

Oxytonergic circuitry sustains and enables creative cognition in humans

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Creativity enables humans to adapt flexibly to changing circumstances, to manage complex social relations and to survive and prosper through social, technological and medical innovations. In humans, chronic, trait-based as well as temporary, state-based approach orientation has been linked to increased capacity for divergent rather than convergent thinking, to more global and holistic processing styles and to more original ideation and creative problem solving. Here, we link creative cognition to oxytocin, a hypothalamic neuropeptide known to up-regulate approach orientation in both animals and humans. Study 1 ($N = 492$) showed that plasma oxytocin predicts novelty-seeking temperament. Study 2 ($N = 110$) revealed that genotype differences in a polymorphism in the oxytocin receptor gene *rs1042778* predicted creative ideation, with GG/GT-carriers being more original than TT-carriers. Using double-blind placebo-controlled between-subjects designs, Studies 3–6 ($N = 191$) finally showed that intranasal oxytocin (vs matching placebo) reduced analytical reasoning, and increased holistic processing, divergent thinking and creative performance. We conclude that the oxytonergic circuitry sustains and enables the day-to-day creativity humans need for survival and prosperity and discuss implications.

Keywords: neurohormones; creative cognition; oxytocin; polymorphism; divergent thinking

INTRODUCTION

Humans have a strong capacity for creative thought and innovation, allowing them to adapt flexibly to changing circumstances, to manage complex social relations and to survive and prosper through social, technological and medical innovations. Indeed, the ability to generate novel and potentially useful ideas and problem solutions (viz., creativity) has been proposed as a key driver of human evolution. Cultural advances, including the inventions of agriculture, for example, may have accumulated to a ‘tipping point’ that supported the great human expansion out of Africa and into the Near East and Eurasia (Wynn *et al.*, 2009; Henn *et al.*, 2012). In addition, throughout evolution nothing would select more potently for increased social intelligence than a within-species coalitionary arms race in which success depended on effectiveness in social competition, and creative insights and solutions may have provided exactly that competitive advantage (Alexander and Borgia, 1978; Flinn *et al.*, 2005). Today, creativity is among the most valued and sought after competencies in contemporary societies that struggle with complex problems and compete for technological and economic supremacy (Runco, 2004).

Because creativity provides fitness functionality, it stands to reason that (i) the human brain evolved to sustain and promote creative thinking and (ii) we should be able to identify brain circuitries and neurohormonal modulators of creative cognition and performance (Flaherty, 2005; Dietrich and Kanso, 2010). Here we link human creativity to oxytocin, a hypothalamic neuropeptide pivotal in pair-bond formation and pro-social approach (Donaldson and Young, 2008).

Functioning as hormone and neurotransmitter, oxytocin targets the amygdala and hippocampus, interacts with the hypothalamic–pituitary–adrenal axis involved in the down-regulation of stress and up-regulates the dopaminergic, reward processing circuitries in the nucleus accumbens shell and in the ventral tegmental area (Skuse and Gallagher, 2005; Carter *et al.*, 2008; Donaldson and Young, 2008; Bartz *et al.*, 2011).

Direct linkages between oxytocin and creative cognition have heretofore not been reported. However, and largely due to its anxiolytic effects, oxytocin up-regulates approach orientations in both human and non-human animals (Kosfeld *et al.*, 2005; Carter *et al.*, 2008; Striepens *et al.*, 2012). Administering oxytocin to female rats leads to more exploration of unfamiliar environments (Windle *et al.*, 1997), and compared with knock-out mice without forebrain oxytocin receptors (OXTR), normal mice explore their novel cage mates to a greater extent and display greater cognitive flexibility (Ferguson *et al.*, 2000; Sala *et al.*, 2011). Furthermore, compared with low novelty-seeking rats, rats exhibiting high novelty-seeking behaviors have elevated oxytocin mRNA levels in the supraoptic nucleus of the hypothalamus (Clinton *et al.*, 2010). In humans, exogenous oxytocin promotes both trust and cooperation (Kosfeld *et al.*, 2005), and defensive aggression against threatening intruders (De Dreu *et al.*, 2010, 2011; Hahn-Holbrook *et al.*, 2011; Striepens *et al.*, 2012).

The approach tendencies associated with oxytocin are pivotal in creativity. Approach orientation increases global processing and reduces attention to detail (Förster *et al.*, 2004), and enhances cognitive flexibility, original ideation and creative insight (Cretenet and Dru, 2009; Mehta and Zhu, 2009; Lichtenfeld *et al.*, 2012). Accordingly, the oxytonergic circuitry may be associated with creative cognition and performance in humans. We examined this possibility by (i) linking naturally fluctuating levels of oxytocin to novelty-seeking tendencies (Study 1), (ii) examining the relationship between a targeted polymorphism in *OXTR* gene and creative performance (Study 2) and by (iii) testing the effects of intranasal administration of oxytocin

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on holistic and flexible processing, divergent thinking and creative ideation and problem solving (Studies 3–6).

STUDY 1: PLASMA OXYTOCIN AND NOVELTY-SEEKING TEMPERAMENT

Study 1 was designed to examine the relationship between endogenous oxytocin and individual differences in traits related to creativity. Work by Cloninger *et al.* (1993, 1994) identified four basic personality dimensions that are highly heritable and grounded in specific brain circuitries that are activated in response to specific environmental stimuli, such as danger, novelty and reward. ‘Novelty Seeking’ reflects a heritable tendency to respond strongly to novel stimuli and cues for reward, with frequent exploratory activity in pursuit of novelty, rewards or impulsive decision making. ‘Harm Avoidance’ reflects a heritable bias to respond strongly to aversive stimuli, leading to inhibition of behavior. ‘Reward Dependence’ reflects a heritable tendency in the maintenance or continuation of behaviors previously associated with reward, which manifests itself as sentimentality and sociability. ‘Persistence’, finally, reflects a heritable tendency to persevere despite goal frustration and fatigue.

Our main hypothesis was that novelty seeking, but not harm avoidance, reward dependence and persistence, would be positively related to naturally fluctuating, endogenous oxytocin. Evidence for this prediction would fit research showing that in individuals diagnosed with major depressive disorder, endogenous oxytocin levels positively predict novelty seeking and reward dependence (Bell *et al.*, 2006). It would also fit work showing that novelty-seeking temperament positively associates to approach and creativity, whereas harm avoidance, reward dependency and persistence are not or negatively related to approach and creativity (Cloninger *et al.*, 1993; Chávez-Eakle *et al.*, 2006).

Method and materials

Study 1 was part of a larger research program on the biological basis of human behavior and decision making in which Han Chinese undergraduate students at the National University of Singapore participated (total $N=1158$; 584 females; mean age = 21.2 years, $s.d.=1.5$). A subset ($N=492$; 228 males) was recruited through advertisement on the Integrated Virtual Learning Environment (IVLE).

At the beginning of the study, participants completed an informed consent form approved by the Institutional Review Board at National University of Singapore. Thereafter, participants were administered the Temperament and Character Index (TCI-R) personality questionnaire (Cloninger *et al.*, 1993, 1994). Sample items of ‘Novelty Seeking’ include ‘I’m slow to get excited about new ideas’ (reverse scored) and

‘I do things spontaneously’. Sample items of ‘Harm Avoidance’ include ‘I get tense and worried in unfamiliar situations’ and ‘I avoid meeting strangers’. Sample items of ‘Reward Dependence’ include ‘I’m strongly moved by sentimental appeals’ and ‘Others think I am too independent’ (reverse scored). Items characteristic of the ‘Persistence’ scale included ‘I often push myself to exhaustion’ and ‘I work long after others give up’. Participants indicated their agreement with each statement on a 5-point Likert scale ranging from 1 = definitively false to 5 = definitively true. The TCI-R has been validated in previous research and shows good internal reliabilities ranging from 0.65 to 0.87 (Cloninger *et al.*, 1993, 1994).

Following TCI-R measurement, blood samples for oxytocin assay were collected from the antecubital vein into pre-chilled 5-ml ethylenediaminetetraacetic acid (EDTA) tubes with 250 KIU of apoprotinin and refrigerated until processing. Plasma was isolated by centrifugation at 1800g, 15 min, 4°C and stored in aliquots at -70°C . Oxytocin immunoreactivity levels were quantified in duplicates using a commercial oxytocin ELISA kit (Enzo Life Sciences, NY, USA, formerly Assays Designs, MI, USA), as recommended in previous publications (Carter *et al.*, 2008). Thawed samples on ice were diluted 1:2 times in assay buffer and assayed according to manufacturer’s instructions. The oxytocin assay had a sensitivity of 11.7 pg/ml, and inter- and intra-assay coefficient of variations <15%.

Results

In a first analysis, we computed the zero-order correlations between each of the four TCI-R scales and (log-transformed) plasma oxytocin. As predicted, we observed a positive correlation only among (log-transformed) plasma oxytocin and TCI novelty seeking, $r(490)=0.121$, $P=0.007$ (Figure 1A), which survives correction for multiple comparison testing ($P=0.028$). Furthermore, the other correlations were not significant; OT-Reward Dependence: $r=-0.026$; OT-Persistence: $r=0.025$; OT-Harm Avoidance: $r=-0.018$, all $P_s > 0.568$.

We then computed ordinary least-squares regressions with gender (0 = male, 1 = female) and age as covariates, log-transformed plasma oxytocin as predictor and the four temperament scales as criterion. Table 1 shows that controlling for gender and age did not change the strength and direction of our results—again, only novelty-seeking temperament was positively associated with (log transformed) plasma oxytocin. These analyses also revealed higher scores on novelty seeking, reward dependence and harm avoidance, and lower persistence scores among female compared with male participants.

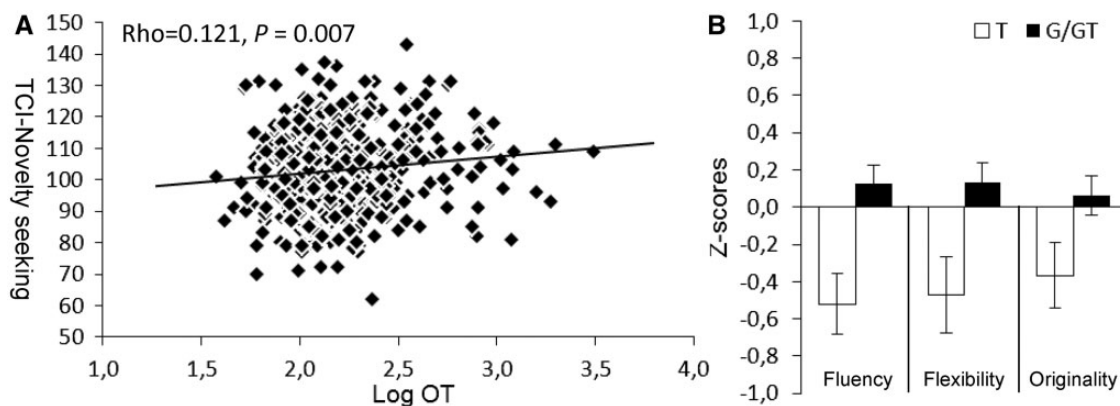


Fig. 1 (A) Study 1: endogenous oxytocin levels predict individual differences in novelty-seeking temperament ($N=492$). (B) Study 2: GG/GT-carriers of the *rs1042778 OXTR* generate more ideas, are more original and display greater flexibility than TT-carriers (displayed z-scores \pm s.e.m.).

Table 1 Ordinary least-squares regression of log-transformed OT on TCI temperaments (unstandardized regression weights) controlling for gender and age (all covariates reported)

	TCI-NS	TCI-RD	TCI-PS	TCI-HA
Log OT	4.864***	−1.800	2.055	−1.905
Gender	3.222***	5.092***	−5.578***	7.045***
Age	−0.110	0.244	−0.269	0.291
Constant	92.743***	94.104***	120.314***	92.070***
R ² (%)	3.26	3.41	2.85	4.01

NS = novelty seeking; RD = reward dependence; PS = persistence; HA = harm avoidance.
 *** $P < 0.001$ ($N = 492$).

Taken together, these results are consistent with our hypothesis that (endogenous) oxytocin associates with creativity, as evidenced here in the positive correlation between plasma oxytocin and novelty-seeking temperament. We note that the evidence is correlational and not informative about causality (something we turn to in Studies 3–6). We also note that while significant, the overall effect size is fairly small.

STUDY 2: POLYMORPHISM IN OXTR GENE AND CREATIVE IDEATION

Study 2 focused on the possible link between creativity and polymorphism in the *oxytocin receptor* (OXTR) gene. The OXTR is a 389-amino-acid polypeptide located on chromosome 3p25, containing three introns and four exons. Of the single-nucleotide OXTR polymorphisms (SNPs), the SNP *rs1042778* at Exon 4-3'-UTR is of specific interest here because GG- and GT-carriers have higher plasma oxytocin than TT-carriers (Feldman *et al.*, 2012), and stronger approach tendencies (Israel *et al.*, 2009; Feldman *et al.*, 2012).

In Study 2, we assessed creativity with an Alternative Uses Test, in which individuals generate as many possible new uses for a particular object (e.g. a tin can; Guilford, 1967). Uses generated by the participants were coded for total number of responses given (fluency), number of semantic categories (flexibility) and originality (infrequency) (Mehta and Zu, 2009; Baas *et al.*, 2011). Originality is generally considered the hallmark of creativity (Guilford, 1967), and we predicted GG- and GT-carriers of the *rs1042778* polymorphism to generate more original ideas than TT-carriers. We anticipated similar differences with regard to flexibility and explored effects on fluency.

Methods and materials

Participants were 110 healthy students recruited from the University of Haifa (43 men and 67 women) whose average age was 24.59 (men: mean age = 24.70 years, s.d. = 1.87; women: mean age = 24.52 years, s.d. = 1.89). All participants were Jewish and fluent in Hebrew. Exclusion criteria were self-reported history of mental disorders, neurological disorders, learning disabilities and traumatic brain injury. Additionally, participants who reported taking chronic medication other than contraceptive pills were excluded. Women who were pregnant, breastfeeding or had been pregnant in the past 12 months, as well as men having children <6 months old, were excluded. All participants gave informed written consent and the genetic study was approved by the local University and Hospital Internal Review Board and the Israeli Ministry of Health (Genetics Section).

Upon arrival, each participant provided two 20 ml of mouthwash samples of DNA by rinsing their mouths vigorously for 60 s with 10 ml of 'Aquafresh' mouthwash and expectorating into a sterile test tube. DNA was extracted using the Master Pure Kit (Epicentre). Genotyping of the OXTR *rs1042778* SNP was performed using the SNaPshot

Method (Applied BioSystems, Foster City, CA, USA) as previously described in our laboratory (Lerer *et al.*, 2008). Amplification of the OXTR was achieved using the following primers. First polymerase chain reaction (PCR primers): F: GGGTTCAGGGTGGTAGAAG, R: AGGCTGTGCTGGCATAAGTG; second PCR primer extensions: (T)₁₂TGAAGCCACCCCAAGGAG. PCR cycling conditions in the SNaPshot Method were as follows: samples were initially heated at 94°C for 5 min followed by 35 cycles of 94°C (30 s), 55°C (30 s) and 72°C (90 s) and a final extension step of 72°C for 5 min. After the first PCR cycle, the PCR product was cleaned with ExoSAP for 37°C for 30 min and then at 80°C for 15 min. The conditions for the second PCR were as follows: 96°C (10 s), 50°C (5 s) and 60°C (30 s) for 25 cycles. The second PCR product was cleaned using shrimp alkaline phosphatase (SAP) initially at 37°C for 1 h followed by 72°C for 15 min.

Following the collection of mouthwash samples, participants were instructed about the Alternative Uses Task (Guilford, 1967; Mehta and Zhu, 2009). Participants were presented with common objects (e.g. button) and were asked to list as many alternate uses as possible for the object. Scoring was carried out by two trained raters and only non-redundant ideas that did not include the common use of the object were included. Scoring was based on the total number of responses given (fluency), number of categories (flexibility) and a measure of infrequency (originality). The flexibility scores included the total number of distinct semantic categories of each response (e.g. button: 'body parts on a doll', 'play with', 'weapon'). Originality scores were calculated using the relative infrequency of ideas based on norms collected in healthy volunteers ($N = 100$, age 18–40 years). For each object, a list was compiled consisting of all possible uses provided across subjects. An originality score was given to each possible use according to the percentage of subjects who provided the answer (a score of 2 was given if <2% of subjects gave the answer, a score of 1 if 2–5% gave the answer and a score of 0 if >5% gave the answer). For each participant in the current study, we averaged the infrequency scores of his or her ideas as a measure of originality.

Results

Planned comparisons showed that compared with TT-carriers, GG/GT-carriers produced more ideas, $F(1,108) = 11.449$, $P = 0.002$ partial $\omega^2 = 0.086$, more original ideas, $F(1,108) = 4.355$, $P = 0.047$, partial $\omega^2 = 0.051$, and displayed greater flexibility, $F(1,108) = 7.004$, $P = 0.014$, partial $\omega^2 = 0.029$ (Figure 1B). These results provide further support to our general hypothesis that the oxytonergic circuitry sustains and enables human creativity. We note that, as in Study 1, results are correlational and do not permit conclusions about causality. We further note that, again, although results are significant and as predicted, effect sizes are fairly small.

STUDIES 3–6: EXOGENOUS OXYTOCIN AND CREATIVE COGNITION AND PERFORMANCE

Our first two studies provided initial evidence for possible linkages between oxytocin and creative cognition and performance. However, as mentioned, the evidence prohibits conclusions about causality, and the effect sizes were small to medium. To further test our predictions, and to further insight in the possible effects of oxytocin on creative cognition and performance, we performed four double-blind, placebo-controlled experiments in which individuals received intranasal oxytocin or matching placebo prior to performing tasks gauged at measuring creative cognition and creative performance. We predicted that individuals given oxytocin rather than placebo engage in more holistic rather than detailed processing (Study 3), display divergent rather

than convergent thinking (Study 4), generate more original ideas (Study 5) and perform better on creative insight tasks (Study 6).

Methods and materials

For Studies 3–6, a total of 191 male subjects (mean age = 21.14 years, *s.d.* = 1.26) were recruited via an on-line system and offered €10 (~USD 13) for participating in a study on medication and psychological testing. Exclusion criteria were significant medical or psychiatric illness, prescription-based medication, smoking more than five cigarettes per day and drug or alcohol abuse. The experiments were approved by the Psychology Ethics Committee of the University of Amsterdam and complied with the Declaration of Helsinki. Participants provided written informed consent prior to the experiments.

Participants were instructed to refrain from smoking or drinking (except water) for 2 h before the experiment and were randomly assigned to the oxytocin or placebo group (double-blind, placebo-controlled study design). Participants self-administered a single intranasal dose of 24 IU oxytocin (Syntocinon Spray, Novartis; three puffs per nostril) or placebo. The placebo contained all the active ingredients except for the neuropeptide, was prepared according to Good Manufacturing Practice (GMP) and Good Clinical Practice (GCP) and delivered in the same bottles as Syntocinon.

For each of the studies, participants were seated in individual cubicles preventing them from seeing or communicating with others, read and signed an informed consent form and self-administered the medication under experimenter supervision. The experimenter left and participants completed a series of unrelated questionnaires and tests that were presented on their computer screen, using the keyboard and computer mouse to answer questions.

Effects of intranasal oxytocin typically plateau ~35 min after administration (Kirsch et al., 2005; Kosfeld et al., 2005; Baumgartner et al., 2008; De Dreu et al., 2010; Striepens et al., 2012). Accordingly, the computer switched to the main experimental tasks after 30 min (De Dreu et al., 2010, 2011). In all four studies, experimental tasks lasted between 7 and 15 min (i.e. between 35 and 50 min following self-administration of the test medication). In Study 3, we counterbalanced the order in which the two tasks (analytical reasoning and Navon task) was given but because order did not interact with treatment this variable is further ignored.

In the ‘Navon task’ used in Study 3 (Navon, 1977; Förster, 2012), participants are asked to respond as quickly as possible to a series of letters that are randomly shown on screen. On the top left of their screen, participants were shown a capital letter H in blue color, corresponding to a blue sticker on the letter A on their keyboard. On the top right of the screen, a capital letter L was shown in red color, corresponding to a red sticker on the letter L on their keyboard. For each trial, participants were asked to focus on a fixation cross in the center of the screen that was presented for 500 ms. Then, one of eight target letters was shown until a participant gave a response. There were eight trial types, and target letters were always an H or L. On 50 trials, target letters were either a large (2.1 × 2.1 cm) H or L consisting of small (0.4 × 0.4 cm) Fs or Ts. In the other 50 trials, target letters were small Hs or Ls composing either a large F or T. The correct response was in half of the trials the blue and thus left response, and in half of the trials the red and thus right response. For each trial, participants were asked to indicate as fast as possible if either the letter H or L was shown in the center of the screen. Only correct trials were included in the analyses (12.4% of trials were answered incorrectly). The average reaction time in milliseconds on the large and small target letters was computed. Trials on which the reaction time was smaller or larger than 3 *s.d.* from the mean of that individual were excluded from analyses

(Ratcliff, 1993). We subsequently computed a composite measure by subtracting the reaction time on the large target letters from the small target letters. A more positive score on this measure thus evidenced a more global, holistic processing style (seeing the large letters faster than the small ones; Förster, 2012).

In the ‘Syllogistic Reasoning Task’ used in Study 3, participants were presented with 16 syllogisms. Syllogisms are arguments about the properties of entities and consist of two premises and a conclusion (Alter et al., 2007; Khemlani and Johnson-Laird, 2012). There are four ‘types’ of premises and conclusions: All A are B, Some A are B, No A are B and Some A are not B. The conclusion that follows the two premises is true when this conclusion is true in every case in which both premises are true. An example of a syllogism with a true conclusion is (1) All A are B. (2) Some A are C. Therefore (3) Some C are B. An example of a syllogism with an untrue conclusion is (1) No A is a B. (2) No B is a C. Therefore (3) All As are Cs. Because performance requires deductive reasoning and close analyzing of the associations that are provided, this syllogism task is often used as indicator of analytical reasoning (Khemlani and Johnson-Laird, 2012). For each of the 16 syllogisms participants indicated whether the conclusion provided was true or not. More correct answers indicate better analytical performance (range 0–16).

In the ‘Pasta-task’, used in Study 4, participants five primes—non-existing pasta names all ending with an ‘i’ (e.g. maloveni, paragoni), and asked to generate as many new pasta names as possible within 3 min (Troyer et al., 1997; Marsh et al., 1999; Dijksterhuis and Meurs, 2006). From their responses, we created indices for fluency (number of names generated, duplicates removed), convergent thinking (number of items ending with an ‘i’, as in the primes), divergent thinking (number of items not ending with an ‘i’), category repetitions (number of times in which participants consecutively generated pasta names with the same ending) and category switches (number of times in which participants switched from one ending to another) (Troyer et al., 1997). Specifically, two coders blind to hypotheses and conditions counted number of names generated (duplicates removed; fluency), assigned each pasta name to one of two categories: those ending with an ‘i’ (converging items, as they are in line with the cue given in the instructions) vs those not ending with an ‘i’ (diverging items), category repetitions (number of times in which participants consecutively generated pasta names with the same ending) and category switches (number of times in which participants switched from one ending, e.g. ‘i,’ to another ending, e.g. ‘a’) (Marsh et al., 1999; Dijksterhuis and Meurs, 2006). Inter-coder agreement was 100%. Category repetitions associated positively with convergent thinking [$r(60) = 0.747$, $P = 0.001$] and negatively with divergent thinking [$r(60) = -0.267$, $P = 0.036$]. Category switches negatively related to convergent thinking [$r(60) = -0.350$, $P = 0.005$] and positively to divergent thinking [$r(60) = 0.667$, $P = 0.001$].

The ‘Alternative Uses Task’ in Study 5 was a variant of the one in Study 2 and used previously in Baas et al. (2011). Ideas generated were coded by a trained rater who was blind to hypotheses and conditions. She counted the number of non-redundant ideas per participant and classified all non-redundant ideas to distinct semantic categories (e.g. a brick to build something, as a musical instrument, as a weapon). A second rater coded a random selection of 30% of the ideas to establish inter-rater reliability, which proved excellent (Cohen’s $\kappa = 0.91$; differences were solved through discussion). For each participant, the number of distinct semantic categories that were accessed during idea generation was used as a measure of flexibility (Guilford, 1967; Baas et al., 2011). Because a reference group was unavailable, originality of ideas was based on the relative infrequency of ideas within the study population (Guilford, 1967; De Dreu et al., 2008; Baas et al., 2011). For each idea we assessed how often it was mentioned by the

participants in this experiment and assigned a percentage score to each idea (e.g. if an idea was mentioned by 12.11% of the participants, it received a percentage score of 12.11; if it was mentioned by 54.01%, it received a score of 54.01). We subtracted percentage scores from 100 to get an infrequency score—the higher the number assigned to an idea, the more original (i.e. less frequent) it is. For each participant, we averaged the infrequency scores of his or her ideas as a measure of originality.

The Remote Associates Test (RAT), used in Study 6, is a creative insight task that asks participants to identify associations among words that are not normally connected (Mednick, 1962). On a particular trial, participants are given three words (e.g. car, swimming, cue) and have to generate a word that associates with all of them (e.g. pool). The RAT has previously been used in a number of studies on creative insight (Mednick, 1962; Schooler *et al.*, 1993; Smith and Kounios, 1996; Harkins, 2006; Rowe *et al.*, 2007; Kounios and Beeman, 2009; Chermahini and Hommel, 2010). Because the initial or dominant response to creative insight problems is likely to be incorrect, these problems often require individuals to actively restructure the presented problem material and approach the problem from multiple angles (Mednick, 1962; Harkins, 2006; Kounios and Beeman, 2009). Once a possible solution has been identified, participants check its appropriateness through convergent analysis. However, to come up with possible solutions, divergent thinking is needed and shows up in brain activity and processing styles that differentiates from that on analytical tasks (Smith and Kounios, 1996; Kounios and Beeman, 2009). Here, the RAT was introduced as a study on complex problem solving and participants were shown, on their computer screen, a string of three words and asked to provide a fourth word that connected the three words given. Upon entering their answer, they were presented with a new string of three words. In total, participants received 30 RATs.

Results

Study 3 ($n=49$) showed that oxytocin produced holistic processing and reduced analytical reasoning. Holistic processing was assessed with the Navon task. Here, average reaction time in milliseconds on holistic trials was subtracted from detailed trials so that a higher score reflects more holistic processing (identifying large target letters faster than small target letters). Analysis of variance (ANOVA) showed that, compared with placebo, individuals given oxytocin engaged in more global processing, $F(1,47)=6.354$, $P=0.015$, partial $\eta^2=0.119$ (Figure 2A).

In Study 3, analytical reasoning was assessed with the syllogistic reasoning task. Analyses of the number of correctly solved items revealed that oxytocin undermined performance on the syllogistic reasoning task, $F(1,47)=5.165$, $P=0.028$, partial $\eta^2=0.099$ (Figure 2B). This result suggests that oxytocin up-regulates creative cognition (i.e. holistic processing) specifically, and not performance in general.

Study 4 ($n=62$) assessed convergent and divergent thinking using the pasta task. A $2(\text{Treatment}) \times 2(\text{Convergent/Divergent Thinking})$ mixed model ANOVA showed no effect on fluency, $F(1,60)=0.185$, $P=0.669$, and significant effects for Thinking, $F(1,60)=6.071$, $P=0.017$, and the Thinking \times Treatment interaction, $F(1,60)=7.172$, $P=0.016$ (Figure 2C). Compared with placebo, oxytocin reduced convergent and increased divergent thinking [directional $t(60) > 1.722$, $P < 0.05$; partial $\eta^2=0.047$ and 0.061 , respectively]. Furthermore, oxytocin reduced repetitions, $F(1,60)=6.443$, $P=0.014$, partial $\eta^2=0.072$, and increased switching among cognitive categories, $F(1,60)=4.668$, $P=0.035$, partial $\eta^2=0.097$ (Figure 2D). These findings corroborate those in Study 3, that oxytocin reduces analytical reasoning (akin to convergent processing) yet stimulates creative thinking (i.e. divergent thinking).

Study 5 ($N=44$) tested treatment effects on creative ideation, as measured with the Alternative Uses Test (Study 2). ANOVA showed that oxytocin, compared with placebo, did not affect fluency, $F(1,42)=2.477$, $P=0.123$ (partial $\eta^2=0.056$), increased flexibility, $F(1,42)=4.608$, $P=0.038$ (partial $\eta^2=0.099$; Figure 3A), and originality, $F(1,42)=4.527$, $P=0.039$ (partial $\eta^2=0.097$; Figure 3B). Controlling for flexibility rendered the effect of Treatment on originality non-significant, $F(1,41)=1.00$, $P=0.324$ (regression of flexibility on originality is $B=29.776$, $t=4.694$, $P=0.001$). It thus appears that oxytocin increases original ideation because it enables cognitive flexibility. This fits the results on holistic processing (Study 3) and on divergent processing (Study 4), both of which are considered to be pivotal to cognitive flexibility.

Study 6 ($n=36$) examined divergent thinking and activation of more remote informational links using the RAT. Consistent with findings reported above, the number of correct RAT solutions (range 0–30) was higher in the oxytocin compared with placebo condition, $F(1,34)=9.66$, $P=0.004$, partial $\eta^2=0.221$ (Figure 3C). No effects were found for misses or wrong answers, all $F(1,34) < 2.838$, all $P > 0.110$.

Taken together, Studies 3–6 support the hypothesis that exogenous oxytocin (*vs* placebo) increases global, divergent and flexible processing of material. Furthermore, although oxytocin promotes original ideation and betters creative insight, it reduces convergent thinking and analytical performance.

DISCUSSION AND CONCLUSIONS

Creativity allows individuals and their groups to thrive and prosper. Here we uncovered that creative cognition and performance is enabled by the evolutionary ancient neuropeptide oxytocin. Endogenous oxytocin positively associates with novelty-seeking temperament, polymorphism in the *OXTR rs1042778* associates with cognitive flexibility and original thinking, and intranasal administration of oxytocin led to increased holistic processing, more flexible thinking, more original ideas and better creative problem solving. Concurrently, administering oxytocin reduced convergent processing and impeded analytical reasoning.

Predictions were grounded in the well-established finding that oxytocin down-regulates anxiety and motivates social approach in humans (Skuse and Gallagher, 2005; Carter *et al.*, 2008; Donaldson and Young, 2008; Bartz *et al.*, 2011), and that oxytocin is involved in exploration in non-human animals (Windle *et al.*, 1997; Ferguson *et al.*, 2000; Sala *et al.*, 2011). One possible mechanism not investigated here is that oxytocin-induced approach is, at least in non-human mammals, mediated by up-regulated dopaminergic circuitry involved in reward processing (Flaherty, 2005; Skuse and Gallagher, 2005). Indeed, in humans, biomarkers of dopaminergic activation, such as eye-blink rates, associate with increased divergent and decreased convergent thinking (Dreisbach *et al.*, 2005; Chermahini and Hommel, 2010). Possibly, oxytocin impedes analytical reasoning yet simultaneously stimulates a suite of processes conducive to creative performance because it up-regulates the dopaminergic circuitry and associated approach orientation.

Although significant, the relationships between endogenous oxytocin and *OXTR* polymorphism on the one hand and novelty-seeking temperament and original ideation on the other were relatively weak. Stronger effects were observed in the administration studies. Possibly, administration studies induce a peak in brain oxytocin that exceeds the levels of endogenous oxytocin, and the path from *OXTR* polymorphism to brain-level oxytocin remains largely unknown. New research is needed to further substantiate current findings and to uncover when and how intranasal administration of oxytocin mirrors naturally

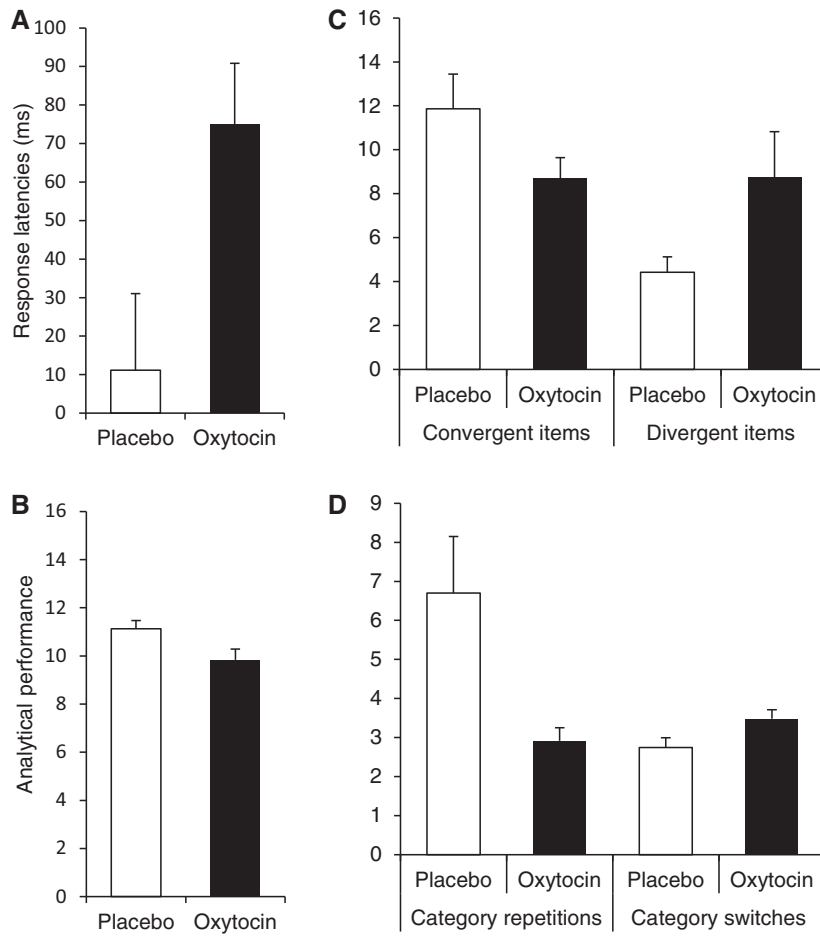


Fig. 2 (A) Study 3: response latencies for detailed vs holistic targets in the Navon task (higher score reflects more holistic processing; displayed \pm s.e.m.). (B) Study 3: oxytocin reduces number of solved syllogistic reasoning problems (ranging from 0 to 16, displayed \pm s.e.m.). (C) Study 4: number of generated convergent and divergent pasta names as a function of oxytocin (displayed \pm s.e.m.). (D) Study 4: number of category repetitions and switches during the generation of pasta names as a function of oxytocin (displayed \pm s.e.m.).

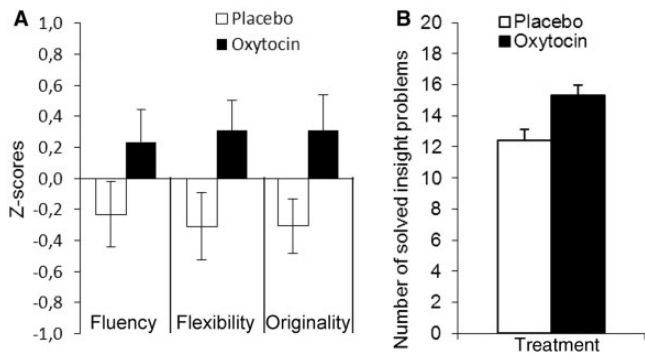


Fig. 3 (A) Study 5: oxytocin stimulates fluency, flexibility and originality in the generation of alternate uses (displayed \pm s.e.m.). (B) Study 6: oxytocin increases number of solved insight problems (RATs; ranging from 0 to 30, displayed \pm s.e.m.).

fluctuating levels of oxytocin and interacts with OXTR polymorphism to up-regulate creative functioning in humans. The strong convergence in findings presented here renders such new research both important and promising.

We studied ‘small c’ creativity—the type of creativity humans display in their day-to-day functioning, and cannot generalize to ‘big C’ creativity—the creative inventions and breakthroughs that lead to radical and long-lasting changes in society. Furthermore, we considered the relationship between oxytocin and creative functioning in individual

settings and ignored the social context. However, oxytocin is strongly implicated in pair-bond formation (Carter *et al.*, 2008), and positive social bonds are important in creativity. Indeed, a principal feature of creative art is exhibiting and it may be that associations between art and courtship displays—exhibiting feathers, singing, performing courtship dances—have their neurobiological linkage in the oxytonergic circuitry (Zaidel, 2010). Second, oxytocin is a pivotal mediator in cooperative exchange within groups (Kosfeld *et al.*, 2005; De Dreu *et al.*, 2010), and cooperative groups are more creative than groups dominated by competition (Bechtoldt *et al.*, 2010; also see Farrell, 2001). New research is needed to test the hypothesis that cooperative settings facilitate the release of oxytocin which, in turn, up-regulates human creativity. Evidence for such a hypothesis would further substantiate the possibility that the evolutionary ancient neuropeptide oxytocin functions to facilitate the divergent thinking and creative problem solving needed to flexibly adapt to changing circumstances and to protect and promote both oneself and one’s kin and kith.

AUTHOR CONTRIBUTIONS

R.P.E. and S.H.C. designed Study 1. T.T. supervised and designed the plasma oxytocin assay in Study 1 and Y.J. analyzed the data. N.M. and S.G.S.-T. designed Study 2 and analyzed the data. C.K.W.D.D., M.B., D.J.S. and M.R. designed Studies 3–6. M.B., D.J.S. and M.R. programmed Studies 3–6 and coordinated data collection. C.K.W.D.D., D.J.S. and M.B. analyzed the data. C.K.W.D.D., M.B. and S.G.S.T. wrote the article.

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Conflict of Interest

None declared.

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