Supporting Information

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SI Materials and Methods

Age Effects. In an exploratory analysis, we evaluated age-related changes in brain activity by calculating the correlation coefficients between age in months and the beta coefficients from the regions of activity identified in the key treatment × task interaction analysis (summarized in Table 1). The magnitude of the treatment × task interaction increased with age in the striatum ($r = 0.56$, $P = 0.02$) and decreased with age in the precuneus and left parahippocampal regions ($r = -0.65$, $P = 0.005$ and $r = -0.57$, $P = 0.02$, respectively).

Order and Dose Effects. To evaluate potential order effects [receiving oxytocin (OT) or Placebo first], we averaged the beta coefficients from all brain regions identified in each of the functional MRI analyses across the first and second visits for each participant. We then conducted an independent samples *t* test on the resulting scores with order of receiving OT as the group variable. These analyses revealed no effects of order. Similarly, we modeled potential dose effects (12, 18, or 24 international units) in random effects analysis of covariance. Dose did not significantly ($P > 0.05$, corrected) predict the level of Eyes > Vehicles activity in any brain region. This negative result is consistent with previous behavioral studies that have used age-dependent dosing (1, 2), where age serves as a rough proxy for weight. Dose effects are indeed found in other types of OT studies, where different doses are given to individuals of the same age (3).

Other Medications. Eight participants were not on medications during the study period, whereas three were (Allegra and Cingulair, usually Tenex and Adderall also; Focalin and Clonidine; and Vyvanse and Abilify) but did not take them on both study days. The remaining 10 children were on a medication [Norditropin (growth hormone); Lamictal and Abilify; Prozac; two participants were taking Sertraline; Abilify and Cingulair; Effexor and Abilify; and Nasonex, Risperidol, and Zyrtec) regime that remained consistent across both study visits.

We assessed potential effects of medications taken by participants (other than OT) on brain function in regions that were identified in our key contrasts. We created two dichotomous variables describing medication status: (*i*) "Day": participants ($n = 8$) who were not on any prescribed medication(s) during the study visits vs. participants ($n = 9$) who were taking their medication(s) on those days and (*ii*) "Chronic": participants who were on some kind of medication regime during the study period ($n = 12$) vs. those who were not on any medication(s) ($n = 5$). We used these variables as grouping variables in parametric (independent samples *t* test) and nonparametric (Mann–Whitney *U* test) analyses with beta coefficients from Placebo and OT visits as dependent variables to evaluate the possible impact of medication. For brain regions identified in the OT > Placebo and Eyes > Vehicles contrasts, there were no significant differences in beta coefficients for either Day or Chronic. Within regions exhibiting significant interaction effects (OT > Placebo × Eyes > Vehicles), for the Day variable, there was a significant difference in the left parahippocampal region when labeling vehicles under OT ($P = 0.03$ in the parametric test and $P = 0.04$ in the nonparametric test). Children on medication had higher beta coefficients compared with children who were not medicated. This difference did not remain significant after correcting for multiple comparisons. Similarly, after correction for multiple comparisons, there were no significant effects for the Chronic variable. Medication status did not have an impact on behavioral performance on the "Reading the Mind in the Eyes Test" (RMET). In a repeated measures analysis of variance, accuracy scores and reaction times did not differ as a function of the Day or Chronic variable. There were also no interactions between medication status, treatment (OT or placebo), and condition (social or nonsocial). Note that the medications participants were taking during the study were intended to treat comorbid conditions and not to target social dysfunction or skills relevant to performance on the RMET.

Baseline Levels of OT in Saliva. We compared baseline and reactive OT levels, regardless of treatment, to assess if there was an order of visit effect. Overall, baseline levels of salivary OT were lower [student's *t* test coefficient, $t_{(14)} = 3.09$, $P = 0.008$] on the second visit (M = 7.49 pg/mL, SE = 4.23) compared with the first visit (M = 11.08 pg/mL, SE = 5.70). Reactive salivary levels were not significantly different [$t_{(15)} = 0.44$, $P = 0.66$] between the first (M = 829.68, SE = 612.60) and second (M = 517.15, SE = 242.97) visits.

OT's Effect on the Magnitude and Individual Variability of Brain Activity. We calculated event-related averages separately for the regions identified in the social (Eyes > Vehicles: orange map in Fig. 1, *Lower*) and nonsocial (Vehicles > Eyes: blue map in Fig. 1, *Lower*) contrasts on the day participants received the Placebo, including the time points from 2 s before a block onset (at 0 s) to 28 s after the block onset. We then examined the effect of OT on the magnitude and variability of the responses from these social and nonsocial regions. In Fig. S2, we observed that the error bars for the responses to social judgments (Eyes; solid lines) in the social regions (Eyes > Vehicles) were approximately twice as large in the Placebo condition (blue translucent ribbons) relative to OT condition (red translucent ribbons). OT reduced the variability in the blood oxygenation level-dependent response during social judgments. However, this effect was specific to social stimuli (Eyes) and was not observed during nonsocial judgments (Vehicles, dotted lines). In the nonsocial (Vehicles > Eyes) areas, the error bars did not differ between task conditions and the administration of OT did not reduce the error bars relative to Placebo during social or nonsocial judgments. Extending and refining the results of Dinstein et al. (4), we observed that greater variability in event-related brain responses is specific to social relative to nonsocial areas. We further observed that OT selectively increases the reliability of evoked responses in social vs. nonsocial brain areas while simultaneously increasing the amplitude of the responses to social stimuli and attenuating the responses to nonsocial stimuli in these very same areas. OT also reduces the magnitude of the response to nonsocial stimuli in social areas relative to Placebo, and OT reduces the response to Vehicles in nonsocial areas.

1. Dadds MR, et al. (2013) Nasal Oxytocin for Social Deficits in Childhood Autism: A Randomized Controlled Trial. *J Autism Dev Disord* 43(7):1–11.
2. Guastella AJ, et al. (2010) Intranasal oxytocin improves emotion recognition for youth with autism spectrum disorders. *Biol Psychiatry* 67(7):692–694.
3. Ebitz RB, Watson KK, Platt ML (2013) Oxytocin blunts social vigilance in the rhesus macaque. *Proc Natl Acad Sci USA* 110(28):11630–11635.
4. Dinstein I, et al. (2012) Unreliable evoked responses in autism. *Neuron* 75(6):981–991.

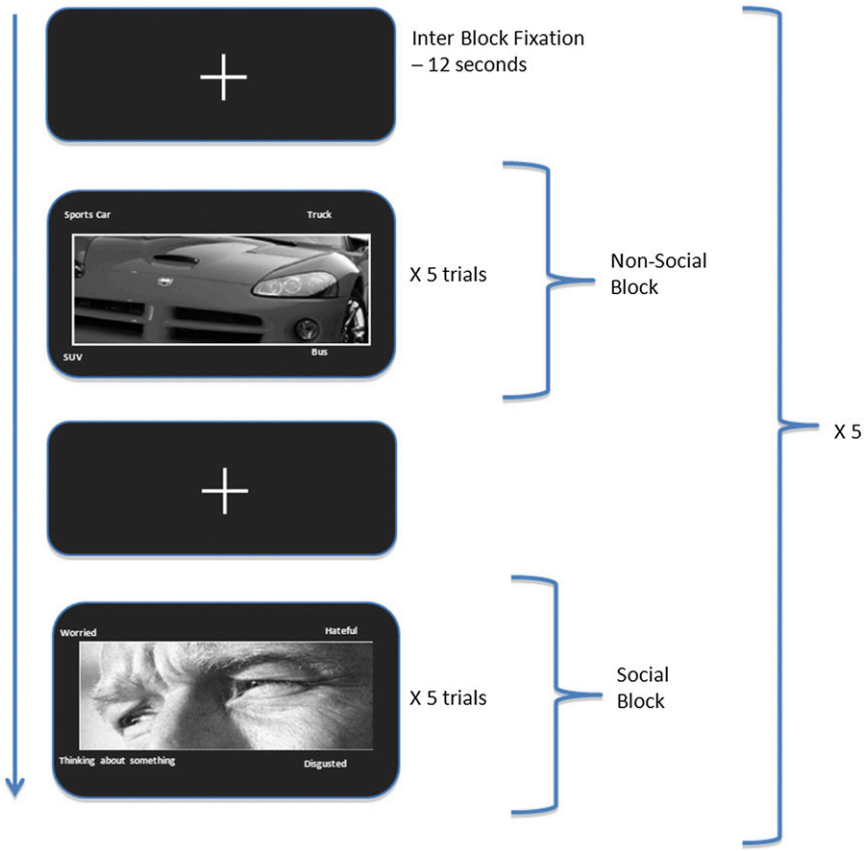

Fig. S1. Procedure and stimuli presented during the functional MRI (fMRI) task. Each block consisted of a 12-s initial fixation followed by five consecutive presentations of static images of either Eyes or Vehicles (a trial). Each trial lasted for 5 s. When participants chose a label, the outline of the label turned green to provide the participant with feedback concerning the registration of his or her selection.

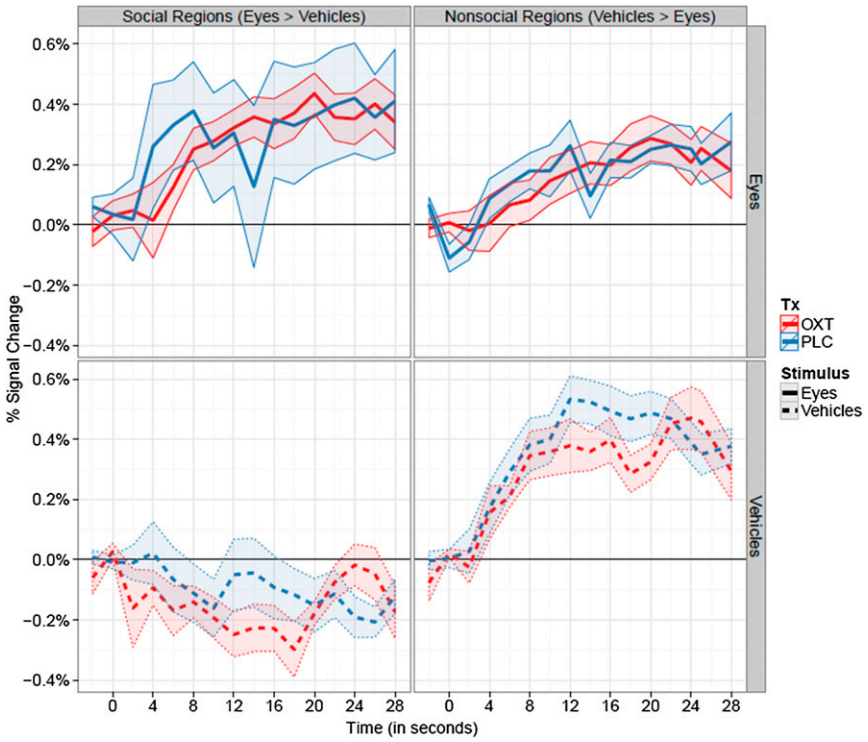

Fig. S2. Style of the lines represents the stimulus type, with solid lines indicating epoch averages of the blood oxygenation level-dependent (BOLD) response to Eyes and dotted lines indicating the same to Vehicles. Colors indicate OT (red) or Placebo (PLC; blue). The lines represent the epoch-averaged BOLD response over time and include the baseline time points from 2 s before the onset (at 0 s) of a stimulus block to 28 s after the block onset. The translucent ribbons around the lines portray the SEMs. (*Left*) Responses from the social (Eyes > Vehicles) regions are displayed. (*Right*) Responses of the nonsocial (Vehicles > Eyes) regions are exhibited. Comparing *Upper Left* and *Lower Left* reveals that OT selectively reduces the variability of responses during social judgments but not during nonsocial judgments. OT also reduces the magnitude of the response to nonsocial stimuli in social regions relative to Placebo in social areas. (*Right*) OT does not affect the variability of the BOLD responses in nonsocial regions. (*Lower Right*) OT reduces the response to Vehicles in nonsocial regions.

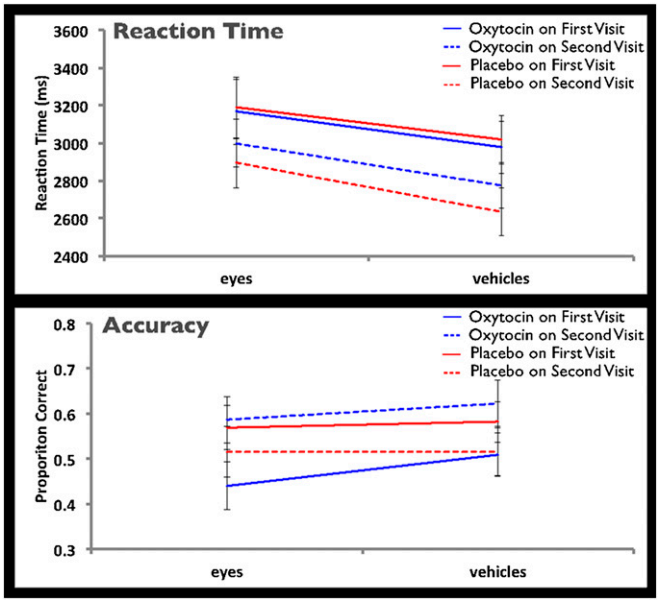

Fig. S3. Reaction time (*Upper*) and accuracy scores (*Lower*) from the RMET and Control tasks. Accuracy did not differ by treatment (OT vs. Placebo) or task (social and nonsocial judgments). Reaction times were significantly shorter in the second visit compared with the first visit, indicating a practice effect. Participants were faster to label Vehicles than Eyes. Because OT was randomized to be given either on the first or second visit, the order of treatment is also depicted. There was no order effect or interaction between treatment order and treatment condition.

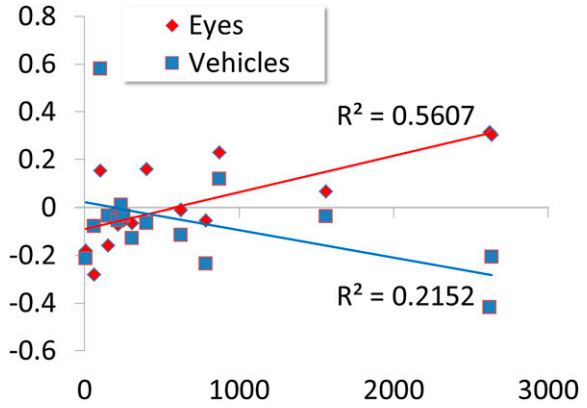

Fig. S4. Scatterplot depicting the correlations between salivary changes in OT levels when OT was administered (*X* axis) and beta coefficients from the amygdala and Brodmann's area 25 (BA 25) region of interest (ROI), separately for Eyes (red line and markers) and Vehicles (blue line and markers).

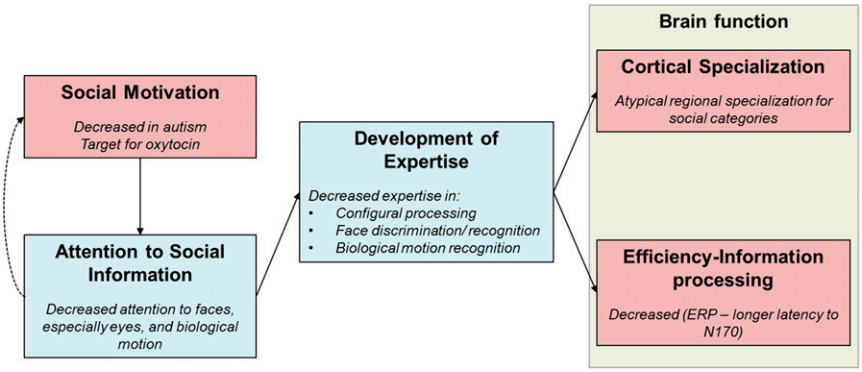

Fig. S5. Illustration of the social motivation hypothesis and predictions of altered brain development in autism spectrum disorder (ASD). ERP, event-related potential.