Genotype and dose-frequency determine acute and chronic effects of oxytocin on amygdala fear responses in humans: therapeutic implications

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Running title: Dose-frequency and genotype-dependent effects of oxytocin on brain and behavior

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Abstract

Background: There is considerable interest in therapeutic application of intranasal oxytocin in psychiatric disorders, but while clinical trials typically use daily dosing protocols it has not been established whether this is optimal or if there are moderating influences of oxytocin receptor genotype.

Methods: In a randomized, placebo-controlled pre-registered trial on 138 adult male subjects we investigated effects of single and repeated (24IU daily versus alternate days for 5 days) doses of oxytocin on two neural biomarkers (attenuated amygdala fear reactivity and increased intrinsic amygdala-prefrontal functional connectivity) and modulating effects of oxytocin receptor polymorphisms rs53576 and rs2254298 strongly associated with autism.

Results: Findings confirmed that after a single dose, amygdala responses to fear faces were reduced and its resting state connectivity with medial frontal cortex increased. Suppression of amygdala responses to fear faces was restricted to AA homozygotes of rs53576 and A+ carriers of rs2254298, whereas resting state effects were not genotype-dependent. Importantly, amygdala responses to fear faces were absent after daily oxytocin treatment but maintained after treatment every other day with infrequent dosing additionally resulting in reduced behavioral ratings of emotional arousal and intensity after 5 days. In contrast, oxytocin effects on intrinsic amygdala-prefrontal coupling were similar following daily or infrequent dose protocols after 5 days.

Conclusions: Overall, results suggest that infrequent rather than daily doses of oxytocin may be more effective therapeutically and that its actions in reducing amygdala responses to fear are strongly genotype-dependent.

The study was pre-registered at Clinical Trials.gov (NCT03610919).

Introduction

Intranasal oxytocin (OT) has been proposed as a potential therapy for social dysfunction in psychiatric disorders in relation to autism spectrum disorder, schizophrenia and social anxiety [1–3] as well as in the context of fear-extinction [4] and as an adjunct to the placebo effect for working memory deficits [5]. To date the functional effects of intranasal OT administration have been based primarily on a single dose and there is evidence that a 24IU dose may be optimal [6]. However, initial clinical trials reporting some therapeutic efficacy have typically used twice-daily treatment protocols lasting a number of weeks [1,7–11], even though no studies have investigated if this is an optimal strategy. This is an important issue since clinical trials to date have reported relatively modest or inconsistent effects of chronic daily intranasal OT treatment and there is evidence from animal studies for rapid desensitization of OT receptors in some brain regions [12], most notably in the amygdala which mediates many of OTs functional effects on social cognition and anxiety [1]. Rodent models have reported that in contrast to single doses, chronic administration of OT can actually produce social impairment [13–15] and reduced receptor expression in the amygdala and nucleus accumbens [15]. Furthermore, chronic versus single administration of OT can produce differential neurochemical changes in both the rodent and human frontal cortex [16].

Different OT receptor (OXTR) genotypes have been associated with social behaviors and may also influence sensitivity of behavioral and neural responses to intranasal OT. In particular, OXTR polymorphisms rs53576 and rs2254298 have been associated with autism[17], deficits in social and emotional processing including empathy [18–20] and individual variations in behavioral and neural responses to intranasal OT [21,22]. Variants of rs2254298 may also be a more general biomarker for social dysfunction across a number of psychiatric disorders [23].

While single doses of OT have been reported to produce numerous functional effects two have emerged as promising candidate neural biomarkers: reduced amygdala responses to fear faces and increased resting state functional connectivity

between the amygdala and medial prefrontal cortex[1,6]. Both biomarkers may be particularly relevant in the context of anxiety in terms of reduced responses to social threat and enhanced top-down control of emotion [24], although OT effects on the amygdala are important for a range of social cognition functions[1–3, 6]. In the current pre-registered neuroimaging study we therefore conducted a double-blind, randomized between subject placebo (PLC)-controlled design experiment including 138 adult male subjects to investigate the effects of acute (single dose) and repeated doses (daily or every other day for 5 days) of 24IU OT versus PLC on these two biomarkers and valence, arousal and intensity ratings of fear faces. Additionally, we assessed the influence of OXTR rs53576 and rs2254298 polymorphisms on the acute and repeated dose effects of intranasal OT and associations with trait autism [25].

Material and Methods

Participants. A total of 147 healthy, right-handed healthy adult male subjects were enrolled according to common inclusion and exclusion criteria for human OT-administration studies. This subject number achieves >90% power for a medium effect size of 0.45. A total of 9 subjects were excluded due to failure to complete the study or excessive head movement (see **Fig 1**). Subjects were randomly assigned to repeated intranasal treatment (single daily dose on five consecutive days) of (1) placebo (PLC; n = 46, M ± SD, 22.46± 2.3 years), (2) oxytocin ($OT_{5;}$ n = 49, M ± SD, 21.78 ± 2.3 years), or interleaved OT and PLC (OT on days 1, 3, 5, PLC on days 2, 4; OT_3; n = 43, M ± SD, 21.02 ± 2.0 years) (see **SI**). To ensure compliance all subjects were required to come to the center every day and supervised during self-administration of nasal sprays. To control for between-group differences in potential confounders pre-treatment levels of anxiety, depression, and empathy were assessed using validated scales. Measures of trait autism were assessed using the AQ [25]. There were no significant differences between the OT and PLC groups (**Table S4**). The study was approved by the local ethics committee (Institutional Review Board, University of Electronic Science and Technology of China) and subjects provided written informed consent. The study was in accordance with the latest

revision of the Declaration of Helsinki, pre-registered at Clinical Trials.gov (NCT03610919) and in line with recommendations for trials in psychological experiments [26] (see **Fig. 1** for Consort flow diagram). Subjects received monetary compensation for participation.

Experimental procedures.

The study employed a double-blind, randomized, placebo-controlled, between-subject design. The OT and PLC sprays used in the 3 groups were both supplied by Sichuan Meike Pharmaceutical Co. Ltd, Sichuan, China in identical dispenser bottles containing identical ingredients (glycerine and sodium chloride) other than OT. In line with recommended guidelines experiments started 45 minutes after intranasal administration [27]. In post-treatment interviews collected on days 1 and 5 subjects were unable to identify better than chance whether they had received OT or PLC ($\chi^2 < 0.1$, ps > 0.2, **Table S5**) confirming successful blinding over the entire study period. For OXTR genotyping subjects provided buccal swaps on the 1st day for analysis of OXTR rs2254298, rs53576 SNPs (see **SI** and [28]).

For the implicit face-emotion processing task 208 grayscale facial stimuli displaying happy, neutral, angry or fearful facial expressions (n = 26 per category, 50% female) were used. Stimuli were initially rated with respect to arousal and valence by an independent group of subjects and two matched independent sets of stimuli were produced for use on the 1st and 5th days (all ps > 0.3, see **SI** for details and **Table S6**). The presentation order of the two sets was counter balanced. To ensure attentive processing subjects were required to identify the gender of each face picture (see **Figure S2**).

Primary outcomes and analysis plan.

Face emotion-related amygdala responses were assessed using the event-related implicit face processing fMRI paradigm on treatment days 1 and 5. Intrinsic amygdala connectivity was assessed by means of two resting state fMRI assessments (before and after the task-paradigm). Valence, arousal and intensity ratings (scale: 1-9) for the

facial stimuli were collected immediately after MRI acquisition as additional behavioral outcomes (further details see **SI**). In line with the main aim of the study changes in amygdala fear reactivity and amygdala intrinsic connectivity between the 1st and 5th day served as primary outcome measures. Changes in valence, arousal and intensity ratings for the fear faces represented an associated behavioral outcome measure.

Imaging acquisition and analysis.

MRI data was acquired using standard sequences on a 3T GE MR750 system. In addition to the functional time series high resolution T1-weighted structural MRI data was acquired at both time points to improve normalization and control for acute and chronic effects of treatment on brain structure. MRI data was preprocessed using validated procedures in SPM12 [29] (Statistical Parametric Mapping; http://www.fil.ion.ucl.ac.uk/spm) and Data Processing Assistant or Resting-State fMRI [30] (DPARSFA; http://rfmri.org/DPARSF) (for details see **SI**). First level General Linear Models (GLM) for the task-related fMRI data included separate regressors for the four emotional conditions, gender identity rating period and 6 movement parameters and appropriate contrasts were subjected to a second level random effects analysis.

Analysis strategy

To identify OT-sensitive regions and confirm previous findings on suppression of amygdala reactivity following single-dose OT-administration[2] a voxel-wise whole-brain two-sample t-test was conducted in SPM comparing neural activity in OT- and PLC-treated subjects on the1st day. For all subsequent analyses a 6-mm sphere centered at the maximum t-values of the acute OT effects in the amygdala served as target region to determine different trajectories of amygdala functioning following acute versus repeated treatment (for similar approach see [6]).

Primary outcomes: amygdala fear-reactivity and intrinsic connectivity.

Differences in stimulus-induced amygdala fear reactivity were examined by means of

mixed ANOVAs with treatment (PLC, OT_3, OT_5) as between-subject factor, time point (1st day, acute effects; 5th day, chronic effects) as within-subject factor and extracted target region amygdala-reactivity towards fearful faces as dependent variable (parameter estimates extracted using Marsbar, http://marsbar.sourceforge.net) followed by appropriate Bonferroni-corrected post-hoc comparisons.

Differences in amygdala connectivity were determined using a voxel-wise seed-to-whole-brain ANOVA as implemented in the SPM flexible factorial design with treatment (PLC, OT_3, OT_5) as between-subject factor, time point (1st day, acute effects; 5th day, chronic effects) as within-subject factor and amygdala connectivity maps as dependent variable. To account for potential effects of task-engagement on intrinsic amygdala connectivity the primary analysis focused on pre-task resting state maps. A subsequent ROI analyses on the post-task data (focusing on extracted estimates from a 6mm sphere centered at vmPFC determined by the pre-task data) served as a replication and further validation.

Secondary outcome measures: OXTR genotype and trait autism associations.

For rs2254298 subjects were divided into A+ carriers (AA and AG) and A- non-carriers (GG) and rs53576 into G+ carriers (GG and GA) and G- non-carriers (AA). To explore effects of genotype as a secondary outcome measure, OXTR group was included as additional between-subject factor in the corresponding ANOVAs and amygdala fear reactivity, amygdala-vmPFC intrinsic functional connectivity and behavior rating response served as dependent variables. Associations between neural and behavioral effects of OT and trait autism were carried out by analyzing correlations with AQ scores.

Control for treatment effects on brain structure.

To control for potential confounding effects of single- and repeated OT-administration brain structure, a voxel-based morphometry (VBM) analysis was conducted on the T1-weighted images acquired on both testing days using SPM12

standard procedures[31,32]. Effects of single- and repeated dose administration were explored concordant with the fMRI analyses (see **SI**).

Thresholding and statistical implementation.

Voxel-wise whole brain analyses in SPM were thresholded at a cluster-based Family-wise error (FWE) corrected $p < .05$ with an initial cluster forming threshold of $p < .001$ (in line with recent recommendations [33,34]. Behavioral and neural (extracted parameter estimates) indices were analyzed using SPSS 22.0 and appropriate ANOVA models. Partial eta squared (η^2_p) and Cohen's *d* were computed as measures of effect size. Group differences in parameter estimates extracted from significant main effect in SPM were further evaluated using two-sample t tests. Associations between neural and behavioral changes and AQ scores were computed using Pearson correlation. All reported p values were Bonferroni-corrected, two-tailed, and $p \leq 0.05$ considered significant.

Results

Acute effects of OT on neural responses to emotional faces

In accordance with the primary outcome measure of the trial analyses focused on the neural responses to fearful faces, however no significant effects of OT were found for happy or angry faces. Comparison of single-dose OT- and PLC-treated subjects (1st day) revealed significantly decreased right amygdala reactivity towards fearful faces on the whole brain level ($k = 78$, $p_{FWE} = 0.043$, x=27, y=-4, z=-13) (**Fig.2A**). Cytoarchitectonic probabilistic localization (Anatomy toolbox V1.8 [35]) mapped the peak coordinate with >80% probability to the basolateral amygdala sub-region. In addition, OT also decreased fear-reactivity in the right superior frontal gyrus and bilateral primary visual cortex (see **SI** and **Table S1**). There were no significant differences between the OT_3 and OT_5 groups on the 1st day.

Primary outcome measures: effects of repeated doses on OT-evoked changes

Mixed ANOVAs with treatment (PLC, OT_3, OT_5) and time point (1st day, acute effects; 5th day, chronic effects) as factors and right amygdala fear reactivity as dependent variable revealed a significant main effect of treatment ($F_{2, 135} = 7.854$, $p = 0.001$, $\eta^2_p = 0.104$) and a treatment x time point interaction ($F_{2, 135} = 5.737$, $p = 0.004$, $\eta^2_p = 0.078$). Post-hoc Bonferroni corrected comparisons between groups on the 5th day revealed that the OT_3 group exhibited a suppression of right amygdala fear reactivity relative to both the PLC ($p = 0.001$, Cohen's $d = 0.70$) and OT_5 groups ($p = 0.018$, $d = 0.52$) but the OT_5 group did not ($p = 0.266$, $d = 0.24$, relative to the PLC group). Within group comparisons revealed that whereas amygdala reactivity did not change on day 1 relative to day 5 in the PLC group ($p = 0.090$, $d = 0.29$), its suppression was significantly enhanced in the OT_3 group ($p = 0.019$, $d = 0.40$) and attenuated in the OT_5 one ($p = 0.044$, $d = 0.38$) (**Fig. 2B**).

For the behavioral ratings mixed ANOVAs with treatment and time point as within-subject factors revealed a significant main effect of treatment for arousal, but not intensity ratings ($F_{1, 135} = 3.56$, $p = 0.031$, $\eta^2_p = 0.05$, intensity: $F_{1, 135} = 1.24$, $p = 0.292$, $\eta^2_p = 0.018$), and time point for both emotional arousal and intensity ratings (arousal: $F_{1, 135} = 12.59$, $p = 0.001$, $\eta^2_p = 0.085$, intensity: $F_{1, 135} = 13.25$, $p < 0.001$, $\eta^2_p = 0.09$) although no significant two-way interactions (arousal: $F_{1, 135} = 0.72$, $p = 0.487$, $\eta^2_p = 0.011$, intensity: $F_{1, 135} = 1.24$, $p = 0.292$, $\eta^2_p = 0.018$). An exploratory post hoc analysis showed that both emotional arousal and intensity ratings for fear faces in the OT_3 group were decreased on the 5th day (arousal: $p = 0.01$ versus PLC, $d = 0.55$, $p = 0.02$ versus OT_5, $d = 0.47$; intensity: $p = 0.05$ versus PLC, $d = 0.42$) but not on the first day ($ps > 0.27$) (**Fig.3A-B**). No significant main effects or interactions were found for valence ratings ($ps > 0.12$).

Right-amygdala seed-to-whole brain fMRI resting-state analysis by mixed-effect ANOVA revealed a main effect of treatment (OT_3, OT_5 and PLC) on amygdala functional coupling with vmPFC (peak MNI x = -3, y =53, z = -19, $F_{2, 135} = 16.55$, $p_{FWE} = 0.001$, k = 88) before subjects underwent the face paradigm, whereas no brain regions showed a significant time point x treatment interaction. Post-hoc analyses demonstrated that right amygdala intrinsic connectivity with the vmPFC was stronger

in both the OT_3 (k = 74, p_{FWE} = 0.014, x = -3, y = 53, z = -19) and OT_5 groups (k = 127, p_{FWE} = 0.001, x = -3, y = 53, z = -19) relative to PLC. Subsequent confirmatory analyses of resting state functional connectivity in this pathway acquired after the face task paradigm confirmed a significant main effect of treatment ($F_{2, 135}$ = 7.081, p = 0.001, η^2_p = 0.095). Post hoc comparisons showed both groups exhibited increased connectivity in this pathway after a single OT dose on the 1st day (OT_3, p = 0.001, *d* = 0.71; OT_5, p = 0.063, *d* = 0.40; relative to PLC) and after repeated doses on the 5th day (OT_3 p = 0.047, *d* = 0.46; OT_5, p = 0.001, *d* = 0.69; relative to PLC). The OT_3 and OT_5 groups did not differ significantly on the 1st (p = 0.140) or 5th (p = 0.208) day (**Fig. 4B**).

Although not included in our primary outcome measures the (calcarine) visual cortex showed the same reduced responsivity to daily OT as the amygdala, but the superior frontal gyrus did not (see **SI**). Voxel based morphometry analysis revealed no evidence for acute or repeated dose effects of OT on gray matter volume (see **SI**).

Associations with OXTR genotype and trait autism

The number of G-carriers and G-non-carriers of rs53576 as well as A-carriers and A-non-carriers of rs2254298 did not differ between the three groups and both SNPs satisfied the Hardy Weinberg Equilibrium (see **Tables S2 and S3**). With Bonferroni-correction for the multiple SNPs and alleles (i.e. 2 x 2 = 4), p < 0.0125 was considered significant. For amygdala responses there was a significant treatment x genotype interaction for rs53576 ($F_{2, 105}$ = 6.01, p = 0.003, η^2_p = 0.10) but not for rs2254298 ($F_{2, 105}$= 1.48, p = 0.232, η^2_p = 0.03). For rs53576, OT-induced amygdala suppression on day 1 was only significant in G-non-carriers (p < 0.001, *d* =1.00) and also on the 5th day in the OT_3 group (p < 0.001, *d* =1.41). An exploratory post hoc analysis for rs2254298 revealed that OT-induced suppression on the 1st day across treatment groups was only significant in A-carriers (p = 0.001, *d* = 0.91) and also on the 5th day in the OT_3 group (p = 0.004, *d* =0.81) (see **Fig. 5**). Similar patterns of genotype association were found for the visual cortex but not superior frontal gyrus responses to fear faces (see **SI**). For both emotional arousal and intensity ratings there

was a significant treatment x genotype interaction for rs2254298 (arousal: $F_{2, 105}$= 7.82, p = 0.001, η^2_p = 0.13, intensity: $F_{2, 105}$= 6.25, p = 0.003, η^2_p = 0.11). Post-hoc analyses revealed no differences on the 1st day between OT and PLC groups all ps>0.10) but on the 5th day the reductions in arousal and intensity ratings in the OT_3 group were only significant in A-carriers (arousal: p < 0.001, *d* =1.14, intensity: p < 0.001, *d* =1.19) (**Fig. 5**). No associations with trait autism scores (AQ) achieved significance.

Since comparable patterns of OT effects were observed on pre- and post-task resting state data right amygdala-vmPFC functional connectivity values were pooled to increase power (**Fig. 4B**). No significant main or interaction effects of genotype for either SNP (rs 2254298 all ps > 0.262; rs53576 all ps > 0.396) were found although a negative association between total AQ scores and strength of functional connectivity was observed in the PLC group on the 1st day (r = -0.32, p = 0.029) which was significantly reduced by OT in both groups on the 1st day (OT_3, r = 0.21 p = 0.170; Fisher's *z* = 2.51, p = 0.012; OT_5, r = 0.10, p = 0.500; *z* = 2.07, p = 0.038). The same effect was also seen on the 5th day (PLC: r = -0.33 p = 0.025; OT_3, r = -0.03 p = 0.837; *z* = 1.41, p = 0.16; OT_5 group, r = 0.10 p = 0.475; *z* = 2.11, p = 0.035) (**Figs. 4C-4D**).

Discussion

Overall, our findings firstly validate the use of OT-reductions in amygdala responses to fear-faces and associated emotional intensity ratings together with increased resting state functional connectivity between the amygdala and vmPFC as robust markers for its effects. Intriguingly, these task-dependent and resting-state effects of OT show a markedly different sensitivity to repeated intranasal doses and OXTR genotype, although our results indicate that to achieve both maximal task and resting-state changes an optimal protocol using the standard 24IU dose may be to administer it every other day rather than daily. Indeed, amygdala and particularly behavioral anxiolytic responses to fearful faces were more pronounced after 5 days when OT was

administered every other day, and even with the resting-state and superior frontal gyrus changes there was no advantage of giving OT daily as opposed to every other day.

Our findings are therefore consistent with those in animal models demonstrating OXTR desensitization following repeated doses of OT in some brain regions [12] and that chronic administration can reduce brain OXTR expression [15] and altered patterns of neurochemical release [16]. While we did not use the twice daily administration protocol employed to date in clinical trials we anticipate that this would likely produce even stronger receptor-desensitization effects. However, at this point we have only demonstrated repeated-dose effects on amygdala and visual cortex fear reactivity in this respect and those on other behavioral and neural domains remain to be established. Nevertheless, the amygdala is one of the main targets for functional effects of OT and is dysfunctional in many psychiatric disorders including social impairments and anxiety [36,37]. Interestingly, chronic doses of OT in rodents fail to produce anxiolytic effects normally seen with single doses [15] and thus daily repeated doses in humans might also reduce its efficacy in decreasing social anxiety.

Our second major finding is that the effects of OT on reducing amygdala and visual cortex responses to fear faces are highly dependent on OXTR genotype. Only G-non-carriers of rs53576 (i.e. AA) and A-carriers of rs2254298 (i.e. AA and AG) and AA homozygotes for rs53576 and A+ carriers of rs2254298 were significantly responsive to OT. A-carriers of both SNPs have frequently, although not universally, been associated with social dysfunction in autism as well as empathy [17,18]. A recent haplotype-based analysis of OXTR SNPs including rs53576 and rs2254298 also indicated that individually they have some association with sensitivity to OT-effects on face recognition [22]. Again, while the current study clearly indicates that OT modulation of amygdala and visual cortex responses to fear are strongly associated with the AA genotype (Cohen's *ds* from 0.81-1.41), its effects on other regions and behaviors might show a different association. Limitations to the findings are that subject numbers are still relatively low for establishing robust genetic

associations and that the AA allele of rs53576 occurs more frequently in Asian compared with Caucasian populations [38]. Also rs53576 exhibits some sex-dependent differences in social cooperation effects of OT [21] and our current study focused only on males to avoid potential menstrual cycle effect issues.

Interestingly, task-related and intrinsic network changes produced by OT showed a strikingly different sensitivity to repeated doses and OXTR genotype and only the resting state changes were actually significantly associated with trait autism. However, importantly there was no advantage of giving OT daily as opposed to every other day. Intrinsic networks may be less influenced by repeated doses of OT or OXTR genotype than those activated by tasks, although this remains to be more fully established. Future studies should measure differential OT effects on both task-related and intrinsic networks.

In conclusion, the current study provides strong evidence for an important influence of dose frequency and receptor genotype on the neural and behavioral actions of intranasal OT in response to fear faces in healthy human subjects. Dose frequency should therefore be taken into consideration when designing future clinical trials using repeated doses of OT as an intervention in psychiatric disorders, particularly in relation to reducing social anxiety.

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Author contributions: JK and KMK designed the experiment. JK, YZ and CS carried out the experiment. JK, KMK, CM, FZ and BB analyzed the experiment and JK, KMK, CM and BB wrote the paper. All authors contributed to the conception of the study and approved the paper.

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Competing interests

The authors declare that they have no competing interests.

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Figure legends

Fig.1 CONSORT flow diagram of the clinical trial.

Fig.2 The effect of intranasal oxytocin (OT) treatment on neural responses to fearful faces on the 1st day. (A) The t-map of the treatment effect (FWE c = 78, t = 3.93, p = 0.043) showed an activated cluster peaking at the right amygdala (x = 27, y = −4, z = −13). (B) Parameter estimates extracted using a 6-mm radius sphere centered at the peak MNI coordinates at the right amygdala on the 1st and 5th day separately revealed that OT treatment on alternate days (OT_3) decreased amygdala responses on both the 1st and 5th days whereas for the daily OT treatment group (OT_5) group the decrease only occurred on the 1st day. * $p < 0.05$, ** $p < 0.01$, two-tailed t-test. Bars indicate M ± SE.

Fig.3 Oxytocin decreased intensity and arousal ratings of fearful faces only on the 5th day of treatment in the group receiving OT on alternate days (OT_3) compared with placebo (PLC). *$p \leqslant 0.05$. Bars depict M ± SE.

Fig.4 The effects of oxytocin (OT) on resting state functional connectivity (A) schematic showing functional connection between the right amygdala and ventromedial medial prefrontal cortex (vmPFC). Whole brain functional connectivity (FC) used the right amygdala as a region of interest (6mm sphere, x=27, y=-4, z=-13) and (B) revealed significant increased functional connectivity between vmPFC and right amygdala ($p_{FWE} <0.05$, x=-3, y=53, z=-19) in both OT treatment groups (every day – OT and every other day - OT on both days 1 and 5. Data for the two resting state periods before and after the face emotion task were similar and are therefore showed here combined. (C) Regression graphs showing correlations between resting-state functional connectivity and autism spectrum quotient scores (AQ) in the

three treatment groups on day 1 and (D) day 5. Bar graph illustrates the extraction of parameter estimates from right amygdala connectivity with vmPFC (M ± SE). * $p < 0.05$, ** $p < 0.01$, two-tailed t-test. Bars indicate M ± SE.

Fig.5. Influence of oxytocin receptor genotype on right amygdala responses to fearful faces (n = 111 subjects). (A)-(B): for rs 53576 only G-non carriers (i.e. AA) showed reduced amygdala response to fearful faces and for rs2254298 only A-carriers (i.e. AA and AG) in the groups with intranasal oxytocin treatment either daily (OT_5) or every other day (OT_3). (C)-(D): A similar pattern was found for rs2254298, but not rs53576 for intensity ratings of fearful faces although only on day 5 in the OT_3 group. (E)-(F): A similar pattern was found for rs2254298, but not rs53576 for arousal ratings of fearful faces although only on day 5 in the OT_3 group. ** $p < 0.001$, * $p < 0.01$, # $p < 0.05$, two-tailed t-test (Bonferroni corrected significance threshold of $p = 0.0125$). Bars indicate M ± SE.

Figure 1

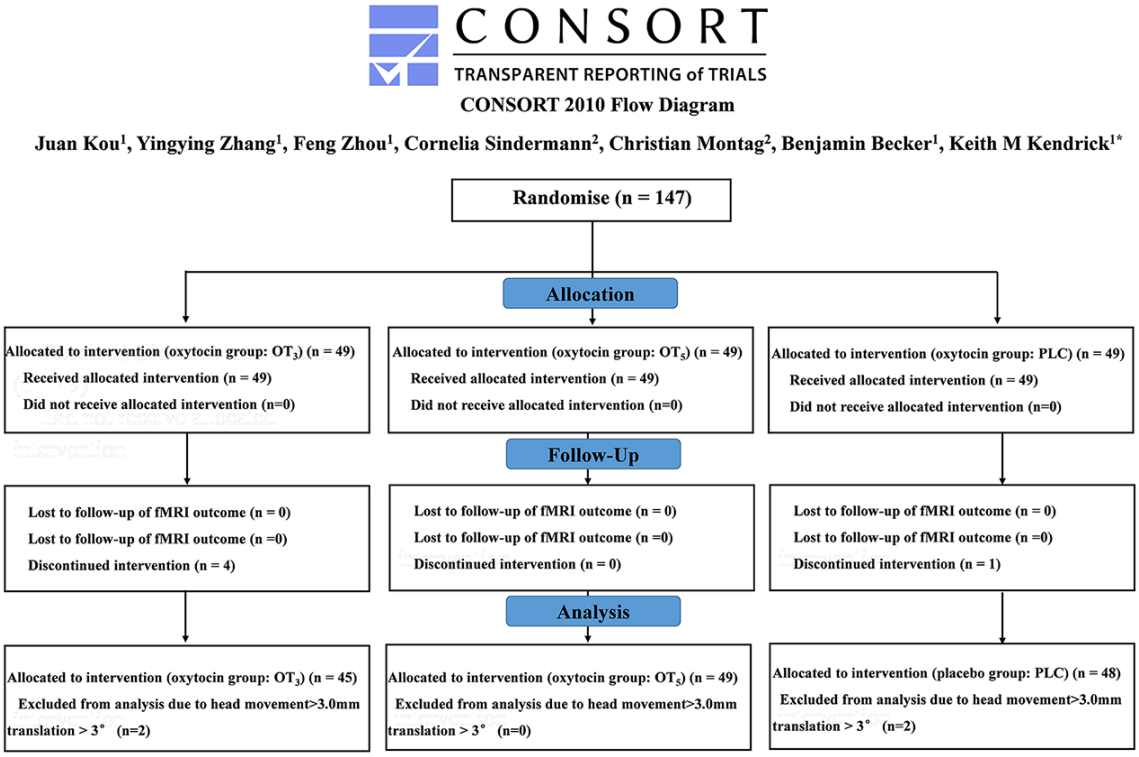

Fig.1

Figure 2

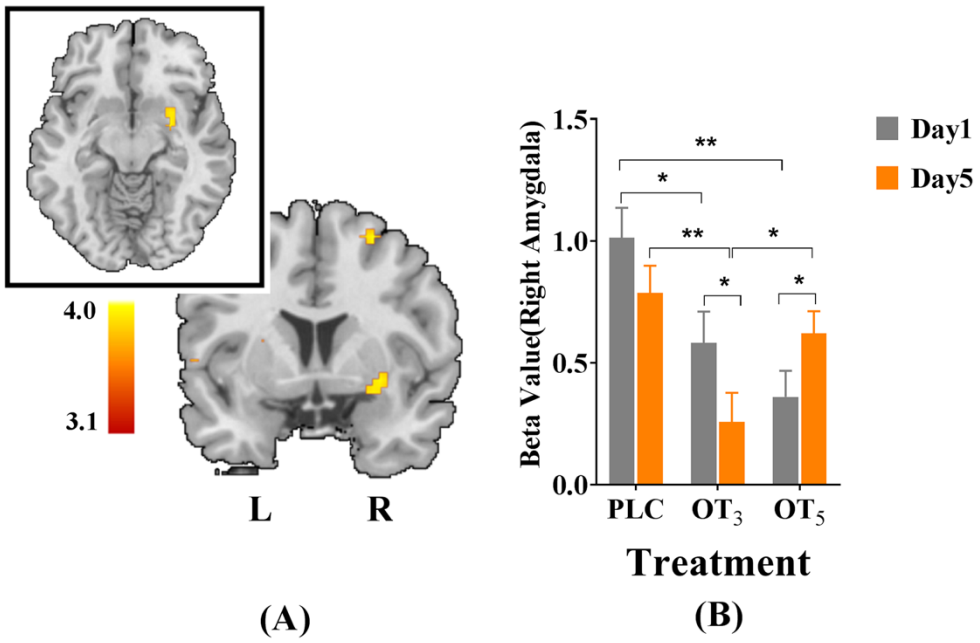

Fig.2

Figure 3

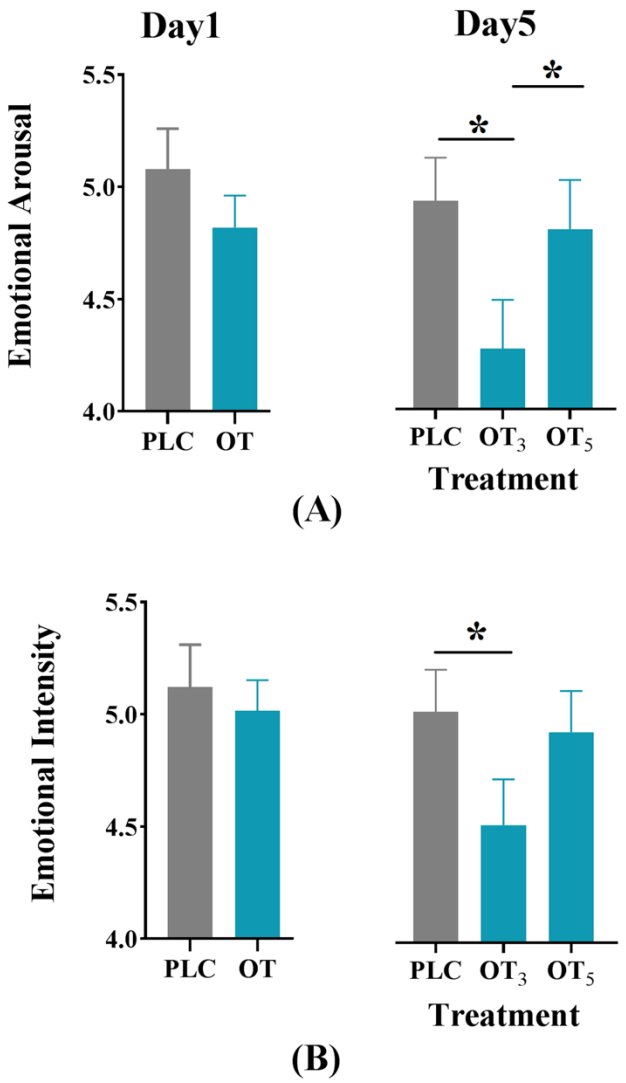

Fig.3

Figure 4

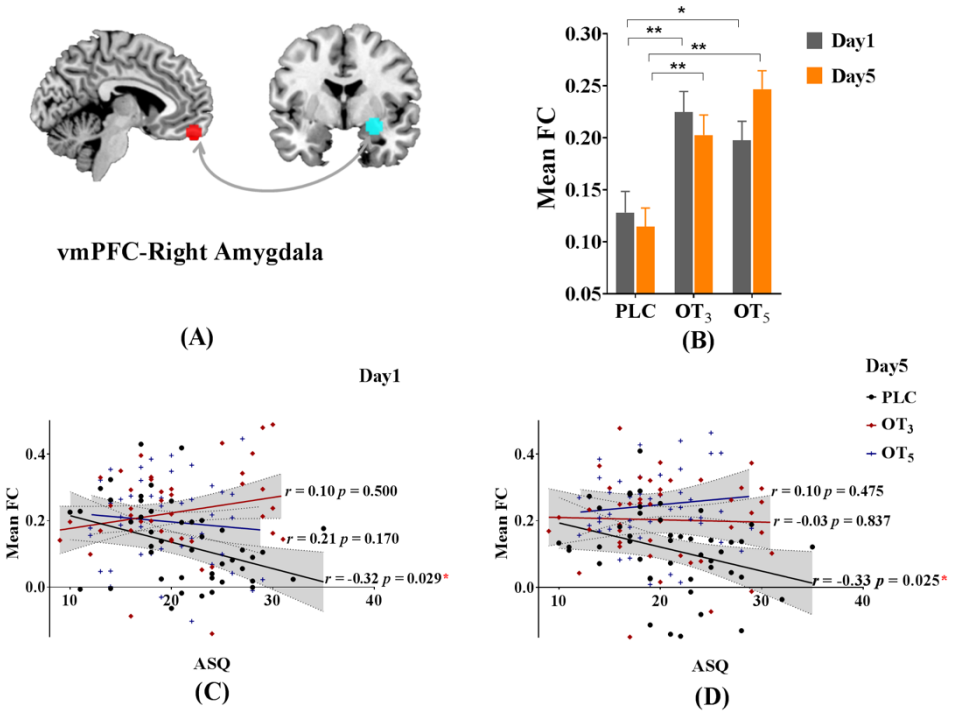

Fig.4

Figure 5

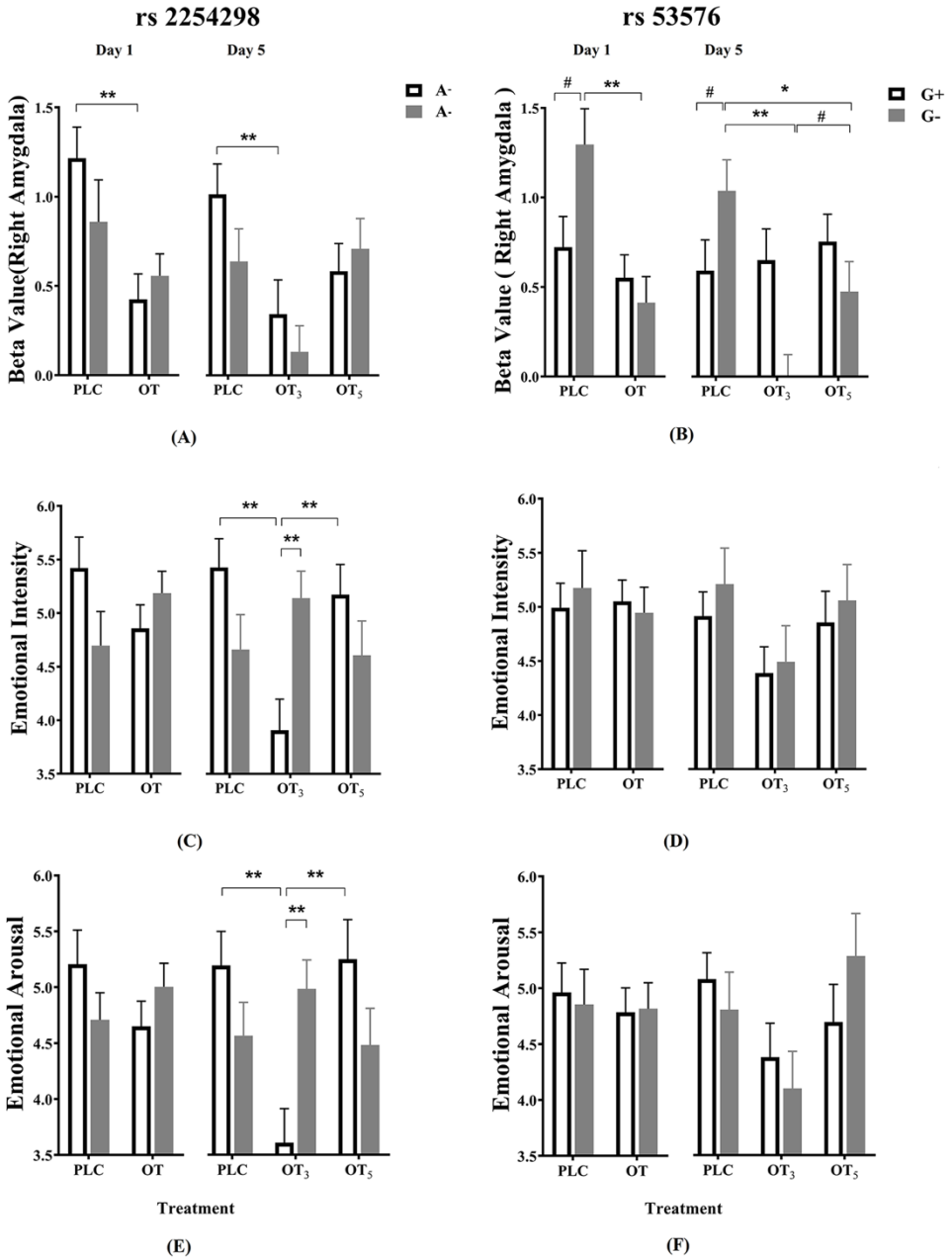

Fig.5