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The effect of intranasal oxytocin on the perception of affective touch and multisensory integration in anorexia nervosa: protocol for a double-blind placebo-controlled crossover study

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ABSTRACT

Introduction Anorexia nervosa (AN) is an eating disorder characterised by restriction of energy intake, fears of gaining weight and related body image disturbances. The oxytocinergic system has been proposed as a pathophysiological candidate for AN. Oxytocin is a neuropeptide involved in bodily processes (eg, breast feeding) and in the onset of social behaviours (eg, bonding). Studies investigating the effect of intranasal oxytocin (IN-OT) in AN showed that it can improve attentional bias for high-calorie food and fat bodies stimuli, and related stress. However, less is known about the effect of IN-OT on bodily awareness and body image distortions, key features of the disorder linked to its development, prognosis and maintenance. Here, we aim to investigate the effect of IN-OT on the perception of affective, C-tactile-optimal touch, known to be impaired in AN and on multisensory integration processes underlying a body ownership illusion (ie, rubber hand illusion). For exploratory purposes, we will also investigate the effect of IN-OT on another interoceptive modality, namely cardiac awareness and its relationship with affective touch.

Design, methods and analysis Forty women with AN and forty matched healthy controls will be recruited and tested in two separate sessions; self-administering IN-OT (40 IU) or placebo, intranasally, in a pseudo-randomised manner. The data from this double-blind, placebo-controlled, cross-over study will be analysed using linear mixed models that allow the use of both fixed (treatment levels) and random (subjects) effects in the same analysis. To address our main hypotheses, separate analyses will be run for the affective touch task, where the primary outcome dependent variable will be the pleasantness of the touch, and for the rubber hand illusion, where we will investigate multisensory integration quantified as subjective embodiment towards the rubber hand. In the latter, we will manipulate the synchronicity of touch and the size of the hand.

Ethics and dissemination Ethics approval has been obtained by National Research Ethics Service NRES Committee London (Queen's Square Committee, ref number 14/LO/1593). The results will be disseminated through conference presentations and publication in peer-reviewed journals.

Strengths and limitations of this study

- The first experimental study to investigate the effect of intranasal oxytocin on the perception and integration of interoceptive and exteroceptive modalities, and their role in body representation, in people with anorexia nervosa.
- The first study to examine the role of intranasal oxytocin on explicit and implicit, experimental measures of body image and representation in anorexia nervosa.
- One of the few studies to have sufficient power (0.80) to investigate the effect of intranasal oxytocin on embodied, behavioural and affective tasks in a double blind, placebo-controlled, crossover study in a female sample, combining participants with and without anorexia nervosa.
- A limitation of this study is that it will investigate the effect of a single dose of intranasal oxytocin; therefore, no conclusions about dose-response or longitudinal treatment effects can be drawn.
- Future studies could include a group who have recovered from anorexia nervosa to provide a better understanding of the relationship between oxytocin, malnutrition and body image distortions.

INTRODUCTION

Anorexia nervosa (AN) is an eating disorder characterised by restriction of energy intake, fears of gaining weight and related body shape and size disturbances.[1] AN is associated with severe morbidity and yields the highest mortality rate of any psychiatric illness (5%–7%[2]). The aetiology is not fully understood; however, there is significant progress in formulating mechanism-based rather than diagnosis-based models and the appreciation that AN is heterogeneous and shares dimensions of psychopathology with other psychiatric illnesses.[3 4] Nevertheless, despite this progress, treatment outcomes

to date are modest and randomised control trials have higher drop-out rates than other psychiatric conditions.[5] One reason is AN's 'ego-syntonic' nature, with some patients experiencing their restrictive eating as adaptive given their anxieties about their body image and fears of losing control over it.[6] Unfortunately, body awareness and related body image distortions fall outside the scope of current biopsychosocial models of AN[3] (but see ref 7 for recent conceptualisations). This study will explore for the first time the relation between multisensory body awareness, including interoceptive perception and awareness (ie, the sense of the physiological condition of the body[8]), and a pathophysiological candidate for AN, namely the oxytocinergic system.

Recent studies suggest that oxytocin (OT) may be involved in the pathophysiology of AN (see refs 9 10 for reviews). OT is a neuropeptide consisting of nine amino acids, synthesised in the hypothalamus. OT acts both peripherally as a hormone and centrally as a neurotransmitter (see ref [11] for reviews). Patients with AN have reduced central[12] (see ref 13 for a systematic review and meta-analysis) and peripheral level[14] of OT at baseline and in response to stimulation with estrogens.[15] In underweight patients, low OT levels might enhance the retention of cognitive distortions of the negative consequences of food intake, therefore reinforcing these patients' perseverative worrying with weight gain.[9] Other studies reported low basal serum OT levels in women with AN[14] and those with a history of AN who are now weight-restored and in partial or full recovery.[16 17] These data seem to suggest that OT level may be low in women with AN regardless of their weight and raise the question of whether low OT levels may contribute to symptoms. A recent study showed that lower OT levels are associated with increased severity of social-emotional functioning impairment and greater severity of alexithymia in AN.[18] Double-blind, placebo-controlled studies in AN showed that the administration of 40IU intranasal oxytocin (IN-OT) can improve attentional bias towards food images and stress perception[19–22] but not emotional recognition.[22] Furthermore, it has been suggested that OT might positively support recovery, by reducing the stress associated with food intake[23] (but see ref [24]). However, to our knowledge, only two recent studies[25 26] so far have investigated the effect of IN-OT on interoceptive accuracy in healthy population reporting inconsistent findings (see below for details), but no study investigated such effects in AN and in relation to body awareness and body image distortions. As aforementioned, body awareness and body image distortions are important and long-identified facets of the disorder, linked to development, prognosis and maintenance of AN, as well as its relapse.[27–29] Nevertheless, these have not received sufficient neuroscientific attention as other facets of the disorders such as anxiety, cognitive control, or appetitive motivation.[30 31]

Body awareness and body image distortions can be investigated using bodily illusions such as the rubber hand illusion (RHI[32]). The RHI involves conflicts between internally felt sensations (eg, proprioception) and externally seen sensations (eg, touch on the other body). Recent studies have investigated multisensory integration across interoceptive (ie, cardiac awareness) and exteroceptive modalities in the RHI. Specifically, interoception accuracy, in the sense of how good or bad participants perform in a heartbeat counting task[33] seems to predict the susceptibility to the RHI, considered as a measure of malleability of the sense of body ownership[34–36] (but see ref 37).

Computational approaches to multisensory integration[38] illusions such as the RHI[39] have shown that such cross-modal conflicts are resolved in a Bayes-optimal manner, by differential weighting of the various sensory signals.[40 41] Specifically, Zeller and colleagues showed that in order to resolve the uncertainty between the conflicting visual, proprioceptive and tactile information in the RHI, the brain downregulates the precision (the inverse of variance in their model[42];) of ascending somatosensory prediction errors so that they will have less influence on top-down, predicted sensory signals about the body.[41 43] In support of this idea, Zeller and colleagues found that touch-evoked electroencephalography potentials derived by brush-strokes during the RHI are selectively attenuated by reducing their precision.[43] These results are consistent with the idea that in the RHI the precision of somatosensory signals (vs precision of visual signals) needs to be attenuated in order to resolve conflicting perceptual hypotheses about the most likely cause of sensations.[41 43]

People with AN, as well as sub-clinical eating disorders, are particularly susceptible to the visual manipulations of multisensory integration paradigms (ie, 'visual capture' effect), in the sense that they show increased feelings of ownership of a fake body part, irrespective of synchronicity between the seen and felt touch.[44–46] One possible explanation could lie on the fact that they have low precision or even deficits in internal, somatosensory and interoceptive signals from the body, and thus an over-reliance on visual bodily signals from the outside. Indeed, our group and others have already provided some evidence for tactile and interoceptive deficits in this population, such as perception of taste, pain, cardiac awareness and more recently 'affective touch'.[47–52] Most importantly for this study, a newly discovered class of C tactile (CT) afferents in the human skin that respond preferentially to low pressure and slow-velocity dynamic touch are associated with the perception of tactile pleasantness,[53] and positive emotions.[54] Accordingly, this modality has been redefined as an interoceptive modality, providing information about the internal, physiological state of the body and clearly separated from other discriminatory, exteroceptive sensations[8] (see refs 55 56 for reviews). Functional imaging studies in humans suggest the posterior insular cortex as a primary cortical target for CT-optimal touch (see refs 57 58 for a meta-analysis), an area containing a primary representation of the physical condition of the body and declared as interoceptive cortex.[8 59] Thus, CT afferents share more characteristics with interoceptive

compared with exteroceptive modalities, not least considering the slow, affective nature of the percept.[59] Several researchers continue to use the term interoception in its classic meaning; however, here we embrace this new reclassification of interoception, which includes both internally and externally originated bodily signals,[56] and we think offers an important view on homeostatic and affective regulation.[8 37 60]

Importantly, affective touch has been found to play a particularly important role on feelings of body ownership in healthy subjects. Specifically, several independent studies using the RHI paradigm have now shown that this modality enhances the subjective feelings and in some studies also objective measures of body ownership towards the rubber hand during optimal (synchronous) conditions for multisensory integration.[37 61–63] However, people with AN show reduced subjective pleasantness and abnormal brain processing in response to CT-optimal touch in comparison to healthy controls,[52 64] and no study has assessed whether such tactile anhedonia may relate to how individuals with AN respond to multisensory integration paradigms such as the RHI. As aforementioned, their tendency to report feelings of body ownership for a rubber hand even during suboptimal multisensory integration conditions may relate to the fact that somatosensory and interoceptive signals from the body are not as strong in this population. The present study will be addressing this hypothesis, as well as the possibility that IN-OT can enhance feelings of tactile pleasure and hence body ownership during optimal multisensory integration conditions (ie, synchronous touch during the RHI).

Interestingly, interoceptive abnormalities have been associated with altered activity in the insular cortex (eg, refs 51 65) This area and particularly the right anterior insula was recently linked also to feelings of body satisfaction during a body representation task.[66] Yet, the influence of interoception on body representation in AN, and the potential effect of IN-OT on this relationship, remain surprisingly unexplored and will be investigated in this study as specified below.

Primary aims and hypotheses

This study follows a double-blinded, placebo-controlled, crossover design, with treatment (oxytocin vs placebo) as the within-subjects factor (40 IU; two separate sessions; randomised allocation AB/BA[67]). The main aims of the study will be to investigate the effect of a single dose of IN-OT versus placebo on (1) the perceived pleasantness of affective, CT-optimal touch and emotionally neutral, non-CT optimal touch and (2) the multisensory integration processes underlying the classic RHI, as well as (3) an enhanced version in which we manipulated the size of the rubber hand, in women with AN and healthy controls. Our related predictions are outlined below.

First, we hypothesise that IN-OT would enhance the perceived pleasantness of touch (both CT-optimal and non-CT optimal touch) to a greater extent in people with AN compared with healthy controls, that is oxytocin will improve the tactile anhedonia which characterises AN (ie, main effect of compound; main effect of group and significant interaction compound X group, irrespective of velocity). We expect to see a greater difference in pleasantness ratings between groups under the placebo condition; in contrast, we anticipate that we will observe a smaller difference in pleasantness ratings between groups following administration of IN-OT.

A recent behavioural study did not find any effect of IN-OT on the hedonic experience of affective touch.[68] However, it should be pointed out that the study did not control for contextual effects that could have played a role in the experimental setting, such as the gender of the person delivering the touch. Furthermore, the sample comprised both men and women, with female participants recruited in different phases of their menstrual cycle, and without considering the use of contraceptive (see ref 69 for evidence that plasma oxytocin varies across the menstrual phase and effect of contraceptive pill on hormonal levels). Also, the experimenter delivered the touch with his/her hand covered with a silk glove, rather than by means of the traditional brush used in studies investigating the perception of CT optimal touch[53 70] and at a CT optimal velocity only. These aspects of the experimental design might have played a role in the perceived pleasantness of the touch, and they do not allow firm conclusions to be made regarding the specific involvement of the CT afferents system, since a non-CT optimal control condition was not included. Therefore, the potential effect of IN-OT on tactile pleasantness remains an open question, and it should be compared with the potential modulation of emotionally neutral touch using standard procedures while controlling for velocity of touch, gender of the toucher and testing time within the menstrual cycle.

Second, we anticipate that IN-OT will lead to stronger feelings of subjective embodiment during a RHI paradigm compared with placebo, and the effect will be modulated by synchronicity of touch during the illusion, in the sense that IN-OT would have a larger effect following synchronous touch compared with asynchronous touch (ie, main effect of synchronicity, significant interaction synchronicity X compound, irrespective of group). We expect a main effect of group in the subjective embodiment, in the sense that we expect the AN group to have a stronger experience of the RHI regardless of synchronicity of visuotactile simulation (as in ref 71). Finally, we predict that IN-OT will enhance the multisensory integration process also during the RHI with a larger hand. We will observe a main effect of group, in the sense that only people with AN will have a higher susceptibility to the illusion when they will see a larger hand compared with a regular hand, given the body image distortions which characterise the disorder.

We also expect a significant interaction between group and compound, with IN-OT increasing this effect in people with AN only.

Any significant interaction relative to our main hypotheses will be followed up by appropriate post hoc analyses (ie, t-test corrected for multiple comparisons).

Secondary exploratory aims and hypotheses

Given that no previous studies on AN or IN-OT have assessed some of the cognitive and affective domains of interest, and the available time window of IN-OT effects, this study also explores a number of secondary hypotheses. These will be accordingly analysed with exploratory statistical analyses, the results of which will need to be further examined in future confirmatory studies. Specifically, a secondary aim of this study is to explore whether any of the hypothesised effects on affective touch in the AN group (see above) are specific to this modality or they can be generalised to other interoceptive modalities such as cardiac awareness. We hypothesise that people with AN will show a reduced interoceptive accuracy compared with healthy controls. Since interoceptive accuracy can be considered as a trait measurement stable in time[72] and in light of recent studies showing inconsistent effects of IN-OT on this modality,[25 26] no main effect of IN-OT versus placebo on cardiac awareness per se is expected. However, we expect to observe differences in the effect of IN-OT on interoceptive accuracy between groups (ie, a compound by group interaction). Specifically, since IN-OT seems to improve attentional bias in AN, we expect IN-OT to have a larger effect in improving cardiac awareness in AN compared with healthy controls. Additionally, we aim to investigate the relationship between interoceptive accuracy and affective touch (as in ref 37) and multisensory integration as measured by means of the RHI. We are planning to do so by means of correlational analysis and by analysing the effect of velocity of touch (CT optimal vs non-CT optimal) on the embodiment of the rubber hand.

The same hypotheses described above for the subjective embodiment in the RHI will also be investigated in exploratory analyses with the perceived location of the participant's hand (ie, proprioceptive drift) as a behavioural outcome measure of the illusion. Additionally, in the subjective measure of the RHI, we will analyse the total embodiment score, as well as considering interindividual and intraindividual analysis of variance for each of the 12 items of the embodiment questionnaire separately.

Another secondary aim of this study is also to explore whether the effect of IN-OT would be modulated by individual differences, such as eating disorders symptomatology, measured by means of the Eating Disorders Examination Questionnaire (EDE-Q[73]). Recent studies suggest that (non-clinical) EDE-Q scores might relate to body satisfaction following manipulation of illusory body size,[46] suggesting that this measure can capture sensitivity to different body size in healthy population.

METHODS AND MEASURES

Participants and recruitment

Inclusion and exclusion criteria

Forty healthy women will be recruited through the University College London subject pool system; 40 women with AN will be recruited at the National Health Service North East London Foundation Trust (NELFT) and Central and North West London Foundation Trust (NoCLOR). All patients will meet the Diagnostic and Statistical Manual of Mental Disorders, fourth Edition (1) criteria for AN restrictive subtype, as assessed using the Structured Clinical Interview for DSM-IV Axis I Disorders. Healthy participants will be recruited in the follicular phase of their menstrual cycle (between the 5th and 14th day) to control for hormonal levels.[69] All participants will be heterosexual and not taking the contraceptive pills.[69] Exclusion criteria for both groups include being pregnant or breast feeding,[74] being below 16 or above 40 years of age, any visible scar, tattoo or skin condition (eg, psoriasis) on the left arm, use of any drugs within the last 6 months, and consumption of more than five cigarettes per day. Exclusion criteria for the healthy controls group include a history of any medical, neurological or psychiatric illness and body mass index (BMI) out of the range 18.5–24.9. AN patients will be of restrictive-type only.

Participants will be asked to refrain from consuming any alcohol the day before testing and any alcohol or coffee on the day of testing. All participants will provide informed consent to take part and will receive a compensation of £40 for travelling expenses and time. The study will be carried out in accordance with the provisions of the Declaration of Helsinki of 1975, as revised in 2008.

Patients' involvement

Patients were not involved in the development of the research question and design of the study. However, clinical psychologists, dieticians, psychiatrists and psychotherapists working in the eating disorders units associated to the project are involved in the screening of patients in order to control for eligibility and asses burden of the research study in the ongoing treatment. The Information Sheet approved by the National Research Ethics Service committee specifies the voluntary basis of the patients' participation, their right to withdraw without explanation or consequences and their right for a cooling-off period of 7 days. No participant will be recruited without written, inform consent. Patients who complete the study will be notified with an email about the results of the study. Furthermore, findings will be disseminate at research days taking place in eating disorders units and in public engagements events involving clinicians, patients and carers.

Randomisation, blinding and storage

We will use a cross-over design, where each participant will receive both IN-OT and placebo. However, the order in which participants receive oxytocin/placebo will be counterbalanced, by pseudo-randomly assigning

to a treatment order (IN-OT—placebo or the reverse) following the stratified method of minimisation, which takes into account the age of all the participants, and the BMI for the healthy controls group and the years of illness for the AN group. This pseudo- randomised procedure will be used so as to ensure in each group (AN, healthy controls) an equal number of people have received the same treatment order (eg, 10 participants will be assigned to oxytocin-placebo and 10 participants to the reverse order).

Active and placebo sprays will not be identifiable by the research team (they will be contained in identical bottles marked as spray A and B), ensuring that both researchers and participants are blind regarding treatment. The blinding letter is in possession of an institutional administrator not otherwise involved in the study and the researchers will be unblinded at the end of the study and on completion of data analysis. Both active sprays and placebos are safely stored under controlled conditions at the laboratories in the Department of Clinical, Educational and Health Psychology University College London. They are stored in a lockable, refrigerator with temperature monitoring and power failure support features between 2°C and 8°C as required by the manufacturer. The lab is always locked and access is strictly controlled and limited to authorised personnel.

Oxytocin and placebo intranasal spray administration

In the present study, participants will receive 40 IU of oxytocin (Syntocinon-Spray, Novartis, Basel, Switzerland) and placebo (containing the same ingredients as Syntocinon except without the active ingredient oxytocin, Victoria Apotheke Zuerich, Switzerland) by means of a nasal spray. Two practice bottles containing water will be used for the participants to familiarise themselves with the procedure; one for the experimenter to demonstrate and one for the participant to practice. Participants will self-administer a puff containing 4IU every 30 s alternating between nostrils (five for each nostril) for a total of 10 puffs. Half of the sample will start the administration on the right nostril, and half on the left nostril. The self-administration procedure will take about 9 min, including 3 min of rest at the end.[67]

Study design

The study employs a double-blind, placebo-controlled, cross-over design, with compound (oxytocin vs placebo) as the within-subjects factor. Each subject (AN or healthy control) will participate in two identical sessions, the first one lasting approximately 2 hours and the second lasting 1.5 hours, and scheduled between 1 to 3 days apart; this is to ensure that participants are tested in the same phase of the menstrual cycle, to ensure consistency of hormonal levels.[69] Testing sessions will take place between 09:00 and 12:00 hours, and the time of the day will be kept consistent within participants. In one session, participants will be asked to self-administer 40 IU of oxytocin and in the other session placebo (see the Session procedure section for details and figure 1) in a counter-balanced and double-blinded manner. Participants will be pseudorandomly allocated to the nasal spray sequence (AB/BA); so that half of the participants receive placebo on the first visit and IN-OT on the second visit, whereas the order is reversed for the other participants.

Measures

Demographic and psychological characteristics

Demographic and psychological characteristics will be collected at the beginning of the first testing session. Demographics include age, BMI, medication use, medical history and relationship status. Participants will complete (1) the Depression Anxiety Stress Scales (DASS),[75] a 42-item self-report instrument designed to measure the three related negative emotional states of depression, anxiety and stress; (2) the Self-Objectification Questionnaire,[76] to assess the extent to which participants perceive themselves from an external/objectified point of view; (3) the Body Awareness Questionnaire,[77] an 18-item scale designed to assess self-reported attentiveness to body processes, such as sensitivity to body cycles and rhythms, ability to detect small changes in normal functioning, and ability to anticipate bodily reactions; (4) the Autism Spectrum Quotient (AQ-10),[78] to measure the degree to which an individual possesses symptoms typical of the autistic spectrum autistic traits (see ref 79 for recent neurobiological evidence supporting the behavioural link between AN and autistic traits); (5) the Toronto Alexithymia Scale (TAS-20),[80] to assess difficulties in identifying and describing feelings and (6) EDE-Q,[81] to assess disordered eating behaviours and attitudes over the past 28 days; the questionnaire consists of 36 items on a 7-point forced choice rating scale, and it measures weight, shape, eating concerns and dietary restrain.

Affective touch

Procedure

For the affective touch procedure, two rectangles will be drawn on the hairy skin of the participants left forearm, each measuring 4 cm x 9 cm (as in ref 61). Participants will place their left arm on the table with palm facing down and they will be asked to wear a blindfold to avoid visual feedback of the tactile stimuli. Tactile stimulation (ie, stroking) will be administered for three seconds using a soft cosmetic make-up brush (Natural hair Blush Brush, N◦7, The Boots Company) at two different velocities: one CT-optimal (3 cm/s: one stroke in 3 s) and one not CT-optimal (18 cm/s: six strokes in 3 s). In the present study, a total of 16 tactile stimuli will be delivered, eight at slow velocity (3 cm/s) and eight at fast velocity (18 cm/s). The order of velocity will be randomised and tactile stimulation alternated between the rectangles drawn on the skin, to minimise habituation.

Outcome measure

After each brush stroke participants will verbally rate the pleasantness of the touch using a scale from 0 (not at all

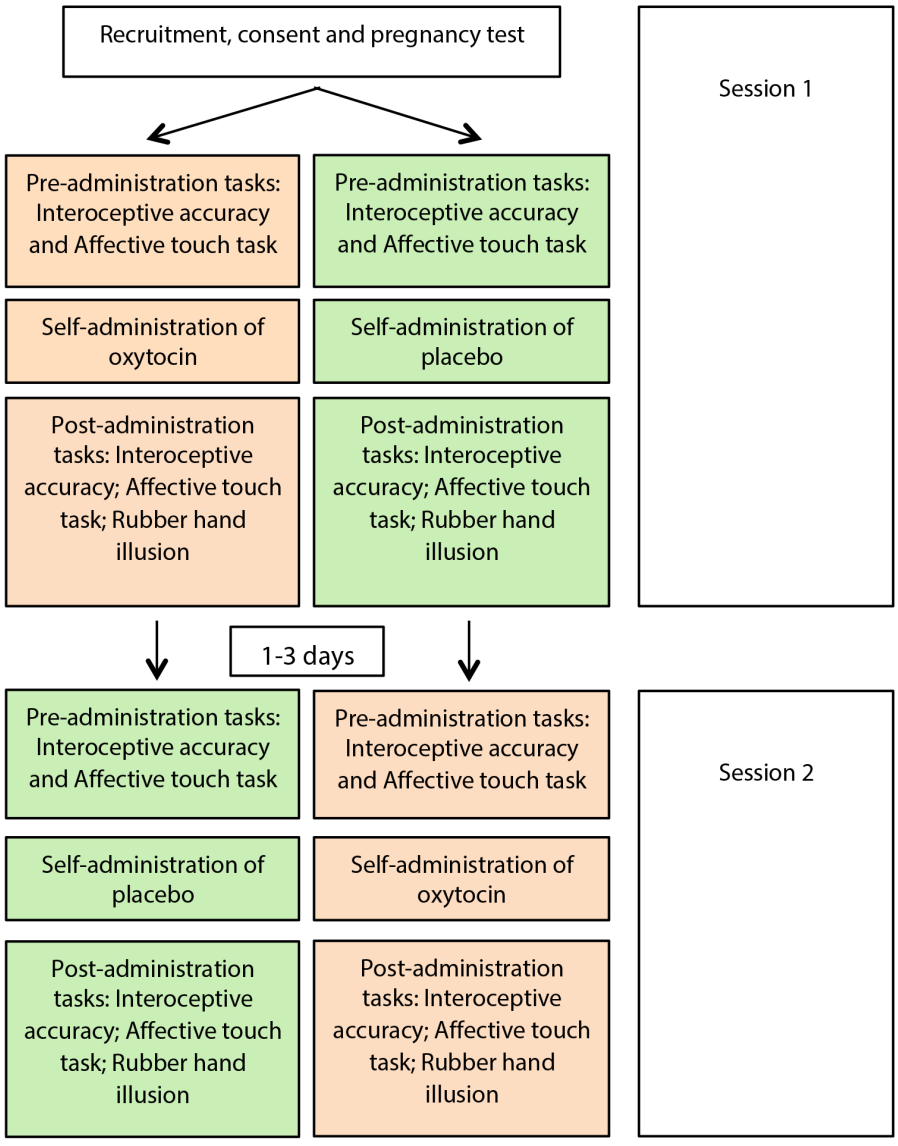

Figure 1 Study design and flow chart.

pleasant), to 100 (extremely pleasant). A copy of the scale will be placed on the table for reference. The affective touch task will be performed twice at each testing session: before and after nasal spray administration.

Body ownership: classic, affective and hand size RHI

Procedure

The RHI will be conducted to investigate the effect of IN-OT versus placebo on: (1) the *classic RHI* manipulation, which involves comparing synchronous and asynchronous visuotactile stimulation; (2) the *affective RHI*, which investigates the effect of velocity of touch on the occurrence of the illusion (slow vs fast touch); (3) the *hand size RHI*, which explores the effect of hand size on the occurrence of the illusion (regular vs larger hand). The RHI will be performed following the procedure fully described in.[37 61] Briefly, in each condition, the experimenter will place the participant's left hand (palm facing down; fingers pointing forwards) at a fixed point inside a wooden box. Subsequently, the rubber arm will be positioned in the right half of the box, in front of the participant's body midline and in the same direction as the participant's actual left arm. The distance between the participants' left arm and the visible arm (on the sagittal plane) will be approximately 25 cm. In this study, the experimenter then will sit opposite the participant and will stroke the previously identified stroking areas[82] for 1 min using a speed of 3 cm/s (slow/pleasant) or 18 cm/s (fast/neutral). In the synchronous conditions, the participant's left forearm and the rubber forearm will be stroked such that visual and tactile feedback will be congruent, whereas in the asynchronous conditions, visual and tactile stimulation will be temporally incongruent. The asynchronous condition will be run only at slow velocity to control for the occurrence of the illusion, while the synchronous condition will be repeated three times; one at slow velocity, one at fast velocity to control for the effect of velocity on the embodiment process and one in which participants will be asked to look at a larger

hand (in size). The latter condition has been included in order to control for the effect of size of the hand on the occurrence of the illusion and the effect of IN-OT on body size representation. The order of the four conditions (slow/synchronous, slow/asynchronous, fast/synchronous, larger hand/synchronous) will be randomised between participants, but it will be kept constant within participants. Prior to commencing the next condition, they will be given a 60 s rest period, during which they will be instructed to freely move their left hand.

Illusion measures

A pre-stroking estimate of finger position will then be obtained (for the measurement of *proprioceptive drift*) using a tailor's tape-measure placed on top of the box lid. The experimenter will move her finger along the top of the box lid on the sagittal plane and participants will be asked to say 'stop' when the experimenter's finger is in the position where they feel that their own left index finger is inside the box. The experimenter then will measure and record the difference between the actual and perceived position of the participant's left index finger. After the stimulation period, the felt and actual location of the participant's left index finger will be again measured following the pre-induction procedure. The difference between pre and post-stroking finger position will give *a measure of the proprioceptive drift*.

An *embodiment questionnaire*[83] is used to capture the subjective experience of the illusion (12 statements rated on a 7-point Likert-type scale; −3, strongly disagree; +3, strongly agree). In each condition, the questionnaire is administered prestroking (ie, embodiment due to the visual capture effect) and poststroking, and we will calculate their difference to obtain a measure of subjective embodiment due to visuotactile integration.[37 61] This questionnaire consists of three sub-components: *felt ownership*, that is related to the feeling that the rubber hand is part of one's body; *felt location* of own hand, that is related to the feeling that the rubber hand and one's own hand are in the same place; *affect*, that includes items related to the experience being interesting. We will examine this difference between pre- and post-stroking (*change in embodiment*) for each of the statements separately, as well as for an overall 'embodiment of rubber hand'[83] score, that will be obtained by averaging the scores of the two subcomponents specifically related to embodiment, namely ownership and felt location that did not relate to affect. The affect sub-component will also include a measurement of the perceived pleasantness of the tactile stimulation using a visual analogue scale ranging from 0 to 100 (as in the affective touch procedure, see above).

Heartbeat baseline and interoceptive accuracy

The participant's actual heartbeat will be recorded using a Biopac MP150 Heart Rate oximeter, and data will be analysed using AcqKnowledge software V.3.9.2. In the present study, a heartbeat baseline of 5 min will be recorded three times throughout the experiment; immediately after the end of the administration nasal spray (non-active post-OT administration, $HB1_{pre}$), at the beginning of the nasal spray active window (active post-OT administration, $HB2_{during}$) and at the end of the experiment (non-active post-OT administration, $HB3_{post}$).

Interoceptive accuracy will be assessed by means of the well-established heartbeat detection task,[33] where participants are asked to count their own heartbeat without feeling their chest or taking their pulse. The counting procedure will be repeated three different lengths time intervals (25, 45 and 65 s) presented in a randomised order and separated by a resting time of 30 s. Participants will not receive any feedback regarding their performance and the interval length. The estimated and actual number of heartbeats per time intervals will then be combined in the following formula:

$$1/3 \sum (1 - (|\text{recorded heartbeats} - \text{counted heartbeats}|) / \text{recorded heartbeats})$$

The interoceptive accuracy scores obtained following this transformation can vary between 0 and 1, with higher scores indicating a better estimation of the heartbeats (ie, smaller differences between estimated and actual heartbeats).

Session procedure

The experiment is run by two female experimenters. After signing the consent form and in the first session only, participants are asked to provide a urine sample and a pregnancy test (Pregnancy test device, SureScreen Diagnostics) is carried out by one experimenter to exclude the possibility of any ongoing, unknown pregnancy. This is done for safety reasons given the role of oxytocin on labour. After confirmation of the negative result of the pregnancy test the experimental procedure starts. Participants are familiarised with the pleasantness ratings scale and with the experimental procedure (above). They are asked to place their left arm resting on the table, palm down and the two rectangular areas on the forearm are marked. Participants then wear the blindfold and are asked to rate the pleasantness of the touch.

Subsequently, participants self-administer, under both experimenters' supervision, either IN-OT or the placebo. The order of the treatment is counterbalanced across participants, and both experimenters and participants are blind to the treatment order. Experimental instruction about the aim of the nasal administration, the position of the head and of the nasal spray inside the nasal cavity, and breathing technique are given to the participants. Participants are familiarised to the administration procedure by means of a practice nasal spray as described above. Before the beginning of the self-administration procedure, all the participants are asked to blow their nose. Thirty-seconds breaks are given between puffs and participants are specifically instructed to not blow their nose during the administration procedure.

At the end of the last puff, participants are given 3 min of resting time in which they are instructed to rest. After

that, the first heartbeat baseline reading is recorded for 5 min ($HB1_{pre}$). During the 25 min time post-spray administration (see refs [67 74] for optimal temporal window) no social contact between the participant and the experimenters takes place beyond necessary experimental instructions. Participants are asked to refrain from checking their phones or doing any personal reading. During the waiting time, participants are offered the opportunity to complete a Sudoku. At the beginning of the active oxytocin window (25 min after the end of the administration procedure), the second heartbeat baseline is recorded for 5 min ($HB2_{during}$).

Participants then complete the heartbeat detection task for the assessment of interoceptive accuracy (see above). Following this, the affective touch task and the RHI tasks are completed in a counterbalanced order (half of the sample follows the post administration order of affective touch task-RHI and half of the sample follows the post administration order of RHI-affective touch task). After completion of the full experimental procedure (that will take approximately 45 min), the heartbeat baseline is recorded for the last time ($HB3_{post}$). At the end of each testing session, participants are asked to guess whether they received IN-OT or placebo to control for any potential effect of expectations on the observed effects. Our experience to date with hundreds of volunteers[84] has shown that if proper placebo (ie, a nasal spray identical in all excipients to Syntocinon except for oxytocin) is used, participants cannot distinguish between oxytocin and placebo. Participants are fully debriefed and reimbursed £40 for their time at the end of the second study visit.

Monitoring adverse events

In the unlikely event that a participant shows side or adverse effects to IN-OT, the participant will be withdrawn from the study and a new participant will be recruited. The study principal investigator will be contacted immediately, she will be un-blinded regarding the nature of the compound the participant received in the specific visit (IN-OT or placebo) and she will check and monitor the participant until they are sure that they are safe to leave the premises. After testing, the participant will be advised that they will receive a telephone call the next day. The principal investigator will telephone the participant to check that all is well and report any side or adverse effects to the Research Steering Committee following the appropriate procedures at the end of the study.

Data analysis

Sample size calculation

We performed a priori sample size calculation (using G*Power 3 software[85]), based on four previous studies which investigated the main effect of IN-OT versus placebo on behavioural tasks in AN. Specifically, Kim and colleagues (2014) investigate the effect of IN-OT versus placebo on attention to emotional social stimuli. They tested 31 AN patients and 33 healthy controls; following a repeated measures procedures they obtained an effect size of 0.13. In another study, Kim *et al*[21] investigated the impact of oxytocin on food intake and emotion recognition. They tested 35 patients with AN and 33 healthy controls (as well as 34 patients with bulimia nervosa). They showed a significant effect on emotion recognition, obtaining an effect size of 0.16. Leppanen *et al*[22] investigated the effect of IN-OT on the interpretation and expression of emotions in AN. Thirty patients with AN and 29 healthy controls completed the study, which showed no significant differences between IN-OT and placebo, with an effect size of 0.17. In another study, Leppanen *et al*[22] investigated the effect of IN-OT on attentional bias towards food. The sample consisted of 30 patients with AN and 29 healthy controls. The repeated measures analysis showed a significant main effect of IN-OT in reducing attentional avoidance to food items, with an effect size of 0.19. So on the basis of the studies that have looked at the effect of IN-OT on behavioural measures in AN we can expect an effect size of between 0.13 and 0.19. Here, we run a power calculation on our main, primary analyses by looking at the effect of IN-OT versus placebo in the two groups on three behavioural measures; affective touch, embodiment in the classic RHI and embodiment in the enhanced RHI with a larger hand. We took also into account the main three interactions of interest (group X compound X manipulation of interest); therefore, we corrected for multiple comparisons obtaining an α of 0.017. We run a power calculation and we observed that when α=0.017, considering the standard deviation of 1, a sample of 30 participants per group will be sufficient to obtain a power of 0.80. A drop-out rate (ie, participants completing only one session) of 30% is assumed for sample size calculation to coincide with similar drop-outs rates of previous studies[86]; therefore, we aim to recruit 40 healthy controls and 40 AN patients.

Statistical analysis plan

Preliminary analyses

Participants who did not follow experimental instructions, or drop-out after one session will not be considered in the data analyses and data will be disposed immediately. Outliers (above or below 3 SD from the mean in each group) will be considered and removed in each condition (oxytocin vs placebo) and task separately (ie, affective touch; interoceptive accuracy; RHI). We will then check the data distribution by means of visual exploration (by looking at Q-Q-Plots) and Shapiro-Wilk tests. In the case of a non-normal distribution, appropriate log, square root and reciprocal transformations will be applied to attempt to correct for the normality violations. If following the transformations the data are not normally distributed, appropriate non-parametric tests will be used to analyse the data (see below).

Preliminary correlation analyses will be conducted to investigate the relationships between the psychometric measures, namely EDE-Q; DASS; AQ-10; TAS-20 and the outcome measures of RHI (embodiment questionnaire and proprioceptive drift), pleasantness of touch

and interoceptive accuracy. These preliminary analyses will inform the inclusion/exclusion of these psychometric measures as co-variates in subsequent analyses. In case of a significant correlation between the psychometric measures and the outcome measures, these will be included in the analyses as covariates. We will also explore the reciprocal relationships between the various psychometric measures to check for multicollinearity and hence reduce any such variables.

Main analyses

The data will be analysed using linear mixed models (LMM) that allow the use of both fixed and random effects in the same analysis. Fixed effects have levels that are of primary interest and would be used again if the experiment were repeated. Random effects have levels that are not of primary interest, but rather are thought of as a random selection from a much larger set of levels. For example, subject effects are usually treated as random effects, while treatment levels are almost always fixed effects. An advantage offered by mixed-effects models is that hypotheses about the structure of the variance-covariance matrix can be tested by means of maximum likelihood methods that are now in common use in many areas of science, medicine and psychophysiology.[87 88]

Here, separate LMM analyses will be run to test the main hypotheses related to (1) pleasantness of touch in the affective touch task and measures of embodiment following, (2) a classic RHI paradigm (testing body ownership) and (3) the enhanced RHI with manipulation of the hand size (testing body image). In these analyses, order of nasal spray administration (oxytocin-placebo or placebo-oxytocin) will be included as a covariate.

Specifically, the perceived pleasantness of touch will be analysed by means of a 2×2×2 LMM analysis, where the primary outcome dependent variable will be the pleasantness of the touch; velocity of touch, group and compound will be the three variables of interest (independent variables). The preadministration baselines measurements of pleasantness from both the experimental sessions will be entered as covariates in the LMM analysis.

As specified in our main hypotheses, the data relative to the subjective embodiment in the RHI will be analysed by means of two separate 2 (compound) x 2 (synchronicity) x 2 (group) LMM analyses. One analysis will be run to test the effect of synchronicity only on the subjective occurrence of the illusion (ie, *classic RHI*, comparison between synchronous and asynchronous touch condition) and the interaction between synchronicity, group and nasal spray. The second analysis will be run to test the effect of hand size in synchronous conditions only on the subjective occurrence of the illusion (ie, *hand size RHI*, comparison between normal and larger hand in synchronous condition only) and the interaction between hand size group and nasal spray.

Any significant interactions from the above analyses will be followed up by appropriate post hoc analyses, correcting for multiple comparisons.

Secondary analyses

As a secondary analysis, we will explore the effect of IN-OT on interoceptive accuracy, in the sense of cardiac awareness. The interoceptive (cardiac awareness) scores are obtained before and after the nasal spray administration and, therefore a LMM analysis will be run with interoceptive accuracy postnasal spray administration as the dependent variable, and interoceptive accuracy pre-nasal spray as covariate.

Previous research suggests that oxytocin might increase heart rate variability[89] and therefore the three measurements taken at different stages of the testing procedure allow a critical observation of any change in resting heartbeat activity during the entire study. As mentioned above, outliers (above or below 3 SD from the mean in each group) will be considered and removed in each condition (oxytocin vs placebo) and for each trial separately. For the LMM analysis of heart rate variability, 5 min heart rates will be recorded for three times throughout the testing session in order to control for any change due to the effect of nasal spray based on different time effects. The primary outcome measures are the heart rates, and the interaction between time of recording ($HB1_{pre}$ vs $HB2_{during}$ vs $HB3_{post}$) and nasal spray will be analysed.

We will also explore the relationship between interoceptive accuracy and affective touch by means of correlational analyses.[37] We will also explore the extent to which interoceptive accuracy and affective touch can predict the susceptibility to the RHI by means of a hierarchical regression, where possible confounds would be entered on step one and the main variable on interest on step 2 (as in ref 37).

In addition, analyses will be performed without the subjects who do not show sensitivity to CT optimal stimulation for exploratory purposes (ie, negative difference between the pleasant of slow touch and the pleasantness of fast touch). This is a procedure used in previous studies,[37] which allow to check for the slow versus fast manipulation which is the basis of subsequent manipulation in the RHI paradigm. Given previous evidence showing an impairment in the perception of affective touch in AN,[52] this procedure will be applied only to the healthy participants group.

Finally, the same pattern of LMM analyses described for the subjective embodiment in the RHI will also be conducted with proprioceptive drift as a secondary outcome measure of the illusion to explore the effect of IN-OT on the objective mis-location of the participant's hand. In addition, we will explore the effect of IN/OT on the *affective* RHI. We will run a 2×2×2 LMM analysis to test the effect of velocity in synchronous conditions only on the subjective and objective occurrence of the illusion (ie, *affective RHI*, comparison between slow and fast touch in synchronous conditions only) and the interaction between velocity of touch, group and nasal spray. Pleasantness ratings will also collected and analysed as a manipulation check that slow touch is perceived and rated as more pleasant than fast touch at the group level.

All the analyses will be conducted to investigate differences between groups (ie, differences between conditions between subjects) as well as at the group level (ie, differences between conditions for within subjects). Additionally, we will analyse the total embodiment score (ie, by averaging the scores of the different items of the embodiment questionnaires), as well as considering inter- and intra- individual analysis of variance for each of the 12 items of the embodiment questionnaire separately.

DISCUSSION

This experimental study aims to mainly explore the effect of IN-OT as compared with placebo in AN (compared with healthy controls) on (1) the perceived pleasantness of affective, CT-optimal touch and emotionally neutral, non-CT optimal touch; (2) on multisensory integration processes underpinning the sense of body ownership in the classic RHI and (3) in an enhanced version where we manipulate the size of the hand. Furthermore, secondary, exploratory aims of this study include the investigation the effect of IN/OT on another interoceptive modality (namely cardiac awareness) and on the relationship between interoceptive accuracy, affective touch and multisensory integration as measured by means of the RHI. We also aim to explore whether the effect of IN-OT would be modulated by individual differences, such as self-objectification and eating disorders symptomatology.

In the last two decades, a growing body of research has explored the effect of IN-OT on human behaviour; nevertheless, the neural processes and the specificity of its effects on socio-affective functioning and bodily awareness are not fully understood. IN-OT shows some promising effects on the core symptoms on AN, such as social cognition and as support to food therapy (eg, ref 23). However, there is a lack of investigation on the potential effect of IN-OT on other key features of AN, namely body image distortions and perception of interoceptive signals, such as affective touch and cardiac awareness (but see ref 26). To date, there is no pharmacological treatment which can specifically address the body image distortions in AN. To the best of our knowledge, this is the first study to systematically investigate the effect of IN/OT versus placebo in AN at different levels of socio-affective functioning and bodily-related awareness. Due to the multi-measures approach and the use of different experimental paradigms, this study can provide new insights in the functional mechanisms of OT on some of the core symptoms of AN patients. AN is the psychiatric disorders with the highest mortality rate.[2] People with AN show a severe lack of awareness and often do not realise the severity of their condition. This unawareness might trigger a maintenance mechanism and discourage patients to engage with therapy. Hence, novel approaches targeting the awareness of illness (ie, both from inside [interoceptively] and outside [exteroceptively] the body) with the final aim of improving therapeutic engagement must be developed. A 'healthy' psychological experience of our own body is central to mental health, as revealed by eating and psychosomatic disorders, but also the somatic dimensions of other conditions such as depression and anxiety. Therefore, re-balancing the relationship between internal and external bodily signals can help not only develop treatments specific for AN patients, but also to prevent the development of such disorders in young people, targeting ages when they might be more sensitive to bodily as well as emotional changes.

One of the main aims of this study is to elucidate, by using neurobiological and behavioural methodologies, whether IN-OT could improve the balance between interoceptive and exteroceptive signals in relations to body representation. By targeting for the first time the relation between the oxytocinergic system and social, tactile anhedonia, interoceptive awareness and body representation, we aim to provide a novel but promising perspective on the understanding of AN. One strength of this study is that all the methodologies (ie, affective touch, cardiac awareness, RHI) have been used with AN patients in previous separated studies from our group and others[49 52 71]; this provides a solid base for this more challenging clinical and pharmacological investigation. In addition, the design of the present study has been informed by previous research investigating the effect of intranasal compounds on the perception of touch. For example, a recent study provided support to the modulation of top-down expectations on the perception of touch, by showing that positive expectations on an inactive nasal spray (ie, placebo) can enhance the perceived pleasantness of touch.[90] This evidence highlighted the necessity to apply a double-blind methodology in order to avoid any potential influence, even if unwanted, coming from both the participant and/or the experimenter.

A limitation of this study is that only female subjects will be tested and thus findings cannot be generalised to males, which are increasingly being diagnosed with AN.[91] However, this limitation also increases the internal validity of this trial and allows for tight control of extraneous variables that might differ between male and female with AN. In addition, this study will investigate the effect of a single dose of IN-OT (40 IU); therefore, no conclusions about the longitudinal treatment effects can be drawn. Although the placebo-controlled within subject nature of the study offers high internal validity, it is no possible to conclude whether IN-OT can be used in a therapeutic setting as such. Hence, we hope that this study will inform future clinical trials to investigate the effect of multiple doses of IN/OT following longitudinal approaches and multi-point outcome measurements, and to explore the possibility to pair oxytocinergic therapy to other ongoing treatments to improve body image distortions and body awareness, and ultimately treatment outcome in AN.

Ethics and dissemination

Women only (16–40 years old) are selected due to differences in the perception of affective touch and oxytocin

levels. Participants will be recruited from the collaboration teams (LS, NELFT and PR, NoCLOR) and they will be provided with written information and the opportunity to discuss the study. The Information Sheet approved by the NRES committee specifies the voluntary basis of the patients' participation, their right to withdraw without explanation or consequences and their right for a cooling-off period of 7 days. No participant will be recruited without written, inform consent. Matched healthy controls will be recruited by the University College London subject pool.

The results will be disseminated through conference presentations and publication in peer-reviewed journals.

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