Title

Nasal oxytocin administration does not influence eye gaze or perceived relationship of male volunteers with physicians: a randomized, placebo-controlled trial

Authors

Jongerius, C.^{*1,2}, Hillen, M.A.^{1,2}, Smets, E.M.A.^{1,2}, Mol, M.J.¹, Kooij, E.S.¹, de Nood, M.A.¹, Dalmaijer, E.S.³, Fliers, E.⁴, Romijn, J.A.⁵, Quintana, D.S.^{6, 7,8}

*Correspondence to: Chiara Jongerius, Amsterdam UMC, Location AMC, Meibergdreef 9, 1100 DD, Amsterdam, The Netherlands, T: +31205667787 E: c.jongerius@amsterdamumc.nl

1. Amsterdam UMC, location University of Amsterdam, Medical Psychology, Meibergdreef 9, Amsterdam, The Netherlands
2. Amsterdam Public Health, Quality of Care, Amsterdam, The Netherlands
3. MRC Cognition and Brain Sciences Unit, University of Cambridge, Cambridge, United Kingdom
4. Amsterdam UMC, location University of Amsterdam, Department of Endocrinology & Metabolism, Amsterdam Gastroenterology, Endocrinology & Metabolism, Meibergdreef 9 Amsterdam, The Netherlands
5. Amsterdam UMC, location University of Amsterdam, Department of Medicine, Amsterdam Gastroenterology, Endocrinology & Metabolism, Meibergdreef 9, Amsterdam, The Netherlands
6. Department of Psychology, University of Oslo, Oslo, Norway
7. NevSom, Department of Rare Disorders, Oslo University Hospital, Oslo, Norway
8. Norwegian Centre for Mental Disorders Research (NORMENT) and KG Jebsen Centre for Neurodevelopmental Disorders, University of Oslo, Oslo, Norway

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Abstract

The patient-physician relationship is a critical determinant for patient health outcomes. Verbal and non-verbal communication, such as eye gaze, are vital aspects of this bond. Neurobiological studies indicate that oxytocin may serve as a link between increased eye gaze and social bonding. Therefore, oxytocin signaling could serve as a key factor influencing eye gaze as well as the patient-physician relationship. We aimed to test the effects of oxytocin on gaze to the eyes of the physician and the patient-physician relationship by conducting a randomized placebo-controlled crossover trial in healthy volunteers with intranasally administered oxytocin (24IU, number 2018-004081-34). Eye gaze of sixty-eight male volunteers was studied using eye-tracking. Volunteers engaged in a simulated video call consultation with a physician who provided information about vaccination against the human papilloma virus. Relationship outcomes, including trust, satisfaction and perceived physician communication style, were measured using questionnaires and corrected for possible confounders (social anxiety and attachment orientation). Additional secondary outcome measures were recall of information and pupil diameter and exploratory outcomes were mood and anxiety. Oxytocin did not affect eye tracking parameters of volunteers' gaze towards the eyes of the physician. Moreover, oxytocin did not affect parameters of bonding between volunteers and the physician, nor other secondary and exploratory outcomes. Bayesian hypothesis testing provided evidence for the absence of effects. These results contradict the notion that oxytocin affects eye gaze patterns or bonding.

Keywords: Oxytocin, crossover trial, eye gaze, eye-tracking, patient-physician relationship

1. Introduction

The patient-physician relationship is critical for patients' health. For example, optimal trust and therapeutic alliance positively affect patients' psychological well-being, adherence to medication, and treatment response (Piette et al. 2005; Graves et al. 2017), and can even influence their healthcare use and intention to vaccinate (Kundi et al. 2015; Weiss and Blustein 1996). Therefore, improvement of patient-physician relationships has the potential to positively affect healthcare at large. Consequently, it is worthwhile to investigate the underlying mechanisms of *how* patients and physicians bond, from a psychological as well as a neurobiological perspective.

Communication is a crucial constituent of patient-physician relationships, both verbal and non-verbal (De Haes and Bensing 2009). Verbal communication encompasses, for instance, the content or amount of information that is shared (De Haes and Bensing 2009). Non-verbal communication, which is any communication that is not verbal (such as body language), also contributes to the patient-physician relationship (De Haes and Bensing 2009). A salient aspect of non-verbal communication is the degree of eye contact between patient and physician (MacDonald 2009). Through eye contact, the physician enters a critical first stage of social engagement with the patient (MacDonald 2009). Eye contact can be defined as mutual gaze towards the eye region of others (Jongerius et al. 2020). Gaze towards the eyes ("eye gaze") regulates aspects of communication, such as turn-taking in conversation (Bailly, Raidt, and Elisei 2010). Furthermore, eye gaze transmits social and attentional information (Freeth, Foulsham, and Kingstone 2013; Jokinen et al. 2010), both of which are important elements in patient-physician communication and may therefore affect the quality of the relationship. Sub-optimal levels of eye gaze between physicians and patients can negatively affect patient-physician relationships, including reduced trust of patients in their physicians (Mast 2007; MacDonald 2009). Similarly, a higher degree of mutual eye gaze leads to higher levels of patient trust in their physician (Hillen et al. 2015).

The neurological basis for gaze towards the eyes is often studied as an integral part of the processing of faces. Neuroimaging studies show that activity in specific brain areas, such as the amygdala, is at the basis of face processing (Domes et al. 2013; Labuschagne et al. 2010). Many of these studies link oxytocin to the processing of facial stimuli, and especially of eye gaze (Domes et al. 2013; Labuschagne et al. 2010). Therefore, oxytocin could serve as an underlying neurobiological mediator directing eye gaze (Auyeung et al. 2015; Guastella, Mitchell, and Dadds 2008; Hubble et al. 2017), and even the patient-physician relationship (Zilcha-Mano et al. 2020).

Oxytocin is a nine amino acid neuropeptide influencing human attachment and social behavior (Carter et al. 2008). Oxytocin functions both as a neurotransmitter and as a hormone. Intranasally

administered oxytocin has been used to investigate the effects of oxytocin on social cognition and behavior in humans (Burley and Daughters 2020) as it increases oxytocin concentrations in the central nervous system (Quintana et al. 2020). Studies show, for example, that oxytocin administration improves people's recognition of facial emotional expressions (Shahrestani, Kemp, and Guastella 2013) and increases their sensitivity to socially salient cues (Shamay-Tsoory and Abu-Akel 2016). Such effects of oxytocin have been explained by the social salience hypothesis, which posits that the effects of oxytocin on various social behaviors are dependent both on contextual social cues (such as a competitive or a cooperative environment) and on baseline individual differences such as personality traits or degrees of psychopathology (Bartz et al. 2011). According to this social salience hypothesis of oxytocin, oxytocin increases the salience or noticeability of social cues, influencing cognitive processes and behaviors that depend on this information. This social salience hypothesis of oxytocin also proposes that by increasing the salience of social cues, visual attention is drawn to socially relevant stimuli, like the eye region (Burley and Daughters 2020). Therefore, it is expected that oxytocin administration increases gaze towards the eyes in socially salient stimuli. Some studies examining the effects of intranasally administered oxytocin have indeed shown increased gaze on the eye region (Auyeung et al. 2015; Guastella, Mitchell, and Dadds 2008; Hubble et al. 2017; Domes et al. 2013; Gamer, Zurowski, and Büchel 2010). In contrast, other studies found no effect of oxytocin administration on gaze to the eye region (Lischke et al. 2012). Many of the aforementioned studies researching the effect of oxytocin on eye gaze and relational outcomes have been statistically underpowered (Quintana 2020). Therefore, more substantial evidence is needed for the effects of oxytocin on eye gaze, using study designs that can reliably detect a wider range of effect sizes (Quintana 2020).

The aims of the current study were to assess whether oxytocin administration changes (1) the level of eye gaze towards the eye area of a physician, and (2) the patient-physician relationship. To that end, we designed a pre-registered, placebo controlled, randomized experiment, in which we compared the effects of intranasal administration of oxytocin and placebo on gaze of healthy volunteers' towards the eye region of a physician. We expected oxytocin to change gaze towards the eye region. In addition, we compared the effects of oxytocin and placebo on the relationship (primarily on the levels of trust in the physician, and secondarily satisfaction with the physician and perception of physician communication style), and expected oxytocin to change the relationship. Other secondary outcome measures were recall of information, pupil diameter and exploratory outcomes were mood and state anxiety. Social anxiety and attachment orientation were included as possible confounders (Declerck et al. 2020).

2. Methods

2.1. Volunteers

Volunteers from the general and student community were recruited through online and paper pamphlets. Volunteers had to be aged between 18 and 35 years, and speak sufficient Dutch for participation. They were instructed to refrain from alcohol, smoking, caffeine and drug-use 24 hours before the experiment, and from food, drinks (except water) as well as intensive exercise two hours before the experiment (Guastella et al. 2010). Volunteers were excluded if they reported a hypersensitivity to oxytocin or to any of the excipients of oxytocin or the placebo spray formulations. Females were excluded to rule out possible confounding effects of sex-specific oxytocin activity and therefore a potential heterogeneous response (Gao et al. 2016).

The study was pre-registered at [ClinicalTrialsRegister.eu](https://www.clinicaltrialsregister.eu) (number 2018-004081-34) and approved by the local institutional review board (NL69901.018.19). All experimental procedures were performed in accordance with relevant guidelines and regulations. All participants gave written informed consent.

2.2. Study design

We conducted a randomized crossover trial with 24IU intranasally administered oxytocin (Syntocinon 40 IE/mL, Alfaisigma S.p.A., Bologna, Italy) (one puff of 12 IU per nostril) as the intervention and, on another occasion, a placebo (with similar ingredients as the oxytocin solution, such as chlorobutanol; one puff per nostril) as the control condition. The dose was determined based on previous studies reporting statistically significant results on gaze (Guastella, Mitchell, and Dadds 2008; Auyeung et al. 2015; Hubble et al. 2017). Both researchers and volunteers were blinded with respect to the intervention. The sequence of oxytocin and placebo administration was determined by balanced assignment. Volunteers visited the lab twice with a washout period of exactly seven days and at precisely the same time of the day, to account for possible variations in circadian oxytocin levels (Amico et al. 1983). Volunteers engaged in a simulated Skype consultation with the physician. We used eye-tracking hardware to assess volunteers' gaze towards the physician on the video and to assess pupil size (as a possible indicator of trust (Kret and De Dreu 2017)), and questionnaires to assess self-reported outcome measures. The study lab consisted of two adjacent rooms, one for the researcher (including the control of the hardware and software) and one for the volunteers (with only artificial lightning to improve eye-tracking quality).

2.3. Procedure

Figure 1 illustrates a graphical representation of the procedures. Upon arrival at the lab, the participants provided written informed consent and were screened for the study inclusion criteria.

Volunteers first completed baseline questionnaires assessing sociodemographic and background characteristics. Subsequently, the researcher administered the medication or placebo intranasally, randomized by the local pharmacy. Medication was administered using the Intranasal Mucosal Atomization Device, which was previously successfully used with oxytocin (Skvortsova et al. 2018). This device atomizes the nasal medication into a fine mist of particles 30-100 microns in size, which is the optimal size for absorption across mucosal membranes into the bloodstream avoiding first-pass metabolism (Corrigan, Wilson, and Hampton 2015). The device has a soft conical plug on the tip that forms a seal with the nostril, preventing expulsion of fluid. During the administration, researchers followed the guidelines of the nasal device manufacturer, in combination with the standardized recommendations of Guastella and colleagues (Guastella et al. 2013). Intranasal administration was followed by a wait time of 40 minutes, during which volunteers had access to magazines depicting neutral images of nature or architecture. The waiting time was based on earlier studies (Guastella, Mitchell, and Dadds 2008; Auyeung et al. 2015; Lischke et al. 2012; Hubble et al. 2017; Kosfeld et al. 2005).

Figure 1. Graphical illustration of the procedure and timeline of the experiment

For the primary experimental task, volunteers were informed they would have an interaction with a physician about human papilloma virus (HPV) vaccination. Subsequently, they participated in a standardized, simulated Skype call (similar to previous research (Mansour and Kuhn 2019)) depicting a real physician who directly addressed them, creating the illusion of a real-time online interaction. The Skype call had been video-recorded using a webcam, to enhance realism. The physician gazed as much as possible into the webcam, establishing direct gaze towards the participant. Figure 2 shows an illustration of this task. During this simulated video call, the physician provided arguments in favor of and against vaccination of males to prevent HPV. This topic was likely to be engaging to the study population because of its relevance to society and to their own health (Thompson et al. 2020). While participating in the experiment, gaze and pupil size of the participants were tracked. They rested their head on a chin and forehead rest to enhance stability and ensure the quality of measurement. After the simulated video call, participants completed a second questionnaire assessing primary, secondary and exploratory outcome measures. During the second study visit, seven days later, a second simulated video call was shown, including different pros and cons of HPV vaccination. Appendix A documents the arguments for HPV vaccination of both sessions with equivalent characteristics. The order of the two videos was randomly counterbalanced to exclude learning effects.

Figure 2. Screen shot depicting the Skype call setup

Note: Figure 2 is published with permission of the displayed physician.

2.3. Parameters

2.3.1. Questionnaires:

To assess patient-physician relationships we used three validated outcome measures. Our primary relationship outcome measure was volunteers' trust in the physician, assessed using the Wake Forest Physician Trust Scale (WFPTS) (Bachinger, Kolk, and Smets 2009). We omitted one item that was not applicable to our communication process (referring to the listening capabilities of the physician). The questionnaire consisted of 9 items, answered on a 5-point Likert scale ("completely disagree" to "completely agree"), and in our sample had a Cronbach's alpha of .84.

As secondary outcome measure of the patient-physician relationship we assessed self-reported satisfaction of the participants with the physician, using one visual analogue scale ranging from 0 (not likely at all) to 100 (most likely) stating: "I would recommend this doctor to a friend or family member." We additionally assessed volunteers' perception of physicians' communication style, using the validated 17 Physicians' Communication Style items (translated to Dutch for this study with forward-backward translation) on two subscales: 12 items for affiliativeness and 5 items for dominance/activity (Buller and Buller 1987). Three items of the original scale were deleted that were

not applicable to our setting. Items are answered on a 5-point Likert Scale (“strongly disagree” to “strongly agree”), and Cronbach’s alpha was .81.

For information recall, we assessed both free recall and recognition of the information regarding HPV vaccination provided in the videos, using 5 self-developed items. The free recall items were open ended questions, such as “The physician has just told you that a type of cancer caused by HPV is on the rise at the moment. What kind of cancer is this?” and the recognition items were the open-ended questions with multiple choice answers. Volunteers received 0 (incorrect), 0.5 (partially correct) or 1 (correct) point per question. Two authors manually double scored all answers and resolved discrepancies through discussion with two additional authors.

We included social anxiety and attachment orientation as possible confounders and change in mood and state anxiety as exploratory outcome measures. Social anxiety was measured with the six item Social Interaction Anxiety Scale and six item Social Phobia Scale (SIAS-6, SPS-6) (Peters et al. 2012). The questionnaire comprised 12 items in total (e.g. ‘I find it difficult to look at other people’), answered on a 5-point Likert scale (from 1 ‘does not apply to 5 ‘completely applicable’). Our sample yielded a Cronbach’s alpha of .86.

Attachment orientation was measured with the Experiences in Close Relationship Scale-Short Form (ECRS-SF), which scores on two dimensions: attachment avoidance and attachment anxiety (Kooiman et al. 2013). This questionnaire consisted of 12 items (e.g. ‘I usually discuss my problems and concerns with my partner’) answered on a 7-point Likert scale (1 ‘totally disagree’ to 7 ‘totally agree’). Our sample had a Cronbach’s alpha of .71.

We measured change in mood (i.e., positive and negative affect), using the 20-item Positive And Negative Affect Schedule (PANAS) before and after the consultation (Engelen et al. 2006). Items [e.g., I feel ‘Interested’ (positive affect) or I feel ‘nervous’ (negative affect)] are answered on a 5-point Likert scale (from 1 ‘not or hardly’ to 5 ‘very strongly’). Our study sample recorded a Cronbach’s alpha of .74.

Change in state anxiety was assessed using the 6-item short form of the Spielberger State-Trait Anxiety Inventory, state scale (STAI-S) before and after the consultation (van der Bij et al. 2003). This measured the volunteers’ anxiety at the given moment (e.g., ‘I feel tense’), answered on a 4-point Likert scale (1 being ‘Not at all’ to 4 being ‘Very much’). Cronbach’s alpha was acceptable, at .68.

2.3.2. Eye tracking:

We used an SMI-RED 500 screen eye-tracker (SensoMotoric Instruments; retailed by iMotions, A/S, Copenhagen, Denmark) complemented with a head and chin rest to capture our primary eye gaze outcome. The distance between the eye-tracker and the eyes was 70 centimeters. We calibrated eyes

of the participants in the SMI Experiment software. We used a 5 point calibration method, which evaluates the measurement accuracy of the gaze coordinates for five fixed points spread across all parts of the screen following the iView X system manual.

The eye tracker was also used to measure pupillometry, a non-invasive method of measuring pupil diameter over time. The pupil data were recorded in millimeters for both eyes, as a direct effect of oxytocin on pupil dilation and a possible indicator of trust (Kret and De Dreu 2017). For gaze location and for pupil diameter we exported the raw eye-tracking data (meaning that no filters, such as a fixation filter, were used) using SMI Experiment Center Be-Gaze.

2.4. Data preparation

For the gaze towards the eye region, we exported raw eye-tracking data for every participant using the gaze location based on both eyes. To calculate the amount of volunteer gaze towards the eye region of the physician as Area-of-Interest, we used a validated face recognition algorithm (Hessels et al. 2018). For an elaborate description of the analysis see Appendix B. Results were exported to SPSS for Windows, version 24.0 (IBM Corp. Armonk, New York, USA) to calculate percentages of gaze location.

For the pupillometry analysis we first pre-processed the raw data to remove blinks and artefacts (Kret and Sjak-Shie 2019). We excluded both pupil diameters when the value of either the left or the right eye was missing (median=3.30% of time, range=.30%-14.21%). Then we calculated mean pupil diameter by averaging over time of the stimulus (Burley and Daughters 2020).

To assess eye-tracking data quality, we exported the accuracy for both eyes from the eye-tracking software. We used a cut-off of 2.0 degrees for either the right or left eye. Second, we controlled for the total summed amount of data loss and used a cut-off of 20% of data loss. Third, we calculated the data precision, Root Mean Squared, for both eyes in MATLAB R2020b (The MathWorks, Inc., Natick, Massachusetts, United States) used a precision cut-off of 1.0 degrees for both eyes.

2.5. Statistical analysis

We planned to include 76 healthy young male volunteers, to enable detecting an effect size of .33. This is conventionally considered as a medium-to-small effect (Cohen 1988). Previous comparable studies found effect sizes ranging from .35 to 1.2 (Hubble et al. 2017; Auyeung et al. 2015; Guastella, Mitchell, and Dadds 2008), but given the risks of effect size inflation in published studies (Simonsohn, Nelson, and Simmons 2014) we powered our study to detect a smaller effect size, two-tailed α of .05, with 80% statistical power.

Data cleaning was done in SPSS for Windows, version 24.0 (SPSS Inc. 26 ed. Chicago, IL, USA, 2020). Because of the within-subject design we conducted a Wilcoxon signed-rank test for differences in treatment (control versus treatment). Furthermore, we ran a mediation analysis to test whether the level of eye gaze mediated the effect of oxytocin on trust. We excluded missing data listwise and specified the number of missing data. We repeated the same multilevel analysis with our secondary outcome measures (satisfaction with physician, physician communication style (affiliativeness and dominance), recall of information (free recall and recognition) and pupil diameter) and exploratory outcome measures (change in positive mood, negative mood, and state anxiety). Finally, to investigate any influence of participant characteristics, we correlated age, education level, and attachment style, to delta values of the main outcomes, gaze and trust. Hypothesis testing was done using the R statistical programming language (R Development Core Team, Vienna, Austria) with a-priori defined two-tailed α -value of .05 for all frequentist tests and R scripts are available following this link: <https://osf.io/2b4z8/>. Additionally, we used Bayesian hypothesis testing for the Wilcoxon Signed-Rank tests in JASP (Love et al. 2019). Bayesian inference can be used to assess the relative evidence of a null model to an alternative model. Therefore, Bayesian mixed models were used to complement the regression and mediation analyses to examine the relative strength of evidence for both the null and the alternative hypotheses using the non-informative Cauchy distribution as a prior, given our non-directional hypothesis (Rouder et al. 2009). A Bayes factor (BF_{10}) value less than 0.33 suggests that the null model is more than 3 times more favored than the alternative model, given the data. A BF_{10} over 3 suggests that the alternative model is more than 3 times more favored than the null model, given the data. We supplemented our frequentist analyses with Bayes Factors, because they provide a continuous measure of evidence. This allowed us to differentiate between evidence for the absence or effects and evidence for data insensitivity (Dienes 2014).

3. Results

3.1. Descriptives

We included 68 volunteers in the final analyses. Figure 3 provides the details of the CONSORT flow diagram, which includes reasons for dropout and data exclusion, and Table 1 provides the sociodemographic and psychological characteristics of the sample. Median age of the participants was 22 years (range 18 to 33 years). The quality of the eye-tracking data in our sample was as follows: a median accuracy degrees of .47 for the X axis and .41 for the Y axis (range= .010 – 1.31), a median precision of .04 RMS degrees for the X and Y axis (range= .02 – .73), and a median of 3.38% of data loss (range= .29 - 18.49). Table 1 provides descriptive statistics for gaze towards the eyes, trust in physician, satisfaction with physician, physician affiliativeness, physician dominance, recall of information,

recognition of information, and pupil size, and exploratory measures (change in positive mood, negative mood, and anxiety) per condition.

Table 1. Sociodemographic and psychological characteristics of our sample

Sociodemographic or psychological characteristic	Value
<i>Self-identified nationality (N (%))</i>	
Dutch	63 (92.6%)
Other European nationalities	1 (1.5%)
South American	1 (1.5%)
Middle East	2 (2.9%)
Other (not specified)	1 (1.5%)
<i>Education level (N (%))</i>	
None/primary school	1 (1.5%)
Secondary/lower level vocational school	44 (64.7%)
College/university	23 (33.8%)
<i>Social anxiety (MDN (range)) (SIAS-6 SPS-6)</i>	4 (0-29)
<i>Avoidant attachment orientation (MDN (range)) (ECRS-SF)</i>	18 (9-34)
<i>Anxious attachment orientation (MDN (range)) (ECRS-SF)</i>	8 (8-29)

Figure 3. CONSORT flow diagram

3.2. Effects of oxytocin on gaze to the eyes and trust

Oxytocin did not affect gaze towards the eye region as indicated by our rank biserial correlation of $rrb = .103$ $p = .397$ (Table 2; Fig. 4). Furthermore, oxytocin did not significantly affect trust in the physician as indicated by our rank biserial correlation of $rrb = .015$ $p = .908$.

Bayesian hypothesis tests were consistent with the frequentist analyses. The Bayes factor for the gaze towards the eyes model was 0.162, suggesting 6.2 times more evidence for a null model relative to an alternative model. Therefore, the data suggest that it is unlikely that oxytocin had an effect on gaze towards the eyes. Similarly, the Bayes factor for trust in the physician is .133, suggesting that the null model is 7.5 times more likely than the alternative hypothesis. Therefore, it is unlikely that oxytocin had an effect on trust in the physician either.

Furthermore, the level of gaze towards the eyes did not mediate the effect of oxytocin on trust as indicated by a Baron and Kenny mediation analysis ($\beta = .00$, $p = .88$).

3.3. Effect of oxytocin on secondary outcome measures

Oxytocin did not affect our secondary outcome measures as indicated by our rank biserial correlations. There was no significant association between oxytocin and satisfaction with the physician ($rrb = .045$, $p = .711$, $BF_{10} = .210$), physician affiliativeness ($rrb = .074$, $p = .$, $BF_{10} = .204$), physician dominance ($rrb = .094$, $p = .479$, $BF_{10} = .295$), free recall of information ($rrb = .174$, $p = .168$, $BF_{10} = .896$), information recognition ($rrb = .175$, $p = .231$, $BF_{10} = .382$) or pupil diameter ($rrb = .092$, $p = .489$, $BF_{10} = .165$). Furthermore, there was no effect of oxytocin on our exploratory outcome measures, i.e. change in positive affect ($rrb = .023$, $p = .909$, $BF_{10} = .138$), negative affect ($rrb = .096$, $p = .427$, $BF_{10} = .207$) and anxiety ($rrb = .025$, $p = .892$, $BF_{10} = .144$).

3.4. Correlations between participant characteristics and the effect of oxytocin

Age, education, attachment anxiety and avoidance all had weak correlations with the delta values of gaze ($r = -.06$; $r = .11$, $r = -.06$; and $r = -.11$ respectively) and trust ($r = -.06$; $r = .12$; $r = .05$; and $r = -.15$ respectively).

Table 2. Descriptive statistics for all outcome measures per condition

	Oxytocin		Placebo		Difference/Test
	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)	Rank-biserial correlation (<i>P</i>)
<i>Primary outcome measures</i>					
Gaze towards the eye region (% of time)	29.9 (18.0)	25.3 (28.4)	31.5 (19.9)	29.9 (30.9)	.103 (.397)
Trust in the physician (WFPTS, range=1-5)	3.8 (0.6)	3.7 (0.9)	3.8 (0.7)	3.8 (1)	.015 (.908)
<i>Secondary outcome measures</i>					
Satisfaction with physician (range=0-100)	60.5 (23.1)	67.0 (26)	61.9 (22.4)	67 (26.8)	.045 (.711)
Physicians' Communication Style - affiliativeness (range = 0-60)	42.8 (6.6)	44.0 (7)	42.3 (6.2)	43.5 (7)	.074 (.506)
Physician's Communication Style - dominance/activity (range = 0-25)	9.3 (2.9)	9.0 (4)	9.7 (2.7)	9.0 (3)	.093 (.479)
Free recall of information (range = 0-5)	3.7 (1.0)	4.0 (1.5)	3.4 (1.1)	3.5 (1.5)	.174 (.168)
Recognition of information (range = 0-5)	4.0 (0.9)	4.0 (1)	3.7 (0.9)	4.0 (1)	.175 (.231)
Pupil diameter (in millimeters)	4.3 (0.5)	4.3 (0.6)	4.3 (0.5)	4.2 (0.7)	.092 (.489)
<i>Exploratory measures</i>					
Change in positive affect (PANAS)	-1.3 (4.3)	-1.0 (4.5)	-1.4 (4.6)	-1.0 (5.3)	.022 (.909)
Change in negative affect (PANAS)	-0.8 (2.6)	-1.0 (2)	-1.0 (2.6)	-1.0 (3)	.095 (.427)
Change in State Anxiety (STAI-S)	-0.6 (2.2)	0.0 (3)	-0.5 (2.3)	0.0 (2.3)	.025 (.892)

Figure 4. Raincloud plot distributions of primary outcomes. Panel A illustrates a comparison of oxytocin and placebo's effects on eye gaze percentage. Panel B illustrates a comparison of oxytocin and placebo's effects on trust in physician.

Note: The raincloud plot combines an illustration of data distribution (the 'cloud') with jittered raw data (the 'rain'). All individual data points of the participants are connected through a trace line and the raincloud plots are supplemented with boxplots.

4. Discussion

We tested the effects of oxytocin administration on participants' gaze towards a physician's eye region and on patient-physician relationships in a double-blind randomized crossover trial. Sixty-eight healthy men were eye-tracked during a standardized simulated video-call with a physician. Oxytocin did not increase gaze towards the eye region, nor increased trust in the physician. Oxytocin did not affect other indicators of patient-physician relationships. Similarly, secondary analyses indicated that oxytocin did not influence recall and recognition of information by the participants nor pupil diameter. Lastly, there were no effects of oxytocin administration on mood and anxiety. In sum, oxytocin did not affect any of our outcome parameters.

Whereas previous studies reported that intranasal oxytocin administration increased gaze towards the eye region, we found no effects of oxytocin on gaze towards the eye region of the physician (Auyeung et al. 2015; Guastella, Mitchell, and Dadds 2008; Gamer, Zurowski, and Büchel 2010). Methodological differences might explain this discrepancy. Previous studies used static images as facial stimuli, instead we used a dynamic standardized video-call (Guastella, Mitchell, and Dadds 2008; Gamer, Zurowski, and Büchel 2010). In accordance with our results, Lischke and colleagues (Lischke et al. 2012) found no effects of oxytocin on gaze towards the eye region on dynamic facial stimuli. These authors (Lischke et al. 2012) argued that this absence of an effect could be explained by the presentation time of their facial stimuli, which was much longer compared to previously used static facial images. However, this view is contested by findings that oxytocin increased people's gaze to another person's eye region in an interview setting, lasting approximately 5 minutes (Auyeung et al. 2015). To study gaze to the eye region they calculated the transformed mean eye-fixation difference per second (Auyeung et al. 2015). In comparison, we assessed the percentage of time participants gazed towards the eye region in an experimental group with a larger size, and did not replicate these effects. Oxytocin may influence tasks related outcomes such as increased gaze towards the eye region on pictures, or while answering to a semi-structured interview (Auyeung et al. 2015; Hubble et al. 2017). Furthermore, oxytocin may be related to moment-to-moment effects such as eye-fixation per second. However, a longer-duration stimulus, like our video consultation, better represents real-world social behavior. Therefore, it may be that oxytocin has no meaningful role in longer interactions without specific task instructions. This is also suggested in a recent longitudinal trial in which nasal administration of oxytocin did not improve the social interaction of young participants with autism spectrum disorder (Sikich et al. 2021).

Similarly, we found no effects of oxytocin on the patient-physician relationship, such as trust in the physician. Previous studies reporting effects on relational outcomes such as trust, used single items to measure trust (Kosfeld et al. 2005; Declerck et al. 2020): how much money participants were

willing to transfer to another participant (the trustee). Trust in the physician is a multidimensional construct (Bachinger, Kolk, and Smets 2009). Therefore, a single item may not do justice to the patient-physician relation. Moreover, the single item measure for trust may represent a more transactional or economic type of trust, whereas we assessed interpersonal trust, which reflects the relational bond between patient and physician. It could be that oxytocin affects transactional trust but not relational trust.

Our study has some limitations. First, we did not include female participants, to rule out possible confounding effects of sex-specific oxytocin activity and therefore reduce heterogeneity in responses (Gao et al. 2016). Therefore, our results are not generalizable to females, in whom opposite effects of intranasal oxytocin have sometimes been reported (Scheele et al. 2014). Second, while we designed our study to detect a medium effect size it is possible that the effects of oxytocin on gaze towards the eye region and trust are smaller and, therefore, require an even larger sample size to reliably detect. Finally, we administered 24IU with an intranasal mucosal atomization device, which has previously been used to document the effects of oxytocin on eye gaze (Guastella, Mitchell, and Dadds 2008; Auyeung et al. 2015; Hubble et al. 2017; Skvortsova et al. 2018). Therefore, we chose for this dose. However, without a comparison with other dosages, it is unclear whether the absence of effects of oxytocin would have been different with a higher or lower oxytocin dose.

Increased trust and eye gaze were among the first reported responses to intranasal oxytocin administration (Kosfeld et al. 2005; Guastella, Mitchell, and Dadds 2008). However, we found no effects of 24IU intranasal oxytocin administration on gaze towards the eye region, or on trust within the context of the patient-physician relationship, using a larger sample size and a within-subject design compared to these original reports. To advance oxytocin research, prevailing hypotheses need to be tested using approaches that facilitate hypothesis falsification (Winterton et al. 2021). In conclusion, by complementing conventional frequentist hypothesis testing with Bayesian hypothesis testing, we were able to provide strong relative evidence for our null models.

Appendix A.

Information provided during the recorded Skype call: pros and cons of HPV vaccination for men

The below script contains the information that the physician provided during the recorded Skype call. The information encompasses pros and cons of the HPV vaccination for men. Both versions, needed for the two visits, had identical greetings before and after the information. The original script was in Dutch, below you will find an English translation of the script.

Version A

Pros:

1. The first reason to vaccinate boys is that homosexual boys are presently not protected. The current system focuses on heterosexual intimacy, where men are protected because women are vaccinated. However, when an infected man has sex with another man, the virus can still spread. Homosexual men therefore do not benefit if only women are vaccinated. This is one reason why people may feel that boys should also be vaccinated.
2. A second argument for the vaccination of boys is that men are currently dependent on the vaccination of girls. A man can contract the virus from a girl who has not been vaccinated. As a result, men have no personal control. Some people think it would be fair if men could also protect themselves by being able to opt for a vaccination themselves. Some men also like the idea that they themselves cannot pass on the virus to others.

Cons:

1. The first disadvantage is that we can better prevent the virus from spreading if 90% of all girls are vaccinated than if 65% of both boys and girls are vaccinated. If 90% of the girls are vaccinated, there are lower chances that the virus will continue to spread. Because with sexual contact, the chance is higher that one of the people involved has been vaccinated. If only 65% of both sexes are vaccinated, it will be more common that one of the people involved in sexual contact is not vaccinated. This means the virus will keep on spreading more easily. For this reason, it would be more effective to vaccinate 90% of girls compared to 65% of boys and girls. It should be kept in mind that this applies to the current system that focuses on heterosexual contact.
2. In addition, 800 boys should be vaccinated compared to 200 girls to prevent the development of one tumor in one person. This is because men and women can both get cancer from the HPV virus, but women are more likely to develop cancer after infection. For the prevention of one tumor, it is therefore more effective to vaccinate girls, because it means that fewer vaccinations are needed in total. Thus, this would not only be the most effective, but also the most cost-effective approach to keep the HPV from spreading.

Version B

Pros:

1. A first argument for vaccinating boys is that the HPV virus is not only harmful to women, but also to men. As you have read, men can also develop different types of cancer from infection with the virus. Often this is oral pharyngeal cancer. This variant is up to 5 times more common in men than in women. In addition, the incidence of anal cancer due to HPV is currently increasing, in both men and women. For these reasons it is important that men are also well protected.
2. A second advantage is that it is more cost-effective to vaccinate boys as well as girls. I will explain why. At the moment, 65% of girls are vaccinated. If in addition 40% of boys are vaccinated, the risk of cancer decreases and the costs of cancer care decrease. Only if at least 80-90% of girls were vaccinated would the additional vaccination of boys no longer be cost-effective. Practice shows that such high vaccination rates for girls are not feasible. For the time being, it is therefore more cost-effective to vaccinate 40% of the boys and 65% of the girls. So this cost-effectiveness can also be a reason to vaccinate boys.

Cons:

1. A first argument for not vaccinating boys is that it is still unknown what the long-term effects of the new vaccine for boys are. For women, the long-term effects over a period of 10 years are known, but not for men. This uncertainty leads to questioning the desirability of vaccinating boys.
2. In addition, it has not yet been proven that the vaccine is effective against oral pharyngeal cancer, whereas that type of cancer is relatively common in men. The reason is that pharyngeal cancer cannot be recognized at an early stage. This means that it is not known whether the vaccination is effective against this type of cancer. This uncertainty can be a reason not to vaccinate boys.

Appendix B.

Calculation of gaze towards the eye region

To calculate a percentage of volunteer gaze towards the eye region of the physician, several steps had to be undertaken. First, the stimulus (i.e., the video), was synchronized to match the eye-tracking data using a command-line interpreter. This was needed because the refresh rate of the video was 25 Hz and the eye-tracking data was 120 Hz. Second, to analyze the synchronized eye-tracking data on the physician's face, we used the "AutomaticAOIconstruction" tool in MATLAB R2020b (The MathWorks, Inc., Natick, Massachusetts, United States). This tool includes an algorithm that creates Areas-of-Interest using face recognition. The Areas-of-Interest are created using the noise-robust Limited-Radius Voronoi Tessellation method (Hessels et al. 2018). This method first assigns the center of an Area-of-Interest on facial features: left eye, right eye, nose and mouth. Each center is assigned a fixed radius creating a so-called cell. The gaze location of the participant is then matched to the closest Area-of-Interest center of the physician within the fixed radius. When the gaze coordinates exceeded the maximum radius for all the Areas-of-Interest cells, the gaze location was assigned as not belonging to an Area-of-Interest (Hessels et al. 2018).

Acknowledgements

The authors thank all volunteers who participated in the experiment. Furthermore, the authors extend their gratitude to prof. dr. Louis Vermeulen for his kind help in the setup of the experiment. Many thanks also to Soraya Bresser, prof. dr. Julia van Weert, and the University of Amsterdam lab collaborators. Finally, dr. Aaron Caldwell has provided precious feedback on the statistical analyses.

References

- Amico, Janet A, Ruben Tenicela, Jann Johnston, and Alan G Robinson. 1983. 'A time-dependent peak of oxytocin exists in cerebrospinal fluid but not in plasma of humans', *The Journal of Clinical Endocrinology & Metabolism*, 57: 947-51.
- Auyeung, Bonnie, Michael V Lombardo, Markus Heinrichs, Bhisma Chakrabarti, A Sule, Julia Brynja Deakin, RAI Bethlehem, L Dickens, Natasha Mooney, and JAN Sipple. 2015. 'Oxytocin increases eye contact during a real-time, naturalistic social interaction in males with and without autism', *Translational psychiatry*, 5: e507-e07.
- Bachinger, S. M., A. M. Kolk, and E. M. A. Smets. 2009. 'Patients' trust in their physician-Psychometric properties of the Dutch version of the "Wake Forest Physician Trust Scale"', *Patient Education and Counseling*, 76: 126-31.
- Bailly, Gérard, Stephan Raidt, and Frédéric Elisei. 2010. 'Gaze, conversational agents and face-to-face communication', *Speech Communication*, 52: 598-612.
- Bartz, Jennifer A, Jamil Zaki, Niall Bolger, and Kevin N Ochsner. 2011. 'Social effects of oxytocin in humans: context and person matter', *Trends in cognitive sciences*, 15: 301-09.
- Buller, M. K., and D. B. Buller. 1987. 'Physicians Communication Style and Patient Satisfaction', *Journal of Health and Social Behavior*, 28: 375-88.
- Burley, Daniel T, and Katie Daughters. 2020. 'The effect of oxytocin on pupil response to naturalistic dynamic facial expressions', *Hormones and Behavior*, 125: 104837.
- Carter, C Sue, Angela J Grippo, Hossein Pournajafi-Nazarloo, Michael G Ruscio, and Stephen W Porges. 2008. 'Oxytocin, vasopressin and sociality', *Progress in brain research*, 170: 331-36.
- Cohen, Jacob. 1988. 'Statistical Power Analysis for the Behavioral-Sciences ', *Perceptual and Motor Skills*, 67: 1007-07.
- Corrigan, Megan, Suprat Saely Wilson, and Jeremy Hampton. 2015. 'Safety and efficacy of intranasally administered medications in the emergency department and prehospital settings', *American Journal of Health-System Pharmacy*, 72: 1544-54.
- De Haes, Hanneke, and Jozien Bensing. 2009. 'Endpoints in medical communication research, proposing a framework of functions and outcomes', *Patient education and counseling*, 74: 287-94.
- Declerck, Carolyn H, Christophe Boone, Loren Pauwels, Bodo Vogt, and Ernst Fehr. 2020. 'A registered replication study on oxytocin and trust', *Nature Human Behaviour*, 4: 646-55.
- Dienes, Z. 2014. 'Using Bayes to get the most out of non-significant results', *Frontiers in Psychology*, 5.
- Domes, Gregor, Markus Heinrichs, Ekkehardt Kumbier, Annette Grossmann, Karlheinz Hauenstein, and Sabine C Herpertz. 2013. 'Effects of intranasal oxytocin on the neural basis of face processing in autism spectrum disorder', *Biological psychiatry*, 74: 164-71.
- Engelen, Ute, Steven De Peuter, An Victoir, Ilse Van Diest, and Omer %J Gedrag en gezondheid Van den Bergh. 2006. 'Verdere validering van de Positive and Negative Affect Schedule (PANAS) en vergelijking van twee Nederlandstalige versies', 34: 61-70.
- Freeth, Megan, Tom Foulsham, and Alan Kingstone. 2013. 'What affects social attention? Social presence, eye contact and autistic traits', *PloS one*, 8: e53286.

- Gamer, Matthias, Bartosz Zurowski, and Christian Büchel. 2010. 'Different amygdala subregions mediate valence-related and attentional effects of oxytocin in humans', *Proceedings of the National Academy of Sciences*, 107: 9400-05.
- Gao, S., B. Becker, L. Z. Luo, Y. Y. Geng, W. H. Zhao, Y. Yin, J. H. Hu, Z. Gao, Q. Y. Gong, R. Hurlmann, D. Z. Yao, and K. M. Kendrick. 2016. 'Oxytocin, the peptide that bonds the sexes also divides them', *Proceedings of the National Academy of Sciences of the United States of America*, 113: 7650-54.
- Graves, Tiffany A, Nassim Tabri, Heather Thompson-Brenner, Debra L Franko, Kamryn T Eddy, Stephanie Bourion-Bedes, Amy Brown, Michael J Constantino, Christoph Flückiger, and Sarah Forsberg. 2017. 'A meta-analysis of the relation between therapeutic alliance and treatment outcome in eating disorders', *International Journal of Eating Disorders*, 50: 323-40.
- Guastella, A. J., I. B. Hickie, M. M. McGuinness, M. Otis, E. A. Woods, H. M. Disinger, H. K. Chan, T. F. Chen, and R. B. Banati. 2013. 'Recommendations for the standardisation of oxytocin nasal administration and guidelines for its reporting in human research', *Psychoneuroendocrinology*, 38: 612-25.
- Guastella, Adam J, Stewart L Einfeld, Kylie M Gray, Nicole J Rinehart, Bruce J Tonge, Timothy J Lambert, and Ian B Hickie. 2010. 'Intranasal oxytocin improves emotion recognition for youth with autism spectrum disorders', *Biological psychiatry*, 67: 692-94.
- Guastella, Adam J, Philip B Mitchell, and Mark R Dadds. 2008. 'Oxytocin increases gaze to the eye region of human faces', *Biological psychiatry*, 63: 3-5.
- Hessels, Roy S, Jeroen S Benjamins, Tim HW Cornelissen, and Ignace TC Hooge. 2018. 'A validation of automatically-generated areas-of-interest in videos of a face for eye-tracking research', *Frontiers in psychology*, 9: 1367.
- Hillen, Marij A, Hanneke CJM de Haes, Geertjan van Tienhoven, Nina Bijker, Hanneke WM van Laarhoven, Daniëlle M Vermeulen, and Ellen MA Smets. 2015. 'All eyes on the patient: the influence of oncologists' nonverbal communication on breast cancer patients' trust', *Breast cancer research and treatment*, 153: 161-71.
- Hubble, Kelly, Katie Daughters, Antony SR Manstead, Aled Rees, Anita Thapar, and Stephanie HM van Goozen. 2017. 'Oxytocin increases attention to the eyes and selectively enhances self-reported affective empathy for fear', *Neuropsychologia*, 106: 350-57.
- Jokinen, Kristiina, Kazuaki Harada, Masafumi Nishida, and Seiichi Yamamoto. 2010. "Turn-alignment using eye-gaze and speech in conversational interaction." In *Eleventh Annual Conference of the International Speech Communication Association*.
- Jongerius, Chiara, Roy S Hessels, Johannes A Romijn, Ellen Smets, and Marij A Hillen. 2020. 'The Measurement of Eye Contact in Human Interactions: A Scoping Review', *JOURNAL OF NONVERBAL BEHAVIOR*.
- Kooiman, C. G., E. R. Klaassens, J. Q. V. Lugt, and A. M. Kamperman. 2013. 'Psychometrics and Validity of the Dutch Experiences in Close Relationships Revised (ECRr) in an Outpatient Mental Health Sample', *Journal of Personality Assessment*, 95: 217-24.
- Kosfeld, Michael, Markus Heinrichs, Paul J Zak, Urs Fischbacher, and Ernst Fehr. 2005. 'Oxytocin increases trust in humans', *Nature*, 435: 673-76.
- Kret, Mariska E, and Carsten KW De Dreu. 2017. 'Pupil-mimicry conditions trust in partners: Moderation by oxytocin and group membership', *Proceedings of the Royal Society B: Biological Sciences*, 284: 20162554.
- Kret, Mariska E, and Elio E Sjak-Shie. 2019. 'Preprocessing pupil size data: Guidelines and code', *Behavior research methods*, 51: 1336-42.
- Kundi, Michael, Patrick Obermeier, Stephanie Helfert, Hiba Oubari, Stefan Fitzinger, Jeong A Yun, Martin Brix, and Barbara Rath. 2015. 'The impact of the parent-physician relationship on parental vaccine safety perceptions', *Current drug safety*, 10: 16-22.
- Labuschagne, Izelle, K Luan Phan, Amanda Wood, Mike Angstadt, Phyllis Chua, Markus Heinrichs, Julie C Stout, and Pradeep J Nathan. 2010. 'Oxytocin attenuates amygdala reactivity to fear in generalized social anxiety disorder', *Neuropsychopharmacology*, 35: 2403-13.

- Lischke, Alexander, Christoph Berger, Kristin Prehn, Markus Heinrichs, Sabine C Herpertz, and Gregor Domes. 2012. 'Intranasal oxytocin enhances emotion recognition from dynamic facial expressions and leaves eye-gaze unaffected', *Psychoneuroendocrinology*, 37: 475-81.
- Love, Jonathon, Ravi Selker, Maarten Marsman, Tahira Jamil, Damian Dropmann, Josine Verhagen, Alexander Ly, Quentin F Gronau, Martin Šmíra, and Sacha Epskamp. 2019. 'JASP: Graphical statistical software for common statistical designs', *Journal of Statistical Software*, 88: 1-17.
- MacDonald, Kai. 2009. 'Patient-clinician eye contact: social neuroscience and art of clinical engagement', *Postgraduate medicine*, 121: 136-44.
- Mansour, Hassan, and Gustav Kuhn. 2019. 'Studying “natural” eye movements in an “unnatural” social environment: The influence of social activity, framing, and sub-clinical traits on gaze aversion', *Quarterly Journal of Experimental Psychology*, 72: 1913-25.
- Mast, Marianne Schmid. 2007. 'On the importance of nonverbal communication in the physician–patient interaction', *Patient education and counseling*, 67: 315-18.
- Peters, L., M. Sunderland, G. Andrews, R. M. Rapee, and R. P. Mattick. 2012. 'Development of a short form Social Interaction Anxiety (SIAS) and Social Phobia Scale (SPS) using nonparametric item response theory: the SIAS-6 and the SPS-6', *Psychol Assess*, 24: 66-76.
- Piette, John D, Michele Heisler, Sarah Krein, and Eve A Kerr. 2005. 'The role of patient-physician trust in moderating medication nonadherence due to cost pressures', *Archives of internal medicine*, 165: 1749-55.
- Quintana, Daniel S. 2020. 'Most oxytocin administration studies are statistically underpowered to reliably detect (or reject) a wide range of effect sizes', *Comprehensive Psychoneuroendocrinology*, 4: 100014.
- Quintana, Daniel S, Alexander Lischke, Sally Grace, Dirk Scheele, Yina Ma, and Benjamin Becker. 2020. 'Advances in the field of intranasal oxytocin research: lessons learned and future directions for clinical research', *Molecular Psychiatry*: 1-12.
- Rouder, Jeffrey N, Paul L Speckman, Dongchu Sun, Richard D Morey, and Geoffrey Iverson. 2009. 'Bayesian t tests for accepting and rejecting the null hypothesis', *Psychonomic bulletin & review*, 16: 225-37.
- Scheele, Dirk, Nadine Striepen, Keith M Kendrick, Christine Schwering, Janka Noelle, Andrea Wille, Thomas E Schläpfer, Wolfgang Maier, and Rene Hurlemann. 2014. 'Opposing effects of oxytocin on moral judgment in males and females', *Human brain mapping*, 35: 6067-76.
- Shahrestani, Sara, Andrew H Kemp, and Adam J Guastella. 2013. 'The impact of a single administration of intranasal oxytocin on the recognition of basic emotions in humans: a meta-analysis', *Neuropsychopharmacology*, 38: 1929-36.
- Shamay-Tsoory, Simone G, and Ahmad Abu-Akel. 2016. 'The social salience hypothesis of oxytocin', *Biological psychiatry*, 79: 194-202.
- Sikich, Linmarie, Alexander Kolevzon, Bryan H King, Christopher J McDougale, Kevin B Sanders, Soo-Jeong Kim, Marina Spanos, Tara Chandrasekhar, MD Pilar Trelles, and Carol M Rockhill. 2021. 'Intranasal oxytocin in children and adolescents with autism spectrum disorder', *New England Journal of Medicine*, 385: 1462-73.
- Simonsohn, Uri, Leif D Nelson, and Joseph P Simmons. 2014. 'p-curve and effect size: Correcting for publication bias using only significant results', *Perspectives on Psychological Science*, 9: 666-81.
- Skvortsova, A., D. S. Veldhuijzen, H. Van Middendorp, O. Van den Bergh, and A. W. M. Evers. 2018. 'Enhancing Placebo Effects in Somatic Symptoms Through Oxytocin', *Psychosom Med*, 80: 353-60.
- Thompson, Erika L, Christopher W Wheldon, Brittany L Rosen, Sarah B Maness, Monica L Kasting, and Philip M Massey. 2020. 'Awareness and knowledge of HPV and HPV vaccination among adults ages 27–45 years', *Vaccine*, 38: 3143-48.
- van der Bij, A. K., S. de Weerd, R. J. Cikot, E. A. Steegers, and J. C. Braspenning. 2003. 'Validation of the dutch short form of the state scale of the Spielberger State-Trait Anxiety Inventory: considerations for usage in screening outcomes', *Community Genet*, 6: 84-7.

- Weiss, Linda J, and Jan Blustein. 1996. 'Faithful patients: the effect of long-term physician-patient relationships on the costs and use of health care by older Americans', *American journal of public health*, 86: 1742-47.
- Winterton, Adriano, Lars T Westlye, Nils Eiel Steen, Ole A Andreassen, and Daniel S Quintana. 2021. 'Improving the precision of intranasal oxytocin research', *Nature Human Behaviour*, 5: 9-18.
- Zilcha-Mano, Sigal, Simone Shamay-Tsoory, Tohar Dolev-Amit, Orna Zagoory-Sharon, and Ruth Feldman. 2020. 'Oxytocin as a biomarker of the formation of therapeutic alliance in psychotherapy and counseling psychology', *Journal of Counseling Psychology*, 67: 523.