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Title: **The role of oxytocin in modulating interpersonal space: A pharmacological fMRI study**

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Highlights

- We show that intranasal oxytocin (OT) increases personal distance from strangers.
- OT reverses the activity of the left dorsomedial prefrontal cortex (dmPFC).
- Under OT we observed higher activation in the dmPFC when a friend is approaching.
- The effect of OT on personal space depends on the protagonist.

Abstract

Interpersonal space is a nonverbal indicator of affiliation and closeness. In this study we investigated the effects of oxytocin (OT), a neuropeptide known for its social role in humans, on interpersonal space. In a double blind placebo controlled study we measured the effect of intranasal OT on the personal distance preferences of different familiar (friend) and unfamiliar (stranger) protagonists. Behavioral results showed that participants preferred to be closer to a friend than to a stranger. Intranasal OT was associated with an overall distancing effect, but this effect was significant for the stranger and not for the friend. The imaging results showed interactions between treatment (OT, placebo) and protagonist (friend, stranger) in regions that mediate social behavior including the dorsomedial prefrontal cortex (dmPFC), a region associated with the mentalizing system. Specifically, OT increased activity in the dmPFC when a friend approached the participants but not when a stranger approached. The results indicate that the effect of OT on interpersonal space greatly depends on the participant's relationship with the protagonist. This supports the social salience theory, according to which OT increases the salience of social cues depending on the context.

Key words: interpersonal space, oxytocin, dorsomedial prefrontal cortex, mentalizing

Introduction

Interpersonal distance or personal space is the distance we choose to share with other social agents. Our preferred interpersonal distance may vary according to numerous variables, such as the level of familiarity with the person with whom we share the space or a general desire for closeness (Hayduk, 1978; Perry, Mankuta, & Shamay-Tsoory, 2015). Interestingly, proximity to others has been shown to be a reliable indicator of underlying affiliative relationships, not only in humans but also in capuchins and other primates (Visalberghi et al., 2009). Similarly, in humans, interpersonal distance may signal responsiveness and feelings of comfort and safety with others (Birtchnell, 1996; Feeney, 1999; Kaitz, Bar-Haim, Lehrer, & Grossman, 2004; Meisels & Guardo, 1969; Roberts, 1997). Specifically, it has been suggested that potential interpersonal zones may range from a close and intimate space to a distant space that is impersonal. For example, we expect friends that we know and are usually open with to stand close to us, while we expect strangers to stand farther away, indicating that interpersonal space can be a reliable measure of affiliation (Güroğlu et al., 2008).

Given that affiliative behaviors are supported by neural mechanisms associated with the "social brain," including the medial prefrontal cortex, the anterior cingulate and the temporal lobes (Adolphs, 2003; Barrett & Satpute, 2013; Frith, 2007; Stanley & Adolphs, 2013), it is possible that interpersonal distance is also mediated by this network. These areas have been shown to be activated when individuals construct representations of relationships between the self and others and when they use this information to understand and guide social behavior (Adolphs, 2001, 2010; Gobbini et al., 2011). One core region of the social brain particularly involved in mentalizing and social cognition is the dorsomedial prefrontal cortex (dmPFC) (Denny, Kober, Wager, & Ochsner, 2012). This region has been linked to social network size, both in humans and primates, and to the ability to create representations of the mental state of other individuals (Amodio & Frith, 2006; Sallet et al., 2013). Activity in this region has been linked to self-other distinction (Amodio & Frith, 2006) and is thought to depend on how close we are to other individuals and how similar we feel to them (Krienen, Tu, & Buckner, 2010). Specifically, researchers have shown that the dmPFC is activated when we make inferences about the mental state of dissimilar others as compared to similar others (Mitchell, Macrae,

Banaji, & Hall, 2006). Thus, the dmPFC appears to be a core region that mediates social interest and represents the mental state of other individuals, particularly when these individuals are dissimilar or unfamiliar. Similar to the dmPFC, the anterior cingulate (ACC), the posterior cingulate and the temporoparietal junction (TPJ) have been shown to play a part in mental state reasoning (Adolphs, 2001, 2003). Previous studies showed that these regions can represent the position of the body in space and can help determine where an individual looks (Frith & Frith, 2006). The ACC was also found to be active in self-monitoring, such as in recognizing ourselves and others (Frith & Frith, 2006; Gallagher & Frith, 2003). Together, these areas can all be considered as playing a role when measuring interpersonal space, because when others approach us we try to understand them and their intentions.

In addition to cortical networks, it is possible that interpersonal space regulation also involves subcortical regions that mediate affiliation. Areas such as the amygdala, the NAcc and the putamen are all regions that have been shown to play a major role in social affiliation. The NAcc and the amygdala are known to be related to social affiliation and social reward, and these regions have been shown to be regulated by the OT system (Feldman, 2012, Keverne & Curley, 2004). The amygdala was also found to play a key role in personal space. Kennedy et al. (2009) showed that in healthy individuals the amygdala is activated when someone enters our personal space and especially when personal space is invaded. The study further showed that a patient with bilateral amygdala damage did not feel uncomfortable even when standing extremely close to the experimenter. Consequently, the authors concluded that the amygdala is especially relevant to personal space invasion (Kennedy et al., 2009). Furthermore, it has been shown that the putamen is involved in early stages of romantic love and is activated when seeing a picture of a loved one, perhaps through the activation of the reward and motivation system (Aron et al., 2005). The putamen was also found to be activated when watching films depicting scenes of affiliation compared to films depicting scenes of power (Quirin et al., 2013). Overall, it seems that subcortical areas such as the NAcc and the putamen are all related to social affiliation, with the amygdala specifically related to personal space discomfort.

Interestingly, the neurohormone oxytocin (OT), known for its role as a strong mediator of social interaction and social approach, has also been found to regulate social distance (Liu, Guastella, & Dadds, 2012; Scheele et al., 2012). Scheele et al. (2012) showed that the distance people prefer to stand from others can be manipulated

with OT administration, and that this manipulation depends on the relationship status of the participants. Specifically, Scheele et al. (2012) found that following OT administration, participants (only male participants were included in this study), who were in a committed relationship chose to stand farther away from attractive women than did participants who were single and not in such a relationship. This result suggests that the effects of OT on interpersonal distance depend on relationship with the protagonist.

Indeed, numerous studies exploring the effects of OT on human social affiliation indicate that context and relevance of information to the participant play a crucial role in the direction of the effect (e.g., Bartz, Zaki, Bolger, & Ochsner, 2011; Feldman, 2012; Strathearn, Iyengar, Fonagy, & Kim, 2012). For example, not only does OT promote positive emotions, it also augments negative emotions such as envy and gloating (Shamay-Tsoory et al., 2009), suggesting that OT increases the salience of social agents and therefore may increase threat in hostile contexts and trust in cooperative social situations (Bartz et al., 2011; Shamay-Tsoory & Abu-Akel 2016). Similarly, in the context of interpersonal distance, OT may induce closeness or separation, depending on situational cues such as familiarity with the protagonist and individual differences reflected in personality traits. Perry et al. (2015) showed that OT affects an individual's preferred distance depending on that individual's empathy level, and Scheele et al. (2012) showed that OT affects an individual's preferred distance according to status of the relationship with the other. In fact, in the study by Scheele et al. (2012), OT had only a distancing effect. Following OT administration, those in a relationship chose to be farther away from a female stranger than did those who were not in a relationship. This evidence is compatible with in-group/out-group bias theory (De-Dreu, 2012;De- Dreu et al., 2010), according to which OT promotes closeness to someone we consider part of our group (such as a friend) but may promote negative feelings towards someone we consider a member of an out-group and potentially a stranger. Notably, increasing evidence shows that the OT system regulates the activity of regions that may mediate social distance including prefrontal regions and subcortical networks that mediate reward and affiliation (Feldman, 2012; Lim et al, 2004; Scheele et al., 2013).

Taken collectively, these findings appear to suggest that the OT system regulates the salience of social cues in that it may diminish interpersonal distance in positive or safe relationships and increase distance in threatening relationships.

The current study used a pharmacological-fMRI approach to examine the neural correlations of the effects of OT on personal distance. We compared two types of protagonists, a friend and a stranger, while participants were scanned following OT or placebo (PL) administration[1]. Considering that levels of personal space are indicators of psychological closeness, we hypothesized that the stranger would be stopped at a greater distance than the friend would. In addition, according to the social salience hypothesis of oxytocin, we hypothesized that OT would affect personal space preferences differently for a stranger and for a friend, such that following OT administration the friend would be stopped even closer while the stranger would be stopped farther away. In addition, we hypothesized that OT would modulate dmPFC activity depending on familiarity with the protagonist (friend, stranger).

Methods

Participants

Thirty male participants were recruited for the experiment. Nine participants were excluded from the analysis since their head movement exceeded 2 millimeters. Two additional participants were excluded from the study for not following the experimental protocol, leaving a total of 19 participants who took part in the analysis. The age range of the participants was 18-30 (M= 26.05, SD= 3.51). All participants were fluent in Hebrew, right handed, and did not report any history of psychiatric or neurological disorders as confirmed by a screening questionnaire and interview. None of the participants reported taking drugs or any regular medication. Participants were asked to refrain from alcohol, nicotine and caffeine during the evening prior to the scanning and during the morning before the scanning. Participants received 200 New Israeli Shekels (approx. $50) for their participation. The study was approved by the Institutional Review Board (IRB) of the Tel-Aviv Sourasky Medical Center.

[1] This was conducted as a part of a larger experiment that also included a ball figure and a boss figure.

Procedure

The participants attended two scanning sessions a week apart. In the first stage, participants completed a consent form that provided them with all the relevant information regarding OT, fMRI and the experiment protocol.

Task and stimuli

The task was based on a modified version of the comfortable interpersonal distance (CID) task originally validated in the 1970's by Duke and Kiebach (1974) and used in prior experiments (Duke and Nowicki, 1972; Perry et al., 2013). In the original paper-and-pencil version, participants were asked to imagine the point at which they would prefer to stop an entering protagonist. In the current version, we created nine computerized drawings of realistic figures. Prior to the scanning session, the participants were asked to choose three protagonists from these figures: a figure that best resembles themselves, one that resembles a close friend and one that would act as a stranger. We previously validated performance in this task with real-life interpersonal distance (Perry et al., 2015). In that experiment, we found a significant correlation between performance on the CID task and a measure of interpersonal distance between the participant and the experimenter in the lab. In addition, early studies of the CID task also showed a strong correlation between the computerized task and real life decisions regarding personal space (Duke and Kiebach, 1974). Finally, to examine the current version of the CID task, we conducted a pilot study with ten participants. The results of the pilot confirmed that participants stopped the friend figure closer to them than they stopped the stranger figure. There was a significant difference in the reaction time scores, showing that it took longer to stop the friend (M=30.48.13, SD= 1.70) than the stranger (M= 37.42, SD= 2.60); t (2.67), p=0.02.

The current version of the CID consisted of eight blocks, with 20 trials in each block. There was a separate block for each figure, so that in the case of a friend protagonist, each figure was repeated for twenty trials and then the block ended. Before each block, a fixation point appeared for 15 seconds and then the block began. In each trial, the participants were shown a circular room on the screen, with the figure depicting the participant in the center and the stranger or friend at one of four entrances to the room (randomly at 0, 90, 180 and 270 degrees, e.g., Figure 1). This was followed by a 3000 ms animation in which one of the figures approached the participant figure standing at the center of the room. Each figure appeared five times

randomly in each block. Participants were instructed to press the response box with their right index finger to signal when they wanted the figure to stop. The animation stopped when the participant pressed the response box. In the absence of a press, the animation stopped after 3 seconds, when the character and the participant's figure collided. The radius between the room's center and an entrance was 120 mm. This procedure was repeated 20 times in each block, five times randomly for each entrance. Blocks were counterbalanced across participants, and each block lasted 60 seconds. The total functional scanning session lasted for 10 minutes and the anatomical scanning lasted for four additional minutes.

Figure 1 to be inserted near here.

Training session

Prior to the scanning, participants were trained on a computer to select the figures and practice the task. Participants were asked to choose from a bank of figures and to complete a few practice steps from the CID task with the figures they chose in order to make sure they understood the instructions. In addition, at the end of each trial, a question appeared asking the participant to identify whether the figure that appeared was a friend or stranger, to ensure that the participants remembered the figures they chose. The training session included 16 trials and was completed only after the participants answered 90% or more of the trials correctly, which in all the cases occurred before 16 trials. The training sessions were carried out to ensure that the participants were able to relate to the protagonist they selected.

Substance administration

Each participant randomly received either 24 international units (250 ml) of intranasal OT (Syntocinon spray, Defiante, Sigma) or sterile saline as placebo treatment (PL, consisting of the same saline solution in which the hormone was dissolved, but without the hormone itself). Both treatments were self-administered using a nasal spray, three puffs per nostril, with each puff containing 4 IU. Neither the experimenter nor the participant knew whether the participant was receiving OT or the placebo, but session order was randomized such that half the participants received OT in the first session and the other half received OT in the second session.

Following treatment, participants were asked to wait 45 minutes from the time of administration to ensure that the OT levels in the central nervous system would reach a plateau (Evans, Dal Monte, Noble, & Averbeck, 2014). During this time, they were given a nature journal to read. At the end of these 45 minutes, the participants were debriefed again, and the experiment began.

Behavioral analysis

Reaction time (RT) ranged from zero, denoting maximum personal distance (the participant pressed the button right away, before the protagonist started approaching) to 3000 milliseconds, representing no distance at all between the approaching protagonist (friend or stranger) and the participant in the middle (self). We transformed the data into distance units by calculating the score of the raw data (RT)*(radios/maximum reaction time). We subtracted this score from 90 in order to measure the distance the protagonist covered while approaching the target before it was stopped. It is important to note that by this calculation we measured the distance that remained between the protagonist and the self. We carried out a 2 X 2 (OT/PL, friend/stranger) repeated-measures ANOVA design to measure the effect of OT upon the different protagonists. In addition, for each participant we created a "distance index" per protagonist, calculated by subtracting the RT under the PL condition from the RT under the OT condition. This created two separate index scores, one for friend and one for stranger, indicating a change in distance between PL and OT. A positive score indicated that there were longer reaction times under OT and therefore a closer distance, while a negative score indicated that there were faster reaction times under OT and thus a greater distance.

MRI data acquisition and analysis

Participants were scanned at the functional brain-imaging center at the Wohl Institute for Advanced Imaging, Tel-Aviv Sourasky Medical Center, using a 3T GE Signa Excite scanner with an 8-channel head coil. Functional whole-brain scans were conducted with gradient echo-planar imaging sequence of functional T2*-weighted images (TR/TE=3,000/35ms; flip angle=90 º; FOV=200 × 200 mm; slice thickness=3mm; no gap; 39 interleaved top-to-bottom axial slices per volume). Anatomical T1-weighted 3D axial spoiled gradient (SPGR) echo sequences

(TR/TE=7.92/2.98ms; flip angle=15º; FOV=256 × 256 mm; slice thickness=1mm) were acquired to provide high-resolution structural images.

BrainVoyager (version 2.6) was used for preprocessing and analysis. Preprocessing included high frequency temporal filtering and removal of linear trends. Head motions were corrected by rigid body transformations using three translation and three rotation parameters and the first volume as a reference. Slice scan time was corrected using sinc interpolation and the first slice as a reference. The temporal smoothing process included linear trend removal and application of high pass filter of three cycles per time course. A 6-mm FWHM Gaussian spatial smoothing was used to reduce noise (Dvash et al., 2010)

fMRI analysis

The BOLD response was modelled per participant using a general linear model that included two protagonists, friend and stranger, and corrections for head movements. For the whole brain neuroimaging analysis, a random effects general linear model was used with two predictors, treatment (oxytocin/placebo) and protagonist (friend/ stranger), in order to create a 2 X 2 factorial design. This was conducted in order to assess the BOLD signal upon the different conditions. Activations were considered significant at $q<0.05$ False Discover Rate (FDR) correction for multiple comparisons. ROIs were chosen from significant regions found in the treatment by protagonist interaction map. Then, mean beta values were extracted from those specific ROIs for each condition for further analysis (Tuckey) by using SPSS.

Brain-Behavior analysis

To examine the effect of OT on activation in the selected ROIs and the role of the ROIs in interpersonal distance preferences, we carried out an ANCOVA analysis between each protagonist's "distance index score" and activation of all the areas from the interaction. We used the contrast of PL<OT in order to examine whether activation within the related areas correlates with the "distance index score" for stranger and for friend separately. Such a correlation can help us understand whether OT differentially affected the distance decision for each of the figures. This analysis can help us examine the correlation between a specific activation in a related area and a specific behavior demonstrated by a participant.

Results

Behavioral results

We observed a main effect for protagonist [F (1,18)=26.39, p<0.02], indicating that the stranger was stopped farther away (M= 39.83. SE= 1.7) than the friend, who was stopped at a shorter distance away (M= 30.36, SE= 1.04). We also observed a main effect for treatment [F(1, 18)= 5.57 , p<0.001], indicating that following intranasal administration of OT, participants preferred a greater distance (M=40.20 , SE=1.4) compared to in the PL condition (M=30.62, SE=1.3).

The protagonist by treatment interaction was not significant [F (1, 18) = 0.28 n.s)]. Nevertheless, given that we had an a priori hypothesis regarding the differential role of OT in modulating interpersonal space in friends and strangers, we carried out follow-up t-test analyses. These analyses revealed a significant treatment effect in the stranger condition [t(18,1=2.44,p< 0.05] but not in the friend condition [t(18,1=1.27, p<N.S]. This result indicates that OT had a significant distancing effect for the stranger but not for the friend (see Figure 2).

Figure 2 to be inserted near here.

Neuroimaging results

Main effects:

For the neuroimaging analysis, we tested a similar 2 X 2 factorial design. Whole brain analysis revealed a main effect for protagonist, showing stronger activations for friend than for stranger in several regions including frontal regions (see Table 1 for full results). No regions showed an opposite significant effect. There was no main effect for treatment, either for OT>PL or for PL<OT.

Table 1 to be inserted near here

Treatment X Protagonist Interaction

The interaction revealed six significant areas (FDR, $q<0.05$ (see Table 2): left dorsomedial prefrontal cortex (BA9/10), right anterior cingulate (BA24), right posterior cingulate (BA23), right parahipocampal gyrus (BA34), right post central gyrus (BA2), and right putamen.

Table 2 to be inserted near here

Based on our hypothesis, we conducted a follow-up ROI analysis in SPSS in order to test for simple effects. Figure 3 shows a demonstration of beta activity for the relevant areas extracted from Brainvoyger.

Figure 3 to be inserted near here

Follow-up t-tests of beta values extracted from the left medial prefrontal cortex simple effects analysis showed significant difference between the friend and stranger condition under PL ($t(18)= -4.25$), $p= 0.01$) as well as between friend and stranger condition under OT ($t(18)= 1.63$), $p= 0.1$).

Similarly, follow-up t-tests of beta values extracted from the right anterior indicated significant difference between the friend and stranger condition under PL ($t(18)= -3.26$), $p= 0.04$) and between friend and stranger condition under OT ($t(18)= 2.89$), $p= 0.01$). In addition, there was a significant difference between OT and PL in the friend condition ($t(18)= -2.02$), $p= 0.05$).

Follow-up t-tests of beta values extracted from the right posterior anterior cingulate showed significant difference between the friend and stranger condition under PL ($t(18)= -3.11$), $p= 0.06$).

Finally, follow-up t-tests of beta values extracted from the right parahipocampal gyrus indicated significant difference between the friend and stranger condition under PL ($t(18)= 2.19$), $p= 0.09$) as well as between friend and stranger condition under OT ($t(18)= 2.03$), $p= 0.05$).

Brain-Behavior analysis

Left dmPFC

The results show a positive correlation between the variables within the dmPFC: the less activity in the dmPFC, the smaller the "index score" for the stranger. A small "index score" indicated that OT administration resulted in less interest, as indicated by greater distance. This finding demonstrates that lower activation in the dmPFC under OT in the stranger condition is associated with preference for greater distance. In the friend condition, the direction of the correlation was the same, though this did not reach significance.

Figure 4 to be inserted near here

Discussion

In line with the assumption that proximity to others is a reliable indicator of underlying affiliative relationships caused by social interest, the behavioral findings indicate that overall, participants preferred to stand close to friends as opposed to strangers. Administering OT had the effect of increasing the preferred distance, replicating similar findings by Scheele et al. (2012). We extend these results by showing that OT in fact significantly increased the preferred distance from a stranger but not from a friend. These findings partially support the social salience hypothesis, according to which OT has a general effect on increasing the salience of social agents depending on context and social relevance and consequently increases the distance for a stranger and decreases the distance for a friend (Bartz et al., 2011; Abu-Akel and Shamay-Tsoory, 2016). It appears that when the context is unfamiliar (a stranger approaching), OT increases attention to threat signals and therefore the stranger is stopped farther away. Contrary to our hypothesis, we did not find an opposite effect for a friend (OT did not promote closeness). One possibility is that since the friend was already stopped at a very close distance, there was no room left for the OT to act and decrease the distance from the friend.

The neuroimaging findings point to differential activations for the friend protagonist compared to the stranger protagonist in several regions, including the left superior frontal gyrus (BA10), the temporal lobes, the cingulate gyrus (BA32), and the

premotor cortex (BA6). These areas were activated when the friend was approaching as opposed to the stranger, indicating a strong social interest and affiliation with someone who is familiar compared to someone who is not. For the main effect, we also found activation in the left pre-motor area (BA6) which could imply activation in the mirror system network when the participants saw someone familiar approaching them (Rizzolati, 2005). The activity in this region may indicate that participants simulated the approach of a friend more than the approach of a stranger. Activity in these regions reflects higher social interest and affiliation when someone is familiar to us and we attempt to understand their intentions. These findings are in line with previous work that also connects these areas to the "social brain," to theory of mind, and more specifically to social interest and affiliation (Amodio & Frith, 2006; Frith & Frith, 2009).

In the interaction between OT and the protagonists, we found that OT reverses the activity of the left dmPFC such that following OT administration we observed higher activation during the friend condition than in the stranger condition. It is possible that under PL individuals are more interested in the stranger but under OT they become more interested in the friend. These findings are in line with the social salience hypothesis (Abu-Akel & Shamay-Tsoory, 2016) as well as with the in-group hypothesis, according to which OT increases the tendency for in-group bias and promotion of ethnocentrism (De-Dreu, 2012; De-Dreu et al., 2010). Accordingly, there is evidence that under OT participants prefer people that are familiar to them and are considered in-group members, as opposed to those they consider as part of an out-group whom they find dissimilar and unfamiliar. Our results support this theory by showing heightened activation in the friend condition under OT compared to activation under PL, and less overall activation in the stranger condition under OT in the left dmPFC area. In addition to the dmPFC, we also observed a similar pattern of activity in the ACC and the PCC, which are also considered areas of the social brain and are related to understanding others (Amodio & Frith, 2006).

In addition, we found activation in the right putamen, an area that is related to social approach as well as with the reward system (Aron et al., 2005). Studies show that the putamen is activated when a positive reward is processed (Izuma, Saito & Sadato, 2008) or when decisions outcomes are rewarding (Haruno & Kawato, 2006). In addition, the parahippocampal gyrus was found to be activated in this analysis. In addition to this region role in memory encoding (Tsukiura & Cabeza, 2008), this

region has been associated with understanding social context (Rankin et al., 2008), indicating that the personal space regulation involves understanding of social context.

Although we found areas related to understanding others, contrary to our hypothesis we did not find any significant activation in the TPJ. it is possible that since the TPJ plays a more specific role in reasoning about the contents of mental states in others (Saxe & Kanwisher, 2003), this region does not participate in personal space tasks that do not involve specific contents of mental states. Some studies that found activation in the TPJ used a different task that included listening to stories and focused more on "theory of mind." Others found that the TPJ was activated when it came to decisions against others in a game, once again not the focus of our task (Carter, Bowling, Reeck, Huettel, 2012). Furthermore, studies have found that these areas are related to action monitoring. In particular, the ACC is activated during monitoring tasks involving conflict and is thought to play a key role in guiding decision-making (Frith, 2007, Etkin, Egner, Kalisch, 2011).

In contrast with our hypothesis, we did not find significant activation in the amygdala related to social distance. A possible reason might be that, as previously shown, the amygdala is usually activated during threat, especially when personal space is invaded (Kennedy et al., 2009). It is possible that the task did not provoke sufficiently high levels of distress and feelings of discomfort to activate the amygdala. Furthermore, the brain-behavior analysis showed that the distancing effect was enhanced under OT, especially for the stranger condition and not for the friend condition. These findings support the notion that dissimilar protagonists lead to dmPFC activation more than do similar protagonists (Mitchell et al, 2006).

Interestingly, some of the activated regions (dmPFC, PCC) which were found to be activated in the interaction, are also part of the default mode network (DMN), a network that is known to be activated during self-referential processes (Sheline et al., 2009). The DMN was also found to be correlated with mind wandering (Mason et al., 2007) and even more specifically with thinking about the "self" and "internal" conditions (Gusnard, Akbudak, Shulman, & Raichle, 2001). Thus, it is possible that self-referential processes and self-navigation in space are related to personal space regulation. Thus, it is possible that self-referential processes and self-navigation in space are related to personal space regulation.

Finally, although we used a controlled design with balanced conditions, there are several limitations to the study. First, the ecological validity of the protagonist we used is limited. Future studies should examine the effect of OT during real-life interactions between humans. Second, in the current study we examined only male participants who interacted with other male participants, so that our conclusions are limited to relationships between men. Nonetheless, our results show that individuals prefer to be closer to friends and farther away from strangers confirming that the task may represent real-life relationships. Furthermore, we show that OT, which resulted in maintaining farther distances from strangers but had no significant effect on friends, can modify these preferences. Future studies should use real protagonists and various interactions between men and women.

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Fig 1. CID task: The figure that represents the self is in the middle of the circle. In a trial- the figure approaches until the participant stops the figure when he starts to feel uncomfortable.

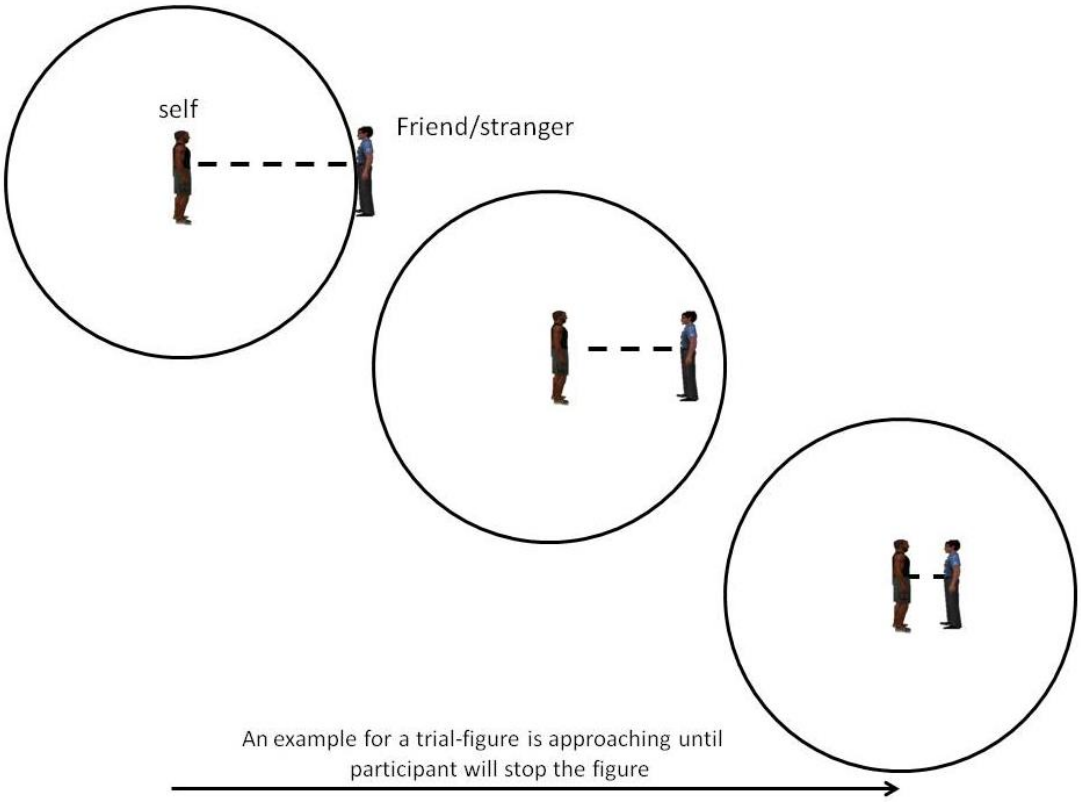


Figure 2. Results of the 2X2 ANOVA interaction. The x-axis represents the type of protagonist, and the y-axis represents the distance in millimeters where the figure was stopped, showing the difference between OT and PL within the different protagonists. The error bars represent standard error (SE) calculation. Blue indicates behavior choices under the placebo condition and red indicates behavior choices under the influence of oxytocin.

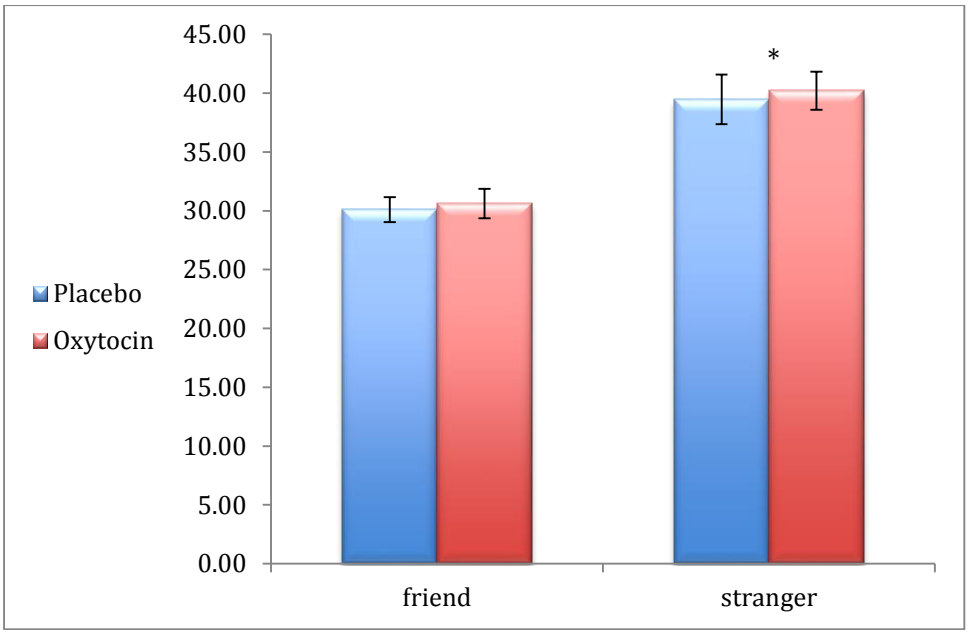


Figure 3a. Results of left medial prefrontal cortex beta values in the interaction between treatment (OT/PL) and type of protagonist. The x-axis represents the type of protagonist, and the y-axis represents the beta activity values. The error bars represent standard error (SE) calculation. Blue indicates brain activation under OT condition and red indicates activation under placebo.
3b. Results of right anterior cingulate beta values in the interaction between treatment (OT/PL) and type of protagonist. The x-axis represents the type of protagonist, and the y-axis represents the beta activity values. The error bars represent Standard error (SE) calculation. Blue indicates brain activation under OT condition and red indicates activation under placebo.
3c. Results of right posterior anterior cingulate beta values in the interaction between treatment (OT/PL) and type of protagonist. The x-axis represents the type of protagonist, and the y-axis represents the beta activity values. The error bars represent Standard error (SE) calculation. Blue indicates brain activation under OT condition and red indicates activation under placebo.
3d. Results of right parahipocampal gyrus beta values in the interaction between treatment (OT/PL) and type of protagonist. The x-axis represents the type of protagonist, and the y-axis represents the beta activity values. The error bars represent Standard error (SE) calculation. Blue indicates brain activation under OT condition and red indicates activation under placebo.

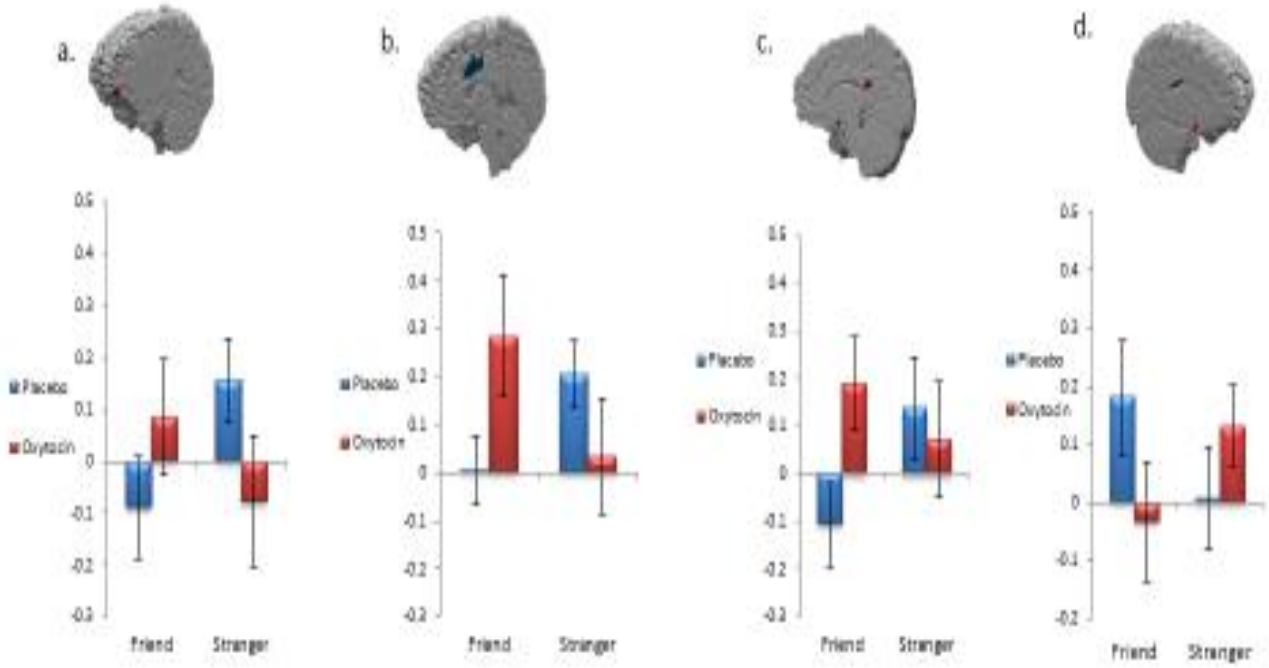
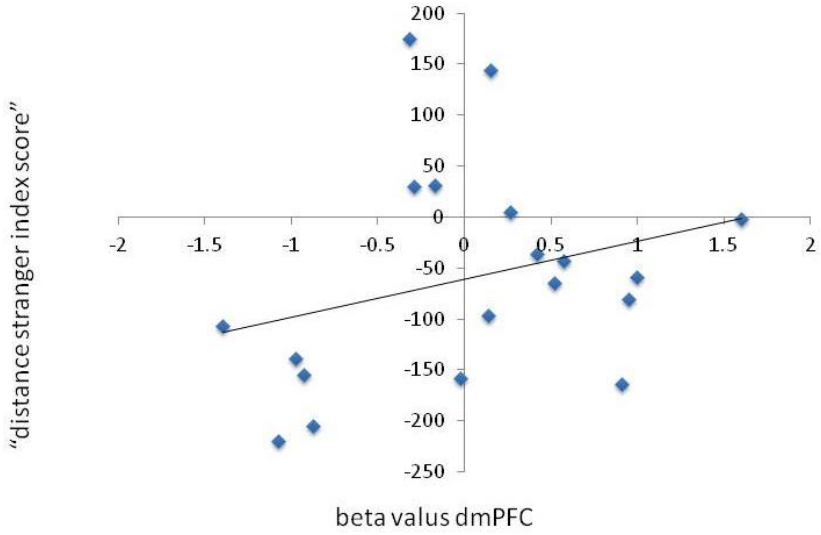


Figure 4: The figure shows the relationship between activity in the dmPFC (mean beta values extracted from the whole brain interaction analysis) and the "distance index score" for the stranger condition. The index represents the extent of change in distance following intranasal OT as compared to PL and is calculated by subtracting distance from the stranger in the PL condition from distance from the stranger in the OT condition. The negative correlation indicates that increased distance following intranasal OT is related to decreased activity in the dmPFC. The X- axis represents the beta values of the dmPFC. The y- axis represents the distance stranger index score. The friend condition analysis did not reach significance.



Tables

Table 1: Main effect for protagonist

Name	Talairach coordinates	Brodmann area	Number of Voxels	**p value**
Right temporal lobe	X=50 Y=-32 Z=9	BA41	390	0.0019
Right occipital lobe	X=32 Y=-92 Z=-3	BA18	1544	0.0016
Left superior frontal gyrus	X=-22 Y=58 Z=6	BA10	2829	0.0008
Left premotor	X=-10 Y=-8Z=60	BA6	714	0.0015
Right middle temporal gyrus	X=41 Y=1 Z=-33	BA21	337	0.0019
Left subthalamic nucleus	X=-10 Y=-14 Z=-6		655	0.0002
Left cingualte gyrus	X=-16 Y=-26 Z=39	BA31	425	0.0007
Left inferior frontal gyrus	X=-25 Y=13 Z=-9	BA47	1255	0.0009
Left parahipocampal gyrus	X=-28 Y=-23 Z=-21	BA35	501	0.0012
Left middle occipital gyrus	X=-40 Y=68 Z=0	BA37	1853	0.0007
Left inferior parietal lobule	X=-43 Y=-47 Z=51	BA40	371	0.0020

Table 1: Areas activated for the friend protagonist compared to the stranger protagonist

Table 2: Significant areas for the treatment X protagonist interaction

Name	Talairach coordinates	Brodmann area	Number of voxels	**p value**
Left medial prefrontal cortex	X=-16 Y=25 Z= 27	BA9/BA10	907	0.001635
Right anterior cingulate	X=13 Y=7 Z= 30	BA24	116	0.000238
Right posterior cingulate	X=11 Y=-39 Z= 23	BA23	92	0.000137
Right parahipocampal gyrus (BA34)	X=14 Y=1 Z=-18	BA34	163	0.000195
Right post central gyrus	X=50 Y=-26 Z=39	BA2	173	0.000566
Right putamen	X=26 Y=-2 Z=-21		105	0.001970

Table 2: Areas activated for the interaction between OT and protagonist