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Oxytocin selectively modulates brain response to stimuli probing social synchrony

Jonathan Levy, Abraham Goldstein, Orna Zagoory-Sharon, Omri Weisman, Inna Schneiderman, Moranne Eidelman-Rothman, Ruth Feldman *

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ABSTRACT

The capacity to act collectively within groups has led to the survival and thriving of *Homo sapiens*. A central group collaboration mechanism is "social synchrony," the coordination of behavior during joint action among affiliative members, which intensifies under threat. Here, we tested brain response to vignettes depicting social synchrony among combat veterans trained for coordinated action and following life-threatening group experience, versus controls, as modulated by oxytocin (OT), a neuropeptide supporting social synchrony. Using a randomized, double-blind, within-subject design, 40 combat-trained and control male veterans underwent magnetoencephalography (MEG) twice following OT/placebo administration while viewing two social vignettes rated as highly synchronous: pleasant male social gathering and coordinated unit during combat. Both vignettes activated a wide response across the social brain in the alpha band; the combat scene triggered stronger activations. Importantly, OT effects were modulated by prior experience. Among combat veterans, OT attenuated the increased response to combat stimuli in the posterior superior temporal sulcus (pSTS) – a hub of social perception, action observation, and mentalizing – and enhanced activation in the inferior parietal lobule (IPL) to the pleasant social scene. Among controls, OT enhanced inferior frontal gyrus (IFG) response to combat cues, demonstrating selective OT effects on mirror-neuron and mentalizing networks. OT-enhanced mirror network activity was dampened in veterans reporting higher posttraumatic symptoms. Results demonstrate that the social brain responds online, via modulation of alpha rhythms, to stimuli probing social synchrony, particularly those involving threat to survival, and OT's enhancing versus anxiolytic effects are sensitive to salient experiences within social groups.

Introduction

The capacity to act collaboratively toward social goals has long been suggested to underpin the success and thriving of social species, including *Homo sapiens* (Wilson, 2012). Beginning with the early entomologists, social synchrony – the online coordination of behavior between group members during joint action – has been described as a central evolutionary mechanism supporting group collaboration (Wheeler, 1928; Rosenblatt, 1965). As members of a social species, humans enter synchronous experiences readily: group singing, band marching, or joint harvesting. Such coordination carries profound effects on group cohesion and has been utilized throughout human history as a powerful enhancer of social belonging. Synchrony tightens when individuals face life-threatening circumstances: Medical crews during operation, soldiers in battle, or firefighters saving captives from flames – groups highly trained for coordinated performance – synchronize action within split seconds, and this ability has played a key evolutionary role in increasing the survival of our species under harsh conditions (Feldman, 2012; Yamasue et al., 2012).

In mammals, synchrony is learned within the mother–infant bond via processes of *bio-behavioral synchrony* — the online coupling of coordinated behavior and matched physiological response between social partners (Feldman, 2012; Hofer, 1995). Experiences of parent–infant synchrony profoundly affect the development of human sociality, for instance, understanding others' minds and engaging in social reciprocity with group members (Feldman and Masalha, 2010; Feldman et al., 2013; De Dreu et al., 2010). Oxytocin (OT), a neuropeptide synthesized in the hypothalamus and implicated in mammalian socialization and affiliation (Rilling and Young, 2014; Carter, 2014), underpins the expression of social synchrony within human social bonds, including parents, couples, and close friends, and plays a central role in group identity (Feldman, 2012; De Dreu et al., 2010). The OT system supports group cohesion in mammals, particularly when facing environmental threats that may lead to dispersal, by increasing salience to social cues and regulating the stress inherent in group living under life-threatening conditions (Yamasue et al., 2012). Such mechanisms are similarly described in human imaging research, which showed both salience-enhancing and anxiety-reducing effects of OT administration in response to threatening stimuli (Bartz et al., 2011; Kirsch et al., 2005).

Although few data are available on the mechanisms underlying brain response to social synchrony, recent studies highlight the involvement of critical nodes in the social brain. EEG synchronization between

* Corresponding author at: Department of Psychology and the Gonda Brain Sciences Center, Bar-Ilan University, Ramat-Gan 52900, Israel.
E-mail address: feldman.ruth@gmail.com (R. Feldman).

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two brains in the alpha band was found in mirror regions when individuals engaged in motor synchrony (Dumas et al., 2010). Mothers and fathers synchronized their brain response to their 4-month-old infant's video in areas of the mentalizing and mirror networks including the inferior frontal gyrus (IFG) and inferior parietal lobule (IPL) (Atzil et al., 2012), demonstrating brain-to-brain synchrony in these areas in survival-related contexts. Regions in mothers' social brain were activated in response to videos depicting mother–infant synchrony, and the mother's behavioral synchrony during interaction with her infant predicted her brain response to synchrony in others (Atzil et al., 2011, 2014). These studies suggest that brain mechanisms underpinning participation in social synchrony also support neural response to stimuli depicting synchrony in others, particularly to viewing vignettes high in social synchrony. This is consistent with research on pain perception, which showed overlapping activations to first-person experience and third-person observation, a parallel response thought to underlie the human capacity for empathy and affective sharing (Decety, 2010; Singer and Lamm, 2009).

Overall, the sharing of others' emotions and recognition of others' mental states rely on two networks that globally form the "social brain" (Keysers and Gazzola, 2007). The *mentalizing system* includes the precuneus, temporo-parietal junction (TPJ), posterior superior temporal sulcus (pSTS), and medial prefrontal cortex (Amodio and Frith, 2006). The *mirror neuron system* (MNS) includes the IPL, pSTS, and IFG (Rizzolatti and Craighero, 2004; Iacoboni and Dapretto, 2006). The mentalizing system allows individuals to predict the relationships between external events and internal states, whereas the MNS responds to both action performance and action observation (Bernhardt and Singer, 2012). Together, these networks enable humans to participate in joint action and share the feelings of others — the prerequisites of social life. Inasmuch as infants develop these abilities on the basis of parent–infant synchrony and the OT system, the salience of prior experiences in social synchrony may tune responses in these regions to stimuli probing social synchrony. Intranasal administration of OT acts upon the social brain (Born et al., 2002; Meyer-Lindenberg et al., 2011), and OT's unique mode of peptidergic release is primed by past experience, particularly salient social experiences, for activity-dependent release that can reorganize neural networks (Carter, 2014; Ludwig and Leng, 2006).

While research on the social brain has mainly utilized fMRI technology, we focused on induced neuronal oscillations measured by magnetoencephalography (MEG), which have scarcely been studied in social neuroscience (Stanley and Adolphs, 2013). Of special interest were alpha-band oscillations (8–12 Hz), the predominant oscillations in the awake, conscious brain that reflect higher intrinsic cortical functioning and serve an integrative role by synchronizing brain activity in different rhythms. Alpha rhythm functions through inhibition; an alpha oscillatory increase reflects suppressed cortical reactivity whereas alpha oscillatory suppression indexes enhanced reactivity and cortical recruitment (for a review, see Jensen and Mazaheri, 2010). Evidence highlights the role of alpha rhythms in supporting social functions (Whitmarsh et al., 2011), biological motion (Ulloa and Pineda, 2007), and inter-individual synchronized actions (Dumas et al., 2010). Furthermore, EEG research showed that OT regulates alpha rhythms during social processing, possibly via modulation of MNS (Perry et al., 2010).

In the current study, we utilized a unique cohort of combat veterans who were highly trained for coordinated group performance and following life-threatening combat to tap the social brain's response to cues depicting social synchrony in combat versus social contexts. Employing a randomized, double-blind, placebo-control crossover design, we integrated, for the first time, assessment of alpha oscillations in the social brain, the influence of prior synchrony experience in survival-related contexts, and the modulating effects of OT administration. Using MEG after OT/placebo administration in two sessions a week apart, we compared the brain responses of two groups of male military veterans, those with enhanced training for coordinated action and controls, while they viewed two video vignettes: (a) pleasant male social gathering (social scene — SS) and (b) coordinated unit during combat (combat scene — CS). Both scenes were judged by independent raters as being high on social synchrony with no differences in the degree of synchrony. MEG uniquely combines the temporal resolution of fast neural rhythms and their underlying cortical generators and can thus assess induced alpha rhythms in distinct areas across the social brain. The following hypotheses were proposed: (a) Regions across the social brain would respond online to stimuli probing social synchrony; such response would be mediated by alpha rhythms; and alpha responsivity would increase when stimuli involve threat to survival. (b) Consistent with research indicating that OT administration effects are context-bound, shaped by powerful social experiences (for a review see Bartz et al., 2011), and impact alpha oscillations in MNS (Perry et al., 2010), we expected differential alpha modulation in MNS as a function of prior experiences within the social group. (c) Brain response to OT may follow both anxiolytic and social-enhancing mechanisms, the two mechanisms by which OT has been shown to impact brain activity (Neumann, 2008; Bartz et al., 2011). And (d) among combat veterans, the degree of posttraumatic symptoms would shape brain response to combat and social vignettes.

Methods

Participants

We recruited two groups of young (21–35 years; M = 27.77 ± 2.38 years) male veterans of the Israel Defense Force who finished their mandatory military service within the past 8 years and all reported being physically healthy. The 26 combat veterans had served in a highly-trained combat unit, received intense training within their unit, and spent at least 12 months in daily training for coordinated performance. These veterans had participated in life-endangering combat with their unit where they witnessed one or more comrades of their unit getting severely wounded or dead a few years before the experiment (4.81 ± 1.40 y).

The 14 controls were matched for age and education and served during the same period in non-combat units (intelligence, technical support). As we expected greater variability in the brain response of the combat-trained group, we recruited a smaller group of controls. All participants reported to be functional in their daily life and under no regular use of medication. The study was approved by the Institutional Review Board of Bar-Ilan University. Participants were recruited via advertisement in the community and were matched for demographic status. Subjects were right-handed as measured by the Edinburgh Handedness Questionnaire except for three subjects from the combat group who were neutral ($n = 1$) or left-handed ($n = 2$). Exclusion criteria included serious physical injury, current or past neurological disorders, and serious medical problems. Participants completed the Posttraumatic Diagnostic Scale (PDS) to assess posttraumatic symptom severity (Foa et al., 1997). All combat veterans reported mild to medium PDS symptoms (M = 16.13, SD = 6.98), whereas none of the controls showed any symptoms related to any traumatic events of any sort (M = 0, SD = 0).

Experimental procedure

The study used a double-blind, placebo-control, within-subject design. Each subject participated in two similar experimental sessions approximately a week apart (mean = 7.5 days, SD = 2) after inhaling either OT or PBO. Upon arrival, participants self-administered 24 IU of either OT or placebo. 45 min later (at the putative peak influence of OT), the MEG recording began. Spontaneous brain activity was measured using MEG while participants watched two consecutive 1-minute video excerpts (social and then combat) with brief resting break between. Excerpts were taken from commercial films: the social

scene (SS) from *Mumford* (Kasdan, 1999) and a combat scene (CS) from *Platoon* (Stone, 1986). Both vignettes were rated by 10 blind independent judges at highly synchronous (M = 4.08, 4.12 on scale of 1–5 for social and combat scenes respectively) with no differences between scenes. Finally, outside the MEG, participants watched the video vignettes again and rated them for valence, arousal, and familiarity on a five-point Likert scale (for further details *SI Materials and Methods*).

Recordings, spectral analysis, source dynamics and statistics

Ongoing brain activity was recorded (sampling rate, 1017 Hz, online 1–400 Hz band-pass filter) using a whole-head 248-channel magnetometer array (4-D Neuroimaging, Magnes 3600 WH) in supine position inside a magnetically shielded room. Reference coils located approximately 30 cm above the head oriented by the x, y, and z axes were used to remove environmental noise. Five coils were attached to the participant's scalp for recording the head position relative to the 248 sensor-array. External noise (e.g., power-line, mechanical vibrations) and heartbeat artifacts were removed from the data using a predesigned algorithm for that purpose (Tal & Abeles, 2013). Spectral analysis was performed using Matlab 7 (MathWorks, Natick, MA, USA) and the FieldTrip toolbox (Oostenveld et al., 2011). Data were segmented into 1000 milliseconds epochs, and trials containing muscle artifacts and signal jumps were rejected from further analysis by visual inspection. Data were then filtered in the 1–200 Hz range with 10 s padding and were then resampled to 400 Hz. Finally, spatial component analysis (ICA) was applied in order to clean eye-blinks, eye movements, and heart-beats (which survived the previous step of heart-beat cleaning), in total cleaning on average approximately three components per participant.

A Hanning taper was applied to each epoch of the 248-sensor data in order to calculate the Fast Fourier Transform (FFT) for short sliding time windows of 0.5 s in the 2–40 Hz frequency range, resulting in a spectral resolution of 2 Hz. To analyze the location of the sources in the frequency bands of interest, we computed the cross-spectral density matrix between all MEG sensor pairs from the Fourier transforms of the tapered data epochs. Spatial filters were constructed for each grid location, based on the identified frequency bin, and the Fourier transforms of the tapered data epochs were projected through the spatial filters. To facilitate analysis at the source level, for each subject, a single shell brain model was built based on a template brain (Montreal Neurological Institute), which was modified to fit each subject's digitized head shape using SPM8 (Wellcome Department of Imaging Neuroscience University College London,www.fil.ion.ucl.ac.uk). The head shape was manually digitized (Polhemus Fastrak digitizer), and the subject's brain volume was then divided into a regular grid. The grid positions were obtained by a linear transformation of the grid positions in a canonical 1 cm grid. This procedure facilitates the group analysis, because no spatial interpolation of the volumes of reconstructed activity is required. For each grid position, spatial filters (Gross et al., 2001) were reconstructed with the aim of optimally passing activity from the location of interest, while suppressing activity that was not of interest.

Statistics were implemented in the FieldTrip toolbox (Oostenveld et al., 2011) by applying a nonparametric cluster-based procedure (Maris and Oostenveld, 2007) (*SI Materials and Methods*), and cortical maps were illustrated using BrainVoyager QX (Brain Innovation BV, the Netherlands). SPSS (IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp) and G*Power (Faul et al., 2007) were also used for complementary statistic measures.

Results

One-way ANOVA on the sensor data (for all participants, sessions, and the 248 MEG sensors), revealed a significant effect ($p < .005$, cluster-level corrected) in the 8–14 Hz band, confirming our hypothesis regarding alpha oscillations for the total sample. Post-hoc analyses revealed a parametric decrease in alpha power ($r = -0.39$, $p < .000005$) from Baseline through SS to CS (Fig. 1A). Post-scan behavioral ratings of the video vignettes (Fig. 1B) revealed significant differences between conditions for arousal, affective valence, and familiarity (see ANOVA results in tables S1–3 in the *SI* section).

Participants rated higher arousal for the CS (M = 3.52, SD = 1.17) compared to the SS (M = 1.92, SD = 1.52), ($t(77) = -9.24$, $p < 10^{-13}$, FDR-corrected), and more negative valence for the CS (M = 1.97, SD = 1.05) compared to the SS (M = 3.17, SD = .92), ($t(77) = 8.29$, $p < 10^{-11}$, FDR-corrected). Likewise, participants rated higher familiarity for the CS (M = 1.43, SD = 1.74) compared to the SS (M = 0.38, SD = 0.86), ($t(77) = -4.74$, $p < 10^{-5}$, FDR-corrected), (see ANOVA results in table S3 the *SI* section), but this is related to a marginal proportion of subjects who reported having known any of the movies; namely 16% of participants were confidently familiar with any of the movies (26% with CS and 8.5% with SS).

Inasmuch as synchrony was rated by independent judges as comparable between CS and SS (Fig. 1B, right panel), the stronger modulation in alpha rhythm during CS may indicate higher arousal and more negative valence independent of the vignettes' degree of social coordination.

We next performed source localization for each of the two vignettes across the whole sample (for all participants, sessions and the 248 MEG sensors). As seen in Fig. 2, source localization revealed that both vignettes activated a network ($p < .001$, cluster-level corrected) comprising visual areas as well as regions involved in social processing, including the occipital cortex, cunei, frontal gyri, inferior and superior parietal lobules, posterior superior temporal sulci, supplementary motor areas, precunei and cingulate cortex (posterior, middle, and anterior). Moreover, SS activated the orbito-frontal cortex and CS activated the precentral gyri and temporal–parietal junctions, yet, no area was recruited significantly more for one vignette than for the other (see *SI Results*). These findings confirm our main hypothesis and show that probing social synchrony activates a wide response throughout the social brain. As hypothesized, the threatening CS elicited more robust activations than the SS.

Next, repeated-measures ANOVA examined group (combat/non-combat) and condition (OT/placebo) effects on activations (Fig. 2) in response to each of the two vignettes (see summarized results in Tables S4 and S5 for SS and CS, respectively). In response to SS, significant condition effect emerged for the right IPL (R-IPL) ($F(1,38) = 5.83$, $p = .02$), whereas in response to CS, a significant group by condition interaction effect emerged for the left pSTS ($F(1,38) = 8.21$, $p = .007$). Furthermore, a whole-brain two-way repeated-measure ANOVA (see *SI Results*) confirmed the two significant effect (for R-IPL and L-pSTS, although only the latter survived whole-brain correction for multiple comparisons), and additionally revealed a third activated region, the left IFG (L-IFG; in a cluster including the left anterior insula), demonstrating a significant condition by group interaction in response to CS.

In response to CS, post-hoc t-tests indicated a stronger recruitment of the left pSTS by the combat group under placebo ($p < .05$, with statistical power of 60%); however, this effect was canceled out under OT ($p > .25$) (Fig. 3, left panels). Similarly, the left IFG also indicated a stronger recruitment by the combat group under placebo ($p < .05$, with statistical power of 40%); this effect was then reversed under OT ($p < .005$, with statistical power of 83%) (Fig. 3, right panels). In contrast, in response to SS, post-hoc t-tests revealed no group-differences in the R-IPL (Fig. 4A,B). Nevertheless, combat-trained veterans activated this region only under OT ($p < .05$, with statistical power of 43%), not under PBO ($p > .80$).

Overall, results indicate that the mirror network, indexed by L-pSTS, R-IPL, and L-IFG, responds selectively to social synchrony pending OT intake and prior social-group experiences. In response to CS, OT attenuated (in pSTS) or reversed (in IFG) group differences, whereas in response to SS, OT induced activity (in IPL) in combat-trained veterans. Given the integrative role of the pSTS in social perception, action observation, and theory-of-mind (Yang et al., 2015), the increased recruitment of this

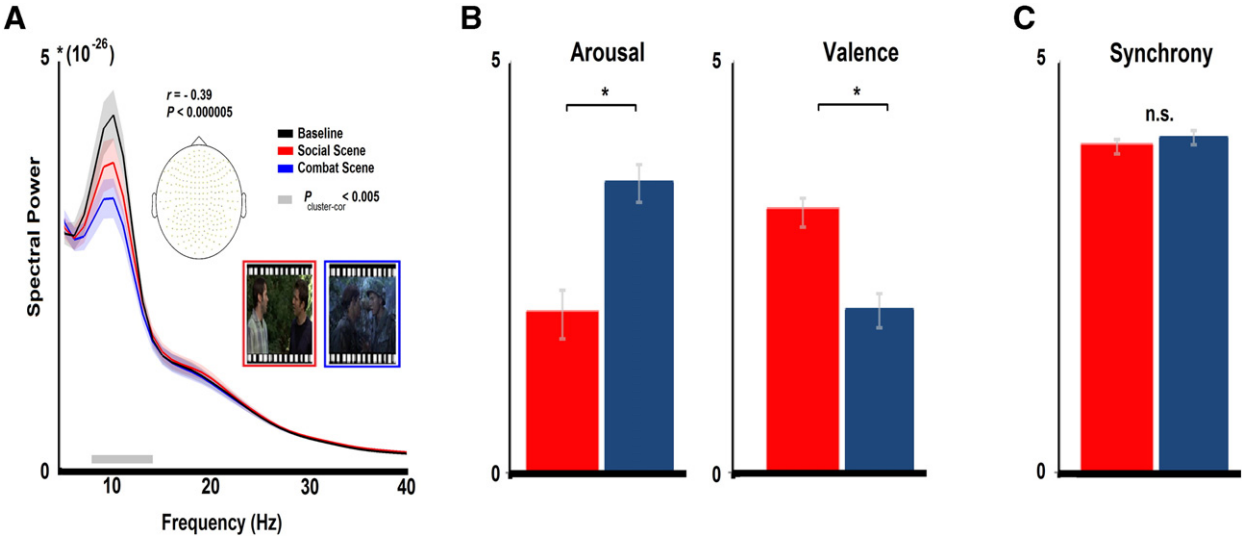

Fig. 1. Participants' overall brain and behavioral responses to combat and social vignettes. (A) Participants' alpha power (power is in 10^{-26} units) spectrum modulation averaged over all sensors. (B) Participants' mean behavioral (Likert) ratings of vignettes' arousal (from calm — 0 to high — 5), valence (from unpleasant — 0 to pleasant — 5) and (external judges') mean ratings of synchrony (from non-synchronous — 0 to synchronous — 5). *($p < 10^{-11}$).

area by combat-trained participants likely reflects stress-related over-activity, possibly related to increased sensory re-experiencing of combat-related cues. Such over-activity of the pSTS under PBO was attenuated under OT, thereby possibly reflecting an anxiolytic influence of OT on stress-induced brain activation. In contrast, the IPL and the IFG structures of the MNS represent response to observed actions. Hence, the OT-driven recruitment of the MNS regions sensitive to observed actions (i.e., IFG and IPL) may demonstrate a selective social salience mechanism that involves increased salience to pleasant social stimuli in the combat veterans and to threatening combat stimuli in the controls.

Finally, we examined associations between brain region activations with the participants' posttraumatic symptoms and affective (valence, arousal, and familiarity) rating of the selective video vignettes. Controls were screened for posttraumatic symptoms of any sort and scored zero on the PDS (see *Materials and Methods, Participants* section below). Among the three selective regions (and their corresponding vignettes and groups), only the R-IPL yielded significant correlations (Table S6). As seen in Fig. 4, findings revealed that the combat veterans' increase in R-IPL activation under OT (higher alpha suppression) was significantly related to their lower posttraumatic symptoms ($r = 0.56$, $p < .001$, FDR-corrected), suggesting that posttraumatic symptoms may inhibit the mirror network's response to social synchrony. Similarly, the combat group's OT-driven R-IPL response correlated with the degree of arousal induced by the viewing ($r = -0.54$, $p < .003$, cluster-level corrected; note also a statistical tendency for the degree of valence),

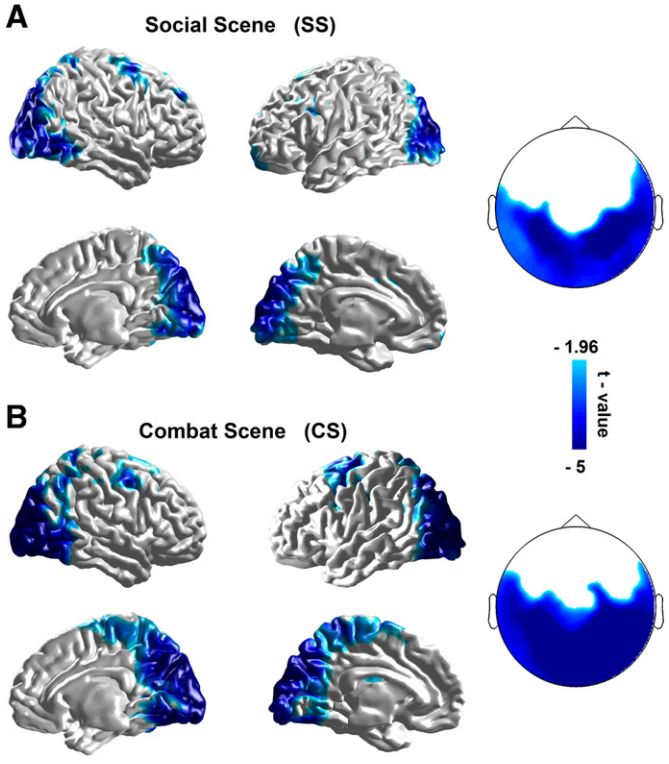

Fig. 2. Localized brain response to (A) the social vignette and (B) the combat vignette. Activity ($p < .005$, cluster-level corrected) is normalized, with rest as baseline, and is represented on overlaid cortical (left) surfaces (Montreal Neurological Institute template) and on head topographies (right).

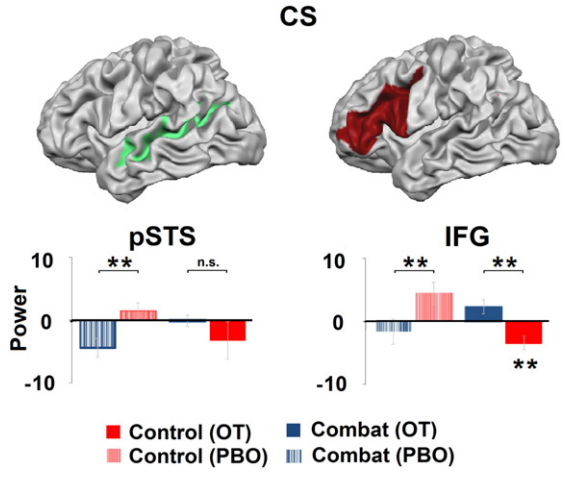

Fig. 3. Cortical representations of group by condition interaction effects while watching CS (combat scenes). With PBO, combat-trained participants recruited the pSTS (posterior superior temporal sulcus) more than non-combat controls did, while OT canceled out this effect. By contrast, with PBO, non-combat controls inhibited the IFG (inferior frontal gyrus) more than combat-trained participants did, while OT reversed this effect. OT = oxytocin; and PBO = placebo. **Activity significantly differed between groups ($p < .005$, FDR-corrected). Power is in 10^{-7} units.

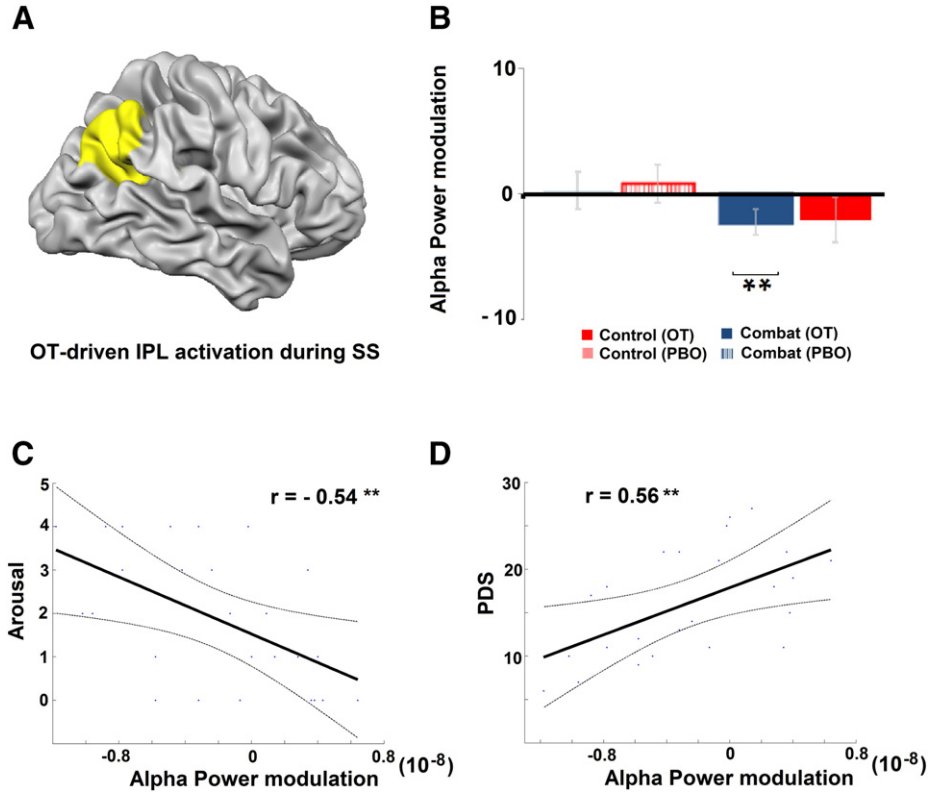

Fig. 4. Oxytocin-driven inferior parietal lobule (IPL) activation. (A + B) cortical surface of the IPL; (C) its Pearson correlations with arousal, and (D) posttraumatic symptom severity. Arousal rated from calm — 0 to highly arousing — 5. Posttraumatic symptoms rated on Posttraumatic Diagnostic Scale (PDS). **Statistically significant correlations ($p < .005$, FDR-corrected). Power is in 10^{-8} units.

despite the fact that arousal rating for SS did not show a condition effect or group-by-condition interaction (see Table S1). This suggests that activation of R-IPL reflects a resonance effect driven by OT intake.

Discussion

Social synchrony is a powerful bio-behavioral mechanism supporting the survival of social species through the neurobiology of bonding and collaboration (De Dreu et al., 2010; Feldman, 2015). The current study is the first to integrate brain mechanisms of social synchrony, salient social-group experiences, and OT administration by using a unique cohort to tap this issue. Our results highlight two important findings regarding the neural mechanisms of social synchrony. First, we demonstrate that the human social brain responds online, via modulation of alpha oscillations, to stimuli probing social synchrony. Cues depicting synchronous group activity in both pleasant and dangerous contexts elicit a wide neural response, with the latter triggering more robust activations. Second, we show that OT regulates this mechanism as a function of salient experiences in social groups, specifically in the mirror neuron system.

Human research has pinpointed the role of mirror mechanisms in various social phenomena, including imitating facial expressions (Carr et al., 2003), experiencing pain (Singer et al., 2004), and recognizing emotions (Bastiaansen et al., 2009; Goldman and Sripada, 2005), and has demonstrated overlapping circuits in observer and experiencer. It can thus be concluded that observing others engage in social synchrony triggers overlapping neural circuits to those occurring during participation in group coordination, albeit such hypothesis awaits validation in real-time brain coordination. Our findings extend human mirroring research in several directions within a social neuroscience framework. Following the call for social neuroscience to include more ecologically-valid paradigms (Stanley and Adolphs, 2013), we utilized vignettes of real-life social events; integrated neuronal and behavioral data in groups that differ by powerful social experience; and probed alpha rhythms using MEG in social neural substrates to address important aspect of social behavior.

Intranasal OT administration impacts social information processing in general (for review Guastella and MacLeod, 2012) and the expression of human synchronous interactions in particular (De Dreu et al., 2010; Feldman, 2012). In a previous study, we demonstrated that OT administration to one attachment partner can have parallel effects on the other via the increase in synchronous interactions (Weisman et al., 2012). In parallel, we found that plasma OT levels can predict the degree of activity in central substrates of the social brain, yet only among mothers who were high on social synchrony with their infants (Atzil et al., 2011). The current study extends prior research on the link between OT and synchrony by providing evidence for a neural response to stimuli high in social synchrony and by describing how intranasal OT administration modulates this response as a function of salient synchronous experience.

OT was found to regulate response to social synchrony via both suppressive/anxiolytic mechanisms (in pSTS) and social-enhancing mechanisms (in IPL, IFG). Research has shown that OT administration exerts both suppressing and enhancing effects on brain activation patterns and neuroendocrine systems. For instance, in animals and humans OT reduced cortisol levels (Ditzen et al., 2009; Gordon et al., 2008; Heinrichs et al., 2003) and inhibited amygdalar response (Domes et al., 2007; Keysers and Gazzola, 2007; Peters et al., 2014; Viviani et al., 2011). Furthermore, studies have shown selective OT effects; whether OT exerted suppressing, enhancing, or no effect depended on individual and contextual factors or the nature of the stimulus. For instance, OT increased amygdalar response depending on the valence of social stimuli (Gamer et al., 2010) or on the participants' gender (Domes et al., 2010). Similarly, OT increased amygdalar response during face processing only among individuals with autism spectrum disorder (Domes et al., 2013). Synchronous experiences also seem to moderate

physiological response to OT administration. Following OT administration to parent, infants' HPA reactivity was either suppressed or enhanced in response to parental "still-face" pending on the degree of parent–infant synchrony prior to the still-face (Weisman et al., 2013). These inconsistencies led to the hypothesis that OT acts in a highly person- and context-specific manner (Bartz et al., 2011).

Our findings lend support to this complex view of OT action in the brain. We found that OT can operate via both social salience mechanisms that enhance activation in areas that process social stimuli (Yamasue et al., 2012) or suppression mechanisms that attenuate response in over-active areas thereby reducing anxiety (Kirsch et al., 2005) and that such selective OT effects depend on past experiences, such as combat exposure, and contextual factors, such as the nature of the social stimuli. Overall, the combination of prior experiences and current reminders determine, to a large extent, the social effects of OT (Bartz et al., 2011). Our participants' powerful experiences in affiliated social groups and the nature of contextual cues (type of social stimuli) shaped the effects of OT on the brain. OT enhanced social salience in the non-combat group during combat stimuli and in the combat-trained group during social stimuli. As such, this is one of the first studies to show that OT can operate via both enhancement and suppression mechanisms in different brain regions in the same individual when exposed to different stimuli.

Whereas several previous independent lines of research described the importance of both the OT system (Bethlehem et al., 2013; Feldman, 2012; Meyer-Lindenberg et al., 2011; Rilling and Young, 2014; Yamasue et al., 2012) and alpha rhythms (Dumas et al., 2010; Ulloa and Pineda, 2007; Whitmarsh et al., 2011) for functioning of the social brain, here we demonstrate for the first time the interaction of these two biological mechanisms as mediated by specific regions within the MNS. Previous EEG research showing increased "mu rhythm" suppression following OT in response to videos of biological motions suggested that the observed modulation of alpha rhythms possibly originated from MNS, although source localization was not performed (Perry et al., 2010). The current findings support and extend these results, pointing to an OT-driven mechanism originating in the MNS via the modulation of alpha rhythms for regulating stress or enhancing social perception as a function of individual and contextual cues.

OT exerted a modulatory influence on alpha rhythm as a function of prior experiences. The pleasant male gathering likely elicited positive memories from young men; however, the combat group's experiences of intense and lengthy daily group training, joint life-threatening combat, and loss of group members, may have reorganized these veterans' brain circuits in the MNS (L-pSTS, R-IPL, and L-IFG) (Iacoboni and Dapretto, 2006). Single-cell recording studies with monkeys confirmed that visual input in the pSTS is propagated to the IPL, from which it passes to the IFG (Keysers and Perrett, 2004), suggesting that these areas form a coherent network. Whereas OT exerted "resonating" influence in the IPL and IFG by tuning into experience-incongruent cues (SS for combat veterans; CS for controls), it exerted anxiolytic influence in pSTS by suppressing a potentially stress-driven response (CS for combat veterans). This suggests that the pSTS may process the social cues differently than the other mirror regions. Generally, the pSTS has not been proposed as exclusively supporting mirror system functioning; rather, it has also been implicated in mentalizing and social perception (Dufour et al., 2013). Researchers have pointed to the integrative role of pSTS in all three systems and have demonstrated its connection to other regions in each system (Yang et al., 2015). Hence, in contrast to the IPL and IFG that exclusively underpin mirroring in social contexts, the pSTS additionally extracts social and intentional cues to facilitate mental inference. The finding that combat veterans typically recruit the pSTS during observation of combat stimuli (under PBO) possibly suggests that the pSTS extracts intentional and social information driven by the veterans' personal history and powerful experiences during combat. Inasmuch as such recall may be associated with stressful experiences and post-traumatic re-experiencing, the suppressive-anxiolytic influence of OT on pSTS over-activity may reflect OT anxiolytic influences and may be important for future pharmacological interventions (Bartz et al., 2011; Kirsch et al., 2005). The current findings support and extend this model by pinpointing the regulatory role of OT on this network via alpha rhythm modulation to influence stress experience or social perception. Thus, we show that OT induces social resonance in line with the resonance properties of the IPL and IFG, which reflect automaticity and lower level processing. In contrast, OT reduces stress in line with the integrative properties of the pSTS, which may implicate a more controlled and higher level processing.

We suggest that the lengthy training for coordinated activity with intimate comrades and the survival-related combat experience reorganized the combat veterans' MNS response to social stimuli. However, it is also possible that the veterans' posttraumatic symptoms may have contributed to this effect. Posttraumatic symptoms are associated with social avoidance, intrusive thoughts, and hypervigilance. However, the brain mechanisms underpinning the social dysfunction in posttrauma, particularly following combat, is an area of much current debate (Foa et al., 1997; Richardson et al., 2010). The influence of posttraumatic symptoms on the effects found here in the combat-trained veterans (i.e., IPL activation under OT during CS and pSTS activation under PBO during SS) was therefore probed and we found that posttraumatic symptoms correlated with IPL activation under OT (Fig. 4) but not with pSTS activation under PBO (see Table S6). It thus appears that posttraumatic symptoms interfered with MNS activity under OT, but not under PBO, suggesting potential disruptions to the interface of the oxytocinergic and mirror-neuron systems following traumatic combat. Although this hypothesis requires much further research, our findings may have potential implications for the use of OT-based treatments in combat-related post-traumatic symptoms. Much future research is required to examine how salient combat experiences shape MNS functioning using larger samples of combat-trained participants both with and without posttraumatic symptoms.

We found that survival-related circumstances enhance the social brain's response to group synchrony and induce OT effects in critical regions implicated in resonating and understanding others' states of mind. However, the downside of such mechanisms for group cooperation is the potential defensive aggression toward group outliers. Indeed, studies suggest that OT motivates in-group favoritism and out-group derogation (De Dreu et al., 2010). From a socio-political perspective, the findings point to an ancient biological mechanism that supports the human capacity for cooperation and thriving within affiliated groups but on the other hand favors ethnocentrism and may be, at least partly, responsible for intergroup conflict and violence. In the context of psychiatric disorders, despite the social bonding effect that military veterans experience during life-endangering combat, such experiences may result in a high prevalence of posttraumatic stress disorder, which may yield lifetime impairments in cognitive processing, social relationships, and emotion regulation (Richardson et al., 2010).

It is important to examine our results in light of a recent review, which claims that results of OT administration studies should be examined with caution (Leng and Ludwig, 2015). This review suggests that only very small amounts of the applied intranasal OT reach the cerebrospinal fluid and possibly minimal doses, if any, reach the brain tissue itself. At the same time, the amounts of OT applied intranasally often largely exceed the physiological concentrations, thereby possibly interacting with peripheral OT receptors which mediate body functions (e.g., metabolism, feeding, sexual regulation, cardiac functioning) that can yield important behavioral consequences which should not be overlooked. Hence, it is suggested that additional controls (e.g., dose–responses and control subjects for peripheral effects) should benefit future intranasal OT studies. Finally, the authors point to additional issues that may weaken reliability of findings obtained in intranasal OT research, including publication bias, questionable statistical practices, and methodological rigor. It is important to note that while these concerns are certainly valid and OT findings should be interpreted with

caution, such problems are not unique to intranasal OT research and may point to general issues the scientific community must address (Freedman et al., 2015; Ioannidis, 2005). Despite the answers provided to Leng and Ludwig (2015) points [see commentary by Carson et al. (in press) and correspondence by Quintana and Woolley (2015)], these concerns are important and should contribute to improving future intranasal OT research.

Expanding on the final concern raised by Leng and Ludwig (2015), another recent review suggests that most behavioral intranasal OT studies are underpowered and may not represent true effects (Walum et al., 2015). Here, however, the reported cortical effects were not underpowered (see Results section). This may not be at odds with Walum et al. (2015), who mainly addressed behavioral studies. Future studies should thus review statistical power and effect sizes of cortical effects resulting from intranasal OT administration. Moreover, future behavioral and neuroimaging studies of intranasal OT administration should be gauged by the suggestions and guidelines set by Walum et al. (2015) and Leng and Ludwig (2015), that is, improving reliability by increasing statistical power, calculating and increasing pre-study odds, disclosing methods and findings transparency, and collaborating to replicate findings.

One caveat of the present design relates to the skewed ratio between combat-trained and control participants (26 vs 14). As we expected greater variability in the combat-exposed group, we recruited a larger group of combat veterans but the non-equal group size is a study limitation. The lack of female participants is another limitation of this study. Finally, the interpretation of the current findings is also limited due to the acquisition setup: participants viewed vignettes rated high on social synchrony by independent judges, but we did not measure social synchrony directly, during participation in coordinated performance. Although much research in social neuroscience lends support to the hypothesis that overlapping mechanisms exist in viewer and experiencer, the brain basis of social synchrony requires validation in real brain-to-brain studies among group members.

In sum, our findings indicate that stimuli probing social synchrony within life-threatening contexts elicit a stronger response compared to non-threatening contexts across the social brain via modulation of alpha rhythm. OT appears to play a key role in this process by supporting sociality that is strongly shaped by powerful personal experiences and increases salience to specific features of individuals and contexts to promote affiliative bonding. Substantial further research testing real-time brain-to-brain synchrony during coordinated social action is needed to provide better understanding of social synchrony. Combining MEG with fMRI technologies may further advance understanding of the neural mechanisms and underlying rhythms that support the human capacity to engage in joint actions with affiliated partners during both pleasant social events and dangers to human social units.

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Appendix A. Supplementary data

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