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Intranasal oxytocin modulates EEG mu/alpha and beta rhythms during perception of biological motion

Anat Perry [a,*], Shlomo Bentin [a,b], Idan Shalev [c], Salomon Israel [a], Florina Uzefovsky [a], Dori Bar-On [a], Richard P. Ebstein [a]

[a] *The Department of Psychology, Hebrew University of Jerusalem, Mt. Scopus, 91905 Jerusalem, Israel*
[b] *The Interdisciplinary Center of Neural Computation, Hebrew University of Jerusalem, Israel*
[c] *The Department of Neurobiology, Hebrew University of Jerusalem, Israel*

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Summary Oxytocin (OT) plays a determining role in social and pair bonding in many vertebrates and increasing evidence suggests it is a social hormone also in humans. Indeed, intranasal administration of OT modulates several social cognitive processes in humans. Electrophysiological studies in humans associated the suppression of EEG in the mu/alpha and beta bands with perception of biological motion and social stimuli. It has been suggested that mu and beta suppression over sensory-motor regions reflects a resonance system in the human brain analogous to mirror neurons in the monkey. We therefore hypothesized that OT, a social hormone, would enhance this suppression, hence, for the first time, link the action of this neuropeptide with a human correlate of mirror neuron activity. Twenty-four students were administered 24 IU of OT or placebo intranasally in a robust, double-blind within-subject design. 45 min later participants were shown a point-light display of continuous biological motion of a human figure's walk. In the 8—10 Hz (low alpha/mu band) and in the 15—25 Hz beta band, a significant main effect of treatment showed that suppression was significantly enhanced in the OT versus the placebo conditions and that this suppression was widespread across the scalp. These results are a first step linking OT to the modulation of EEG rhythms in humans, suggesting that OT may have a role in allocating cortical resources to social tasks partly mediated by mirror neuron activity.
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1. Introduction

Oxytocin (OT), a neuropeptide hormone best known for its role in lactation and parturition, has been linked with a wide range of human social cognitive and emotional functions (Kirsch et al., 2005; Lee et al., 2009). Recent studies have provided evidence for the role of OT in facilitating the recognition of complex mental states and emotions (Domes

* Corresponding author. Tel.: +972 2 5883589; fax: +972 2 5825659.
E-mail address: anat.perry@mail.huji.ac.il (A. Perry).

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et al., 2007a), improving memory for faces (Rimmele et al., 2009), increasing gaze towards eye regions (Guastella et al., 2008a), enhancing the encoding of positive social memories (Guastella et al., 2008b) and the recognition of positive social words (Unkelbach et al., 2008), modulating trust and altruism during interpersonal transactions (e.g. Zak et al., 2005) and reducing endocrine and psychological responses to social stress (Heinrichs et al., 2003). OT has been shown to affect the activation of brain areas involved in emotion regulation and cognitive control, including the amygdala and midbrain regions (Kirsch et al., 2005; Domes et al., 2007b; Baumgartner et al., 2008) and the genetic polymorphism of the OT receptor gene has been associated with prosocial behavior in social value orientations tasks (Israel et al., 2009). Although most studies relate OT to prosocial behaviors, recent studies reported that OT also enhanced feelings of envy and gloating (Shamay-Tsoory et al., 2009), and enhanced fear recognition (Fischer-Shofty et al., 2010) thus relating it to a wider range of social emotion-related behaviors.

A recent behavioral study examined the effect of OT on the perception of point-light biological and non-biological motion stimuli and demonstrated that OT specifically enhances the ability of humans to detect biological motion in noise, but had no effect on a detection of a rotating shape (Keri and Benedek, 2009). In addition to strengthening the notion that OT specifically modulates the perception of socially relevant stimuli, the proven ability of OT to modulate biological motion perception opened a venue for associating this modulation to neural activity.

Neural activity reflected in EEG oscillations has been shown to reliably manifest perception as well as execution of biological motion. In particular, mu rhythms, measured between 8 and 12 Hz over somato-motor regions, are desynchronized and their power attenuated when engaging in motor activity (Gastaut, 1952), and also while observing actions executed by someone else (e.g. Muthukumaraswamy et al., 2004). These characteristics led authors to tentatively link the suppression of mu rhythms with a human mirror-neuron system (for a review see Pineda, 2005). The mirror-neuron system (MNS), originally discovered in the monkey (Rizzolatti et al., 1996), is thought to have evolved in humans into a wider neural system, enabeling simulation (and from it understanding) of other's intentions, thoughts and feelings (Gallese et al., 2004). In the last few years, several studies of typical participants linked EEG mu suppression to higher social information processing including social skills (Oberman et al., 2007), Theory of Mind (Pineda and Hecht, 2009; Perry et al., 2010) and empathy (Cheng et al., 2008a,b). Using similar paradigms, other studies found deactivation also in a higher frequency range (beta range, 15—25 Hz, e.g. Muthukumaraswamy and Singh, 2008). Supporting a link between social cognition and this EEG manifestation several studies of autistic spectrum disorders (ASD) found abnormal mu suppression when ASD individuals viewed actions performed by others despite normal suppression when they performed the same actions (Martineau et al., 2004; Oberman et al., 2005, 2008; but see Raymaekers et al., 2009).

Another EEG oscillation which might be modulated by the perception of biological movement is the alpha rhythm. Mu rhythms have been tentatively distinguished from alpha rhythms which oscillate in the same frequency range (Berger, 1929; see also, for example, Goodman et al., 1980) but culminate over the occipital cortex (for a review see Klimesch, 1999). The alpha frequency dominates the EEG when the brain rests (''idling rhythms'', e.g. Pfurtscheller et al., 1996) and suppression of alpha waves probably reflects enhancement of neural activity induced by a perceptual event, which leads to asynchronous neural firing. An overall decrease in alpha power has been linked to increasing demands of attention, alertness, episodic memory, and task-load in general (for reviews see Klimesch, 1999; Sauseng and Klimesch, 2008). Consequently, it should also be responsive to the perception of biological movement. One of the basic findings within alpha frequency range research is that alpha desynchronization is not a unitary phenomenon. Studies have differentiated at least two distinct patterns of desynchronization: lower alpha desynchronization (starting at 6 or 8 Hz, and ending around 10 Hz; see different studies in Klimesch, 1999), which is topographically widespread over the entire scalp and is assumed to reflect general task demands, expectancy and attentional processes, and upper alpha which is topographically restricted and develops during processing of sensory-semantic information (Klimesch, 1999).

In a recent study Perry and colleagues found stronger suppression of EEG oscillations in the alpha/mu (8—12 Hz) range as well as in the beta (15—25 Hz) range following perception of point-light biological displays compared to non-biological ones (Perry et al., 2010; see also Ulloa and Pineda, 2007). Importantly, the suppression was distributed over parieto-occipital as well as central sites suggesting the involvement of both attentional and somato-motor mechanisms in this activity.

In the present study, we relied on these findings and investigated the effect of externally administered OT on the suppression of EEG rhythms in the low and high alpha/mu bands (8—10, 10—12 Hz respectively), and in the beta band (15—25 Hz) using the same point-light stimuli and design used by Perry et al. (2010). We hypothesized that OT, a neuropeptide that partially shapes human social cognition, would enhance alpha/mu and beta suppression.

2. Materials and methods

2.1. Participants

A total of 24 male participants took part in this double-blind, placebo-controlled, within-subject study. All were undergraduate students from the Hebrew University ranging in age from 20 to 35 (mean age 25.3, SD = 3.55), who participated in the experiment for payment. Three of the participants were left-handed. All participants reported normal or corrected to normal visual acuity and had no history of psychiatric or neurological disorders (confirmed by a screening interview). To limit variance, participants were asked to avoid eating or drinking (except water) for 2 h prior the experiment. Written consent was obtained, and ethical approval was provided by The Herzog Hospital and the Israeli Ministry of Health Ethics Committee. One participant was excluded from the data analysis due to excessive artifacts induced by eyes blinks and saccades as well as body movements. Hence, the reported results are based on 23 participants.

2.2. Stimuli, task, and design

The stimuli used were 5 s long video clips presenting point-light displays of continuous biological motion of a human figure's walk. All stimuli were based on a morphable model spanned by 100 different individual walkers as described in more detail elsewhere (Troje, 2002, 2008). "Walkers" used for the current experiment varied along three different dimensions: gender (male or female), expression (sad or happy), and intention (approaching or retreating). All three dimensions were manipulated independently. For example, a point-light display could represent a sad woman walking towards the observer, a happy man walking away, and all other possible combinations (for still examples of the stimuli, see Fig. 1). A pilot study insured that participants were able to easily distinguish these factors (see Perry et al., 2010). The clips were presented on a CRT monitor, 70 cm away from the participant's eyes with the point-light displays subtending on average a visual angle of $11.5^{\circ} \times 4^{\circ}$. For a detailed description of the construction of the stimuli, see Perry et al. (2010).

E-Prime (Psychological Software Tools) was used for stimulus presentation and experimental control. In a blocked design, each block depicted a different task, requesting the processing of only one dimension (gender, emotion, or intention). Each of the three blocks included two types of trials. Each trial was comprised of 20 clips keeping constant one of the levels of the relevant dimension (e.g. a male figure in the gender block) and 3–6 clips presenting the other level (e.g. a female figure in the gender block). The participants were instructed to silently count the occurrence of the rare event and, at the end of each trial, report this number. The two levels of the two other dimensions (emotion and intention in the above example) changed randomly across the 23–26 clips presented in a trial. Hence, although the participants focused on only one of the three dimensions each dynamic point-light display presented all three dimensions. Two types of trials were presented in each block, with the frequent level of the relevant dimension switched, and the order of the trials counterbalanced across participants.

In addition to the three experimental task conditions (gender, emotion, intention), a non-biological movement baseline condition (a right-to-left or left-to-right moving circle composed of the same point-lights) was presented in two separate blocks. In these blocks participants had to report how many times the ball rolled to a pre-defined (rare) direction (left or right). All possible order permutations of the three experimental and baseline conditions were used, yielding a total of 24 orders, each presented to a different observer. To make sure that there were no effects of participants' current state, participants were interrogated with a visual analogue scale (VAS), before and after each session (4 times altogether), with 8 scales that evaluated working abilities, drowsiness, sadness, anxiety, anger, communicativeness, and concentration (e.g. Charney et al., 1987; Wewers and Lowe, 1990).

2.3. Procedure

Each experimental session was scheduled for 1.5 h, starting between 1200 and 1700 h to counter effects of circadian changes of other hormones (e.g., cortisol, testosterone). After signing the informed consent, each participant randomly received either 24 international units (IU) (250 μl) of intranasal OT (Sigma) or sterile saline for the placebo treatment (consisting of the same salt solution in which the hormone was dissolved in except the hormone itself). Both were self-administered in the presence of the experimenter by means of intranasal (IN) drops applied with a medicine dropper. This method was verified in previous studies which demonstrated the central action of IN administration of neuropeptides (Perras et al., 1996, 1997; Pietrowsky et al., 1996; Born et al., 1998, 2002; Thompson et al., 2004, 2006). For application of the nasal drops, participants, while seated, were asked to maximally tilt their head backwards whereby the liquid was applied with a standard medicine dropper into both nostrils. Neither the experimenter, nor the participant knew whether the participant received OT or placebo.

After administration, participants were asked to wait 20 min to ensure that, together with 25 min of putting on the EEG cap and electrodes, the OT levels in the central nervous system would reach a plateau (Illum, 2000). During this waiting period, participants sat in a comfortable quiet room, and received four volumes of a common Israeli nature newspaper, thus keeping to a minimum any social interaction.

Following these 45 min, participants were seated in a comfortable armchair located in an acoustically attenuated

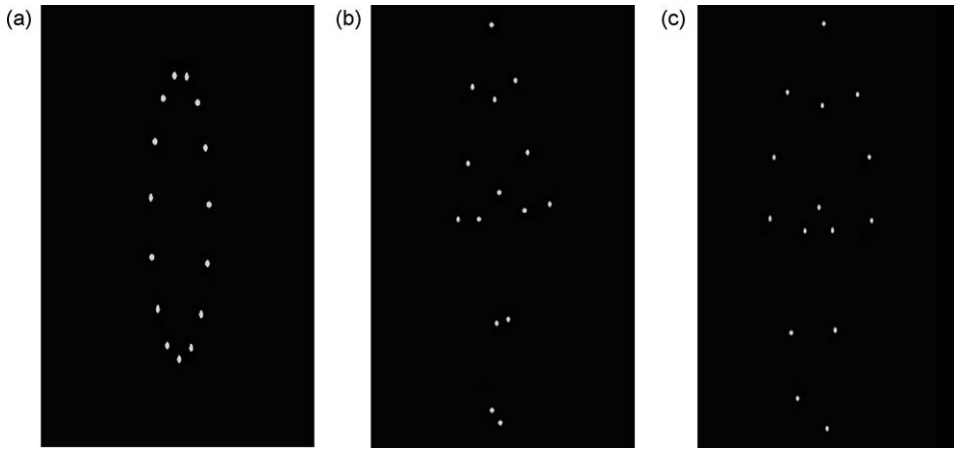

Figure 1 Examples of stimuli: (a) the rolling circle presented in the baseline condition; (b) a female image; (c) a male image.

and electrically isolated chamber, dimly lighted. They were instructed to refrain from any movement during a trial presentation and their overt behavior was monitored by a video-camera. Each block began with a training session of four point-light displays, which the participant had to rate on the pre-determined relevant dimension. The training was repeated if needed, although it was rarely used more than once. The clips within each trial were presented continuously without ISI (yielding 100 s of continuous stimulation). A short break separated the trials. During this break, participants were asked to answer four trivia questions, in order to prevent possible carry-over effects across tasks.

2.4. Data acquisition and analysis

2.4.1. EEG recording

The EEG analog signals were recorded continuously (from DC with a low-pass filter set at 100 Hz) by 64 Ag—AgCl pin-type active electrodes mounted on an elastic cap (Biosemi™, http://www.biosemi.com/headcap.htm) according to the extended 10—20 system, and from two additional electrodes placed at the right and left mastoids. All electrodes were referenced during recording to a common-mode signal (CMS) electrode between POz and PO3 and were subsequently re-referenced digitally (see data processing below). Eye movements, as well as blinks, were monitored using bipolar horizontal and vertical EOG derivations via two pairs of electrodes, one pair attached to the external canthi, and the other to the infraorbital and supraorbital regions of the right eye. Both EEG an EOG were digitally amplified and sampled at 1024 Hz using a Biosemi Active II system (www.biosemi.com).

2.4.2. Data processing

Data were analyzed using Brain Vision Analyzer software (Brain Products; www.brainproducts.com) and house-made Matlab routines. Raw EEG data was initially 0.5 Hz high-pass filtered (24 dB) and re-referenced off-line to the digital average of the two mastoids. Eye movements were corrected using an ICA procedure (Jung et al., 2000). Remaining artifacts exceeding $\pm 100\ \mu V$ in amplitude were rejected. As suggested by Pineda and Oberman (2006) the first 10 s of each block were excluded from the analysis to reduce the possibility of attentional transients due primarily to the initiation of the stimulus. For each 5-s stimulus, the first 2 s were segmented, since this was the maximum time needed to extract the information from the stimulus (see pilot data Perry et al., 2010). For each such segment, the integrated power in the 8—10, 10—12 and 15—25 Hz range were computed using a fast Fourier transform (FFT) performed at 0.5 Hz intervals (based on 2048 points per segment, and using a Hanning window).

A suppression index was calculated as the logarithm of the ratio of the power during the experimental conditions relative to the power during the baseline conditions, and used as dependent variable. The ratio (as opposed to a simple subtraction) was used to control for the variability in absolute EEG power as a result of individual differences such as scalp thickness and electrode impedance (Pineda and Oberman, 2006). Further, since ratio data are inherently not normally distributed as a result of lower bounding, a log transform was also used in order to perform statistical analysis. Hence, a log ratio of less than zero indicates suppression in the EEG amplitude, whereas a value of zero indicates no change and values greater than zero indicate enhancement. Suppression was computed and analyzed at 9 sites: occipital sites, O1, Oz and O2, where classical alpha modulation is expected; central sites, C3, Cz and C4, which are classical mu rhythm sites; and frontal F3, Fz and F4 in order to investigate whether the effect is widespread or local.

3. Results

3.1. 8—12 Hz (alpha/mu band)

The suppression index (see methods) was analyzed using repeated measures ANOVA. The effect of OT was similar in all task conditions (there was no interaction between the Task Condition (intention, emotion, gender) and treatment (OT, placebo), $F(2,44) < 1$, $p = 0.766$), and so these were collapsed for simplicity. Hence there were three factors in the within-subject ANOVA: treatment (OT, placebo), region (frontal, central, occipital) and laterality (left, central, right). When factors included more than two levels, the degrees of freedom were corrected using the Greenhouse—Giesser epsilon (G—GE). Following the literature on alpha and mu (Klimesch, 1999; Pineda, 2005), we looked at the above frequencies divided into low (8—10 Hz) and high (10—12 Hz) ranges. In the 8—10 Hz, a significant main effect of treatment showed that suppression was significantly enhanced in the OT versus the placebo conditions (—0.206 and —0.067 respec-

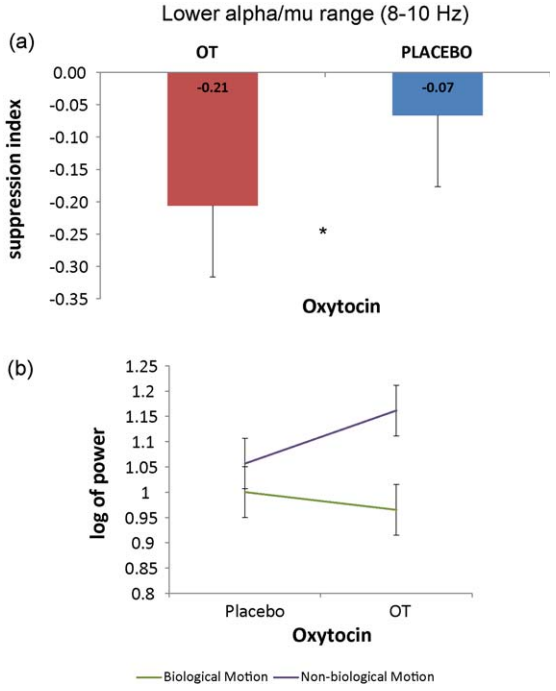

Figure 2 (a) Suppression in the 8—10 Hz range, OT versus placebo. Both bars show suppression for the biological motion conditions compared to the non-biological condition, but this suppression is enhanced significantly by OT. Error bars represent standard error (SE). (b) 8—10 Hz interaction between treatment × motion. OT had an opposite effect on EEG for perception of biological versus non-biological stimuli.

tively; $F(1,22) = 5.79$, $p < 0.05$, see Fig. 2a). There was no main effect of region or laterality; the OT enhanced suppression was widespread across the scalp (occipital, central and frontal regions).

Since the suppression index reflects the ratio between the power during the experimental (biological motion) conditions and the power during the baseline (non-biological motion) condition, the difference between OT and placebo could be caused by either enhanced suppression in the biological motion conditions following the OT treatment, or by a reduced suppression in the non-biological motion condition following this treatment. In order to differentiate between these two alternatives, we conducted a second ANOVA in which the factors were treatment and motion condition (biological, non-biological) and the dependent variable was the log of the power in each condition (across regions and sites). This ANOVA revealed no main effect for treatment ($p > 0.1$), an expected effect of motion [$F(1,22) = 14.98$, $p = 0.001$] and, notably, an interaction between treatment and motion [$F(1,22) = 5.65$, $p < 0.05$], revealing a binary effect of OT, in opposite directions: enhancing suppression for biological motion and reducing suppression for non-biological motion, thus generating the significant interaction (Fig. 2b).

No significant effect of OT was observed in the 10–12 Hz (higher mu/alpha) range.

3.2. 15–25 Hz (beta band)

The same ANOVA was conducted for the 15–25 Hz beta band. This analysis revealed similar effects to those found in the lower mu/alpha range. That is, a significant effect for treatment [$F(1,22) = 4.496$, $p < 0.05$)], with no other significant effects.

The treatment effect showed that suppression was significantly enhanced in the OT versus the placebo conditions (−0.089 and −0.022 respectively; $F(1,22) = 4.396$, $p < 0.05$, see Fig. 3a).

Again, we also carried out a treatment × motion condition ANOVA, comparing the log of the power of the biological and non-biological motion conditions (across regions and sites). As in the 8–10 Hz range, this ANOVA revealed no main effect for treatment ($p > 0.1$), an expected effect of motion [$F(1,22) = 5.801$, $p < 0.05$], and again a binary effect of OT as shown by the interaction between treatment and motion [$F(1,22) = 4.396$, $p < 0.05$]. OT enhanced suppression for biological motion and reduced suppression for non-biological motion, thus generating the significant interaction (Fig. 3b).

3.3. Behavioral measures

The behavioral task was primarily intended to keep participants focused on the stimuli. A significant difference was observed in participants' accuracy measure between the biological and non-biological blocks [mean accuracy rate (SD): 0.80 (0.033) and 0.855 (0.050) respectively, $F(1,47) = 5.449$, $p < 0.05$]. However, there was no effect of treatment by itself on accuracy [$F(1,47) < 1$, $p = 0.922$], and no interaction between treatment and Condition [$F(1,47) < 1$, $p = 0.493$]. There was also no significant interaction between treatment and any of the VAS measures [$F(7,126) = 1.226$, $p > 0.7$].

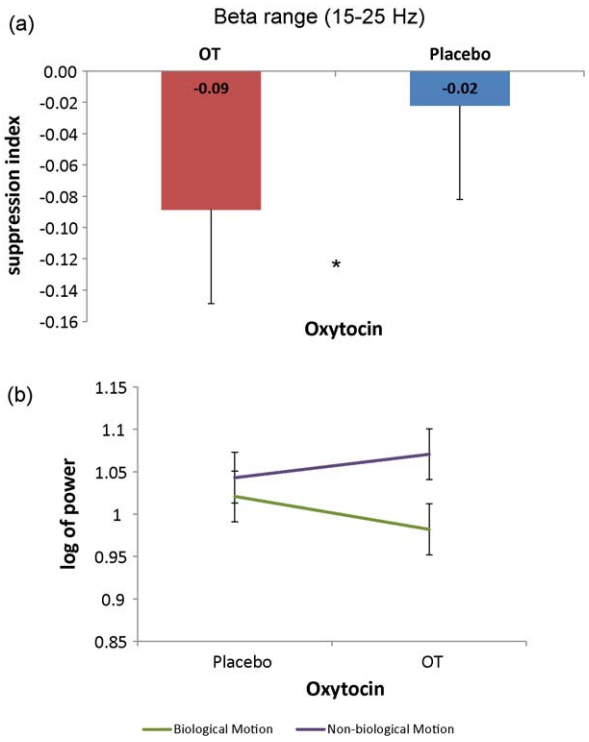

Figure 3 (a) Suppression in the beta range, OT versus placebo. Both bars show suppression for the biological motion conditions compared to the non-biological condition. As in the lower alpha range, this suppression is enhanced significantly by OT. Error bars represent standard error (SE). (b) Beta range interaction between treatment × motion. Like in the lower alpha range, OT had an opposite effect on EEG for perception of biological versus non-biological stimuli.

4. Discussion

This study is a first step in investigating the effects of OT on EEG oscillations in the human brain and demonstrates that this hormone modulates EEG rhythms in the alpha/mu and beta ranges differentially in tasks of biological motion and non-biological motion. Thus, this study serves as a link between previous studies showing an effect of biological motion on suppression in these frequencies (Perry et al., 2010; Ulloa and Pineda, 2007) and the single study showing OT effects on the perception of biological motion (Keri and Benedek, 2009).

Not unexpectedly considering the wide distribution of OT receptors in the brain (Loup et al., 1989, 1991), the suppression following intranasal (IN) administration of this neuropeptides was widespread across the scalp. This widespread OT modulation of the neural response to biological motion might therefore reflect a broader effect than that usually attributed to mu suppression over somato-motor regions. Interestingly, it appears that OT has a general suppressive effect on lower alpha/mu and on the beta rhythms affecting regions that include the somato-motor cortex but are not

limited to it. Specifically, it is possible that the currently observed modulations may reflect not only the activity of an EEG analogue of the human mirror-neuron system (Pineda, 2005; Oberman et al., 2007; Pfurtscheller et al., 2007; Muthukumaraswamy and Singh, 2008; Perry and Bentin, 2009), but also other perceptual and attentional mechanisms. This extended activation, which was reported also by Perry et al. (2010) suggests the there is not an exclusive link between this desynchronization and motor/mirror systems and social cognition. Rather, it suggests a broader network responding differentially to social relevant tasks, which might also include the mirror-neuron system along with other structures.

Alpha suppression in the lower (8—10 Hz) range has been related to expectancy and attentional processes, and suggested that alpha suppression is positively related to the amount of cortical resources allocated to task performance (Gevins et al., 1997; Klimesch, 1999). It has already been shown that the perception of biological motion enhances suppression relative to non-biological motion stimuli, thus probably allocating more cortical resources to the biological motion tasks (Ulloa and Pineda, 2007; Perry et al., 2010). The widespread effect of OT seems to enhance this attentional effect, allocating even more attentional resources when biological stimuli are present and less resources when non-biological stimuli appear. We suggest the notion that the effect of IN OT observed here may be composed of both an effect on alpha rhythms and general attention and on the mu and beta rhythms recorded over somatosensory regions and possibly reflecting a mirror-neuron system. The hypothesis that the widespread OT effect on the EEG rhythms indicates an increase in attention to biological stimuli should be further investigated, perhaps using different paradigms (cf., Keri and Benedek, 2009).

The absence of an OT effect in the 10—12 Hz range is intriguing in light of its "reappearance" in the even higher beta range. This gap might suggest that different neural mechanisms are modulated by biological motion (interacting with OT) in the lower alpha/mu and in the beta ranges. However, the absence of effects in the higher alpha range may be partially explained by the chosen stimuli. Indeed, at least over the central regions, this higher mu range is known to be more specific to hand stimuli (Pfurtscheller et al., 2000; Pineda, 2005). This is the first study demonstrating a differential effect of OT on human EEG rhythms in response to perceiving biological versus non-biological stimuli. Obviously, more research is needed in order to further investigate the effects of OT on these frequencies using different stimuli and paradigms in order to better pinpoint and understand this differential effect.

Finally we should mention that due to local ethical restrictions only male participants were tested in this study. Future studies would benefit from examining female participants and gender differences whenever possible. Future studies of OT and EEG would also benefit from a genetic strategy stratifying modulation of brain waves by genotype. Importantly, considering the interest of OT in relation to autistic spectrum disorders and other disorders related to deficits in social cognition, it would be worthwhile to extend IN OT coupled with EEG recordings to clinical groups. Indeed, experiments are now reported in which individuals with ASD are treated using neurofeedback techniques that modulate EEG rhythms (Pineda et al., 2008; Coben, 2008; Coben and Myers, 2010). Other studies show improvement in social recognition skills in ASD individuals following OT administration (e.g. Hollander et al., 2007). Linking these processes may be an important step at understanding the underlying mechanisms in abnormal social behavior and at a later stage may open a therapeutic window towards improving treatment for disorders of social cognition.

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There was no role of the study sponsor(s) in study design, in the collection, analysis and interpretation of data, in the writing of the report, or in the decision to submit the paper for publication.

Conflicts of interest

The authors report no biomedical financial interests or potential conflicts of interest.

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