Supplementary Materials

Methods

PD game trial:

A timeline for a single PD trial is depicted in Fig. S1. At the beginning of each round, the round number and partner’s photo were displayed for 2 s. Player 1 then had 4 s to choose to cooperate or defect. Players were informed that if they did not decide within this 4 s interval, their response would default to defection. Player 1’s choice was immediately revealed to player 2 and displayed for 1 s. A variable length fixation epoch of either 2, 4 or 6 s followed. Afterwards, player 2 had 4 s to cooperate or defect. Once player 2 decided, the outcome of the round was displayed for 4 s. Finally, the trial concluded with another variable length fixation epoch of either 2, 4 or 6 s. Trials were approximately 20 s long. Five null trials were interspersed among 30 PD trials in each run. Null trials consisted of 14 s of fixation. One run lasted approximately 12 min. E-prime software (Psychology Software Tools, Pittsburgh, PA, USA) was used for stimulus presentation. Stimuli were projected onto a screen that subjects could view through a mirror mounted on the head coil. Subject responses were recorded using a response box.

Fig. S1 A complete timeline for a single trial of PD game.
**PD tutorial and practice trials:**

All subjects completed a 10 min computer tutorial that explained the Prisoner’s Dilemma game, and were given a four-question multiple choice quiz to evaluate their understanding. If any question was answered incorrectly, study personnel explained to participants why that answer was wrong and why another answer was correct. If necessary, subjects repeated the tutorial. Study personnel continued with the experiment only after they were convinced that the subject fully comprehended the task. Subjects then completed four practice rounds of the game using a picture of the response box they would be holding while in the scanner for reference. The practice trials familiarized subjects with the feel of the game and the operation of the response box.

**Rationale for timing of fMRI scan following drug administration**

Following intranasal administration of AVP, CSF concentrations begin rising within 10 min, continue to increase for up to 80 min, and remain above those of placebo-treated subjects at 100—120 min after administration(Born et al. 2002). Previous studies using intranasal OT in human subjects have sampled behavior or brain activity at 50 min post injection(Kirsch et al. 2005; Kosfeld et al. 2005). Thompson et al. (Thompson et al. 2006) tested subjects at 15 and 50 min after intranasal vasopressin administration. Accordingly, our goal was for subjects to be fully immersed in the task at 50 min post drug administration. We therefore aimed to start both the task and fMRI scan at 40 min after drug administration. In actuality, this time period averaged 42 min (s.d. = 3.62) across subjects.

**Imaging Results**
Whole-Brain Analysis Results

Main Effect of Unreciprocated Cooperation (CD > CC) with human partners:

Compared with reciprocated cooperation (CC) from human partners, unreciprocated cooperation (CD) from human partners activated widespread regions, after controlling for both sex and drug treatment effects. These regions include bilateral anterior insula, bilateral amygdala and dorsal anterior cingulate cortex (dorsal ACC) (Fig. S2 (Online Resource 2)).

OT effect 1: Men interacting with assumed same-sex human partners:

OT treatment attenuated activation to CD outcomes within large brain regions that encompassed bilateral amygdala, right anterior insula, hypothalamus, periaqueductal gray matter (PAG), ventral tegmental area (VTA), bilateral hippocampus, tail of the caudate nucleus/stria terminalis, and globus pallidus (GP)/putamen, right nucleus accumbens, left planum polare, bilateral inferior temporal gyrus, right parietal operculum, left precentral gyrus. (Fig.S3 (Online Resource 3))

OT effect 2: Women interacting with computer partners:

OT treatment significantly attenuated activation in response to CD outcomes within large brain regions that encompassed bilateral amygdala, anterior insula, dorsal ACC, caudate, putamen, periaqueductal gray matter (PAG), bilateral hippocampus, tail
of the caudate nucleus/stria terminalis, precuneus, the left frontal pole, frontal medial
cortex, pre/postcentral gyrus, inferior frontal gyrus as well as a portion of cerebellum.
(Fig.S4 (Online Resource 4))

[Fig.S4 about here]

AVP effect 1: Men interacting with assumed same-sex human partners

AVP treatment attenuated activation to CD outcomes primarily in anterior insula,
amygdala, putamen and caudate. This effect is confined to the right hemisphere. (Fig.S5
(Online Resource 5))

[Fig.S5 about here]

Functional ROI analysis results of sex × drug interactions

OT effect on CD with same-sex human partner: Within both functional ROIs
(amygdala and anterior insula) from Fig.2, 2X2 ANOVA revealed a significant sex (M vs.
F) by drug treatment (OT vs. PBO) interaction ($F_{1, 184}=8.41$, $p=0.004$ for anterior insula;
$F_{1, 184}=5.03$, $p=0.026$ for amygdala), in which OT attenuates the response to a greater
degree in men than in women.

OT effect on CD with computer partner: Within only the functional ROI of
amygdala (not anterior insula) from Fig.3, 2X2 ANOVA revealed a significant sex (M vs.
F) by drug treatment (OT vs. PBO) interaction ($F_{1, 185}=7.66$, $p=0.006$), in which OT
attenuates the response to a greater degree in women than in men.

[Fig. S6 about here]
Structural ROI analysis of OT effects on the contrast (CD-CC)

*OT effect 1: Men interacting with assumed same-sex human partners*

OT did significantly decrease the value of the contrast CD-CC within both regions of anterior insula and amygdala. (Fig. S7)

[Fig. S7 about here]

*OT effect 2: Women interacting with computer partners*

OT did significantly (uncorrected p<0.001) decrease the value of the contrast CD-CC within the right amygdala (Fig. S8). However, this OT effect on CC-CD did not survive the multiple comparison correction.

[Fig. S8 about here]
References:


Supplementary Tables/Figure Legends:

Table S1. P-values for association between various Neuroticism facets and average BOLD signal change for fROIs in men (OT, AVP and Placebo groups combined).

<table>
<thead>
<tr>
<th>Neuroticism</th>
<th>Anxiety</th>
<th>Hostility</th>
<th>Depression</th>
<th>Self-consciousness</th>
<th>Impulsiveness</th>
<th>Vulnerability to stress</th>
</tr>
</thead>
<tbody>
<tr>
<td>R Amygdala from Fig.2A</td>
<td>0.046</td>
<td>0.01</td>
<td>0.529</td>
<td>0.065</td>
<td>0.04</td>
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<tr>
<td>R Anterior Insula from Fig.2A</td>
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<td>0.002</td>
<td>0.383</td>
<td>0.116</td>
<td>0.048</td>
<td>0.091</td>
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</tbody>
</table>

Table S2. P-values for association between various Neuroticism facets and average BOLD signal change for fROIs in men (placebo group combined with OT group only).

<table>
<thead>
<tr>
<th>Neuroticism</th>
<th>Anxiety</th>
<th>Hostility</th>
<th>Depression</th>
<th>Self-consciousness</th>
<th>Impulsiveness</th>
<th>Vulnerability to stress</th>
</tr>
</thead>
<tbody>
<tr>
<td>R Amygdala from Fig.2A</td>
<td>0.15</td>
<td>0.01</td>
<td>0.94</td>
<td>0.54</td>
<td>0.15</td>
<td>0.01</td>
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<tr>
<td>R Anterior Insula from Fig.2A</td>
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<td>0.66</td>
<td>0.27</td>
<td>0.31</td>
<td>0.26</td>
</tr>
</tbody>
</table>
Fig. S1: A complete timeline for a single trial of PD game.

Fig. S2 (Online Resource 2): Main effect of Unreciprocated Cooperation (CD > CC) with human partners revealed by whole brain analysis (FWE-corrected p < 0.05 with a primary voxelwise Z > 1.96). The result is in gif animation format.

Fig. S3 (Online Resource 3): OT effects on the neural response to unreciprocated cooperation (CD) from human partners in men revealed by whole brain analysis (FWE-corrected p < 0.05 with a primary voxelwise Z > 1.96). The result is in gif animation format.

Fig. S4 (Online Resource 4): OT effects on the neural response to unreciprocated cooperation (CD) from computer partners in women revealed by whole brain analysis (FWE-corrected p < 0.05 with a primary voxelwise Z > 1.96). The result is in gif animation format.

Fig. S5 (Online Resource 5): AVP effects on the neural response to unreciprocated cooperation (CD) from human partners in men revealed by whole brain analysis (FWE-corrected p < 0.05 with a primary voxelwise Z > 1.96). The result is in gif animation format.

Fig. S6 (Online Resource 6): (a) Average BOLD response to CD human within functional ROIs of the anterior insula and the amygdala from Fig.2 as a function of sex and drug treatment; (b) Average BOLD response to CD computer within functional ROIs of the anterior insula and the amygdala from Fig.3 as a function of sex and drug treatment; (c) Pairwise comparison of average BOLD response to CD human in both fROIs of anterior insula (lower triangle) and amygdala (upper triangle) from Fig.2; (d) Pairwise comparison of average BOLD response to CD computer in both fROIs of the anterior insula (lower triangle) and amygdala (upper triangle) from Fig.3.

AI, AntIns= Anterior Insula, Amyg=Amygdala, mPBO=male Placebo, fPBO=female Placebo, mOXT=male Oxytocin, fOXT=female Oxytocin. *: p < .05, **: p < .01, ***: p < .005. Red line or asterisk: anterior insula; blue line or asterisk: amygdala.

Fig. S7 (Online Resource 7): OT effects on the contrast CD-CC with human partners in men. Analysis was restricted to the anterior insula and the amygdala (delimited with green line). OT treatment decreased activation to CD-CC outcomes with human partners relative to PBO in both anterior insula and amygdala. (FWE-corrected p < 0.05 with a primary voxelwise Z > 1.96).

Fig. S8 (Online Resource 8): OT effects on the contrast CD-CC with computer partners in women. Analysis was restricted to the anterior insula and the amygdala. OT treatment decreased activation to CD-CC outcomes with computer partners relative to PBO in only amygdala. (Uncorrected p < 0.001 with a primary voxelwise Z > 3.3).