. This is consistent with the fact that the medial prefrontal cortex is activated in fMRI studies during trait judgments of oneself vs. others to encode self-relevance of stimuli (Han & Northoff, 2009; Heatherton, 2011; Kelley et al., 2002; Ma & Han, 2011; Ma et al., 2013; Northoff et al., 2006; Wang et al., 2012; Zhu et al., 2007). In addition, OT as a neurotransmitter can reach the medial prefrontal cortex and anterior cingulate cortex through volume transmission (Macdonald & Macdonald, 2010; Meyer-Lindenberg, Domes, Kirsch, & Heinrichs, 2011) where OT receptors are distributed (Macdonald & Macdonald, 2010; Skuse & Gallagher, 2009). Animal studies suggest that OT can produce significant suppression of glutamatergic neurotransmission in the medial prefrontal cortex (Ninan, 2011). Therefore, it is possible that self-referential processing in these brain regions may be inhibited by intranasal OT administration. Although the analysis of LPP amplitudes showed significant interaction of Treatment × Task over the frontal/central electrodes, the LPP showed the maximum amplitude over the parietal region and the results of source estimation suggested that the differential OT effect on self- vs. other-referential processing in the LPP time window may arise from the right parietal cortex. This seemingly inconsistency can be understood if we hypothesize that the positive pole of dipoles in the parietal cortex that underwent OT modulations pointed to the frontal lobe, though this speculation should be examined in future research. The right parietal cortex plays a role in recognition of one's own face (Uddin, Molnar-Szakacs, Zaidel, & Iacoboni, 2006) and the LPP has been shown to be sensitive to evaluative categorization processes, with the LPP amplitude reflecting the extent to which a particular categorization process involves context updating (Cacioppo, Crites, Gardner, & Berntson, 1994). Thus our results suggest that OT treatment may weaken self-related processing in both early encoding of stimulus self-relevance and late evaluative processes. This result makes a key contribution toward understanding of the mechanisms with which OT may

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