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Effects of oxytocin administration on spirituality and emotional responses to meditation

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Abstract

The oxytocin (OT) system, critically involved in social bonding, may also impinge on spirituality, which is the belief in a meaningful life imbued with a sense of connection to a Higher Power and/or the world. Midlife male participants ($N = 83$) were randomly assigned to receive intranasal OT or placebo. In exploratory analyses, participants were also genotyped for polymorphisms in two genes critical for OT signaling, the oxytocin receptor gene (*OXTR* rs53576) and *CD38* (rs6449182 and rs3796863). Results showed that intranasal OT increased self-reported spirituality on two separate measures and this effect remained significant a week later. It also boosted participants' experience of specific positive emotions during meditation, at both explicit and implicit levels. Furthermore, the effect of OT on spirituality was moderated by OT-related genotypes. These results provide the first experimental evidence that spirituality, endorsed by millions worldwide, appears to be supported by OT.

Key words: oxytocin; spirituality; emotion; meditation; OXTR; CD38

Introduction

Spirituality—the belief in a meaningful life imbued with a sense of connection to a Higher Power, the world, or both—is endorsed by millions of people worldwide. What are the neurochemical systems that may undergird these beliefs? Because the oxytocin (OT) system is critically implicated in social bonding, here, we investigate its role in supporting spirituality.

Spirituality and OT

Based on emerging scholarly consensus (see Zinnbauer and Pargament, 2005), here we define spirituality as one's personal affirmation of and relationship to a higher power or to the sacred. Spirituality typically implies the belief in a life infused with meaning and purpose, and the belief in relatedness and interconnectedness with the world and all living beings (Van Cappellen and Rimé, 2014).

OT is a polypeptide synthesized in the hypothalamus, which can be released into the bloodstream as well as to the forebrain. Peripherally, it acts as a hormone and centrally as a neuromodulator affecting many regions of the brain (Lee *et al.*, 2009). OT has received increasing attention among social psychologists for its implication in many social affiliative processes, such as empathy, trust and gaze to the eye region (e.g. MacDonald and MacDonald, 2010). At least in contexts that are not interpreted as competitive or threatening (Olff *et al.*, 2013), OT promotes reduced self-focus (Liu *et al.*, 2013), increased positive focus on others (Bartz *et al.*, 2011), parochial and universal altruism (Israel *et al.*, 2012), and extended affiliation motives (e.g. empathy, even toward the pain of an outgroup; Shamay-Tsoory *et al.*, 2013). An open question is whether the social bonding effect of OT may extend more broadly to support the affiliative components within spirituality's definition. These include a sense of connectedness with the world and all living beings or with a Higher Power, which people tend to conceptualize as a person and can be considered a symbolic figure of attachment

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(Granqvist and Kirkpatrick, 2013). Given the demonstrated social functions of OT, we hypothesized that OT prompts a mindset that supports the emergence and salience of spirituality-like beliefs.

Two recent correlational studies support the idea that OT is involved in spirituality. First, among 79 HIV patients, endogenous OT (assayed from plasma) was positively correlated with two self-report spirituality measures (i.e. one item on how spiritual one considers himself/herself and the Ironson-Woods Spirituality/Religiousness Index; Kelsch *et al*., 2013). Plasma levels of OT were also two times higher among patients who reported a spiritually transformative experience. Second, in a non-clinical sample of 34 devout American Christians, endogenous OT (assayed from saliva) was positively correlated with self-reported spirituality (using a similar one-item measure as in Kelsch *et al*., 2013), even after accounting for church attendance, positive affect, gender and relationship status (Holbrook *et al*., 2015).

These initial correlations suggest that OT is generally related to spirituality. However, experimental evidence is needed to test the causal role of OT on spiritual experiences. By randomizing participants to receive OT or placebo, our first primary aim was to investigate whether an increase in exogenous OT leads to an increase in spirituality. In addition, we reasoned that the boost in spirituality might lead participants to be more engaged and immersed in an activity that is often tied to spirituality and practiced by spiritual people, i.e. meditation. As a consequence, participants in the OT condition would more intensely experience the positive emotions derived from engaging in meditation. Therefore, our second primary aim was to test whether during an initiation to meditation, participants who received OT would experience greater positive emotions, especially ones relevant to spirituality and spiritual practices, i.e. self-transcendent positive emotions such as awe (Saroglou *et al*., 2008; Van Cappellen *et al*., 2013).

Genetic differences in response to OT administration

Intranasal OT administration does not appear to affect everyone uniformly (Bartz *et al*., 2011). Individual differences at the genetic level are likely to be one factor that can moderate the psychological effects of intranasal OT administration. Such effects have been demonstrated for the most commonly studied polymorphism in the OT receptor gene, *OXTR* rs53576 (Marsh *et al*., 2012; Feng *et al*., 2015). Therefore, in exploratory analyses we sought to replicate this effect of rs53576 as well as extend evidence of genetic moderation to the *CD38* gene. *CD38* is crucial for the release of OT from hypothalamic neurons in the brain. Accordingly, mice with the deletion of *CD38* gene show profound social deficits (Jin *et al*., 2007). In a regulatory control region (intron 1) of the human *CD38* gene, there is a polymorphism (rs6449182) that affects transcription factor binding and subsequent expression of the gene (Saborit-Villarroya *et al*., 2011). Consistent with a role for OT in social bonding, rs6449182 has been associated with social emotions (Algoe and Way, 2014; I.S., W,O., E,R.P., B,G., Unpublished data). Another polymorphism (rs3796863) located in a different region of *CD38* (intron 7) has been linked to unextracted plasma OT levels and social attunement (Feldman *et al*., 2012). In exploratory analyses, we tested whether the effect of OT administration on spirituality would be moderated by OT polymorphisms because this provides additional evidence of oxytocinergic involvement in spirituality.

The present study aims to illuminate potential biological mechanisms underlying spirituality by focusing on the OT system. Participants were randomized to receive intranasal OT or placebo. We hypothesized that OT, a neuropeptide critically involved in social bonding, has a facilitative effect on spirituality beliefs and the positive emotions derived from engaging in meditation. In exploratory analyses, we also evaluate who is more susceptible to these effects of intranasal OT by examining variation in genes related to OT signaling.

Materials and methods

Participants and procedure

This study was approved by the Institutional Review Board of the first author's institution and all participants gave written informed consent. Local newspapers, websites and posted flyers recruited mid-life adults (ages 35–64). This study is part of a multiple study grant that specifically targeted mid-life adults, an age during which psychological changes can be critical for later life health. This demographic also offers more generalizability than most studies of OT administration. Exclusion criteria were maintaining regular meditation practice (currently or previously), taking antihypertensive medication and having the ability to read Chinese pictographs (this criterion applied to another task unrelated to the current investigation). The data presented here are part of a larger study testing additional hypotheses not related to the present ones. For the larger study and to test a larger model, based on power calculation, a sample of 240 participants was targeted with a breakdown female–male of 125–115 to reflect the composition of the community from which the sample was drawn. Data collection, which occurred from September 2013 to July 2014, stopped at 239 but despite recruitment effort, the sample is skewed toward females. This report focuses only on the 83 males who took part in the study, which is a slightly higher sample size than most studies investigating the psychological effects of OT among males and seems sufficient to detect effects (recent examples: Israel *et al*., 2014; Bartz *et al*., 2015). Growing evidence suggests that the effects of OT are different for males and females (Feng *et al*., 2015) and most of the current evidence on intranasal OT's psychological effects, which support the current hypotheses, come from studies with exclusively male samples. A separate analysis of female participants, controlling for a series of additional variables related to natural variations in OT (MacDonald, 2012), is ongoing.

A total of 83 mid-life men took part in the study ($M_{Age} = 45.1$, $s.d._{Age} = 8$) in return for $120 in compensation. The majority of participants self-identified as White/Caucasian (86.7%), and the remaining participants were Black/African American (7.2%), or Asian (4.8%), one participant did not report race; additionally, 7.2% of the entire sample identified as being ethnically Hispanic. Participants were Christian (50.6%), Muslim (1.2%), Buddhist (2.4%), Jewish (2.4%), Agnostic (19.3%), Atheist (19.3%) or other (4.8%).

Participants were randomly assigned to one of two conditions: OT ($N = 41$) or placebo ($N = 42$). All received a nasal spray containing either Syntocinon (24 IU) or a placebo, which contained all ingredients except active OT. Under the experimenter's supervision, participants self-administered three full sprays into each nostril, alternating nostrils each time for a total of six sprays. Syntocinon was purchased from the Internationale Apotheke, a Swiss international pharmacy, and bottled for single use by the Triangle Compounding Pharmacy, North Carolina. OT and placebo doses were administered from identical blind-labeled spray vials and had the same color, smell

and pH. Participants, the experimenter and the research staff were blind to experimental condition, which was revealed only once data collection was complete. Experimenters were all thoroughly trained to behave in a professional and neutral way with participants. After the administration of OT or placebo, all participants provided a saliva sample for genotyping. Effects of OT typically emerge after 30–40 min (e.g. Israel *et al.*, 2014); therefore, approximately 40 min after the nasal spray, participants first completed questionnaires assessing spirituality. Then, participants were invited to follow a 20 min guided meditation.[1] Implicit and explicit measures of emotions felt as a result of and during meditation directly followed. A week later, participants ($N = 81$) completed a follow-up measure of spirituality as part of a larger online questionnaire.

Measures

Spirituality. We assessed spirituality through two self-report measures: a single-item assessment of spirituality (a measure devoid of any investigator-established conception of spirituality, allowing participants to project their own definition of spirituality) and a validated and widely used scale of spirituality [Spiritual Transcendence Scale (STS); Piedmont, 1999]. First, we administered the one-item measure of state spirituality: 'Right now, would you say that spirituality is important in your life?' Participants responded using a 8-point Likert type scale (0 = not at all; 7 = *completely;* Van Cappellen *et al.*, 2013). This measure was repeated again 1 week after the laboratory session as part of a larger online questionnaire. Second, we administered the STS (Piedmont, 1999). In creating this scale, Piedmont (1999) defined spirituality as the tendency to orient oneself toward a larger transcendent reality that binds all things into a unitive harmony. It reflects the personal search for connection with a larger sacredness. The subscale Prayer Fulfillment was not included in this study because this measure of spirituality is not clearly distinct from religiosity. Indeed, it has an explicitly religious content (reference to God and religious practices such as prayer) and has been found to relate positively to traditional religious attitudes and behaviors (Piedmont, 1999). Reliability for the items included was satisfactory ($\alpha = 0.86$).

Emotions as a result of meditation. Right after the 20 min guided meditation, participants completed an adaptation of the Implicit Positive and Negative Affect Test (Quirin *et al.*, 2009). Participants were instructed that they would see a list of words (a total of six words) from an artificial language and that these words (e.g. safme) are intended to express various moods. Then, they were asked to rate the extent to which the word conveys each of the following emotions: happy, relaxed, loving, helpless and sad. We chose these emotion words for their relevance to positive or negative experiences during meditation. Participants were asked to let themselves be guided by their spontaneous feelings in making these ratings. Past research has shown that participants tend to rate these artificial words according to how they currently feel (Quirin *et al.*, 2009). Participants responded using a Likert-type scale (1 = does not fit at all, 2 = fits somewhat, 3 = fits quite well, 4 = fits very well). Mean scores are computed across the six artificial words for the three positive emotions and separately for the two negative emotions. Reliability was satisfactory for both the positive and negative emotions scores (respectively, $\alpha = 0.82$, $\alpha = 0.72$). We also used an explicit measure of emotional experience, the 'modified Differential Emotions Scale' (Fredrickson, 2013), which assesses 10 different positive emotions (amusement, awe, gratitude, hope, inspiration, interest, joy, love, pride and serenity) and 10 negative emotions (anger, shame, contempt, disgust, embarrassment, guilt, hate, sadness, fear and stress). Participants were asked to rate the extent to which they felt each emotion during the guided meditation and respond on a Likert-type scale (0 = not at all, 1 = hardly, 2 = some of the time, 3 = often, 4 = most of the time). Mean scores were computed for positive emotions ($\alpha = 0.91$), negative emotions ($\alpha = 0.82$) and self-transcendent positive emotions (awe, gratitude, inspiration and love; $\alpha = 0.87$).

Involvement in organized religion. Participants provided their religious affiliation at the time of registering for the study. We coded their answers to correspond to 1 = affiliated with a religion, 2 = not affiliated with a religion (i.e. agnostics and atheists). Four participants had responded 'other' without specifying it further and were thus excluded through list-wise deletion for the analyses including this variable. Given the specific focus in the present study on spirituality and given that involvement in organized religion is strongly correlated with spirituality (Marler and Hadaway, 2002), we used this variable as a covariate in all analyses for which spirituality was an outcome. This approach is also in keeping with past experimental research that tested the causal role of positive emotions on spirituality and found that having a religious affiliation moderated the primary effect (Van Cappellen *et al.*, 2013). More information is provided in Supplementary Data available online.

DNA extraction and genotyping

All participants provided a saliva sample by passive drool into a 15 ml centrifuge tube right after the OT/placebo administration. Samples were frozen within 5 min. Samples were thawed and DNA was extracted using Qiagen QIAamp DNA Mini Kit according to manufacturer's instructions. Samples were genotyped using Taqman single nucleotide polymorphism (SNP) Genotyping Assays (Applied Biosystems, Inc) according to the standard protocol provided with the kit. Polymerase chain reactions were performed using 20 μl reaction volumes in 96-well plates with 25 ng of DNA. End point reads of fluorescence levels were obtained with an Applied Biosystems Incorporated 7300HT Sequence Detection System. For quality control, 26% of rs6449182 genotypes, 4% of rs3796863 genotypes and 18% of rs53576 genotypes were re-run and showed perfect concordance. Haploview (version 4.2; Barrett *et al.*, 2005) was used to calculate Hardy–Weinberg Equilibrium values using the exact test (Wigginton *et al.*, 2005). The distribution of genotypes did not deviate from Hardy-Weinberg equilibrium (all P's > 0.250). For rs53576, genotyping was unsuccessful for two participants, one in the placebo condition and one in the OT condition. For rs6449182, genotyping was unsuccessful for two participants, one in the placebo condition and one in the OT condition.

Genes were coded in the following fashion: *CD38* rs3796863 was coded in a dominant manner, AA/AC = 0, CC = 1, following Feldman *et al.* (2012); *CD38* rs6449182 was coded in a co-dominant way CC = 0, CG = 1, GG = 2, following Algoe and Way (2014); see Supplementary Data available online for alternative coding and tests. *OXTR* rs53576 was coded in a dominant way, GG = 0, GA/AA = 1, consistent with a meta-analysis of this marker (Bakermans-Kranenburg and van IJzendoorn, 2014).

1 Participants were randomly assigned to either a Mindfulness or a Loving-Kindness meditation but given that meditation type did not interact with OT, these two types will not be further discussed.

Numbers of participants for each genotype by condition are provided in Table S1 in the Supplementary Data available online.

Analyses

All analyses were performed with SPSS v.23. Conditions were dummy coded, Placebo = 0, OT = 1. For models including spirituality variables, we conducted one-way analyses of covariance (ANCOVAs), controlling for a variable that is distinct although strongly correlated with spirituality, religious affiliation. See Supplementary Data available online for additional discussion of this confounding variable and tests for assumptions of ANCOVAs. For the other models, we ran one-way analyses of variance (ANOVAs). These analyses included a total of eight tests and were corrected for multiple comparisons using a false discovery rate (FDR) (Benjamini and Hochberg, 1995) of 0.05. In Table 1, we provide raw *P*-values and FDR adjusted *P*-values. See Table S3 in Supplementary Data available online for FDR per test. Two-way ANOVAS were used to test for effects of conditions, genotype and their interactions. *Post hoc* contrasts were run using ANOVAs. We report exact *P*-values using two-tailed tests.

Results

At the end of the lab session, participants indicated whether they thought they received OT or a placebo, or whether they really did not know. Sixty-two percent of participants responded that they did not know. Among participants who responded that they had taken one treatment over another, a chi-square test of independence was performed to examine whether actual treatment predicted participants' perceived treatment. This test was not significant, χ^2 (1, $N = 31$) = 1.55, $P = 0.213$.

Participants in both groups were similar on a series of relevant baseline measures (i.e. emotions, mindfulness and religious affiliation). See Supplementary Data available online for full results.

Intranasal OT's effects

Spirituality-related outcomes. Means, standard deviations as well as mean differences tests are detailed in Table 1. The one-item measure of spirituality taken in lab and the STS were positively correlated ($r = 0.75$, $P < 0.001$), see Table S2 in Supplementary Data available online for full correlation matrix of dependent variables. Results show that compared to participants in the placebo condition, participants in the OT condition reported greater spirituality during the lab session (on both spirituality scales) and 1 week later. These effects remained significant when controlling for baseline positive and negative emotions and for dispositional mindfulness (see Supplementary Data available online).

We also ran additional analyses on the STS to better understand which items were affected by OT. First, we computed a new mean score excluding three items of the STS that include notions of death and contact with deceased people, which are less typical spiritual beliefs. Removing these items did not change the pattern of results (OT: $M = 5.26$, $SE = 0.1$; Placebo: $M = 4.85$, $SE = 0.1$, $F(2,75) = 4.40$, $P = 0.039$, $\eta_p^2 = 0.055$, mean difference = −0.41, 95% CI [−0.80, −0.02], $d = -0.35$). Then, to better disentangle between the aspects of connection and of meaning in the STS, we computed two scores, one including all items related to interconnectedness (i.e. 'I feel that on a higher level all of us share a common bond'; 'All life is interconnected'; 'There is a higher plane of consciousness or spirituality that binds all people'; 'Although individual people may be difficult, I feel an emotional bond with all of humanity'; 'I believe that on some level my life is intimately tied to all of humankind') and one including all items related to meaning and purpose (i.e. 'I believe that there is a larger meaning to life'; 'I believe there is a larger plan to life'; 'There is an order to the universe that transcends human thinking'). Results reveal that OT increased participants' level on STS interconnectedness (OT: $M = 5.24$, $SE = 0.2$; Placebo: $M = 4.77$, $SE = 0.2$, $F(2,75) = 3.79$, $P = 0.055$, $\eta_p^2 = 0.048$, mean difference = −0.47, 95% CI [−0.94, 0.01], $d = -0.37$) and on STS meaning and purpose (OT: $M = 5.10$, $SE = 0.2$; Placebo: $M = 4.37$, $SE = 0.2$, $F(2,75) = 6.19$, $P = 0.015$, $\eta_p^2 = 0.076$, mean difference = −0.74, 95% CI [−1.33, −0.15], $d = -0.33$).

Emotion outcomes. Means, standard deviations as well as mean differences tests are detailed in Table 1. For positive emotions, self-reported and implicit measures were positively correlated ($r = 0.45$, $P < 0.001$). This was not the case for negative emotions ($r = 0.12$, $P > 0.250$). Results show that compared to participants in the placebo condition, participants in the OT condition reported greater implicit positive emotions following meditation, and greater explicit retrospective reports of self-transcendent positive emotions during meditation. These effects remained significant when controlling for baseline positive and negative emotions and for dispositional mindfulness (see Supplementary Data available online).

Table 1. Means, standard deviations and between-conditions comparisons of all the dependent variables

Variables	Conditions							
	Placebo M (SE)	OT M (SE)	Mean difference 95% CI	*d*	η_p^2	*F*	*P*	*P*(FDR)
Spiritual Transcendence Scale[a]	4.71 (0.1)	5.08 (0.1)	[−0.81, −0.05]	−0.36	0.063	(2, 75) = 5.03	0.028	0.048
Spirituality—1 item—Lab[a]	3.08 (0.3)	4.02 (0.3)	[−1.78, −0.09]	−0.26	0.061	(2, 75) = 4.87	0.030	0.048
Spirituality—1 item—1 Week Follow Up[a]	3.08 (0.3)	4.13 (0.3)	[−1.85, −0.24]	−0.30	0.083	(2, 74) = 6.72	0.011	0.040
Implicit Positive Emotions	1.89 (0.1)	2.13 (0.1)	[−0.43, −0.05]	−0.55	0.070	(1, 81) = 6.14	0.015	0.040
Explicit Positive Emotions	1.73 (0.1)	2.03 (0.1)	[−0.61, 0.02]	−0.42	0.041	(1, 81) = 3.48	0.066	0.088
Explicit Self-transcendent Positive Emotions	1.53 (0.1)	2.03 (0.1)	[−0.88, −0.12]	−0.58	0.078	(1, 81) = 6.87	0.010	0.040
Implicit Negative Emotions	1.60 (0.1)	1.62 (0.1)	[−0.20, 0.17]	−0.05	0.000	(1, 81) = 0.03	0.866	0.866
Explicit Negative Emotions	0.22 (0.1)	0.34 (0.1)	[−0.27, 0.05]	−0.33	0.024	(1, 81) = 1.96	0.165	0.189

[a]Controlling for whether participants are religiously affiliated. *P(FDR)* = False discovery rate adjusted *P*-values (Benjamini and Hochberg, 1995).

Mediation tests. Given that participants in the OT condition reported increased spirituality and positive emotions derived from meditation, we tested whether the increase in spirituality partially accounted for the subsequent increase in positive emotions related to meditation. We ran bootstrapped mediation analyses using the PROCESS macro for SPSS, model 4, 5000 samples (Hayes, 2013). Religious affiliation was used as a covariate for the mediator (spirituality measures) only. In Table 2, for each model tested, we report data parameters and bias corrected 95% confidence intervals of the indirect effect and the direct effect of conditions on the outcome once the mediator is taken into account. Results show that spirituality (one-item measure and STS) mediated the relation between conditions and the positive emotions felt during or as a result of meditation at both the implicit and explicit levels****.

Exploratory analyses of genetic moderation

Interaction effects

Analyses were run using each SNP individually. Interaction effects are detailed in Table 3.

CD38 rs3796863. Interaction tests were significant for the one-item measure of spirituality at lab session. *Post hoc* contrasts revealed that A carriers (AA/AC) showed a significant increase on this measure in the OT condition ($M = 4.46$, $SE = 0.40$) compared to the Placebo condition ($M = 2.54$, $SE = 0.40$), $F(2, 35) = 11.03$, $P = 0.002$, $\eta_p^2 = 0.240$, mean difference $= -1.92$, 95% CI [−3.09, −0.74], $d = -0.55$. For CC homozygotes, there was no significant difference between OT and placebo conditions ($P > 0.250$). There was also a significant interaction for the STS. *Post hoc* contrasts revealed that again A carriers (AA/AC) showed a significant increase on this measure in the OT condition ($M = 5.31$, $SE = 0.18$) compared to the Placebo condition ($M = 4.55$, $SE = 0.18$), $F(2, 35) = 8.45$, $P = 0.006$, $\eta_p^2 = 0.194$, mean difference $= -0.76$, 95% CI [−1.29, −0.23], $d = -0.80$. For CC homozygotes, there was no significant difference between OT and placebo conditions ($P > 0.250$). Finally, there was a marginally significant interaction for the one-item measure of spirituality at the 1 week follow up. *Post hoc* contrasts revealed that A carriers (AA/AC) showed a significant increase on this measure in the OT condition ($M = 4.32$, $SE = 0.40$) compared to the Placebo condition ($M = 2.72$, $SE = 0.41$), $F(2, 34) = 7.38$, $P = 0.010$, $\eta_p^2 = 0.178$, mean difference $= -1.60$, 95% CI [−2.80, −0.40], $d = -0.41$. For CC homozygotes, there was no significant difference between OT and placebo conditions ($P > 0.250$).

CD38 rs6449182. Interaction tests were significant for the one-item measure of spirituality at lab session. *Post hoc* contrasts revealed that CC homozygotes showed a significant increase on this measure in the OT condition ($M = 4.32$, $SE = 0.38$) compared to the Placebo condition ($M = 2.78$, $SE = 0.55$), $F(2, 41) = 8.70$, $P = 0.005$, $\eta_p^2 = 0.175$, mean difference $= -1.56$, 95% CI [−2.63, −0.49], $d = -0.60$. For CG and GG genotypes, there was no

Table 3. Summary of results for condition predicting spirituality-related measures as moderated by variations of CD38 and OXTR

Variables	Main effects and interaction		
	η_p^2	F	P
Spirituality—1 item—Lab			
CD38 rs3796863	0.000	(4,73) = 0.001	0.980
Conditions	0.137	(4,73) = 11.63**	0.001
Interaction	0.081	(4,73) = 6.47*	0.013
CD38 rs6449182	0.004	(4,72) = 0.30	0.583
Conditions	0.116	(4,72) = 9.43**	0.004
Interaction	0.063	(4,72) = 4.88*	0.030
OXTR rs53576	0.001	(4,72) = 0.05	0.823
Conditions	0.015	(4,72) = 1.08	0.302
Interaction	0.004	(4,72) = 0.30	0.583
Spirituality—1 item—Week 1			
CD38 rs3796863	0.000	(4,72) = 0.10	0.922
Conditions	0.116	(4,72) = 9.46**	0.003
Interaction	0.042	(4,72) = 3.12†	0.082
CD38 rs6449182	0.004	(4,70) = 0.31	0.582
Conditions	0.108	(4,70) = 8.47**	0.005
Interaction	0.042	(4,70) = 3.03†	0.086
OXTR rs53576	0.001	(4,70) = 0.05	0.826
Conditions	0.005	(4,70) = 0.35	0.555
Interaction	0.025	(4,70) = 1.82	0.182
Spiritual Transcendence Scale			
CD38 rs3796863	0.001	(4,73) = 0.06	0.815
Conditions	0.130	(4,73) = 10.96**	0.001
Interaction	0.072	(4,73) = 5.70*	0.020
CD38 rs6449182	0.009	(4,72) = 0.62	0.434
Conditions	0.098	(4,72) = 7.83**	0.007
Interaction	0.044	(4,72) = 3.31†	0.073
OXTR rs53576	0.006	(4,72) = 0.46	0.499
Conditions	0.000	(4,72) = 0.00	0.989
Interaction	0.049	(4,72) = 3.68†	0.059

Note: Controlling for whether participants are religiously affiliated.
**P < 0.01,
*P < 0.05,
† P < 0.10.

Table 2. Mediation analyses: conditions predicting positive emotions related to meditation as a result of spirituality

Outcome	Mediator	Indirect effect			c' path		
		PE	SE	95% BC CI	PE	SE	95% BC CI
Implicit Positive Emotions	Spiritual Transcendence Scale	0.05	0.03	[0.01, 0.14]	0.20	0.10	[−0.002, 0.39]
	Spirituality—1 item—Lab	0.06	0.03	[0.01, 0.14]	0.20	0.10	[0.01, 0.39]
Explicit Positive Emotions	Spiritual Transcendence Scale	0.12	0.07	[0.02, 0.30]	0.18	0.16	[−0.14, 0.50]
	Spirituality—1 item—Lab	0.10	0.06	[0.02, 0.26]	0.21	0.16	[−0.11, 0.53]
Explicit Self-transcendent Positive Emotions	Spiritual Transcendence Scale	0.16	0.09	[0.03, 0.38]	0.35	0.19	[−0.03, 0.72]
	Spirituality—1 item—Lab	0.14	0.08	[0.03, 0.34]	0.38	0.19	[0.01, 0.76]

Notes: 5000 bootstrap samples. PE stands for point estimate. 95% BC CI stands for 95% Bias Corrected Confidence Interval. Covariate included for mediator only (controlling for whether participants are religiously affiliated).

significant difference between OT and placebo conditions (all P's > 0.250). There was also a marginally significant interaction for the STS. *Post hoc* contrasts revealed that again CC homozygotes showed a significant increase on this measure in the OT condition ($M = 5.25$, $SE = 0.15$) compared to the Placebo condition ($M = 4.59$, $SE = 0.14$), $F(2, 41) = 10.62$, $P = 0.002$, $\eta_p^2 = 0.206$, mean difference = −0.66, 95% CI [−1.07, −0.25], $d = -0.72$. For CG and GG genotypes, there was no significant difference between OT and placebo conditions (all P's > 0.250). Finally, there was a marginally significant interaction for the one-item measure of spirituality at the 1 week follow up. *Post hoc* contrasts revealed that again CC homozygotes showed a significant increase on this measure in the OT condition ($M = 4.43$, $SE = 0.38$) compared to the Placebo condition ($M = 3.00$, $SE = 0.37$), $F(2, 40) = 7.18$, $P = 0.011$, $\eta_p^2 = 0.152$, mean difference = −1.43, 95% CI [−2.51, −0.35], $d = -0.56$. For the CG genotype, there was no significant difference between OT and placebo conditions ($P > 0.250$), and for GG homozygotes a marginal difference in the opposite direction such that they had lower scores on this measures in the OT condition ($M = 2.34$, $SE = 0.27$) compared to the Placebo condition ($M = 3.77$, $SE = 0.22$), $F(2, 2) = 16.67$, $P = 0.055$, $\eta_p^2 = 0.893$, mean difference = 1.43, 95% CI [−0.08, 2.93], $d = 1.20$.

There were no significant interactions between condition and either SNP regarding emotions felt as a result of or during meditation across either the implicit and explicit measures (all P's > 0.143).

OXTR rs53576. Although there was no interaction between condition and rs53576 with respect to the one-item measures of spirituality, there was a marginally significant interaction with respect to the STS (Table 3). *Post hoc* contrasts revealed that A carriers (AG/AA) showed a significant increase on the STS in the OT condition ($M = 5.32$, $SE = 0.17$) compared to the Placebo condition ($M = 4.58$, $SE = 0.19$), $F(2, 38) = 8.40$, $P = 0.006$, $\eta_p^2 = 0.181$, mean difference = −0.74, 95% CI [−1.25, −0.22], $d = -0.85$. For GG homozygotes, there was no significant difference between OT and placebo conditions ($P > 0.250$). As for the variants in *CD38*, no significant interactions emerged regarding emotions felt as a result of or during meditation across either the implicit and explicit measures (all P's > 0.250).

Discussion

Compared to a placebo, administration of OT increased male participants' levels of self-reported spirituality using two distinct measures. This effect remained significant a week later. Intranasal OT also increased specific positive emotions derived from meditation, an activity commonly practiced by spiritual people, as reflected in both implicit and explicit assessments. These results held after adjusting for the FDR (Benjamini and Hochberg, 1995).

These findings build on prior evidence of correlations between measures of endogenous OT with ratings of spirituality (Kelsch *et al*., 2013; Holbrook *et al*., 2015) in two ways. First, the experimental design employed here takes a step toward establishing causality and provides information on the direction of causality by showing that, at least among men, elevations in OT lead to increases in spirituality. Future experimental research will be necessary to determine whether the other direction of causality—i.e. whether spirituality (beliefs and/or practices) can increase OT—is also possible. Second, the relationship between peripheral measures of OT, whether assayed in the blood or saliva, to OT levels in the brain is unclear (Kagerbauer *et al*., 2013). In contrast, evidence suggests that intranasal administration of OT increases OT levels in the brain (Striepens *et al*., 2013; and in animal research, Dal Monte *et al*., 2014; Modi *et al*., 2014). As such, the data presented here suggest that central OT is in fact driving the increase in spirituality.

Having established a link between OT and spirituality, the next question concerns the psychological processes underlying this phenomenon. We speculate that the effects of OT on social affiliation account for the current findings, although direct testing of this speculation awaits future research. Additional analyses revealed that OT also impacted items of the STS beyond those related to interconnectedness, specifically those targeting belief in larger meaning and purpose in life. Future research should unpack the distinct concepts embedded within definitions of spirituality, aspects that can also be studied separately from the larger construct of spirituality. OT also impacted specific positive emotions participants derived from an initiation to meditation. One potential explanation for this effect, supported by the data, is that the boost in spirituality evident among those in the OT condition led participants to experience more intensely the accompanying positive emotions. OT did not impact negative emotions felt during or as a result of the meditation, which may be attributable to a floor effect. Additionally, measures of positive and negative emotions were uncorrelated in this study (self-reported positive and negative emotions, $r = -0.04$, $P > 0.250$; implicit positivity and negativity, $r = 0.08$, $P > 0.250$), in keeping with a wide range of evidence that positive and negative affective states are independent dimensions of human experience (e.g. Watson *et al*., 1988; Fredrickson *et al*., 2008). Finally, the finding that OT still impacted spirituality a week after the administration merits further research to better understand the underlying mechanisms of action. Although long-term effects of OT have not been reported in past literature, to our knowledge they may not have been directly tested (exceptions include studies on 'repeated' OT administration over several days in clinical samples; e.g. Epperson *et al*., 1996; Guastella *et al*., 2010). Turning to psychological interpretations, one possibility is that OT administration increased the enjoyment of spirituality-related activities over that week and/or the frequency of self-transcendent positive emotions, each of which have been shown to promote spirituality (Van Cappellen and Saroglou, 2012; Van Cappellen *et al*., 2013).

Our exploratory analyses of polymorphisms in the OT system suggest that genetic variation moderates the effects of intranasal OT administration. Because OT can bind to non-OT receptors, for example vasopressin receptors (Gimpl and Fahrenholz, 2001), behavioral effects of OT administration could possibly be a result of these effects. However, the genetic variants moderating the effects of intranasal OT that we studied are in the OT system, which supports the inference that the observed effects of administered OT on spirituality are indeed due to action within the OT system.

The most robust effects on spirituality were found for the variants in *CD38*. That polymorphisms located in two different regions of the *CD38* gene each moderated the effect provides convergent validity for the involvement of *CD38* in moderating the effects of intranasal OT. The genotypes most responsive to intranasal OT (rs3796863: A carriers, AA/AC; rs6449182: CC) were each associated with higher levels of *CD38* expression in immortalized cell lines generated from blood cells (Lerer *et al*., 2010; Riebold *et al*., 2011). Although these measures are based on *in vitro* assessment of expression in peripheral tissue and should thus be interpreted with caution (e.g. Jamroziak *et al*., 2009), this could indicate that greater responses to OT administration in these individuals are due to greater expression of *CD38*. How this

differential expression could impact OT signaling is not clear. One hypothesis is that because CD38 is critical for the release of OT from neurons, this differential expression affects OT release. One potential mechanism accounting for this would arise from the unique property of OT neurons: their ability to autoregulate. OT neurons express the OT receptor on their dendrites (Freund-Mercier *et al.*, 1994). Activation of this dendritically located OT receptor initiates an intracellular signaling cascade that can lead to either the actual release of OT from the dendrites or the priming of this release (Tobin *et al.*, 2012). Once activated, this positive feedback loop can lead to an enduring, self-sustaining release of OT. Because CD38 is a critical intermediary of the intracellular signaling cascade between binding of the dendritic OT receptor and OT release from the dendrites (Salmina *et al.*, 2013), gene variants affecting expression of *CD38* may impact this process. Naturally, with the nascent understanding of how these variants affect oxytocinergic signaling, such a hypothesis should be viewed as speculative as should any links between this autoregulatory capacity of oxytocinergic neurons and psychological changes in response to OT administration.

The most commonly studied polymorphism of *OXTR* (rs53576) also moderated the effects of intranasal OT on one of the three measures of spirituality. The A allele carriers were the most responsive to the OT manipulation. We note that prior literature has found that the GG genotype is more responsive to either exogenous (Marsh *et al.*, 2012; Feng *et al.*, 2015) or endogenous OT (Moons *et al.*, 2014) so the present findings should be considered preliminary. Taken together, these findings indicate that there are individual differences in the OT system that impact the response to intranasal OT.

In the present study, consistent with other research on spirituality (Van Cappellen *et al.*, 2013), we found that controlling for one aspect culture, i.e. involvement in organized religion, was critical to observing the effects of exogenous OT on spirituality (see Saroglou and Cohen, 2013 for a discussion on religion as a cultural system). Religion, or the belief in a Higher Power in a structured way, is related yet distinct from spirituality. Here, we found that when controlling for this confounding variable, OT administration increased all participants' level of spirituality. However, additional analyses (described in the Supplementary Data available online) revealed that this effect is more evident among participants who are not affiliated with an organized religion, potentially because they tend to score lower on measures of spirituality (see similar findings in Van Cappellen *et al.*, 2013). Future research may investigate whether other cultural aspects moderate the psychological outcomes of the OT system (e.g. Kim *et al.*, 2011).

Intriguingly, recent empirical developments have uncovered a host of psychological effects of OT that are strikingly similar to those of spiritual beliefs and practices. Although context and individual differences qualify the effects of OT and of spirituality, they have both generally been related, in separate research literatures, to social affiliation and prosociality (at least to some extent, MacDonald and MacDonald, 2010; Saroglou, 2012) as well as to physical and mental health (OT: Striepens *et al.*, 2011; Spirituality: Koenig *et al.*, 2012; Positive emotions derived from meditation: Fredrickson, 2013; Van Cappellen *et al.*, 2016). Finding that OT can increase spirituality and specific positive emotions derived from practicing meditation allows the generation of new hypotheses on mediating processes. For example, given the evidence that spirituality and the enjoyment of meditation are related to health, the data presented here suggest that they both may represent sustained mechanisms through which OT may impact health.

Because several different neurotransmitters have been implicated in spirituality (McNamara and Butler, 2013), we do not consider OT to be 'the spiritual hormone'. Spiritual beliefs and related practices represent complex phenomena that are shaped by complex and multidimensional processes. However, growing evidence (e.g. Gervais, 2013), including the data presented here, suggests that humans—and perhaps some more than others—are biologically and cognitively predisposed to be receptive to spiritual experiences.

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Supplementary data

Supplementary data are available at *SCAN* online.

Conflict of interest. None declared.

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