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The effects of intranasal oxytocin on smoothie intake, cortisol and attentional bias in anorexia nervosa

Jenni Leppanen[a,*], Valentina Cardi[a], Kah Wee Ng[b], Yannis Paloyelis[c], Daniel Stein[d], Kate Tchanturia[a,e], Janet Treasure[a]

[a] King's College London, Institute of Psychiatry, Psychology, and Neuroscience, Department of Psychological Medicine, United Kingdom
[b] Singapore General Hospital, 20 College Road, Academia, 169865, Singapore
[c] King's College London, Institute of Psychiatry, Psychology, and Neuroscience, Department of Neuroimaging, Division of Neuroscience, United Kingdom
[d] Edmond and Lily Safra Children's Hospital, Chaim Sheba Medical Center, Tel Hashomer, Israel
[e] Department of Psychology, Illia State University, Tbilisi, Georgia

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ABSTRACT

Background: Anorexia nervosa (AN) is characterised by severe malnutrition as well as intense fear and anxiety around food and eating with associated anomalies in information processing. Previous studies have found that the neuropeptide, oxytocin, can influence eating behaviour, lower the neurobiological stress response and anxiety among clinical populations, and alter attentional processing of food and eating related images in AN.
Methodology: Thirty adult women with AN and twenty-nine healthy comparison (HC) women took part in the current study. The study used double blind, placebo controlled, crossover design to investigate the effects of a single dose of intranasal oxytocin (40 IU) on a standard laboratory smoothie challenge, and on salivary cortisol, anxiety, and attentional bias towards food images before and after the smoothie challenge in AN and HC participants. Attentional bias was assessed using a visual probe task.
Results: Relative to placebo intranasal oxytocin reduced salivary cortisol and altered anomalies in attentional bias towards food images in the AN group only. The oxytocin-induced reduction in attentional avoidance of food images correlated with oxytocin induced reduction in salivary cortisol in the AN group before the smoothie challenge. Intranasal oxytocin did not significantly alter subjective feelings of anxiety or intake during the smoothie challenge in the AN or HC groups.
Conclusions: Intranasal oxytocin may moderate the automated information processing biases in AN and reduce neurobiological stress. Further investigation of the effects of repeated administration of oxytocin on these processes as well as on eating behaviour and subjective anxiety would be of interest.

1. Introduction

Anorexia nervosa (AN) is characterised by an intense fear of food and eating with associated avoidance behaviours and severe malnourishment (American Psychiatric Association, 2013). Over time these associations become stronger and cues related to food and eating become linked to changes in brain function and information processing biases begin to develop (Schmidt and Treasure, 2006; Treasure et al., 2012; Yackobovitch-Gavan et al., 2009). To date, a number of studies have demonstrated that relative to healthy individuals, people with AN have elevated plasma and salivary cortisol levels, which suggests a dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis (Bailer and Kaye, 2003; Connan et al., 2003; Lawson et al., 2013b; Licinio et al., 1996). Furthermore, behavioural studies have found that people with AN have elevated autonomic responses to illness-related stimuli, such as food (Léonard et al., 1998; Rigaud et al., 2007; Soussignan et al., 2011; Uher et al., 2004). A study investigating the effect of a blind gastric load of 0, 300, or 700 calories on endocrine responses in AN found that the cortisol response increased with the calorie content of the gastric load in the AN participants (Rigaud et al., 2007). Further work has also demonstrated that relative to healthy participants, people with AN report greater fear and disgust in response to food stimuli, and have elevated corrugator facial EMG (i.e. frowning) and physiological arousal response to food images and when confronted

* Corresponding author.
E-mail address: jenni.leppanen@kcl.ac.uk (J. Leppanen).

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with a test meal (Léonard et al., 1998; Soussignan et al., 2011; Uher et al., 2004).

In addition to elevated anxiety and stress around eating, people with AN also have anomalies in attention towards food (Brooks et al., 2011). A meta-analysis found that people with AN show an increased attentional bias (AB) towards food images (Brooks et al., 2011). Another study utilising eye-tracking methodology found that relative to healthy participants, people with AN showed early AB towards food images, but later avoidance of food images (Giel et al., 2011). Similarly, electroencephalogram (EEG) and magnetoencephalography (MEG) studies have found elevated early and reduced later posterior activation in people with AN compared to healthy individuals in response to food stimuli (Godier et al., 2016; Wolz et al., 2015). Interestingly, a study by Cardi et al. (2013) investigated AB towards food images before and after a standard test meal challenge and found that inpatients with AN showed greater AB towards food images following exposure to a test meal challenge. Thus, taken together, these findings suggest that anomalies in AB towards food images is a prominent feature of AN and is likely fuelled by stress and anxiety around food and eating.

Animal studies have demonstrated that the neuropeptide oxytocin is involved in many regulatory functions in the central nervous system including stress response and food intake (Cochran et al., 2013; Olszewski et al., 2010). A recent meta-analysis found that intranasal oxytocin significantly reduced cortisol response to stressful stimuli among clinical populations of people suffering from a range of disorders, including depression, substance dependence, fragile X syndrome and borderline personality disorder, characterised by a chronic dysregulated and hyperactivated HPA axis (Cardoso et al., 2014). Additionally, emerging evidence from animal studies has demonstrated that central administration of an oxytocin receptor agonist can normalise novelty-induced decrease in food intake in mice, suggesting that oxytocin may play a role in moderating the influence of stress and anxiety on eating (Olszewski et al., 2014). Thus intranasal oxytocin may be helpful facilitating exposure treatment for food restriction fuelled by anxiety.

There has been increasing interest in the possibility that oxytocin may be involved in the pathophysiology of eating disorders (Maguire et al., 2013). A recent meta-analysis reported that peripheral and cerebrospinal fluid (CSF) levels of endogenous oxytocin were significantly lower in AN relative to normal weight controls, which the authors suggested is likely associated with dysregulation of the HPA axis (Rutigliano et al., 2016). Additionally, another study has reported atypical, elevated oxytocin response to food intake in AN, which was associated with pre-meal hypoactivation of the hypothalamus, orbitofrontal cortex, insula, and amygdala in response to food images in AN relative to healthy participants (Lawson et al., 2013b; Lawson et al., 2012). Moreover, a recent proof of concept study found that a single dose of 40IU of intranasal oxytocin reduced anomalies in AB towards images of food, eating, and negative body shape in people with AN (Kim et al., 2014a). The authors also found that intranasal oxytocin led to a reduction in caloric intake in the 24 h following administration in participants with bulimia nervosa (Kim et al., 2015). These findings suggest that intranasal oxytocin can alter anomalies in attentional processes to specific and general aversive stimuli in AN and may alter eating behaviour.

The aim of the current study was to examine the impact of a single dose of intranasal oxytocin on a standard smoothie challenge, as well as neurobiological stress and AB towards food images, as measured with a visual probe task, before and after the smoothie challenge in adult women with AN and gender and age matched healthy control (HC) participants. Based on previous findings outlined above, we hypothesised that relative to HCs, participants with AN would consume less during the smoothie challenge, have elevated anxiety and salivary cortisol, and anomalies in AB towards food images before and after the smoothie challenge. Additionally, we hypothesised that oxytocin administration would decrease anxiety, increase smoothie intake, reduce cortisol and alter anomalies in AB towards food images in participants with AN.

2. Methods and materials

2.1. Participants

Fifty-nine women participated in the study. Thirty women met the DSM-5 criteria for AN, with mean BMI of 16.30 (SD = 2.04) and age of 26.20 (SD = 6.82). Diagnosis was confirmed using the Structured Clinical Interview for DSM-5 (First et al., 2015). Fifteen of the AN participants were recruited from the South London and Maudsley NHS Foundation Trust inpatient unit and were in treatment. The other fifteen AN participants were recruited through ED charities (BEAT, Succeed). Fifteen of the AN participants were taking medication (anti-depressants) during the study.

The HC participants (N = 29), with mean BMI of 23.25 (SD = 3.65) and age of 26.83 (SD = 8.54), were recruited from the community and amongst King's College London students and staff. HC participants were of normal weight and were screened for current or past psychiatric disorders, and alcohol or drug misuse with the Structured Clinical Interview for DSM-5 (First et al., 2015). Participants were excluded from the study if they reported medical or psychiatric problems, a history of or current alcohol or drug abuse, current impairments in cardiovascular functioning, pregnancy or plans to become pregnant during the study. Prior to participating in the study, all participants gave a written informed consent. Ethical approval for the study was obtained from National Research Ethics Service (NRES) committee (14/LO/0128) and all procedures were conducted in accordance with the latest declaration of Helsinki (2008).

The sample size was based on power analysis conducted with G*Power for a repeated measures design (Faul et al., 2007). To ensure adequate power (0.80) to detect an effect in the mixed model, the total recommended sample size was 60 participants.

2.2. Experimental design

The study employed a double blind, placebo controlled, within subjects, crossover design. All participants received a single dose of both oxytocin and placebo in separate sessions. The treatment order was pseudo-randomised so that half of the AN participants and half of the HC participants received oxytocin in the first session and the other half of the AN and HC participants received oxytocin in the second session. Only the Maudsley pharmacy, responsible for dispensing the compounds were aware of the order in which each participant received the compounds. The experimenter and the participants were both blind to treatment order.

The study flow chart is presented in Supplementary Fig. S1 . Prior to administration of the compounds participants were asked to provide a saliva sample for cortisol analysis, and to provide a baseline rating of anxiety on a visual analogue scale (VAS) (for further details see Supplementary information). The intranasal oxytocin and the placebo were self-administered by the participants in ten sprays, five sprays in each nostril every 45 s (for further details see Supplementary information). Fifty minutes after administration, participants gave the second saliva sample and VAS anxiety rating. The first visual probe task was then administered approximately 55 min after administration of the compound (T1; for further details see Supplementary information). This was followed by the smoothie challenge consisting of a 250 ml fruit smoothie (a choice from 3 Innocent smoothie flavours: strawberries and bananas, mangoes and passion fruits, and kiwis, apples and limes).

All labels were kept on the bottles and this contained the calorie content and nutritional information. The participants were encouraged to consume as much of the smoothie as they liked under non-supervised conditions and were left for 15 min to do this. If participants refused to have a smoothie they were informed that they did not have to have it, but were encouraged to try it and left with the smoothie for the duration of the challenge. Following this, participants gave a third VAS anxiety rating and the second visual probe task was administered, approximately 75 min after administration of the compound (T2; for further details see Supplementary information). Finally, the third saliva sample was collected approximately 80 min after administration. The timing was based on previous work investigating the effects of intranasal oxytocin on AB in eating disorders and on cerebral blood flow among healthy individuals (Kim et al., 2014a; Paloyelis et al., 2016).

The two sessions were scheduled a minimum of one day and maximum of five days apart. All HC and AN participants who were menstruating regularly during the study were tested during the follicular phase, 1–15 days following the onset of a menstrual cycle. All participants were asked to refrain from consuming any alcoholic or caffeinated beverages twelve hours prior to the sessions. Additionally, the participants were asked to not consume any food two hours prior to the sessions, in order to minimise effects of fullness and hunger on the tasks.

2.3. Visual probe task

A visual probe detection task was used to investigate AB towards and away from food and neutral, non-food images in AN. The task was amended from that used in a previous study (Cardi et al., 2013), and the food images were acquired from a standardised set of images and depicted a variety of savoury and sweet food items on a blue background (Uher et al., 2004). The food images depicted highly palatable food, and were matched for size and calorie content. The non-food images consisted of neutral images of furniture. In the visual probe detection task participants were presented with two images simultaneously on a computer screen side by side for 500 ms. One of the images then revealed one of two visual probes underneath them and participants were instructed to press specific keys on the keyboard to indicate which probe they saw. The probe was presented until participants responded. The task was presented with E-prime software (Psychology Software Tools, Sharpsburg, USA) and consisted of 96 trials. The task lasted approximately 3 min. Further details regarding the visual probe task are presented in Supplementary information.

2.4. Statistical analysis

All data was analysed using Stata 14 (StataCorp, 2015) and $p < 0.05$ was considered significant. The self-report questionnaire data were analysed with non-parametric two-sample median Chi^2 tests. Effect sizes were estimated with Cramer's ϕ, which can be interpreted as small (0.10), medium (0.30), or large (0.50) (Cohen, 1988).

Due to the highly skewed nature of the smoothie data, logarithm 10 transformation was performed prior to analysis. Group differences in smoothie intake in millilitres (ml) consumed as well as the effect of oxytocin/placebo on consumption were then analysed with a bootstrapped mixed linear model with 1000 repetitions using the *bootstrap* and *mixed* functions in Stata (StataCorp, 2015). Significant interactions were further investigated by computing post-hoc contrasts and pairwise comparisons.

The AB data was analysed separately for the 500 ms and 1250 ms ITI blocks with a $2 \times 2 \times 2$ mixed linear model using the *mixed* function with bootstrapping (1000 repetitions) in Stata 14 (StataCorp, 2015). Drug (oxytocin, placebo), time (before smoothie challenge, after smoothie challenge), and group (AN, HC) were entered as fixed effects with a random intercept and random slope on drug. Similarly, the VAS anxiety and salivary cortisol data were analysed with a $2 \times 3 \times 2$ bootstrapped mixed model with drug (oxytocin, placebo), time (baseline, before smoothie challenge, after smoothie challenge), and group (AN, HC) and a random intercept and random slope on drug. Significant interactions were explored further by calculating contrasts and pairwise post-hoc comparisons using the *contrast* and *pwcompare* functions (StataCorp, 2015).

We additionally explored whether oxytocin induced changes in AB scores correlated with oxytocin induced changes in VAS anxiety ratings and salivary cortisol before and after the smoothie challenge within the AN group. AB delta scores were calculated by first adding a constant to all AB data to ensure no AB scores were negative. The AB scores from the placebo session were then subtracted from the AB scores from the oxytocin session. Thus, negative scores indicated greater AB towards food images in the placebo session and positive scores indicated greater AB towards food images in the oxytocin session. VAS anxiety and salivary cortisol delta scores were calculated in a similar manner. We then conducted correlation analyses to investigate significant correlations between the deltas in Stata using the *spearman* function (StataCorp, 2015).

Effects of medication status on AB, salivary cortisol, and VAS anxiety ratings as well as on the effects of oxytocin are presented in Supplementary information.

3. Results

3.1. Demographic and clinical characteristics

The clinical and self-report questionnaire data is presented in Table 1 and was corrected for multiple comparisons with the false discovery rate set at $q < 0.05$ (Benjamini and Hochberg, 1995). Following correction, $p < 0.04$ was considered significant. The AN and HC groups were matched for age, and as expected the AN group had lower BMI than the HC group. The AN group also scored higher on the EDEQ reporting higher levels of restraint, eating concern, weight concern, and shape concern compared to the HC group. Additionally, the AN group scored higher on the DASS reporting elevated levels of depression, anxiety, and stress relative to the HC group.

3.2. Smoothie intake

Smoothie intake in the oxytocin and placebo conditions are summarised separately for each group in Table 2 (see Supplementary Fig. S2). The mixed model revealed a significant effect of Group, with HC participants consuming significantly more smoothie during the challenge than AN participants across conditions. There was no significant effect of Drug or Drug x Group interaction. Eleven AN participants did not consume any of the smoothie in the placebo condition, and nine of these eleven AN participants also did not consume any smoothie in the oxytocin condition.

3.3. AB: 500 ms ITI blocks

The AB scores in the 500 ms ITI blocks among the AN and HC groups following oxytocin and placebo administration are presented in Table 3 (see Supplementary Fig. S3A,B). P-values were corrected for multiple comparisons with the false discovery rate set at $q < 0.05$ (Benjamini and Hochberg, 1995). Following correction, $p < 0.02$ was considered significant.

The mixed model revealed a significant Drug x Time x Group interactions (Table 3). The 3-way interaction was further investigated in three ways. First we explored the Drug x Time interaction separately within the AN and HC groups. The results revealed

Table 1
Clinical and demographic sample characteristics.

	AN (N = 30) Median	Q1	Q3	HC (N = 29) Median	Q1	Q3	AN vs HC X^2 statistic, p value	Cramer's ϕ
BMI	16.13	14.56	18.14	22.21	20.78	25.51	$X^2 = 35.55$, $p < 0.001$	0.78
Age	24.50	22.00	28.25	25.00	23.00	27.50	$X^2 = 0.02$, $p = 0.875$	0.02
EDEQ total	4.13	3.00	5.13	0.59	0.34	1.00	$X^2 = 35.27$, $p < 0.001$	0.77
EDEQ restraint	3.70	2.60	5.05	0.60	0.00	1.70	$X^2 = 20.79$, $p < 0.001$	0.59
EDEQ weight concern	4.20	2.70	5.65	0.60	0.30	1.40	$X^2 = 31.38$, $p < 0.001$	0.73
EDEQ shape concern	4.86	3.56	5.91	0.75	0.38	1.38	$X^2 = 41.67$, $p < 0.001$	0.84
EDEQ eating concern	4.10	2.90	4.80	0.20	0.00	0.40	$X^2 = 41.67$, $p < 0.001$	0.84
DASS Total	63.00	40.00	86.00	4.00	1.00	10.00	$X^2 = 37.49$, $p < 0.001$	0.80
DASS Depression	21.00	13.50	32.00	0.00	0.00	2.00	$X^2 = 26.61$, $p < 0.001$	0.67
DASS Anxiety	12.00	6.00	21.00	0.00	0.00	2.00	$X^2 = 29.07$, $p < 0.001$	0.70
DASS Stress	25.00	17.50	31.00	2.00	0.00	7.00	$X^2 = 37.49$, $p < 0.001$	0.80

AN = anorexia nervosa, HC = healthy comparison, BMI = Body mass index, EDEQ = Eating Disorder Examination Questionnaire, DASS = Depression, Anxiety, and Stress Scale.

Table 2
Smoothie intake in millilitres (ml) in the AN and HC groups in the oxytocin and placebo conditions.

Drug	AN (N = 30) Mean (SD)	HC (N = 29) Mean (SD)	X^2 statistic, p value
Oxytocin	113.10 (102.94)	224.24 (47.58)	Drug: $X^2 = X^2 = 1.39$, $p = 0.239$
Placebo	99.07 (102.16)	237.52 (30.29)	Group: $X^2 = X^2 = 131.66$, $p < 0.001$
			Drug x Group: $X^2 = X^2 < 0.01$, $p = 0.975$

AN = anorexia nervosa, HC = healthy comparison.

Table 3
AB towards food images before and after the test meal in the AN and HC groups.

ITI	Time	Drug	AN (N = 30) Mean (SD)	HC (N = 29) Mean (SD)	X^2 statistic, p value
500 ms	Before test meal	Oxytocin	−2.66 (33.57)	2.52 (36.79)	Drug: $X^2 = 1.41$, $p = 0.234$
		Placebo	−13.69 (29.27)	13.86 (42.70)	Time: $X^2 = 0.08$, $p = 0.780$
	After test meal	Oxytocin	−13.64 (38.78)	0.41 (43.66)	Group: $X^2 = 3.47$, $p = 0.063$
		Placebo	10.64 (34.42)	−2.99 (42.55)	Drug x Time: $X^2 = 0.09$, $p = 0.764$
					Drug x Group: $X^2 = 1.06$, $p = 0.302$
					Time x Group: $X^2 = 2.81$, $p = 0.093$
					Drug x Time x Group: $X^2 = 6.49$, 0.011
1250 ms	Before test meal	Oxytocin	−5.06 (30.85)	8.66 (43.47)	Drug: $X^2 = 0.41$, $p = 0.524$
		Placebo	2.64 (34.08)	−4.53 (35.44)	Time: $X^2 = 1.97$, $p = 0.160$
	After test meal	Oxytocin	−6.78 (48.86)	−5.24 (67.38)	Group: $X^2 = 0.01$, 0.925
		Placebo	−8.13 (41.65)	−13.95 (44.29)	Drug x Time: $X^2 = 0.03$, $p = 0.863$
					Drug x Group: $X^2 = 1.47$, $p = 0.226$
					Time x Group: $X^2 = 0.18$, $p = 0.669$
					Drug x Time x Group: $X^2 = 0.29$, $p = 0.591$

AN = anorexia nervosa, HC = healthy comparison, AB = Attentional bias, ITI = inter-trial interval.

that the Drug x Time interaction was significant within the AN group ($X^2 = 7.78$, $p = 0.005$), but not within the HC group ($X^2 = 0.94$, $p = 0.333$). The interaction was then further investigated within the AN group by exploring the effects of Drug at T1 and T2. The results revealed that oxytocin administration significantly reduced AB towards food images in the AN group at T2, after the smoothie challenge, ($Z = -2.72$, $p = 0.007$, 95% CI [−41.78, −6.78]), but not at T1, before the smoothie challenge al, ($Z = 1.38$, $p = 0.168$, 95% CI [−4.66, 26.72]).

Finally, we explored the Group x Time interaction separately in the oxytocin and placebo conditions. The results revealed a significant Group x Time interaction only in the placebo condition ($X^2 = 10.03$, $p = 0.002$), but not in the oxytocin condition ($X^2 = 0.38$, $p = 0.540$). When group differences were explored further, the results revealed that AN participants showed significantly more AB away from food images than HC participants at T1, before the smoothie challenge, ($Z = -3.08$, $p = 0.002$, 95% CI [−45.09, −10.02]), but not at T2, after the smoothie challenge, ($Z = 1.56$, $p = 0.118$, 95% CI [−3.46, 30.71]).

We then explored the Group x Drug interaction separately at T1 and T2, which revealed no significant interaction at T1, before the smoothie challenge ($X^2 = 3.06$, $p = 0.080$), or at T2, after the smoothie challenge ($X^2 = 4.13$, $p = 0.042$).

3.4. AB: 1250 ms ITI blocks

The attentional bias scores in the 1250 ms ITI blocks among the AN and HC groups following oxytocin and placebo administration are presented in Supplementary Fig. S4A,B. The drug x time x group mixed model revealed no significant effects or interactions in the 1250 ms ITI blocks (Supplementary Table S1).

3.5. Salivary cortisol

Mean salivary cortisol levels are presented separately for each group in the oxytocin and placebo conditions in Table 4 (see Supplementary Fig. S5). The mixed model revealed a significant effect of Group, with AN participants having significantly higher cortisol levels than HC participants across conditions and time points (Table 4).

The mixed model additionally revealed a significant Drug x Group interaction. The interaction was further explored by exploring the effect of Drug on salivary cortisol separately in each group. The results revealed a significant effect of Drug in the AN group ($Z = -1.99$, $p = 0.046$, 95% CI [−1.30, −0.01]), with AN participants having lower salivary cortisol levels in the oxytocin condition. There was no significant difference between oxytocin

Table 4
Salivary cortisol at each time point in the AN and HC groups.

Time	Drug	AN (N = 30) Mean (SD)	HC (N = 29) Mean (SD)	X^2 statistic, p value
Baseline	Oxytocin	5.35 (5.66)	3.71 (3.68)	Drug: $X^2 = 0.37$, p = 0.542
	Placebo	5.35 (3.31)	3.18 (2.67)	Time: $X^2 = 6.91$, p = 0.032
Before smoothie challenge	Oxytocin	4.81 (3.35)	2.57 (2.10)	Group: $X^2 = 179.21$, p < 0.001
	Placebo	5.54 (4.04)	2.24 (1.75)	Drug x Time: $X^2 = 1.46$, p = 0.482
After smoothie challenge	Oxytocin	4.69 (3.14)	2.59 (1.92)	Drug x Group: $X^2 = 7.22$, p = 0.007
	Placebo	5.93 (4.48)	2.09 (1.57)	Time x Group: $X^2 = 4.33$, p = 0.115
				Drug x Time x Group: $X^2 = 1.38$, p = 0.502

AN = anorexia nervosa, HC = healthy comparison.

and placebo in the HC group (Z = 1.94, p = 0.052, 95% CI [−0.004, 0.84]).

3.6. Self-reported VAS anxiety ratings

Mean VAS anxiety ratings are presented separately for each group in the oxytocin and placebo conditions in Supplementary Fig. S6 . The mixed model exploring group differences in anxiety ratings at different time points in the oxytocin and placebo conditions revealed a significant effect of Time (Supplementary Table S2). VAS anxiety ratings were significantly higher after the smoothie challenge than before the smoothie challenge across groups (Z = 3.62, p < 0.001, 95% CI [0.03, 0.09]). There were no significant differences in self-reported anxiety at baseline and before the smoothie challenge (Z = −1.85, p = 0.064, 95% CI [−0.07, 0.002]) or at baseline and after the smoothie challenge (Z = 1.21, p = 0.224, 95% CI [−0.01, 0.06]).

3.7. Correlations between oxytocin-induced changes in AB, anxiety, and salivary cortisol

The correlational analysis revealed a significant inverse correlation between salivary cortisol delta scores and oxytocin-induced changes in AB before the smoothie challenge (ρ = −0.41, p = 0.026). Inverse correlation between VAS anxiety delta scores and oxytocin induced changes in AB before the smoothie challenge also approached significance (ρ = −0.31, p = 0.097). There were no significant correlations between oxytocin-induced changes in AB and cortisol delta scores (ρ = −0.11, p = 0.574), anxiety delta scores (ρ = −0.08, p = 0.692) after the smoothie challenge, or BMI (before smoothie challenge: ρ = 0.09, p = 0.631, after smoothie challenge: ρ = 0.06, p = 0.752).

4. Discussion

The aim of the current study was to examine the effects of a single dose of intranasal oxytocin on smoothie intake during a standard smoothie challenge as well as on salivary cortisol and AB towards food images before and after the smoothie challenge. As hypothesised, relative to HCs, the majority of the AN participants consumed less smoothie during the smoothie challenge and had elevated anxiety and salivary cortisol levels, and showed anomalies in AB towards food images. Contrary to what was hypothesised, oxytocin administration did not significantly influence smoothie intake among the AN or HC participants nor did it moderate subjective anxiety. However as postulated, oxytocin administration significantly reduced salivary cortisol and reduced the anomalies in AB towards food images in people with AN. Additionally, correlational analysis revealed an association between oxytocin-induced reduction in salivary cortisol and attentional avoidance of food images before the smoothie challenge.

The current findings revealed that relative to the HC group, the AN participants had significantly higher salivary cortisol, and intranasal oxytocin reduced salivary cortisol levels across time points in the AN group only. This supports findings from a recent 6-week pilot trial that reported reductions in salivary cortisol levels and anticipatory cortisol response to an afternoon snack among inpatients with AN following repeated twice-daily administration of 18IU of intranasal oxytocin (Russell et al., 2013). This is also consistent with findings from a recent meta-analysis, which found that intranasal oxytocin reduced the cortisol response to stressful stimuli among clinical populations, with conditions characterised by dysregulation of the HPA axis (Cardoso et al., 2014). These findings suggest that oxytocin is able to moderate both acute and chronic stress response among clinical populations. Previous work has suggested that increased availability of another hypothalamic neuropeptide, vasopressin, plays an important role in dysregulated and elevated neurobiological stress response in AN (Connan et al., 2003). Oxytocin may moderate this system by reducing vasopressin availability, thus, reducing elevated stress response (Heinrichs and Domes, 2008; Heinrichs et al., 2009). Another possibility is that the dysregulation of the HPA axis and associated elevated stress response are due to a failure in the stress-induced up-regulation of endogenous oxytocin (Zheng et al., 2010). Intranasal oxytocin may then moderate the stress response by regulating HPA axis activity (Neumann and Slattery, 2016). Although the exact mechanism of the effects of oxytocin on neurobiological stress is still not clear and need further exploration, these findings raise the possibility that oxytocin might have a role as a neuroenhancer that facilitates extinction learning as has been proposed based on recent findings from animal studies (Eckstein et al., 2015; Hofmann et al., 2015; Stockhorst and Antov, 2016).

The current study also found that relative to HCs, AN participants had anomalies in AB towards food images, showing greater avoidance of food images before the smoothie challenge and greater bias towards food images after the smoothie challenge, although this failed to reach significance. Oxytocin administration altered these anomalies significantly reducing bias towards food images after the smoothie challenge in the AN group. The moderation of the anomalies in AB toward food are in keeping with previous work exploring the effects of intranasal oxytocin on attentional processing in AN (Kim et al., 2014a; Kim et al., 2014b). The authors reported that intranasal oxytocin significantly reduced bias towards illness-related stimuli, including images of food, eating, fat body shape, and disgusted faces in AN (Kim et al., 2014a; Kim et al., 2014b). These findings suggest that intranasal oxytocin can alter automated attentional processing of illness-related stimuli, which would otherwise be difficult to target through talking therapies. Additionally, it has recently been suggested that oxytocin may be a useful supplement to treatment as usual in eating disorders (Maguire et al., 2013; Treasure et al., 2015).

The current study also attempted to explore the mechanism of the effects of oxytocin on attentional processes. The findings revealed a significant inverse correlation between oxytocin-induced reduction in AB away from food images and oxytocin-induced reduction in salivary cortisol before the smoothie challenge. These findings suggest that as intranasal oxytocin reduced salivary cortisol, it also reduced attentional avoidance

of food images before the smoothie challenge. This is in accordance with findings from animal studies demonstrating that central oxytocin release reduces neurobiological stress and stress-related behaviours, such as hiding during an open field test and periods of immobility during forced swimming test (Chaviaras et al., 2010; Zheng et al., 2010). These findings are also supported by a previous functional neuroimaging study, which found that intranasal oxytocin normalises anxiety-induced amygdala hyper-reactivity to threatening, illness related stimuli in generalised social anxiety disorder (Labuschagne et al., 2010). Furthermore, among people with fragile X syndrome, characterised by autism-like difficulties in social processing, intranasal oxytocin has been shown to reduce salivary cortisol and improve eye gaze during social interaction (Hall et al., 2012). However, it is of note that in the current study we were not able to find a significant correlation between oxytocin-induced changes in AB towards food images and salivary cortisol or self-reported anxiety, which may have been due to timing of the final saliva sample collected after the smoothie challenge (Hellhammer et al., 2009). Therefore, further research using functional neuroimaging techniques are needed to further examine the mechanism through which intranasal oxytocin alters attentional processes in AN.

Oxytocin administration did not significantly alter smoothie intake in either the AN or HC group in the current study. Previous findings from studies investigating the effects of a single dose of intranasal oxytocin on eating behaviour in humans are variable (Olszewski et al., 2016). One study reported that intranasal oxytocin reduced food intake during a buffet test meal in healthy men following an overnight fast (Lawson et al., 2015). On the other hand, another study failed to find significant oxytocin-induced reduction in food intake during a buffet breakfast following an overnight fast (Ott et al., 2013). Instead the authors reported that intranasal oxytocin reduced hedonic snacking two hours after the test meal (Ott et al., 2013). Interestingly, the buffet test meal in the Lawson et al. (2015) had more variety and contained more options than that in the Ott et al. (2013) study. Variety has been shown to be an important factor increasing hedonic value of food and intake during buffet test meals (Brondel et al., 2009; Hetherington et al., 2006). The current study conducted in the afternoon and participants had not consumed any food for at least three hours by the time they were introduced to the test meal consisting of a single fruit smoothie. It is probable that clinical status, hedonic hunger, and the context of the test meal may influence the effect of oxytocin on eating.

Considering the important role that chronic neurobiological stress and information processing biases play in the maintenance of disordered eating, it was perhaps surprising that oxytocin-induced reduction in salivary cortisol and in automated AB towards food images did not translate into greater intake during the smoothie challenge and less anxiety throughout the session. It is possible that a test meal disguised as a "taste test" might be a more sensitive outcome as it would allow a covert assessment of intake of various different types of food and micronutrients. Additionally, using ecologically valid assessments such as 24-h food diaries could help to further investigate the effects of intranasal oxytocin on food intake under naturalistic settings. Indeed, a recent proof of concept study by Kim et al. (2015), which used 24-h food diaries, found that a single dose of intranasal oxytocin reduced caloric intake among people with bulimia nervosa. The authors did not find any increase in caloric intake among people with AN (Kim et al., 2015). However, it is of not that the AN participants in the Kim et al. (2015) study were all inpatients undergoing treatment. Thus, further investigation of the effects of intranasal oxytocin on food intake among people with AN under naturalistic conditions would be necessary before recommendations regarding its potential as an add-on treatment can be made.

Finally, the demographic data, including questionnaire responses, age, and BMI, in the current study was skewed. However this is not unusual with questionnaire and other measures that contain natural boundaries, below or above which the data can't reach (Diez et al., 2015). For instance, the age data is skewed because in the current study we only recruited adults over the age of 18. Therefore, we have a natural boundary at 18 years and for this reason the data has a right skew. Similarly, a person's BMI cannot be below a certain point, but there is no clear upper limit, meaning that the data has a natural right skew.

4.1. Limitations

One of the limitations of the current study was the smoothie challenge used in the current study, which differed from test meal challenges employed in other studies (Khalsa et al., 2015; Lawson et al., 2013a; Steinglass et al., 2014). The fruit smoothies are marketed as healthy and previous studies found them to be acceptable for the AN participants (Cardi et al., 2013). However, the smoothie challenge consisted of a single 250 ml smoothie, which in some cases led to ceiling effects. Future studies may benefit from employing test meals that include both high and low calorie options. Additionally, since the smoothie options varied slightly in their calorie content (range: 126–140 Kcal), we were not able to validly analyse the data in calories consumed during the challenge. Future studies using similar smoothie challenge paradigm may benefit from matching the smoothies offered for caloric content.

Additionally, the type of visual probe task used to measure attention in the current study precluded the measurement of timing related changes in AB. Future research may benefit from exploring the effects of oxytocin on early and late attentional processes in AN using eye tracking and functional neuroimaging techniques such as EEG and MEG. Furthermore, the neutral images consisted of pictures of furniture and rooms, which were not similarly standardised as the food images. Although, prior to the study, effort was taken to ensure the images were as visually appealing as the food images, in terms of colour and contrast, this may have added noise to the data. It has also been recently proposed that standardised images should be used in order to improve comparability of studies and increase replicability and reproducibility of findings (Blechert et al., 2014).

Further, the sessions were very close together. Although, this was unlikely to influence the results of the rapid behavioural task and biological measures, it would be beneficial for the current findings to be replicated with a larger study using a longer period between the sessions.

Finally, salivary cortisol measures were taken only at three different time points. It is possible that we did not find a correlation between oxytocin-induced changes in salivary cortisol and AB after the smoothie challenge because the saliva sample was taken too soon after the challenge. It has been suggested that relative to psychological responses, there can be considerable lag in the cortisol response to stressful, anxiety-provoking stimuli (Hellhammer et al., 2009). Future research would benefits from building on these findings and further investigating the timeline of the effects of oxytocin on stress in AN and how these effects may correlate with psychological responses.

5. Conclusions

The current study examined the effects of a single dose of intranasal oxytocin on a smoothie challenge, salivary cortisol, and AB towards food images in AN. The findings revealed that intranasal oxytocin did not significantly increase smoothie intake during the smoothie challenge, but did significantly reduce salivary cortisol in

the AN group. Oxytocin did influence food-related attentional bias, which correlated with oxytocin-induced reduction in salivary cortisol in the AN group. Taken together, these findings suggest that the oxytocin may be helpful in altering automatic information processing biases and inhibiting the hyperactivation of the HPA axis and may enhance the therapeutic benefits of food exposure paradigms in anorexia nervosa. Still, it will be necessary to further examine the exact mechanism through which oxytocin exerts its effects in AN as well as the effects of chronic administration on illness related processes and eating behaviours over the long term, before any recommendation can be made regarding whether intranasal oxytocin could be introduced into treatment of AN.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.psyneuen.2017.01.017.

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