Supplementary material

Increased temporal discounting in social anxiety disorder normalizes after oxytocin treatment

René Hurlemann, Dirk Scheele, Thomas M. Kinfe, Ruben Berger, Alexandra Philipsen, Marisol Voncken, Kim P. C. Kuypers, Koen Schruers

Material and methods

Participants and drug treatment

Participants were recruited from tertiary outpatient clinics in Maastricht, The Netherlands. All participants gave written informed consent. The study was approved by the institutional review board of Maastricht University Medical Center/Maastricht University and was conducted in accordance with the Declaration of Helsinki. The study was registered in the Nederlands Trial Register database (Identifier: NTR3672). The recruitment and testing of the participants took place in Maastricht between July 2013 and July 2016. It was initially planned to include an additional patient group with other anxiety disorders, but this study arm was discarded due to a lack of eligible patients. Screening of the subjects was conducted prior to the test session. Questionnaires included the Social Phobia and Anxiety Inventory [1] to measure social anxiety symptoms, the Center for Epidemiologic Studies Depression Scale Revised (CESD-R) [2] to measure depression symptoms and the Social Connectedness Scale [3] to measure interpersonal closeness. Primary diagnosis was determined by the Mini-International Neuropsychiatric Interview (MINI) [4]. Comorbidities of the social anxiety disorder (SAD) sample included major depressive or dysthymic disorder (n = 12), specific phobia (n = 5), agoraphobia (n = 4), generalized anxiety disorder (n = 3), posttraumatic stress disorder (n = 3), obsessive-compulsive disorder (n = 3), bulimia nervosa (n = 2), drug abuse (n = 1), body dismorphic disorder (n = 1) and irritable bowel syndrome (n = 1). Healthy controls were free of any psychopathology.

Participants self-administered nasal sprays containing either synthetic oxytocin (OXT) or placebo (PLC) at the beginning of the testing session. Participants were randomized over the OXT and PLC condition based on stratification of gender (male versus female) and group (SAD patients and healthy controls). The randomization procedure was done by a person not involved in the study. The administration instructions were in accordance with the latest standardization guidelines [5], and administration was supervised by a trained research assistant. Participants received an OXT dose of 24 IU (three puffs per nostril, each with 4 IU OXT; Novartis, Basel, Switzerland). The PLC solution contained the identical ingredients except for the peptide itself. To examine a possible effect of OXT on prosocial behavior, participants were video recorded during a social interaction task that started 45 minutes after the nasal spray administration. The results of this first task will be reported elsewhere.

The temporal discounting task began 90 minutes after the nasal spray administration. The average duration of the temporal discounting task together with the valuation task was 5 minutes. The strongest effects of intranasal OXT on amygdala activation have been observed 45 minutes after nasal spray administration, but amygdala inhibition has been evident up to a latency of 95 minutes [6]. In fact, a previous study even detected effects of intranasal OXT on emotion intensity ratings after 120 minutes [7].

Temporal discounting task

We used a temporal discounting task to assess the ability to control impulsive preferences (i.e. to suppress the impulsive choice of smaller-sooner incentives over long-term greater benefits) [8, 9]. The temporal discounting task was composed of 36 trials in which the participants chose between smaller-sooner (pseudorandomly drawn from a normal distribution with a mean of EUR 45 and a standard deviation of EUR 15) and larger-later rewards (0.5–75% larger than the smaller-sooner rewards; henceforth “relative difference”). In half of the trials there were immediate smaller-sooner rewards and delayed (two and four weeks) larger-later rewards. In the other half of trials the sooner-smaller option was available in 2 weeks and the larger-later option in four or six weeks. The order of trials was randomized across subjects. The proportion of patient choices (i.e. larger-later rewards) was used as dependent variable. All stimuli were presented using the software Presentation 16 (Neurobehavioral Systems, Albany, CA).

Valuation task

In the valuation task, the participants rated the attractiveness of 12 single options that each provided a specified monetary amount at a specified time point. The options were randomly chosen from the 36 trials of the temporal discounting task and consisted of four time points of delivery ("today", "in 2 weeks", "in 4 weeks", "in 6 weeks") crossed with three levels of reward magnitude (low: approximately EUR 30; medium: approximately EUR 45; and high: approximately EUR 60; actual values varied slightly from these approximate numbers as they were dependent on the values presented in the temporal discounting task). The self-assessment manikin (SAM) [10] was presented below each option and participants rated the attractiveness on a scale of 1 (minimum) – 9 (maximum).

Statistical analysis

Quantitative behavioral data were compared by a mixed-design analysis of variance (ANOVA). Pearson's product-moment correlation (*r*) was used for correlation analysis. Eta-squared and Cohen's *d* were calculated as measures of effect size. The assumption of sphericity was assessed with Mauchly's test, and Greenhouse-Geisser's correction was applied for significant violations. Pearson's chi-squared tests were used for qualitative variables. All reported *P*-values are two-tailed, if not otherwise noted, and *P*-values of $P < 0.05$ were considered statistically significant. Demographical, neuropsychological and behavioral data were analyzed using SPSS 24 (IBM, New York, NY, USA). The discount rate k for each participant was quantified by using a standard one-parameter model of hyperbolic discounting [11], captured by the following term:

$$Subjective\ value = \frac{Reward\ magnitude}{1+k*Delay},$$

where *Delay* is the time of delivery (in weeks) and *k* is the parameter that represents the participant's discount rate. Larger k values indicate steeper discounting of delayed rewards, while 0 indicates no discounting at all. We used the Matlab (Matlab R2017b, The MathWorks Inc., Natick, MA) function *fminbnd* to estimate the k value for each participant which produced the global minimum in the negative log-likelihood of individual choice probability. Extreme k values (k ~ 1) of two participants who rejected all larger-later rewards were discarded.

Supplementary results

Screening data

As expected, SAD patients reported significantly higher levels of social phobia ($t_{(68)}$ = 15.40, P < 0.01, d = 3.74) and depression ($t_{(48.20)}$ = 8.29, P < 0.01, d = 2.08) and significantly lower levels of social connectedness ($t_{(68)}$ = -11.29, P < 0.01, d = -2.74) compared to controls (CTL). Age and gender were comparable between groups (all Ps > 0.30). There were no a-priori differences regarding demographical and psychometric variables between the OXT and PLC groups (cf. **Table S1**). No participant reported any side effects.

Temporal discounting

The pattern of results with the proportion of patient choices (later-larger) as dependent variable did not change when we included gender as an additional between-subject factor. Furthermore, we analyzed possible treatment effects on response time. An additional mixed-design ANOVA with the response time as dependent variable yielded a main effect of relative difference ($F_{(5.34, 346.91)}$ = 3.05, P < 0.01, η^2 = 0.05) and a trend-to-significant group effect ($F_{(1, 65)}$ = 3.01, P = 0.09, η^2 = 0.04). Across treatment groups, patients with SAD were slightly slower in their responses. Interestingly, we also observed a significant interaction of relative difference and treatment ($F_{(5.34, 346.91)}$ = 2.31, P = 0.04, η^2 = 0.03). Under PLC, the response time increased quadratically with the relative difference ($F_{(1, 33)}$ = 10.38, P < 0.01, η^2 = 0.24), suggesting that participants experienced the strongest conflict between larger-later and smaller-sooner options if there was only a modest reward difference. By contrast, this effect vanished after OXT treatment, with the participants showing a linear decrease in response time (i.e. the smaller the relative difference, the faster the participants responded; $F_{(1, 32)}$ = 15.62, P < 0.01, η^2 = 0.33). Interestingly, a correlational analysis revealed a significant association between average response times in the OXT group and the average proportion of patient choices (later-larger) ($r_{(34)}$ = -0.52, P < 0.01) and the discounting parameter k ($r_{(33)}$ = 0.46, P < 0.01). The correlations did not reach significance in the PLC group (all Ps > 0.43).

Valuation task

We applied a mixed-design ANOVA with the between-subject factors “treatment” (OXT, PLC) and “group” (SAD, CTL), the within-subject variables “time points of delivery” (today, in 2 weeks, in 4 weeks, in 6 weeks) and “magnitude” (low, medium, high), and the attractiveness ratings from the valuation task as dependent variable. All participants preferred sooner and larger rewards and the treatment did not affect these ratings, indicating that OXT did not alter the valuation of rewards options, but rather modulated cognitive control which is required when a sooner-smaller reward is directly contrasted with a later-larger option **(**cf. **Table S2)**

Supplementary Discussion

An alternative explanation for the observed effects is related to a possible distortion of time perception in patients with anxiety disorders. The experimental induction of fear and anxiety in healthy subjects causes an overestimation of time intervals [12]. However, if patients with anxiety disorders chose more immediately available smaller rewards because they overestimated the delay for the larger rewards, this perceptual bias should have also influenced their valuation of single options. Moreover, temporal discounting has been associated with various psychological constructs and demographic variables including general intelligence and working memory [13], personality traits such as conscientiousness and neuroticism [14], financial stability and physical health [15] as well as the quality of reward imagination [16]. Previous studies did not find evidence for a modulatory effect of OXT on working memory [17] or conscientiousness and neuroticism ratings [18]. By contrast, OXT is known to increase the ease of imagining compassionate qualities [19], suggesting that OXT could have altered the ability to imagine future rewards. However, the absence of an OXT effect on the valuation of future rewards speaks against this interpretation. Furthermore, well in line with our observation that OXT did not affect the valuation of future monetary rewards, a recent study showed that OXT increased the willingness to work for monetary rewards of other people, but not own monetary rewards in patients with social anxiety disorder [20].

There is a very high rate of comorbidity between anxiety and depression [21] and 36% of the SAD patients in our sample also suffered from dysthymia or major depressive disorders (MDD). Depression affects social-economic decision-making [22] and MDD patients also show higher discounting rates for large-sized rewards [23]. Thus, although it is conceivable that depressive symptoms contributed to the observed differences in temporal discounting, we did not find a significant association between depressive symptoms and the proportion of patient choices in the present study.

Intranasal OXT reduced the proportion of impulsive choices in the temporal discounting task across groups, a finding that is consistent with the idea that OXT improves cognitive control. This interpretation is also corroborated by the observed changes in response time. The conflict between the preference for immediate rewards and larger delayed rewards is reflected by longer response times in trials with a modest reward difference between these options (resulting in an almost equal number of patient and impulsive decisions) and this response time difference was abolished after OXT treatment.

Mesolimbic dopamine signaling has been linked to temporal discounting [24, 25] and there is accumulating evidence that OXT interacts with dopamine pathways. For instance, in mice, hypothalamic oxytocinergic projections regulate midbrain dopamine neuron activity [26] and in humans, positron emission tomography (PET) studies revealed that OXT gene polymorphisms explain interindividual differences in dopamine responses to stress [27] (but see [28]). However, temporal discounting is also dependent on other neurotransmitter pathways. For instance, low serotonin levels have been linked to a preference for small and immediate rewards [29], which may be mediated by increased activity of the ventral part of the striatum [30]. As such, it is also conceivable that OXT modulates temporal discounting via inhibitory regulation of serotonin signaling [31]. Future imaging studies are warranted to decipher the neurobiological mechanisms underlying the effect of OXT on temporal discounting.

The present study has some limitations. First, the prevalence rate of anxiety disorders is significantly higher in women than in men [32] and this distribution is reflected in our sample. The small number of men may have prevented us from detecting sexual-dimorphic effects of OXT which have been observed in several previous studies [33-35]. Second, since we only included medication-free patients we can rule out confounding effects of medication, but future studies are warranted to explore the specificity of our findings by assessing temporal discounting in patients with other anxiety disorders.

Supplemental references

1 Turner SM, Beidel DC, Dancu CV, Stanley MA: An empirically derived inventory to measure social fears and anxiety. Behav Res Ther 1989;1:35–40.

2 Eaton WW, Muntaner C, Smith C, Tien A, Ybarra M: Center for Epidemiologic Studies Depression Scale: Review and revision (CESD and CESD-R); in ME M (ed) The Use of Psychological Testing for Treatment Planning and Outcomes Assessment. Mahwah, NJ, Lawrence Erlbaum, 2004, pp 363-377.

3 Lee RM, Draper M, Lee S: Social Connectedness, Dysfunctional Interpersonal Behaviors, and Psychological Distress: Testing a Mediator Model. J Couns Psychol 2001;48:310-318.

4 Sheehan DV, Lecrubier Y, Sheehan KH, Amorim P, Janavs J, Weiller E, Hergueta T, Baker R, Dunbar GC: The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. J Clin Psychiatry 1998;59 Suppl 20:22-33.

5 Guastella AJ, Hickie IB, McGuinness MM, Otis M, Woods EA, Disinger HM, Chan HK, Chen TF, Banati RB: Recommendations for the standardisation of oxytocin nasal administration and guidelines for its reporting in human research. Psychoneuroendocrinology 2013;38:612-625.

6 Spengler FB, Schultz J, Scheele D, Essel M, Maier W, Heinrichs M, Hurlemann R: Kinetics and Dose Dependency of Intranasal Oxytocin Effects on Amygdala Reactivity. Biol Psychiatry 2017;82:885-894.

7 Cardoso C, Ellenbogen MA, Linnen AM: The effect of intranasal oxytocin on perceiving and understanding emotion on the Mayer-Salovey-Caruso Emotional Intelligence Test (MSCEIT). Emotion 2014;14:43-50.

8 Reynolds B: A review of delay-discounting research with humans: relations to drug use and gambling. Behav Pharmacol 2006;17:651-667.

9 Figner B, Knoch D, Johnson EJ, Krosch AR, Lisanby SH, Fehr E, Weber EU: Lateral prefrontal cortex and self-control in intertemporal choice. Nat Neurosci 2010;13:538-539.

10 Lang PJ, Bradley MM, Cuthbert BN: International affective picture system (IAPS): Affective ratings of pictures and instruction manual. Technical Report A-6. Gainesville, FL: University of Florida, 2005.

11 Mazur JE: An adjusting procedure for studying delayed reinforment; in Commons ML, Mazur JE, Nevin JA, Rachlin H (eds): Quantitative Analyses of Behavior. Hillsdale, N.J., Lawrence Erlbaum Associates, 1987

12 Lake JI, Labar KS: Unpredictability and uncertainty in anxiety: a new direction for emotional timing research. Front Integr Neurosci 2011;5:55.

13 Shamosh NA, Deyoung CG, Green AE, Reis DL, Johnson MR, Conway AR, Engle RW, Braver TS, Gray JR: Individual differences in delay discounting: relation to intelligence, working memory, and anterior prefrontal cortex. Psychol Sci 2008;19:904-911.

14 Manning J, Hedden T, Wickens N, Whitfield-Gabrieli S, Prelec D, Gabrieli JD: Personality influences temporal discounting preferences: behavioral and brain evidence. Neuroimage 2014;98:42-49.

15 Moffitt TE, Arseneault L, Belsky D, Dickson N, Hancox RJ, Harrington H, Houts R, Poulton R, Roberts BW, Ross S, Sears MR, Thomson WM, Caspi A: A gradient of childhood self-control predicts health, wealth, and public safety. Proc Natl Acad Sci U S A 2011;108:2693-2698.

16 Hakimi S, Hare TA: Enhanced Neural Responses to Imagined Primary Rewards Predict Reduced Monetary Temporal Discounting. J Neurosci 2015;35:13103-13109.

17 Tollenaar MS, Ruissen M, Elzinga BM, de Bruijn ERA: Does oxytocin lead to emotional interference during a working memory paradigm? Psychopharmacology (Berl) 2017;234:3467-3474.

18 Cardoso C, Ellenbogen MA, Linnen AM: Acute intranasal oxytocin improves positive self-perceptions of personality. Psychopharmacology (Berl) 2012;220:741-749.

19 Rockliff H, Karl A, McEwan K, Gilbert J, Matos M, Gilbert P: Effects of intranasal oxytocin on 'compassion focused imagery'. Emotion 2011;11:1388-1396.

20 Fang A, Treadway MT, Hofmann SG: Working hard for oneself or others: Effects of oxytocin on reward motivation in social anxiety disorder. Biol Psychol 2017;127:157-162.

21 Kessler RC, Berglund P, Demler O, Jin R, Koretz D, Merikangas KR, Rush AJ, Walters EE, Wang PS, National Comorbidity Survey R: The epidemiology of major depressive disorder: results from the National Comorbidity Survey Replication (NCS-R). JAMA 2003;289:3095-3105.

22 Pulcu E, Trotter PD, Thomas EJ, McFarquhar M, Juhasz G, Sahakian BJ, Deakin JF, Zahn R, Anderson IM, Elliott R: Temporal discounting in major depressive disorder. Psychol Med 2014;44:1825-1834.

23 Dombrovski AY, Szanto K, Siegle GJ, Wallace ML, Forman SD, Sahakian B, Reynolds CF, 3rd, Clark L: Lethal forethought: delayed reward discounting differentiates high- and low-lethality suicide attempts in old age. Biol Psychiatry 2011;70:138-144.

24 Saddoris MP, Sugam JA, Stuber GD, Witten IB, Deisseroth K, Carelli RM: Mesolimbic dopamine dynamically tracks, and is causally linked to, discrete aspects of value-based decision making. Biol Psychiatry 2015;77:903-911.

25 Pine A, Shiner T, Seymour B, Dolan RJ: Dopamine, time, and impulsivity in humans. J Neurosci 2010;30:8888-8896.

26 Xiao L, Priest MF, Nasenbeny J, Lu T, Kozorovitskiy Y: Biased Oxytocinergic Modulation of Midbrain Dopamine Systems. Neuron 2017;95:368-384 e365.

27 Love TM, Enoch MA, Hodgkinson CA, Pecina M, Mickey B, Koeppe RA, Stohler CS, Goldman D, Zubieta JK: Oxytocin gene polymorphisms influence human dopaminergic function in a sex-dependent manner. Biol Psychiatry 2012;72:198-206.

28 Striepens N, Matusch A, Kendrick KM, Mihov Y, Elmenhorst D, Becker B, Lang M, Coenen HH, Maier W, Hurlemann R, Bauer A: Oxytocin enhances attractiveness of unfamiliar female faces independent of the dopamine reward system. Psychoneuroendocrinology 2014;39:74-87.

29 Schweighofer N, Bertin M, Shishida K, Okamoto Y, Tanaka SC, Yamawaki S, Doya K: Low-serotonin levels increase delayed reward discounting in humans. J Neurosci 2008;28:4528-4532.

30 Tanaka SC, Schweighofer N, Asahi S, Shishida K, Okamoto Y, Yamawaki S, Doya K: Serotonin differentially regulates short- and long-term prediction of rewards in the ventral and dorsal striatum. PloS one 2007;2:e1333.

31 Mottolese R, Redoute J, Costes N, Le Bars D, Sirigu A: Switching brain serotonin with oxytocin. Proc Natl Acad Sci U S A 2014;111:8637-8642.

32 Kessler RC, Chiu WT, Demler O, Merikangas KR, Walters EE: Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the National Comorbidity Survey Replication. Arch Gen Psychiatry 2005;62:617-627.

33 Rilling JK, Demarco AC, Hackett PD, Chen X, Gautam P, Stair S, Haroon E, Thompson R, Ditzen B, Patel R, Pagnoni G: Sex differences in the neural and behavioral response to intranasal oxytocin and vasopressin during human social interaction. Psychoneuroendocrinology 2014;39:237-248.

34 Scheele D, Striepens N, Kendrick KM, Schwering C, Noelle J, Wille A, Schlapfer TE, Maier W, Hurlemann R: Opposing effects of oxytocin on moral judgment in males and females. Hum Brain Mapp 2014;35:6067-6076.

35 Scheele D, Plota J, Stoffel-Wagner B, Maier W, Hurlemann R: Hormonal contraceptives suppress oxytocin-induced brain reward responses to the partner's face. Soc Cogn Affect Neurosci 2016;11:767-774.

Table S1. Demographic and psychometric trait data

	Oxytocin (mean ± SD)	Placebo (mean ± SD)	t / χ^2	P
Social anxiety (n = 33)				
Age (years)	33.12 (12.54)	29.19 (10.11)	0.99	0.33
Gender (females)	13	12	0.01	0.92
Depressive symptoms [1]	26.94 (12.08)	22.50 (11.15)	1.10	0.28
Social phobia [2]	132.03 (21.10)	134.03 (19.15)	-0.23	0.82
Social connectedness [3]	65.94 (17.91)	58.31 (12.39)	1.41	0.17
Healthy controls (n = 37)				
Age (years)	35.82 (15.67)	33.30 (13.63)	0.52	0.60
Gender (females)	14	16	0.46	0.50
Depressive symptoms [1]	7.18 (7.21)	4.70 (5.78)	1.16	0.26
Social phobia [2]	53.75 (29.74)	42.70 (21.28)	1.31	0.20
Social connectedness [3]	97.47 (17.24)	104.55 (7.51)	-1.57	0.13

Notes. [1] Depressive symptoms were measured with the Center for Epidemiologic Studies Depression Scale Revised (CESD-R). [2] Social phobia symptoms were measured with Social Phobia and Anxiety Inventory. [3] Social connectedness was measured with the Social Connectedness Scale.

Table S2. Valuation ratings

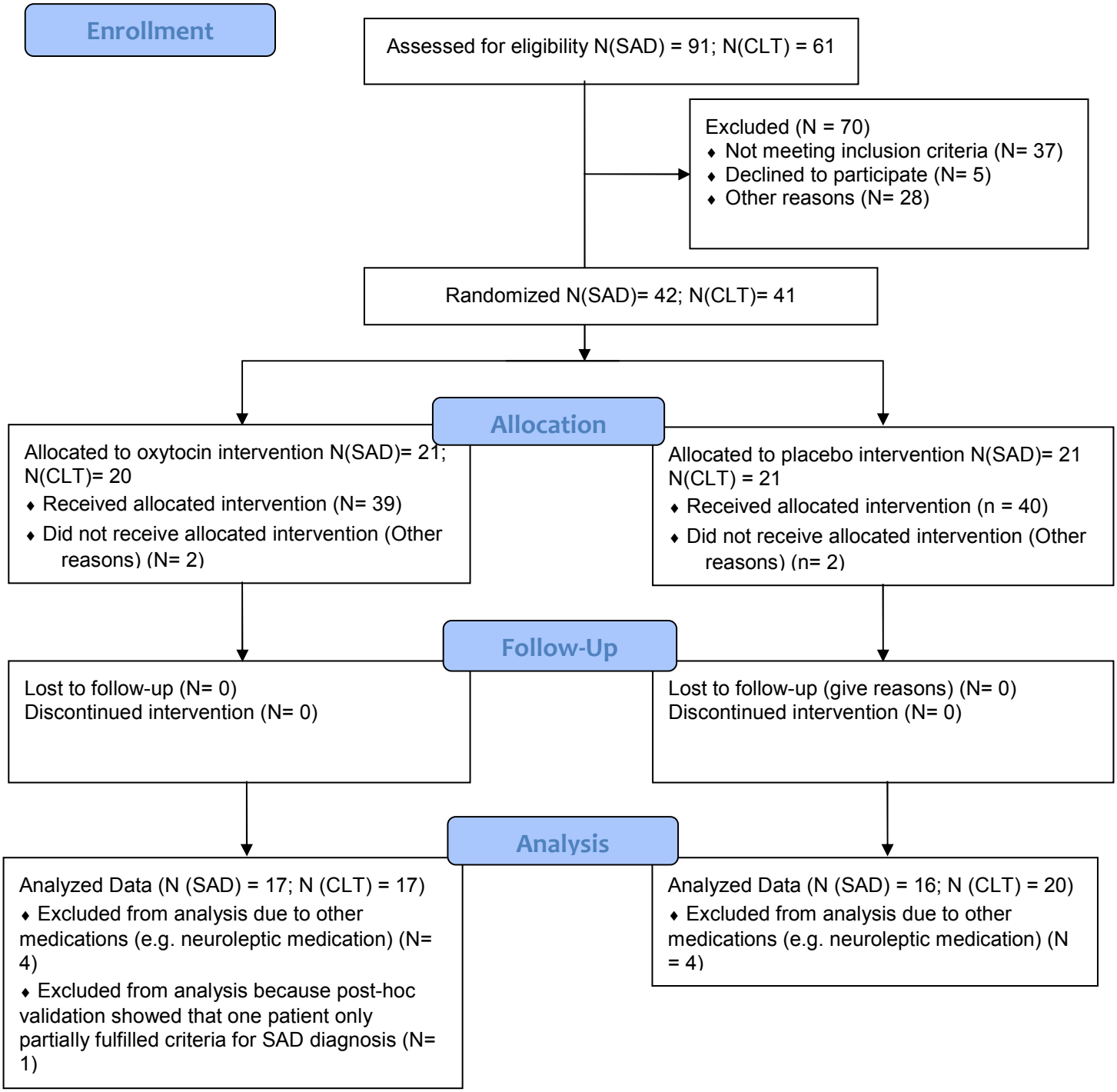
	Oxytocin (mean ± SD)	Placebo (mean ± SD)	*t*	*P*
Social anxiety (n = 33)				
Low amount today	6.47 (2.24)	5.31 (2.33)	1.46	0.16
Low amount 2 weeks	5.06 (2.51)	4.13 (1.86)	1.21	0.24
Low amount 4 weeks	4.65 (1.80)	3.50 (1.75)	1.85	0.07
Low amount 6 weeks	4.71 (2.34)	4.00 (2.31)	0.87	0.39
Medium amount today	7.18 (1.98)	7.19 (2.20)	-0.02	0.99
Medium amount 2 weeks	6.41 (2.00)	6.38 (1.67)	0.06	0.96
Medium amount 4 weeks	6.29 (2.23)	6.38 (1.36)	-0.13	0.90
Medium amount 6 weeks	6.47 (2.10)	5.56 (1.75)	1.35	0.19
High amount today	8.53 (0.79)	8.69 (0.79)	-0.57	0.57
High amount 2 weeks	8.12 (1.05)	7.81 (1.17)	0.79	0.44
High amount 4 weeks	7.76 (1.30)	7.13 (2.00)	1.10	0.28
High amount 6 weeks	7.82 (1.29)	7.56 (1.26)	0.59	0.56
Healthy controls (n = 37)				
Low amount today	6.47 (2.32)	6.15 (2.37)	0.14	0.68
Low amount 2 weeks	5.47 (2.72)	4.90 (2.45)	0.67	0.51
Low amount 4 weeks	5.35 (2.74)	4.40 (2.19)	1.18	0.25
Low amount 6 weeks	5.06 (2.82)	3.95 (2.24)	1.34	0.19
Medium amount today	7.82 (1.94)	7.30 (2.20)	0.76	0.45
Medium amount 2 weeks	7.12 (1.65)	6.70 (2.25)	0.63	0.53
Medium amount 4 weeks	6.71 (1.83)	6.25 (2.53)	0.62	0.54
Medium amount 6 weeks	6.53 (2.07)	6.30 (2.49)	0.30	0.77
High amount today	8.59 (0.80)	8.65 (0.75)	-0.24	0.81
High amount 2 weeks	8.18 (0.95)	8.10 (1.41)	0.19	0.85
High amount 4 weeks	7.41 (1.58)	7.65 (1.84)	-0.42	0.68
High amount 6 weeks	7.29 (1.86)	7.05 (2.58)	0.32	0.75

Notes. Participants rated the attractiveness of the options on a scale of 1 (minimum) – 9 (maximum).

CONSORT

TRANSPARENT REPORTING of TRIALS

CONSORT 2010 Flow Diagram



CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	n.a.
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	2
	2b	Specific objectives or hypotheses	2
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	2, SI Methods
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	SI Methods (p. 2)
Participants	4a	Eligibility criteria for participants	2, SI-Methods
	4b	Settings and locations where the data were collected	SI Methods
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	SI Methods
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	SI Methods
	6b	Any changes to trial outcomes after the trial commenced, with reasons	n.a.
Sample size	7a	How sample size was determined	n.a.
	7b	When applicable, explanation of any interim analyses and stopping guidelines	n.a.
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	SI Methods
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	SI Methods
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	SI Methods
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	SI Methods

Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	SI Methods
	11b	If relevant, description of the similarity of interventions	SI Methods
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	SI Methods
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	SI Methods
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	2, SI Flow Diagram
	13b	For each group, losses and exclusions after randomisation, together with reasons	SI Flow Diagram
Recruitment	14a	Dates defining the periods of recruitment and follow-up	SI Methods
	14b	Why the trial ended or was stopped	n.a.
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	SI Results, SI tables
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	2, SI Flow Diagram
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	2-3
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	SI-Results
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	SI-Results
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	SI Discussion
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	4, SI Discussion
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	4, SI Discussion
Other information			
Registration	23	Registration number and name of trial registry	SI Methods
Protocol	24	Where the full trial protocol can be accessed, if available	
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	5