

***Citation for the published version:***

Crucianelli, L., Paloyelis, Y., Ricciardi, L., Jenkinson, P. M., & Fotopoulou, A. (2019). Embodied Precision: Intranasal Oxytocin Modulates Multisensory Integration. *Journal of Cognitive Neuroscience*, 592-606. DOI: 10.1162/jocn\_a\_01366

***Document Version:*** Accepted Version

***Link to the final published version available at the publisher:***

[https://doi.org/10.1162/jocn\\_a\\_01366](https://doi.org/10.1162/jocn_a_01366)

This article has been accepted for publication in the *Journal of Cognitive Neuroscience*. Published online: 28/02/2019. © 2018 Massachusetts Institute of Technology.

***General rights***

Copyright© and Moral Rights for the publications made accessible on this site are retained by the individual authors and/or other copyright owners.

Please check the manuscript for details of any other licences that may have been applied and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights. You may not engage in further distribution of the material for any profitmaking activities or any commercial gain. You may freely distribute both the url (<http://uhra.herts.ac.uk/>) and the content of this paper for research or private study, educational, or not-for-profit purposes without prior permission or charge.

***Take down policy***

If you believe that this document breaches copyright please contact us providing details, any such items will be temporarily removed from the repository pending investigation.

***Enquiries***

Please contact University of Hertfordshire Research & Scholarly Communications for any enquiries at [rsc@herts.ac.uk](mailto:rsc@herts.ac.uk)

**Embodied precision: Intranasal oxytocin modulates multisensory integration**

Laura Crucianelli<sup>1, 2\*</sup>, Yannis Paloyelis<sup>3</sup>, Lucia Ricciardi<sup>4</sup>, Paul M Jenkinson<sup>2</sup> and  
Aikaterini Fotopoulou<sup>1</sup>

<sup>1</sup>Department of Clinical, Educational and Health Psychology, University College London, UK

<sup>2</sup>School of Life and Medical Sciences, University of Hertfordshire, UK

<sup>3</sup>Department of Neuroimaging, Institute of Psychiatry, Psychology and Neuroscience, King's College London, UK

<sup>4</sup>Neurosciences Research Centre, Molecular and Clinical Sciences Institute, St George's University of London, UK

\* Corresponding author:

Laura Crucianelli, PhD

Department of Clinical, Educational and Health Psychology

University College London

1-19 Torrington Place

London WC1E 7HB

Tel: (+44) 020 3108 3079

Email: [l.crucianelli@ucl.ac.uk](mailto:l.crucianelli@ucl.ac.uk)

## **Abstract**

Multisensory integration processes are fundamental to our sense of self as embodied beings. Bodily illusions, such as the rubber hand illusion (RHI) and the size-weight illusion (SWI), allow us to investigate how the brain resolves conflicting multisensory evidence during perceptual inference in relation to different facets of body representation. In the RHI, synchronous tactile stimulation of a participant's hidden hand and a visible rubber hand creates illusory body ownership; in the SWI, the perceived size of the body can modulate the estimated weight of external objects. According to Bayesian models, such illusions arise as an attempt to explain the causes of multisensory perception and may reflect the attenuation of somatosensory precision, which is required to resolve perceptual hypotheses about conflicting multisensory input. Recent hypotheses propose that the precision of sensorimotor representations is determined by modulators of synaptic gain, like dopamine, acetylcholine and oxytocin. However, these neuromodulatory hypotheses have not been tested in the context of embodied multisensory integration. The present, double-blind, placebo-controlled, crossed-over study (N = 41 healthy volunteers) aimed to investigate the effect of intranasal oxytocin (IN-OT) on multisensory integration processes, tested by means of the RHI and the SWI. Results showed that IN-OT enhanced the subjective feeling of ownership in the RHI, only when synchronous tactile stimulation was involved. Furthermore, IN-OT increased an embodied version of the SWI (quantified as estimation error during a weight estimation task). These findings suggest that oxytocin might modulate processes of visuo-tactile multisensory integration by increasing the precision of top-down signals against bottom-up sensory input.

## Introduction

When we wake up in the morning, we do not question whether our body belongs to us. However, the ability to recognise our body as our own (i.e. sense of body ownership) and related aspects of our coherent, mental representation of our body need to be learned (Gallagher, 2000; Blanke, 2012). Body image involves a conscious process to identify the body as our own, and therefore, it is closely related to our sense of body ownership. It includes visual perceptions and beliefs about our own body, and it is considered to be a fundamental aspect of bodily self-consciousness (see Blanke, 2012 for a review; Dijkerman, 2015).

Experimental methods of multisensory integration allow us to investigate these distinct facets of body representation. For example, the development of experimental paradigms that allow the controlled manipulation of limb ownership in laboratory settings, such as the rubber hand illusion (RHI, Botvinick & Cohen, 1998), provide a unique tool to investigate the sense of body ownership. In this illusion, synchronous touch between a visible rubber hand and the participant's hidden hand produces the illusion of ownership over the fake hand. This feeling of ownership towards the rubber hand arises as a solution to the unlikely conflict between sensory signals from three modalities that need to be integrated - vision, touch and proprioception (i.e. synchronous vision and touch but incongruent proprioception). People select the most plausible cross-modal hypothesis for the causes of these different sensations, i.e. *the (rubber) hand I see being touched (vicarious touch) in synchrony with my own hand (felt via proprioception and epistemically-private touch) is most likely to be mine* (Tsakiris and Haggard, 2005; Apps and Tsakiris, 2014). This hypothesis is more plausible than the hypothesis that this arm belongs to someone else, because I have the prediction that a hand-like stimulus seen in peripersonal space and from a 1<sup>st</sup> person perspective is my own hand. Hence, greater weight is placed to visual signals (i.e. *where I see the rubber hand to be*) relatively to the incompatible proprioceptive signals (i.e. *where I feel my own hand to be*). Due

to the same embodied history, this prediction is even more likely when the hand I see is touched at the same time as the hand I feel, and less likely when the two touches are asynchronous or spatially incompatible (Ferri et al., 2013; Abdulkarim & Ehrsson, 2016; Panagiotopoulou et al., 2017). In the latter case, greater weight is placed to visual signals (i.e. *where and how I see the rubber hand to be touched*) relatively to the incompatible somatosensory signals, comprising both proprioceptive signals (i.e. *where I feel my own hand to be*) and tactile signals (i.e. *where and how I feel the touch to be in an epistemically private manner*). Recent studies have further shown that when proprioception or somatosensation are damaged or become unreliable, this inferential process continues to the point that mere vision of a rubber hand in peripersonal space is sufficient to create strong feelings of rubber hand ownership, even without tactile stimulation (a phenomenon we have previously termed ‘visual capture of ownership’, Martinaud et al., 2017; see also Pavani, Spence and Driver, 2000; Farne et al., 2000; Samad et al., 2015). Taken together, RHI studies in healthy and clinical populations suggest that the sense of body ownership arises as a consequence of the attempt to find the most likely cause of multisensory signals, depending on their reliability (Apps and Tsakiris, 2014; Zeller et al., 2014).

The experience of the RHI can affect both the representation of our own body as well as the representation of the material and physical world beyond our body, e.g. the perception of objects (Haggard and Jundi, 2009). By means of a RHI paradigm, Haggard and Jundi (2009) manipulated body image representation, first explicitly, by inducing participants to embody either a larger or a smaller rubber hand than their own hand. Participants were equally able to embody the larger and smaller rubber hand. Second, they tested whether participants were able to judge the weight of external objects having constant size but different weight, which leads to an embodied version of the size-weight illusion (SWI, Cesari and Newell, 1999; Haggard & Jundi, 2009). Typically, in such illusions the size of an object will influence our expectations

of how heavy this object is (Flanagan and Beltzner, 2000). In this embodied version of the illusion, the size of the object itself is not varied but by varying the size of the embodied hand, any changes in the perception of the object weight are considered a result of the relative size of the object in comparison to the participants' 'own' hand (Haggard & Jundi, 2009). The results revealed that while there was no effect of hand size on explicit feelings of embodiment, the represented size of the participants' hand had an impact on the perceived size and weight of the grasped object, inducing a SWI. In particular, only when participants acquired ownership of a larger hand, they perceived the grasped objects as smaller in size and therefore heavier in weight. This phenomenon can be explained by a violation of perceptual experience due to a mismatch between what we expect (e.g. the size of the object) and what we experience with our senses (e.g. the weight of the object) (Flanagan and Beltzner, 2000; Haggard and Jundi, 2009). Interestingly, the size weight illusion can be considered as an indirect measure of body size representation, in the sense that an induced variation in the perceived body size can be measured indirectly, i.e. not by asking participants but by measuring the modulation of object weight perception. Hence, including this measure can reveal whether body representation is affected differently at an explicit versus implicit level.

These multisensory integration phenomena appear to relate to certain psychometric characteristics, such as eating disorders symptomatology and self-objectification. Indeed, people with eating disorders seem to be particularly susceptible to bodily illusions, in the sense that they score higher than controls during both synchronous and asynchronous conditions of tactile stimulation of their own and a fake, or virtual body, for example (Eshkevari et al., 2012). This susceptibility persists even after otherwise successful recovery (Eshkevari et al., 2015), suggesting a stable trait that is not the mere result of malnutrition at the acute stage of the illness as some other cognitive biases have been found to be (e.g. novelty seeking or emotion recognition, Wagner et al., 2006; Treasure and Schmidt, 2013). In addition, the fact that people

with eating disorders in comparison to healthy controls show greater proprioceptive drift and report stronger feelings of ownership over a fake hand irrespective of whether their own body is touched synchronously or asynchronously suggests that they tend to attribute greater weight to the visual information of a realistic hand in front of them and less weight to correspondence of this visual information with epistemically private proprioceptive signals and somatosensory signals about the felt touch. Recent studies suggest that (sub-clinical) eating disorder symptomatology might relate to body satisfaction following manipulation of illusory body size (Preston and Ehrsson, 2014), suggesting that this measure might influence body size representation in healthy people. Similarly, the extent to which individuals experience their own body as an object to be evaluated based on its appearance rather than effectiveness (i.e. self-objectification), is related to eating disorders symptomatology and seems to affect body shame, anxiety and eating disorders, as well as being a potential precursor to depression and sexual dysfunction (Friedrickson and Roberts, 1997). Additionally, self-objectification accounts for the relative insensitivity of women to their own internal bodily cues, which has been reported in studies of interoception (Tiggemann and Lynch, 2001; Ainley and Tsakiris, 2013).

Computational approaches to multisensory integration illusions (Ernst & Banks, 2002) such as the RHI (Samad et al., 2015) and the SWI (e.g. Buckingham & Goodale, 2013) have shown that cross-modal conflicts are resolved in a Bayes-optimal manner, by weighting the various sensory signals with an appropriate level of confidence or precision (O'Reilly et al., 2012; Zeller et al., 2016). This concept is central to predictive coding theories of perception, which claim that the precision weighting of ambiguous or noisy sensory signals determines how they are used to update predictions about their sources (Friston and Stephan, 2007; Friston, 2008). Specifically, predictive coding is based on the idea that the brain interprets sensory information according to a hierarchical generative model of the world, which generates top-

down representations, against which bottom-up sensory signals are tested to update beliefs about their causes (e.g., Rao & Ballard, 1999; Friston, 2005; Limanowski and Blankenburg, 2015). In this context, perception can be considered as the process of minimizing prediction errors (i.e. difference between predictions and sensory signals) by forming Bayes-optimal, top-down predictions. Crucially, the balance and reciprocal influence between bottom-up signals and top-down predictions depends on their relative uncertainty (or formally its inverse, precision) (Feldman and Friston, 2010) or their reliability (Rohe and Noppeney, 2015; Deroy et al., 2016). The predictive coding architecture we have in mind – to explain multisensory integration in this context – considers ascending prediction errors from multiple modalities that are all competing to update posterior beliefs of an amodal sort. The basic idea here is that if these sources of sensory evidence are in conflict, the ensuing uncertainty can be resolved by downregulating incongruent or incompatible sources of information (e.g. the touch I see vs. the touch I feel; where I see the hand vs. where I feel my hand to be). Technically, according to predictive processing accounts, this corresponds to a decrease in the precision of incongruent prediction errors, relative to consistent and congruent prediction errors. In the experimental setting described below, this form of multisensory integration generally favours visual modalities – at the expense of proprioceptive and somatosensory input – in terms of providing a coherent explanation for the sensory evidence at hand.

For example, using modelling under a predictive coding framework, Zeller and colleagues suggested that in order to resolve the uncertainty between the conflicting visual, proprioceptive and tactile information in the RHI, the brain downregulates the precision of ascending somatosensory prediction errors (Zeller et al., 2014; 2016). In support of their prediction, Zeller et al. (2014) found that touch-evoked EEG potentials elicited by brush-strokes during the RHI are selectively attenuated. These results are consistent with the idea that multisensory integration requires precision weighting of sensations according to their



reliability, such that in the RHI the precision of somatosensory signals (i.e. felt touch and/or proprioceptive signals from the participant's own hand) needs to be attenuated relative to the precision of visual signals in order to resolve conflicting perceptual hypotheses about the most likely cause of sensations in favour of the visually-perceived rubber hand (Zeller et al., 2014; 2016). Similarly, predictive coding models of the SWI suggest that this illusion is the product of perceptual processes specialised for the detection and monitoring of *outliers* in the environment with the final goal of efficient coding of information (Buckingham & Goodale, 2013). In Bayesian terms, our weight perception is driven by our expectations of how heavy something should be. These priors are weighted against bottom up signals and adjusted by the presence of lifting errors. When lifting an object for the first time, participants will apply either excessive or insufficient force; however, in subsequent trials, it is likely that previous experience will reduce the amount or size of such errors (Buckingham & Goodale, 2013).

These Bayesian accounts of multisensory integration seem to suggest that the brain is able to represent and use estimates of uncertainty (more formally precision, namely confidence or the inverse of uncertainty; Friston, 2010; Knill & Pouget, 2004) in order to achieve an optimal coding of information, even if the underlying neural coding principles remain debated (e.g. Ma et al., 2006 vs. Fiser et al., 2010). According to one view, precision is thought to be mediated by the gain or excitability of (superficial pyramidal) cells encoding prediction errors (Feldman and Friston, 2010; Bastos et al., 2012; Shipp et al., 2013). Thus, optimizing precision corresponds to neuromodulatory gain control of neuronal populations reporting prediction error (Feldman & Friston, 2010). On this hypothesis, modulators of synaptic gain (like dopamine, acetylcholine and norepinephrine, as well as neuropeptides such as oxytocin, Quattrocki & Friston, 2014) therefore might play a role in determining the precision of sensorimotor representations encoded by the activity of the synapses they modulate (Fiorillo, Tobler & Schultz, 2003; Yu and Dayan, 2005; Friston et al., 2012). However, to our knowledge these

hypotheses have not been tested in multisensory integration research. The present study specifically aimed to study the role of the neuropeptide oxytocin on multisensory integration and particularly body ownership and body image representation.

Oxytocin is a neuropeptide consisting of nine amino acids, mostly synthesised in the hypothalamus. This neuropeptide acts peripherally as a hormone, such as when it is released during labor and breastfeeding to stimulate uterine contractions and milk ejection, respectively (Burbach, Young & Russell, 2006). Oxytocin also acts centrally as a neuromodulator (Stoop, 2012; Grinevich et al., 2016; Uvnäs-Moberg et al., 2015). It has been proposed that oxytocin might modulate the relationship between sensory information and attentional biases by enhancing the precision of socially relevant information and attenuating the precision of non-social stimuli (Gordon et al., 2013; Quattrocki & Friston, 2014). Oxytocin might interact with the dopaminergic system in order to increase the attention orientation towards social cues (Shamay-Tsoory & Abu-Akel, 2016). The use of nasal sprays has provided a safe and non-invasive route for the administration of oxytocin to target the human brain (MacDonald, Dadds, Brennan, Williams, Levy et al., 2011; Born et al., 2002; Paloyelis et al., 2016). An increasing number of studies have proposed that intranasal oxytocin can modulate social cognition, affiliation and brain function in humans (De Dreu et al., 2010; MacDonald & MacDonald, 2010; Colonnello and Heinrichs, 2016; Uvnäs-Moberg et al., 2015; Rocchetti et al., 2014).

Here, in a parsimonious psychophysical setting, we examined whether (1) intranasal oxytocin affects body ownership during a classic RHI; and (2) intranasal oxytocin modulates body image representation, by means of an enhanced version of the illusion combining the RHI with hands of different sizes and a SWI (as in Haggard and Jundi, 2009). In both instances, individuals had to weigh conflicting sensations derived from the self (somatosensory signals) or rubber hands of different sizes (visual signals). Specifically, based on theoretical proposals about the role of oxytocin on enhancing somatosensory attenuation (Quattrocki & Friston,

2014), we hypothesised that intranasal oxytocin would enhance the embodiment of the rubber hand in the standard and in the enhanced RHI paradigm, by attenuating the precision of somatosensory signals (epistemically-private felt touch) relative to the precision of visual signals (vicarious touch on the rubber hand). In the standard RHI paradigm (1), we predicted that IN-OT would modulate multisensory integration and corresponding subjective (i.e. self-report measure) and behavioural (i.e. the degree to which participants erroneously perceived changes in the position of their own, unseen hand towards the rubber hand, the so-called proprioceptive drift) measures of body ownership over the RHI. We expected to observe these effects in both mere visual capture conditions and during synchronous tactile stimulation of the rubber hand and participants' own hand. In the SWI combined with the RHI (2), we predicted that IN-OT would have an effect on body image representation by increasing the weight estimation error following embodiment of the larger hand; in contrast, no effect on weight estimation was expected following embodiment of the normal size hand.

In sum, we conducted a double blind, placebo-controlled, crossover study to investigate the effect of a single dose of IN-OT compared to placebo on multisensory integration during a standard and an enhanced version of the rubber hand illusion paradigm where we manipulated the synchronicity of touch (synchronous vs. asynchronous) and the size of the rubber hand (normal vs. large). We recorded subjective and behavioural measures of body ownership in both mere visual capture conditions and during synchronous tactile stimulation of the rubber hand and participants' own hand. We measured body image representation by means of weight estimation errors during the SWI. Measures of eating disorders symptomatology (Eating Disorders Examination Questionnaire, EDE-Q, Fairburn & Beglin, 1994) and self-objectification (Self-Objectification Questionnaire, Fredrickson et al., 1998) were also included to control for their potential role in multisensory integration.

## **Materials and Methods**

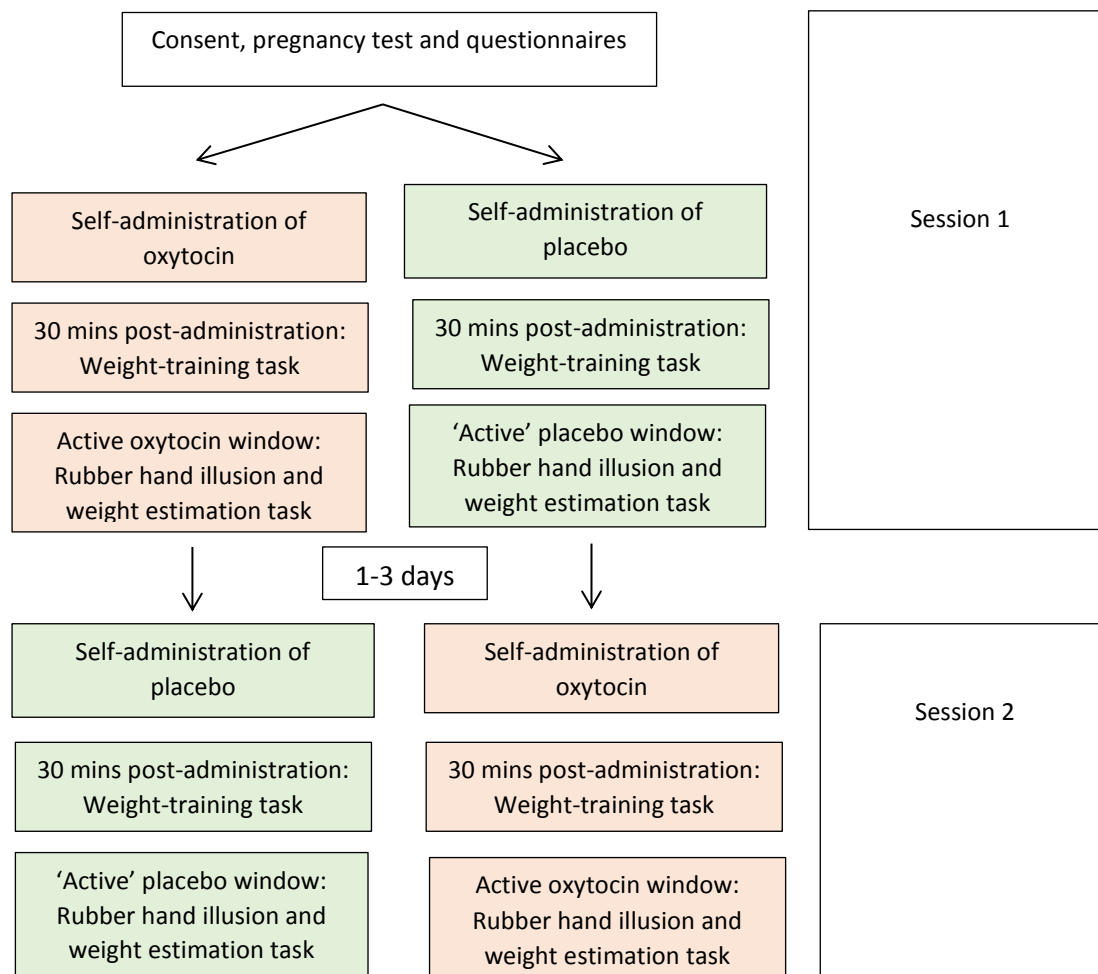
### **Participants**

Forty-one heterosexual females were recruited through the University College London research participation system. They were aged between 18 and 40 years ( $M = 25.13$ ,  $SD = 4.21$ ). Participants were not taking any medication (including the contraceptive pill) and were recruited in the follicular phase of their menstrual cycle (between the 5<sup>th</sup> and 14<sup>th</sup> day) to control for hormonal levels (Salonia et al., 2005). Exclusion criteria included being left handed, pregnant or currently breastfeeding (see MacDonald et al., 2011), a history of any medical, neurological or psychiatric illness, BMI out of the range 18.5 – 24.9 ( $M = 21.38$ ;  $SD = 2.64$ ), use of any illegal drugs within the last six months, and consumption of more than five cigarettes per day. Participants were asked to refrain from consuming any alcohol the day before testing and any alcohol or coffee on the day of testing. All participants provided informed consent to take part and received a compensation of £40 for travel expenses and time. Ethical approval was obtained by University College London and the study was carried out in accordance with the provisions of the Helsinki Declaration of 1975, as revised in 2008. One participant was excluded because she discontinued the study (i.e. she took part in only one of two testing sessions); four participants were later excluded from the analysis as they were found to be extreme outliers in their embodiment scores in the placebo condition (embodiment score  $\pm 3$  SD from group mean). The final sample comprised 36 participants ( $M$  age = 25.03,  $SD = 3.96$ ).

### **Experimental design**

The study employed a double-blind AB/BA (oxytocin-placebo/placebo-oxytocin) cross-over design, with compound (intranasal oxytocin vs. placebo) as the within-subjects factor. Each subject participated in two identical sessions, each lasting between 1.5 and 2 hours and conducted between 1 and 3 days apart; this was to ensure that they were tested in the same

phase of the menstrual cycle. The testing sessions always took place between 09.00 and 12.00. In one session, participants were asked to self-administer 40 IU of oxytocin and in the other session placebo (see Figure 1) in a counter-balanced and double-blinded manner. Participants were randomly allocated to the nasal spray sequence (AB/BA); eighteen participants received placebo on the first visit and intranasal oxytocin on the second visit, while another 18 received the reverse order (intranasal oxytocin on the first visit and placebo on the second visit). The order of administration was included as a covariate in all analyses. The rubber hand illusion and size weight illusion (see below for details of procedure) were administered 30 minutes after nasal spray administration (see MacDonald et al., 2011; Paloyelis, Doyle, Zelaya, Maltezos, Williams et al., 2016 for optimal temporal window). The asynchronous condition of the rubber hand illusion was run only once to establish the presence of the illusion, while the synchronous condition was repeated twice; once with a “normal” size hand and once with a “larger” hand (see below for more details) to investigate the effect of hand size on the embodiment process. The order of the three conditions (normal hand/synchronous, normal hand/asynchronous, larger hand/synchronous) was pseudorandomised between participants (i.e. such that the larger hand was never administered as the first condition so to always obtain the first visual capture measure with the normal size hand) but it was kept constant within participants between the two testing session.



**Figure 1.** Study design and flowchart.

### *Oxytocin and placebo spray*

Participants received 40IU of oxytocin (Syntocinon, Novartis Pharmaceutical, Basel, Switzerland) or placebo (containing the same ingredients as Syntocinon except the active ingredient) by means of a nasal spray. Two practice bottles containing water were used for the participants to familiarise themselves with the procedure; one for the experimenter to demonstrate the correct technique and one for the participant to practice. Experimental instruction about the nasal spray administration procedure, the position of the head and of the nasal spray inside the nose, and breathing technique were given to the participants. Before the

beginning of the self-administration procedure, all the participants were asked to blow their nose. Participants self-administered a puff containing 4IU every 30 seconds alternating between nostrils (five for each nostril) for a total of ten puffs. Half of the sample started the administration on the right nostril, and half on the left nostril. Participants were specifically instructed to not blow their nose during the administration procedure. At the end of the last puff of nasal spray, participants were given three minutes of resting time in which they were instructed to relax. The self-administration procedure took approximately nine minutes, including three minutes of rest at the end (see also Paloyelis et al., 2016).

### ***Rubber hand illusion***

#### *Procedure*

The rubber hand illusion was performed following the procedure fully described in previous studies (Crucianelli et al., 2013; Crucianelli et al., 2018). Two adjacent stroking areas, each measuring 9cm long x 4cm wide were identified and marked with a washable marker on the hairy skin of participants' left forearm (wrist crease to elbow, McGlone, Olausson, Boyle, Jones-Gotman, Dancer et al., 2012). Tactile stimulation (i.e. stroking) was alternated between these two areas to minimise habituation, and congruent stroking area changes were applied to the rubber hand in all instances (Crucianelli et al., 2013). In each condition, the experimenter placed the participant's left hand (palm facing down; fingers pointing forwards) at a fixed point inside a wooden box (34 cm x 65 cm x 44 cm).

A pre-stroking estimate of finger position was then obtained (for the measurement of proprioceptive drift) using a tailor's tape-measure placed on top of the box lid. Subsequently, the rubber arm was positioned in the right half of the box (participant-centred reference frame), in front of the participant's body midline, and in the same direction as the participant's actual left arm. The distance between the participant's left arm and the visible arm (on the sagittal

plane) was approximately 28 cm. A wooden lid prevented visual feedback of the participant's own arm. The participant also wore a black cape to occlude vision of the proximal end of the rubber arm and participant's left arm. The rubber hands were custom made by an artist with expertise in body-part modelling, by means of hand casts obtained from two volunteers, one with a BMI within the healthy weight range (healthy BMI = 18.5-24.9), and one having a BMI in the obese range (obese BMI = 30-39.9). Each cast was subsequently hand painted to create a life-like model hand (Figure 2).

Participants were then asked to look at the rubber hand continuously for 15 seconds, before completing the pre embodiment questionnaire (i.e. *visual capture effect*). Tactile stimulation was then applied for one minute using two, identical, cosmetic make-up brushes (Natural hair Blush Brush, N°7, The Boots Company) using the speed of 3 cm/s (Crucianelli et al., 2013). In the synchronous conditions, the participant's left forearm and the rubber forearm were stroked such that visual and tactile feedback were congruent, whereas in the asynchronous conditions, visual and tactile stimulation were temporally incongruent (i.e. offset by 2 seconds). After the stimulation period, the felt and actual location of the participant's left index finger was again measured following the pre-induction procedure. After the tactile stimulation period, participants completed the post-stroking *embodiment questionnaire*. Prior to commencing the next condition, they were given a 60s rest period, during which they were instructed to freely move their left hand.

### *Outcome measures*

After positioning the hand inside the box, participants were asked to close their eyes and to indicate on the ruler with their right hand the position where they felt that their own left index finger was inside the box. The experimenter then measured and recorded the actual position of the participant's left index finger. After the stimulation period, the felt and actual



location of the participant's left index finger was again measured following the pre-induction procedure. The difference between the pre and post error in location represents a measure of *proprioceptive drift*.

An *embodiment questionnaire* (Longo et al., 2008) was 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 was administered pre- (i.e., embodiment due to the visual capture effect) and post-stroking and we calculated their difference to obtain a measure of subjective embodiment due to visuo-tactile integration (i.e. *change in embodiment*, as in Crucianelli et al., 2013; 2017). 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 examined 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" (Longo et al., 2008) score, that was 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 also included a measurement of the perceived pleasantness of the tactile stimulation quantified by means of a visual analogue scale ranging from 0 (not at all pleasant) to 100 (extremely pleasant).

### ***Size- weight illusion***

#### *Procedure*

The size-weight illusion task was based on the procedures described by Haggard and Jundi (2009). Before the main experiment (see timeline in Figure 1), participants received training in weight estimation. They were asked to lift two opaque cylinders (i.e. metal tea

caddies/containers, Figure 2) that contained wooden beads. Each cylinder was the same size (height = 15.5; diameter = ~7.5cm) but varied in weight (either 100g or 200g). These same cylinders were later used in the actual experimental task. Participants were asked to estimate the weight of the cylinders ten times by lifting them with their left hand and putting them back down; five times they were given the cylinder weighing 100g, and five times they were given the cylinder weighing 200g, in a random order. During this training stage participants were given feedback about their performance (i.e. if they were right or wrong) and were informed about the actual weight of the cylinder after each trial. By the end of the training session, all participants successfully learnt to distinguish between cylinders weighing 100g and 200 g (i.e. the cut off was 8 out of 10 correct trials in a row). This training allowed participants the opportunity to familiarise themselves with the experimental stimuli and ensured that all participants started the main experiment with the same weight reference points (see also Haggard and Jundi, 2009).

Subsequently the baseline weight-estimation took place. The weight estimation task consisted on lifting three cans of the same shape and size (described above), but different weight (125g; 150g; 175g, presented in a random order across conditions and participants). The experimenter placed the can between the participant's left index finger and thumb. Participants were asked to gently lift the can without shaking it, to put it down, and to provide verbally the best estimation about its weight (to the nearest gram). Instructions included the information that the weight could be anything between 100 and 200g but not exactly 100 or 200g; no feedback about the estimation was given at this stage. During the session, participants completed the weight-estimation task twice more: following the rubber hand illusion with the normal size hand, and following the rubber hand illusion with the larger size hand. The difference between the estimated and actual weight was the measure of the SWI (i.e. weight estimation error), which was then compared between the conditions following embodiment of

the normal size or larger hand in order to investigate the relationship between expectations driven by the *illusory* body size perception and the estimated weight of the objects.



**Figure 2.** The size-weight illusion procedure. Firstly, participants completed a RHI procedure where they were asked to look at a regular size rubber hand (on the right) or a larger size rubber hand (on the left). Participants were asked to estimate the weight of three cans, each having identical size but different weights (i.e. 125g, 150g, and 175g). The experimenter passed the can to the participant through the hole in the box. Participants were instructed to lift the can, without shaking it, and to give their best estimation about its weight. No feedback was provided to the participants.

#### *Self-Objectification Questionnaire (SOQ)*

The Self-Objectification Questionnaire (Fredrickson et al., 1998) measures the extent to which individuals see their bodies in observable, appearance-based (i.e. objectified) terms, versus non-observable competence-based terms. The questionnaire consists of ten body attributes (e.g. attractiveness, strength, health, etc.) which participants are required to rank by how important each is to their own physical self-concept, from 0 (for least impact) to 9 (greatest impact). Self-objectification scores are calculated by subtracting the summed ranks given to the 5 competence-based attributes (e.g. health, energy) from the summed ranks of the 5 appearance-based attributes (e.g. physical attractiveness, body measurements). Scores range from 25 to 225, with higher scores indicating greater emphasis on appearance, which is interpreted as greater self-objectification. The SOQ has good test-retest reliability ( $r = .92$ , cited in Miner-Rubino, Twenge and Fredrickson, 2002).

### *Eating Disorders Examination Questionnaire (EDE-Q)*

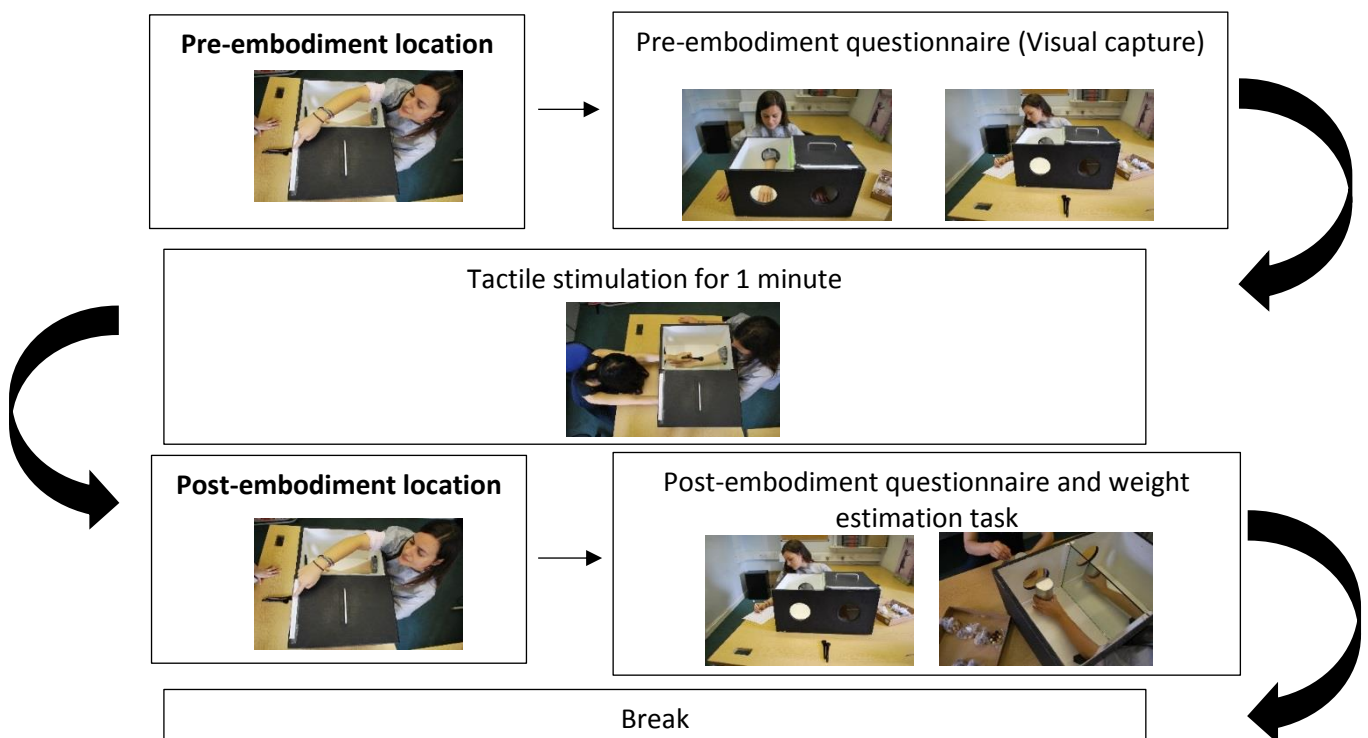
The Eating Disorder Examination Questionnaire 6.0 (EDE-Q; Fairburn & Beglin, 1994), which has good consistency and reliability (global score  $\alpha = .90$ ; Peterson et al., 2007), was used to measure eating disorders symptomatology. The questionnaire consists of 28-items rated on a seven-point Likert scale (ranging from *No days/Not at all* to *Every day/Markedly*), and six items asking about frequency of behaviour. The questionnaire can be divided into four subscales (*dietary restraint*, e.g. Have you been deliberately trying to limit the amount of food you eat to influence your shape or weight?; *eating concern*, e.g. Over the past 28 days, how concerned have you been about other people seeing you eat?; *weight concern*, e.g. Has your weight influenced how you think about yourself as a person?; *shape concern*, e.g. Have you had a definite desire to have a totally flat stomach?), or a single global measure. To obtain an overall or “global” score, the four subscales scores are summed and the resulting total divided by the number of subscales (i.e. four). The clinical cut-off is of 2.8 on the global score (Mond et al., 2008).

### **General Procedure**

The experiment was run by two female experimenters. Upon arrival, in the first session only, participants were asked to provide a urine sample for a pregnancy test (Pregnancy test device, SureScreen Diagnostics), which was carried out to exclude the possibility of any ongoing, unknown pregnancy that might be adversely affected by the administration of intranasal oxytocin. After confirmation of the negative result of the pregnancy test, participants completed the EDE-Q and the SOQ (presented in a random order), and their arm was prepared for later administration of the rubber hand illusion (see Rubber Hand Illusion section above). Subsequently, participants self-administered, under both experimenters’ supervision, either

intranasal oxytocin or the placebo. The order of the treatment was counterbalanced across participants, and both experimenters and participants were blind to the treatment order (as detailed in *Oxytocin and placebo spray* section above).

During the 30 minutes time post-spray administration (see MacDonald et al. 2011; Paloyelis, Doyle, Zelaya, Maltezos, Williams et al., 2016 for optimal temporal window) no social contact between the participant and the experimenters took place beyond necessary experimental instructions. Participants were asked to refrain from checking their phones or doing any personal reading. During this waiting time of oxytocin activation, participants were familiarised with the weight estimation task, before completing the three weight estimations baselines (described in Size-Weight Illusion section above). In the remaining time, participants were offered the opportunity to complete a Sudoku or Word Search. At the beginning of the active oxytocin window, participants completed the rubber hand illusion and the size weight illusion for the following 40 minutes (Figure 3). Participants were fully debriefed and reimbursed £40 for their time at the end of the second study visit.



**Figure 3.** The Rubber Hand Illusion and Size-Weight Illusion procedure

### **Statistical analysis**

The present study aimed to explore whether IN-OT versus placebo would affect (1) the subjective feeling of ownership towards the rubber hand, as measured using an embodiment questionnaire, (2) proprioceptive judgements regarding the location of the position of the real hand relative to the rubber hand (proprioceptive drift), and (3) the representation of body size, as measured by means of a SWI, quantified as weight-estimation error after the embodiment of rubber hands of different sizes.

The multivariable analyses were performed using a purposeful selection of covariates (Hosmer, May & Lemeshow, 2008). Following this procedure, preliminary correlational analyses were conducted to investigate the relationships between the psychometric measures, namely the Self-Objectification Questionnaire (SOQ) and Eating Disorders Examination Questionnaire (EDE-Q), with the subjective measure of the RHI, the proprioceptive drift and the weight-estimation error (see Table 1). In case of a  $p$ -value  $< 0.20$ , we included these variables as covariates in the analyses (Hosmer et al., 2008). According to this criterion, the EDE-Q correlated with the subjective embodiment in the synchronous condition following placebo ( $p = 0.08$ ), and with the weight estimation error following embodiment of the larger hand in the placebo condition only ( $p = 0.12$ ). After running these two linear mixed models, we planned to follow up these with another two, linear mixed model analyses, that included only the variables that significantly contributed to the model at a  $p$ -value  $< 0.05$ , in order to specify the contribution of these variables only to the final model (Hosmer, May & Lemeshow, 2008). The EDE-Q did not meet this criterion in the first and second LMM ( $p = 0.64$  and  $p = 0.84$ , respectively) and therefore it was not included in the final model. The main analyses were conducted by means of linear mixed model (LMM) analyses that allow the use of both fixed

and random effects in the same analysis. Specifically, the effect of IN-OT versus placebo on the rubber hand illusion was analysed by means of three separate LMM analyses. One analysis was run to test the effect of IN-OT versus placebo on the *visual capture* of hands of different sizes (i.e. comparison between normal and larger hand on the pre-embodiment questionnaire only, and the interaction between hand size and oxytocin, on measures of embodiment). The second LMM analysis was run to test the effect of IN-OT versus placebo on the *occurrence* of the illusion (i.e. comparison between synchronous and asynchronous touch condition, and the interaction between synchronicity and oxytocin, on measures of embodiment). The final LMM analysis was run to test the effect of IN-OT versus placebo on the *hand size manipulation* (i.e. comparison between normal and larger hand in synchronous conditions only, and the interaction between hand size and oxytocin, on measures of embodiment). Finally, the latter analysis was repeated with the weight estimation as the dependent variable, in order to investigate the effect of IN-OT versus placebo on the occurrence of the size weight illusion.

In all these analyses, order of compound administration (oxytocin-placebo or placebo-oxytocin), was included as a covariate. The baseline weight-estimation was included in all the analyses of the size-weight illusion effect as a covariate. All data were analysed using SPSS, version 23.

## **Results**

### *Preliminary analyses*

Preliminary correlational analyses showed no significant relationships between self-objectification (SOQ) or eating disorders symptomology (EDE-Q) with the subjective measure of the RHI (embodiment questionnaire), proprioceptive drift, or the weight estimation error in the SWI. Results are reported on Table 1. Given the lack of significant relationships between

the psychometric measures and the main measures of interest, SOQ and EDE-Q were not taken into account in subsequent analyses.

**Table 1.** Pearson’s correlational analyses between Self-Objectification Questionnaire (SOQ) or Eating-Disorders Examination Questionnaire (EDE-Q) and measures of embodiment. The values reported are the correlational coefficients  $r$  in the first row and the  $p$  values in the second row.

		SOQ	EDE-Q
<b><i>Classic rubber hand illusion – Subjective change in embodiment</i></b>			
IN-OT synchronous touch	$r$	-.17	-.19
	$p$	.29	.24
IN-OT asynchronous touch	$r$	.02	-.00
	$p$	.89	.98
PL synchronous touch	$r$	-.06	-.28
	$p$	.71	.08
PL asynchronous touch	$r$	.02	.17
	$p$	.90	.29
<b><i>Classic rubber hand illusion – Proprioceptive drift</i></b>			
IN-OT synchronous touch	$r$	.04	.01
	$p$	.80	.94
IN-OT asynchronous touch	$r$	-.03	-.06
	$p$	.86	.71
PL synchronous touch	$r$	.06	-.15
	$p$	.74	.36
PL asynchronous touch	$r$	.10	-.13
	$p$	.55	.45
<b><i>Size Weight Illusion – Error in weight estimation</i></b>			
IN-OT regular hand	$r$	.02	-.07
	$p$	.88	.67
PL regular hand	$r$	-.01	.15
	$p$	.97	.34
IN-OT larger hand	$r$	.11	-.08
	$p$	.52	.64
PL larger hand	$r$	.04	.25
	$p$	.80	.12

### ***IN-OT Effects on Visual Capture of Hands of different sizes as Measured by Self-Report***

In order to assess whether IN-OT affects the visual capture of hands of different sizes during the RHI, a linear mixed model analysis was run to explore the effect of IN-OT (versus placebo) and watching a larger versus regular size hand on the embodiment resulting from visual capture only. Order of nasal spray administration was considered as a covariate. This analysis showed that neither hand size ( $F(1, 35) = 1.69, p = 0.20; r = 0.46$ ) nor oxytocin ( $F(1,$



35) = 0.74;  $p = 0.39$ ;  $r = 0.09$ ), have a significant main effect on the visual capture. The interaction between nasal spray and hand size was non-significant ( $F(1, 35) = 1.28$ ;  $p = 0.27$ ;  $r = 0.27$ ).

### ***IN-OT Effects on Body Ownership: Synchronous vs. Asynchronous Stimulation***

#### ***Change in Subjective Embodiment as Measured by Self-Report***

In order to assess whether IN-OT affects the subjective reporting of *body ownership* during the RHI, a linear mixed model analysis was run to explore the effect of IN-OT (versus placebo) and synchronous (versus asynchronous) stimulation on the change in embodiment questionnaire scores. The order of administration was considered in the analysis as a covariate. This analysis revealed a main effect of synchronicity ( $F(1, 35) = 8.8$ ;  $p = 0.005$ ;  $r = 0.82$ , see Figure 4), with synchronous touch ( $M = 0.75$ ,  $SE = 0.16$ ) leading to greater embodiment compared to asynchronous touch ( $M = -0.01$ ;  $SE = 0.18$ ). This result confirmed the occurrence of the illusion from a subjective point of view. Nasal spray did not have a significant main effect on the change in embodiment ( $F(1, 35) = 0.48$ ;  $p = 0.49$ ). However, there was a significant interaction between synchronicity and nasal spray ( $F(1, 35) = 4.87$ ;  $p = 0.034$ ;  $r = 0.64$ ). Bonferroni corrected post-hoc analyses (adjusted  $\alpha = 0.025$ ) revealed that IN-OT (compared to placebo) increased embodiment of the rubber hand in the synchronous ( $t(35) = 12.50$ ;  $p = 0.001$ ;  $r = 0.90$ ) but not in the asynchronous condition ( $t(35) = 0.05$ ;  $p = 0.82$ ;  $r = 0.01$ ).

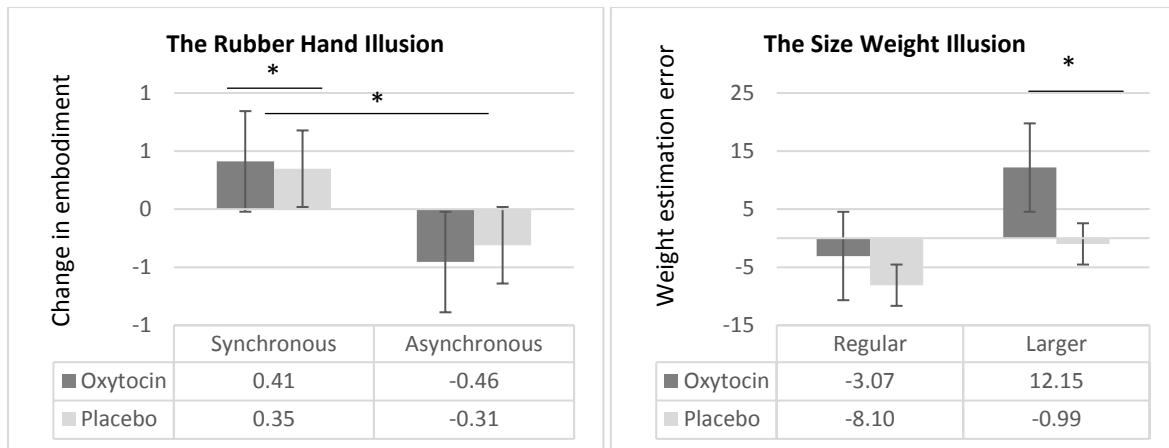
#### ***Embodiment Changes as Measured by Proprioceptive Drift***

In order to assess whether IN-OT affects the perceived location of the hand in the RHI, a linear mixed model analysis was run to explore the effect of IN-OT (versus placebo) and synchronous (versus asynchronous) stimulation on the proprioceptive drift. The order of

administration was considered in the analysis as a covariate. This analysis revealed no significant main effect of synchronicity ( $F(1, 35) = 0.64; p = 0.43; r = 0.12$ ), IN-OT ( $F(1, 35) = 0.29; p = 0.59; r = 0.04$ ), nor a significant interaction between synchronicity and nasal spray ( $F(1, 35) = 0.51; p = 0.48; r = 0.08$ ). Given the lack of findings regarding proprioceptive drift on our main RHI induction, we did not conduct further analyses on proprioceptive drift.

### ***IN-OT Effects on Embodiment of Hands of different sizes as Measured by Self-Report***

In order to assess whether IN-OT affects the embodiment of hands of different sizes during the RHI, a linear mixed model analysis was run to explore the effect of IN-OT (versus placebo) and watching a larger versus regular size hand on the subjective change in embodiment. Order of nasal spray administration was considered as a covariate. This analysis showed a main effect of oxytocin ( $F(1, 35) = 10.51; p = 0.003; r = 0.87$ ), with oxytocin leading to a greater embodiment (embodiment oxytocin,  $M = 0.81, SE = 0.13$ ) compared to placebo (embodiment placebo,  $M = 0.74, SE = 0.14$ ). This result is in line with the one reported above, that is IN-OT seems to enhance the embodiment of the rubber hand more than placebo regardless of the size of the hand, when touch is synchronous (i.e. no asynchronous condition was conducted with the larger hand). Indeed, hand size did not have a significant main effect on the change in embodiment ( $F(1, 35) = 3.43, p = 0.07; r = 0.25$ ). The interaction between nasal spray and hand size was non-significant ( $F(1, 35) = 0.09; p = 0.77; r = 0.02$ ). In sum, 1) we found that IN-OT compared to placebo enhanced the embodiment of the rubber hand, 2) we did not find an effect of hand size on embodiment of the rubber hand, and 3) we did not find that IN-OT enhances the RHI depending on rubber hand size.



**Figure 4.** (a) Mean of raw embodiment scores (mean-corrected) for the synchronous and asynchronous stroking conditions, after administration of oxytocin or placebo. (b) Mean of raw weight estimation error (mean-corrected) following embodiment of the regular and larger size rubber hand, after administration of oxytocin or placebo. Error bars denote standard error. \* indicated a  $p < 0.05$

#### ***IN-OT Effects on Change in Body Size Representation: the Size Weight Illusion***

Finally, a LMM analysis was run to assess the effect of nasal spray and hand size on the weight estimation task, quantified as weight estimation error. The order of administration was considered in the analysis as a covariate, together with the baseline weight estimation. This analysis showed that neither hand size ( $F(1, 35) = 0.04$ ;  $p = 0.95$ ;  $r = 0.01$ ) nor nasal spray ( $F(1, 35) = 1.89$ ;  $p = 0.18$ ;  $r = 0.30$ ) had a significant main effect on the weight estimation task. However, there was a significant interaction between hand size and nasal spray ( $F(1, 35) = 7.2$ ;  $p = 0.01$ ;  $r = 0.77$ , see Figure 3). Bonferroni-corrected post-hoc analyses ( $p = 0.025$ ) showed no effect of oxytocin compared with placebo in weight estimation error for the regular hand ( $t(35) = -0.67$ ;  $p = 0.51$ ;  $r = 0.19$ ). By contrast, oxytocin increases the weight estimation error after embodiment of the larger hand, compared with placebo ( $F(35) = -1.87$ ;  $p = 0.007$ ;  $r = 0.30$ ). These results indicate that IN-OT enhances the size weight illusion in comparison to placebo when a larger hand is used, but not when a regular hand is used.

## **Discussion**

This double blind, placebo-controlled, crossover study aimed to explore the effect of intranasal oxytocin, in comparison to placebo, on multisensory integration in relation to the sense of body ownership (i.e. rubber hand illusion) and body image (i.e. size-weight illusion). Specifically, we investigated whether IN-OT versus placebo would affect (1) the subjective feeling of body ownership, as measured by means of the embodiment questionnaire; (2) the capture of proprioception by touch as measured by means of proprioceptive drift; and (3) the representation of body size, as measured by means of weight estimation error after embodying rubber hands of different sizes (i.e. size weight illusion).

The results showed that IN-OT enhances the subjective feeling of ownership towards a rubber hand to a greater extent compared to placebo. This effect is independent of the size of the seen hand. In fact, participants embodied the large hand to the same extent as the regular size hand, and IN-OT increases the feeling of embodiment regardless of the hand's size. In contrast, IN-OT did not affect the proprioceptive drift differently compared to placebo. Finally, this study showed that IN-OT enhanced the size-weight illusion following embodiment of a large hand only, in the sense that after administration of IN-OT participants tend to overestimate the weight of the cans to a greater extent compared to the placebo control condition. Such effect was not present following embodiment of the regular size hand.

Our findings confirmed our *first hypothesis* that embodiment of the rubber hand would be enhanced following administration of IN-OT only. Specifically, based on theoretical proposals about the role of oxytocin in somatosensory attenuation (Quattrocki & Friston, 2014), we hypothesised that intranasal oxytocin would enhance the RHI effects, by attenuating the precision of epistemically private somatosensory signals relative to the precision of visual signals, such as the vicarious touch on the rubber hand. Our results showed that IN-OT modulated multisensory integration and corresponding subjective measure of body ownership (i.e. embodiment questionnaire) over the RHI only during synchronous tactile stimulation of

the rubber hand and participants' own hand. No effect of IN-OT was observed in the behavioural (i.e. proprioceptive drift) measure of body ownership over the RHI, nor in the mere visual capture conditions. These findings seem to suggest that IN-OT affects the multisensory integration processes only when synchronous tactile stimulation is involved, but not in the condition when only visual and proprioceptive signals need to be integrated (i.e. IN-OT does not enhance the visual capture of ownership seen in previous studies; see Pavani, Spence and Driver, 2000; Samad et al., 2015; Martinaud et al., 2017). In terms of the predictive coding hypothesis we have put forward, this might suggest that oxytocin, as a neuromodulator, plays a role in precision weighting (i.e. increasing precision) of conflicting sensations deriving from the rubber hand (vicarious touch) in contrast with the ones from the self (epistemically private touch). This process reflects in subjective feelings of body ownership towards the rubber hand, but not in an update in the perceived location of the hand (see Rohde, Di Luca & Ernst, 2011; Abdulkarim & Ehrsson, 2016 for experimental evidence on the dissociation between these two measures of the RHI). In addition, the lack of significant findings in the context of visual capture might suggest that intranasal oxytocin does not modulate precision weighting of conflicting proprioceptive sensations deriving from the rubber hand (i.e. where I see the hand to be) and from the participant's own hand (i.e. where I feel the hand to be). This might provide further support to our hypothesis that intranasal oxytocin modulate the precision of sensorimotor, tactile signals.

To the authors' knowledge, only one recent study attempted to explore the relation between oxytocin and the sense of body ownership. Ide and Wada (2017) showed that the subjective but not objective experience of the RHI is associated with oxytocin, in the sense that participants with higher level of salivary oxytocin at baseline showed an increased experience of the RHI. The authors speculated that oxytocin might enhance the precision of tactile stimulation by modulating the activity of the insular cortex, and the higher susceptibility to the

experience of the RHI would be a consequence of an increase in resources (i.e. attention) placed on touch (Ide and Wada, 2017). This interpretation is in line with our hypothesis that intranasal oxytocin might increase the precision of vicarious touch on the rubber hand. However, here we distinguish between vicarious (seen) touch and epistemically private (felt) touch and we also propose that intranasal oxytocin might reduce the precision of the latter relative to visual signals. Moreover, we note that the instability of single measurements of oxytocin in peripheral fluids (Amico et al., 1983), the correlational nature of the findings, the unclear relationship between peripheral oxytocin levels and central oxytocin (Ludwig and Leng, 2006; Kagerbauer, et al., 2013) and the small sample size ( $N = 15$ ) of Ide and Wada's study should warrant caution against premature conclusions relating to their findings.

The present data also partially support our *second hypothesis* that hand size was not expected to have an effect on the rubber hand illusion *per se* (e.g. Farmer, Tajadura-Jimez & Tsakiris, 2012; Haggard and Jundi, 2009) but on the weight estimation error, here included as an indirect measure of body image (Haggard and Jundi, 2009). Indeed, the sense of body ownership (here manipulated by means of the RHI) can be measured by means of an explicit embodiment questionnaire. In contrast, the SWI has been included here as a more implicit measure of body image. We hypothesised that the effect of hand size would be stronger for the implicit compared to the explicit measure of body representation, suggesting a dissociation between explicit and implicit facets of body representation. Our findings are in line with previous studies showing that the rubber hand illusion is object-dependent, in the sense that it occurs as long as the object could be a body part (Tsakiris et al 2010). In addition, the physical characteristics of the hand, such as skin tone (Farmer et al., 2012) do not seem to affect the occurrence of the illusion. Similarly, our findings showed that the size of the hand did not block or reduce the embodiment process towards the rubber hand. In other words, the effect of IN-OT seems to be over and above physical characteristics of the hand, and it is rather dependent

on the synchronicity between seen and felt touch. Furthermore, we predicted that IN-OT would modulate multisensory integration and corresponding behavioural measure as quantified by judgments of the weight of external objects having constant size but different weight following embodiment of the larger hand only (as in Haggard and Jundi, 2009). In other words, we expected IN-OT to increase the error in weight estimation following the embodiment of a large hand only; in contrast, no effect of IN-OT on weight estimation would be observed following the embodiment of the regular size hand. Participants showed a greater weight estimation error following the embodiment of the larger hand as compared to the regular size hand (i.e. main effect of hand size on weight estimation error); however, this effect did not reach significance (see Haggard and Jundi, 2009). Nevertheless, the results confirmed our hypothesis, by showing a significant interaction between hand size and nasal spray. IN-OT seems to promote the occurrence of the size weight illusion compared to placebo, in the sense that it increases the weight estimation error only after embodiment of the larger hand. These findings might suggest that intranasal oxytocin allows more flexibility in terms of body shape and size. We speculate that this process might be related to the role that oxytocin plays in pregnancy, a moment of important bodily and emotional changes in women.

Additionally, the fact that IN-OT influences explicit and implicit measures of the malleability of body representation is in line with previous findings showing that oxytocin sharpens the recognition of basic emotions as well as hidden/implicit emotional facial expressions (Leknes et al., 2013; Leppanen et al., 2017 for a meta-analysis). This explanation supports the idea that oxytocin might play an important evolutionary role, by promoting social affiliation and bonding and by downregulating pain perception associated with reproduction (Insel, 1992; Paloyelis et al., 2015).

In conclusion, our findings are the first to suggest that intranasal oxytocin modulates processes of multisensory integration in relation to both body ownership and body image. We

speculate that this process might follow basic principles of predictive coding. However, the interpretation we put forward in this paper is tentative and we hope it will pave the way for future studies that might investigate the relationship between oxytocin and somatosensory precision more specifically. In particular, studies using computational modelling approaches (e.g. Samad et al., 2015) or measuring synaptic gain (Zeller et al., 2014; 2016) during the RHI with modulation of oxytocin could test our hypotheses and provide unique insight into the mechanisms by which oxytocin may act in order to modulate the subjective feelings of body ownership, as we speculate in this paper. In the context of multisensory integration, oxytocin seems to mediate the precision weighting (or attention) given to descending prior prediction and ascending sensory inputs (prediction errors). When a hand is placed in front of the participant, in peripersonal space and from a first person perspective, the participant has a strong prediction that the hand they see must belong to them. When there are ‘incongruent’ proprioceptive (i.e. where I see the rubber hand to be vs. where I feel my own hand to be) and visuo-tactile signals (i.e. vicarious touch on the rubber hand illusion vs. felt touch on my own hand), then brain must resolve this conflict by downregulating incongruent or incompatible sources of information. In this context, we hypothesised that intranasal oxytocin might attenuate epistemically private sensations in social situations, to allow us to build a self during social interactions characterised by some degree of ‘interpersonal synchrony’ (Fotopoulou & Tsakiris, 2017). Hence, the self is built by ‘identification’ (see Panagiotopoulou et al., 2017), in this context meaning the integration of epistemically private sensations and exteroceptively perceived but ‘synchronous’ sensations from others. We proposed that intranasal oxytocin might enhance this process of identification by increasing the feeling that our body feels like our own, even when we perceive it via exteroception. In other words, intranasal oxytocin might mediate the neurobiological mechanism promoting and sharpening the precision of exteroceptive sensory inputs (e.g. visual signals of a realistic hand in peripersonal space and of



the seen touch) in order to determine the weighting of top-down cognitive predictions against bottom-up, epistemically private sensory information (e.g. felt location and touch), ultimately facilitating multisensory integration.

Furthermore, intranasal oxytocin may modulate the sense of body ownership by means of other possible mechanisms. For example, according to Quattrocki and Friston (2014) oxytocin might act by attenuating interoceptive prediction errors, ultimately increasing the relative precision of exteroceptive information. This interpretation could be partially supported by studies showing physiological changes to the participant's real hand (e.g. a reduction in skin temperature) during the RHI, which are consistent with the idea that interoceptive prediction errors might be attenuated (Moseley et al., 2008). However, recent studies have cast doubt on the replicability of these physiological findings in the context of the RHI and therefore this hypothesis should be interpreted with caution (e.g. de Haan et al., 2017; Crucianelli et al., 2018).

To our knowledge, this is the first study to have investigated whether the oxytocinergic system might modulate process of multisensory integration via embodied synchronicity mechanisms, such as synchronous tactile stimulation on the body. These findings are particularly important not only because the sense of body ownership is a fundamental aspect of our bodily self-consciousness (Blanke et al., 2004; Dijkerman, 2015), but also because the representation of one's own body is not fixed but rather the result of a predictive processing that is constantly updated by means of multisensory processes. Future studies should explore and extend these findings to clinical populations characterised by body image distortions and lack of bodily awareness, such as eating disorders.

### **Authors Contributions**

LC, AF and PMJ conceived and designed the experiment. LR offered medical supervision to the study. LC performed data collection and analysed the data, under supervision of AF, PJ and YP. LC, YP, AF and PMJ wrote the manuscript. All the authors approved the manuscript before submission.

### **Acknowledgements**

Authors would like to thank Dora Tamari-Tutnjević, Mengbing Zhang, Amanda Hornsby, Mariana von Mohr for assistance with data collection. We are grateful to Miss Catherine Maze for her help with the customized rubber hands. The study was supported by a “European Research Council Starting Investigator Award” [ERC- 2012-STG GA313755] to A.K.; a University of Hertfordshire studentship to L.C. and a Neuropsychanalysis Foundation grant to L.C. Funding for the time of A.K. and L.C has been partially provided by the Fund for Psychoanalytic Research through the American Psychoanalytic Association. The Authors would like to thank the anonymous reviewers for their valuable comments and suggestions to improve the quality of the paper.

### **References**

- Abdulkarim, Z., & Ehrsson, H.H. (2016). No causal link between changes in hand position sense and feeling of limb ownership in the rubber hand illusion. *Attention Perception & Psychophysics*, 78(2), 707-720
- Ainley, V., & Tsakiris, M. (2013). Body conscious? Interoceptive awareness, measured by heartbeat perception, is negatively correlated with self-objectification. *PloS one*, 8(2), e55568.
- Amico, J. A., Tenicela, R., Johnston, J., & Robinson, A. G. (1983). A time-dependent peak of oxytocin exists in cerebrospinal fluid but not in plasma of humans. *The Journal of Clinical Endocrinology & Metabolism*, 57(5), 947-951.
- Apps, M. A., & Tsakiris, M. (2014). The free-energy self: a predictive coding account of self-recognition. *Neuroscience & Biobehavioral Reviews*, 41, 85-97.

- Bartz, J. A., Zaki, J., Bolger, N., & Ochsner, K. N. (2011). Social effects of oxytocin in humans: Context and person matter. *Trends in Cognitive Sciences*, *15*, 301-309
- Bastos, A. M., Usrey, W. M., Adams, R. A., Mangun, G. R., Fries, P., & Friston, K. J. (2012). Canonical microcircuits for predictive coding. *Neuron*, *76*(4), 695-711.
- Blanke, O., Landis, T., Spinelli, L., & Seeck, M. (2004). Out-of-body experience and autoscapy of neurological origin. *Brain*, *127*(2), 243-258.
- Blanke, O. (2012). Multisensory brain mechanisms of bodily self-consciousness. *Nature Reviews Neuroscience*, *13*(8), 556-571
- Born, J., Lange, T., Kern, W., McGregor, G. P., Bickel, U., & Fehm, H. L. (2002). Sniffing neuropeptides: a transnasal approach to the human brain. *Nature neuroscience*, *5*(6), 514.
- Botvinick, M., & Cohen, J. (1998). Rubber hands ‘feel’ touch that eyes see. *Nature*, *391*(6669), 756.
- Buckingham, G., & Goodale, M. A. (2013). Size matters: a single representation underlies our perceptions of heaviness in the size-weight illusion. *PLoS One*, *8*(1), e54709.
- Burbach, J.P., Young, L.J., & Russell, J. (2006). Oxytocin: synthesis, secretion and reproductive functions. In Knobil and Neill’s *Physiology of Reproduction*, 3rd edn (ed. J. D. Neill), pp. 3055–3128. Elsevier : London.
- Cesari, P., & Newell, K. M. (1999). The scaling of human grip configurations. *Journal of Experimental Psychology: Human Perception and Performance*, *25*(4), 927.
- Colonnello, V., & Heinrichs, M. (2016). Oxytocin and Self-Consciousness. *Frontiers in human neuroscience*, *10*, 67.
- Crucianelli, L., Metcalf, N. K., Fotopoulou, A. K., & Jenkinson, P. M. (2013). Bodily pleasure matters: velocity of touch modulates body ownership during the rubber hand illusion. *Frontiers in psychology*, *4*, 703.
- Crucianelli, L., Krahé, C., Jenkinson, P. M., & Fotopoulou, A. K. (2018). Interoceptive ingredients of body ownership: Affective touch and cardiac awareness in the rubber hand illusion. *Cortex*.
- De Dreu, C.K.W., Greer, L.L., Handgraaf, M.J.J., Shalvi, S., Van Kleef, G.A., Bass, M, ten Valden, F.S., Van Dijk, E., & Feith, S.W.W. (2010). The neuropeptide oxytocin regulates parochial altruism in intergroup conflict among humans. *Science*, *328*(5984), 1408-1411

- de Haan, A. M., Van Stralen, H. E., Smit, M., Keizer, A., Van der Stigchel, S., & Dijkerman, H. C. (2017). No consistent cooling of the real hand in the rubber hand illusion. *Acta psychologica*, 179, 68-77.
- Deroy, O., Spence, C., & Noppeney, U. (2016). Metacognition in multisensory perception. *Trends in cognitive sciences*, 20(10), 736-747.
- Dijkerman, H.C. (2015). How do different aspects of self-consciousness interact? *Trends in cognitive sciences*, 19(8), 427-428
- Ernst, M. O., & Banks, M. S. (2002). Humans integrate visual and haptic information in a statistically optimal fashion. *Nature*, 415(6870), 429.
- Eshkevari, E., Rieger, E., Longo, M. R., Haggard, P., & Treasure, J. (2012). Increased plasticity of the bodily self in eating disorders. *Psychological Medicine*, 42(4), 819-828.
- Eshkevari, E., Rieger, E., Longo, M. R., Haggard, P., & Treasure, J. (2014). Persistent body image disturbance following recovery from eating disorders. *International Journal of Eating Disorders*, 47(4), 400-409.
- Fairburn, C. G., & Beglin, S. J. (1994). Assessment of eating disorders: Interview or self-report questionnaire?. *International journal of eating disorders*, 16(4), 363-370.
- Fairburn, C. G., & Beglin, S. J. (2008). Eating disorder examination questionnaire. *Cognitive behaviour therapy and eating disorders*.
- Farmer, H., Tajadura-Jiménez, A., & Tsakiris, M. (2012). Beyond the colour of my skin: How skin colour affects the sense of body-ownership. *Consciousness and cognition*, 21(3), 1242-1256.
- Farne, A., Pavani, F., Meneghello, F., & Ladavas, E. (2000). Left tactile extinction following visual stimulation of a rubber hand. *Brain*, 123(11), 2350-2360.
- Feldman, H., & Friston, K. (2010). Attention, uncertainty, and free-energy. *Frontiers in human neuroscience*, 4, 215.
- Ferri, F., Chiarelli, A. M., Merla, A., Gallese, V., & Costantini, M. (2013). The body beyond the body: expectation of a sensory event is enough to induce ownership over a fake hand. *Proceedings of the Royal Society of London B: Biological Sciences*, 280(1765), 20131140.
- Fiorillo, C. D., Tobler, P. N., & Schultz, W. (2003). Discrete coding of reward probability and uncertainty by dopamine neurons. *Science*, 299(5614), 1898-1902.
- Fiser, J., Berkes, P., Orbán, G., & Lengyel, M. (2010). Statistically optimal perception and learning: from behavior to neural representations. *Trends in cognitive sciences*, 14(3), 119-130.

- Flanagan, J. R., & Beltzner, M. A. (2000). Independence of perceptual and sensorimotor predictions in the size–weight illusion. *Nature neuroscience*, 3(7), 737.
- Fotopoulou, A., & Tsakiris, M. (2017). Mentalizing homeostasis: The social origins of interoceptive inference. *Neuropsychoanalysis*, 19(1), 3-28.
- Fredrickson, B. L., & Roberts, T. A. (1997). Objectification theory: Toward understanding women's lived experiences and mental health risks. *Psychology of women quarterly*, 21(2), 173-206.
- Fredrickson, B. L., Roberts, T. A., Noll, S. M., Quinn, D. M., & Twenge, J. M. (1998). That swimsuit becomes you: sex differences in self-objectification, restrained eating, and math performance. *Journal of personality and social psychology*, 75(1), 269.
- Friston, K. (2005). A theory of cortical responses. *Philosophical transactions of the Royal Society B: Biological sciences*, 360(1456), 815-836.
- Friston, K. J., & Stephan, K. E. (2007). Free-energy and the brain. *Synthese*, 159(3), 417-458.
- Friston, K. (2008). Hierarchical models in the brain. *PLoS computational biology*, 4(11), e1000211.
- Friston, K., Adams, R., Perrinet, L., & Breakspear, M. (2012). Perceptions as hypotheses: saccades as experiments. *Frontiers in psychology*, 3, 151.
- Gallagher, S. (2000). Philosophical conceptions of the self: Implications for cognitive science. *Trends in Cognitive Science*, 4, 14–21.
- Gordon, I., Vander Wyk, B. C., Bennett, R. H., Cordeaux, C., Lucas, M. V., Eilbott, J. A., ... & Pelphrey, K. A. (2013). Oxytocin enhances brain function in children with autism. *Proceedings of the National Academy of Sciences*, 110(52), 20953-20958.
- Grinevich, V., Knobloch-Bollmann, H. S., Eliava, M., Busnelli, M., & Chini, B. (2016). Assembling the puzzle: pathways of oxytocin signaling in the brain. *Biological psychiatry*, 79(3), 155-164.
- Haggard, P., & Jundi, S. (2009). Rubber hand illusions and size–weight illusions: self-representation modulates representation of external objects. *Perception*, 38(12), 1796-1803.
- Hosmer, D. W., Lemeshow, S., & May, S. (2008). *Model development. Applied survival analysis: regression modeling of time-to-event data*. 2nd ed. Hoboken (NJ): Wiley-Interscience, 132-68.
- Ide, M., & Wada, M. (2017). Salivary Oxytocin Concentration Associates with the Subjective Feeling of Body Ownership during the Rubber Hand Illusion. *Frontiers in human neuroscience*, 11, 166.

- Insel, T. R. (1992). Oxytocin—a neuropeptide for affiliation: evidence from behavioral, receptor autoradiographic, and comparative studies. *Psychoneuroendocrinology*, *17*(1), 3-35
- Kagerbauer, S. M., Martin, J., Schuster, T., Blobner, M., Kochs, E. F., & Landgraf, R. (2013). Plasma oxytocin and vasopressin do not predict neuropeptide concentrations in human cerebrospinal fluid. *Journal of neuroendocrinology*, *25*(7), 668-673.
- Leppanen, J., Ng, K. W., Tchanturia, K., & Treasure, J. (2017). Meta-analysis of the effects of intranasal oxytocin on interpretation and expression of emotions. *Neuroscience & Biobehavioral Reviews*, *78*, 125-144.
- Limanowski, J., & Blankenburg, F. (2015). Network activity underlying the illusory self-attribution of a dummy arm. *Human Brain Mapping*, *36*(6), 2284-2304.
- Longo, M. R., Schüür, F., Kammers, M. P., Tsakiris, M., & Haggard, P. (2008). What is embodiment? A psychometric approach. *Cognition*, *107*(3), 978-998.
- Ludwig, M., & Leng, G. (2006). Dendritic peptide release and peptide-dependent behaviours. *Nature Reviews Neuroscience*, *7*(2), 126.
- Ma, W. J., Beck, J. M., Latham, P. E., & Pouget, A. (2006). Bayesian inference with probabilistic population codes. *Nature neuroscience*, *9*(11), 1432.
- MacDonald, K., & MacDonald, T. M. (2010). The peptide that binds: A systematic review of oxytocin and its prosocial effects in humans. *Harvard Review of Psychiatry*, *18*, 1-21
- MacDonald, E., Dadds, M. R., Brennan, J. L., Williams, K., Levy, F., & Cauchi, A. J. (2011). A review of safety, side-effects and subjective reactions to intranasal oxytocin in human research. *Psychoneuroendocrinology*, *36*(8), 1114-1126.
- Martinaud, O., Besharati, S., Jenkinson, P. M., & Fotopoulou, A. (2017). Ownership illusions in patients with body delusions: Different neural profiles of visual capture and disownership. *cortex*, *87*, 174-185.
- McGlone, F., Olausson, H., Boyle, J. A., Jones-Gotman, M., Dancer, C., Guest, S., & Essick, G. (2012). Touching and feeling: differences in pleasant touch processing between glabrous and hairy skin in humans. *European Journal of Neuroscience*, *35*(11), 1782-1788.
- Miner-Rubino, K., Twenge, J. M., & Fredrickson, B. L. (2002). Trait self-objectification in women: Affective and personality correlates. *Journal of Research in Personality*, *36*(2), 147-172.
- Moseley, G. L., Olthof, N., Venema, A., Don, S., Wijers, M., Gallace, A., & Spence, C. (2008). Psychologically induced cooling of a specific body part caused by the illusory

- ownership of an artificial counterpart. *Proceedings of the National Academy of Sciences*, 105(35), 13169-13173.
- O'Reilly, J. X., Jbabdi, S., & Behrens, T. E. (2012). How can a Bayesian approach inform neuroscience?. *European Journal of Neuroscience*, 35(7), 1169-1179.
- Paloyelis, Y., Krahé, C., Maltezos, S., Williams, S. C., Howard, M. A., & Fotopoulou, A. (2016). The Analgesic Effect of Oxytocin in Humans: A Double-Blind, Placebo-Controlled Cross-Over Study Using Laser-Evoked Potentials. *Journal of neuroendocrinology*, 28(4).
- Paloyelis, Y., Doyle, O. M., Zelaya, F. O., Maltezos, S., Williams, S. C., Fotopoulou, A., & Howard, M. A. (2016). A spatiotemporal profile of in vivo cerebral blood flow changes following intranasal oxytocin in humans. *Biological psychiatry*, 79(8), 693-705.
- Panagiotopoulou, E., Filippetti, M. L., Tsakiris, M., & Fotopoulou, A. (2017). Affective touch enhances self-face recognition during multisensory integration. *Scientific reports*, 7(1), 12883.
- Pavani, F., Spence, C., & Driver, J. (2000). Visual capture of touch: Out-of-the-body experiences with rubber gloves. *Psychological science*, 11(5), 353-359.
- Preston, C., & Ehrsson, H. H. (2014). Illusory changes in body size modulate body satisfaction in a way that is related to non-clinical eating disorder psychopathology. *PLoS one*, 9(1), e85773.
- Quattrocki, E., & Friston, K. (2014). Autism, oxytocin and interoception. *Neuroscience & Biobehavioral Reviews*, 47, 410-430
- Rao, R. P., & Ballard, D. H. (1999). Predictive coding in the visual cortex: a functional interpretation of some extra-classical receptive-field effects. *Nature neuroscience*, 2(1), 79.
- Rocchetti, M., Radua, J., Paloyelis, Y., Xenaki, L. A., Frascarelli, M., Caverzasi, E., ... & Fusar-Poli, P. (2014). Neurofunctional maps of the 'maternal brain' and the effects of oxytocin: A multimodal voxel-based meta-analysis. *Psychiatry and clinical neurosciences*, 68(10), 733-751.
- Rohde, M., Di Luca, M., & Ernst, M. O. (2011). The rubber hand illusion: Feeling of ownership and proprioceptive drift do not go hand in hand. *PLoS One*, 6, e21659
- Rohe, T., & Noppeney, U. (2015). Cortical hierarchies perform Bayesian causal inference in multisensory perception. *PLoS Biology*, 13(2), e1002073.

- Salonia, A., Nappi, R. E., Pontillo, M., Daverio, R., Smeraldi, A., Briganti, A., ... & Montorsi, F. (2005). Menstrual cycle-related changes in plasma oxytocin are relevant to normal sexual function in healthy women. *Hormones and behavior*, *47*(2), 164-169.
- Samad, M., Chung, A. J., & Shams, L. (2015). Perception of body ownership is driven by Bayesian sensory inference. *PloS one*, *10*(2), e0117178.
- Shipp, S., Adams, R. A., & Friston, K. J. (2013). Reflections on agranular architecture: predictive coding in the motor cortex. *Trends in neurosciences*, *36*(12), 706-716.
- Shamay-Tsoory, S. G., & Abu-Akel, A. (2016). The social salience hypothesis of oxytocin. *Biological psychiatry*, *79*(3), 194-202
- Stoop, R. (2012). Neuromodulation by oxytocin and vasopressin. *Neuron*, *76*(1), 142-159.
- Tiggemann, M., & Lynch, J. E. (2001). Body image across the life span in adult women: The role of self-objectification. *Developmental psychology*, *37*(2), 243.
- Treasure, J., & Schmidt, U. (2013). The cognitive-interpersonal maintenance model of anorexia nervosa revisited: a summary of the evidence for cognitive, socio-emotional and interpersonal predisposing and perpetuating factors. *Journal of eating disorders*, *1*(1), 13.
- Tsakiris, M., & Haggard, P. (2005). The rubber hand illusion revisited: visuotactile integration and self-attribution. *Journal of Experimental Psychology and Human Perceptive Performance*, *31*, 80-91
- Tsakiris, M. (2010). *My body in the brain: A neurocognitive model of body-ownership. Neuropsychologia* *48*, 703-712
- Uvnäs-Moberg, K., Handlin, L., & Petersson, M. (2015). Self-soothing behaviors with particular reference to oxytocin release induced by non-noxious sensory stimulation. *Frontiers in psychology*, *5*, 1529.
- Yu, A. J., & Dayan, P. (2005). Uncertainty, neuromodulation, and attention. *Neuron*, *46*(4), 681-692.
- Wagner, A., Barbarich-Marsteller, N.C., Frank, G.K., Bailer, U.F., Wonderlich, S.A., Crosby, R.D., Henry, S.E., Vogel, V., Plotnicov, K., McConaha, C. and Kaye, W.H., 2006. Personality traits after recovery from eating disorders: do subtypes differ?. *International Journal of Eating Disorders*, *39*(4), 276-284.
- Walum, H., Waldman, I. D., & Young, L. J. (2016). Statistical and methodological considerations for the interpretation of intranasal oxytocin studies. *Biological psychiatry*, *79*(3), 251-257.



- Zeller, D., Litvak, V., Friston, K. J., & Classen, J. (2014). Sensory processing and the rubber hand illusion—an evoked potentials study. *Journal of Cognitive Neuroscience*, 27(3), 573-582.
- Zeller, D., Friston, K. J., & Classen, J. (2016). Dynamic causal modeling of touch-evoked potentials in the rubber hand illusion. *Neuroimage*, 138, 266-273.