Psychoneuroendocrinology 101 (2019) 193–203

Contents lists available at ScienceDirect

Psychoneuroendocrinology

journal homepage: www.elsevier.com/locate/psyneuen

# Foot massage evokes oxytocin release and activation of orbitofrontal cortex and superior temporal sulcus

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ARTICLE INFO

*Keywords:*
Massage
Superior temporal sulcus
Oribitofrontal cortex
Plasma oxytocin
Autism

ABSTRACT

Massage may be an important method for increasing endogenous oxytocin concentrations and of potential therapeutic benefit in disorders with social dysfunction such as autism where basal oxytocin levels are typically reduced. Here we investigated oxytocin release and associated neural responses using functional near infrared spectroscopy (fNIRS) during hand- or machine-administered massage. 40 adult male subjects received 10 min of light foot massage either by hand or machine in a counterbalanced order and then rated pleasure, intensity, arousal and how much they would pay for the massage. Blood samples were taken before and after each massage condition to determine plasma oxytocin concentrations. Neural responses from medial and lateral orbitofrontal cortex, superior temporal sulcus and somatosensory cortex were measured (fNIRS oxy-Hb) together with skin conductance responses (SCR), ratings of the massage experience, autistic traits and sensitivity to social touch. Results showed subjects gave higher ratings of pleasure, but not intensity or arousal, after hand- compared with machine-administered massage and there were no differential effects on SCR. Subjects were also willing to pay more for the hand massage. Plasma oxytocin increased after both massage by hand or machine, but more potently after massage by hand. Both basal oxytocin concentrations and increases evoked by hand-, but not machine-administered massage, were negatively associated with trait autism and attitudes towards social touch, but massage by hand-evoked changes were significant in higher as well as lower trait individuals. Increased neural responses to hand vs. machine-administered massage were found in posterior superior temporal sulcus and medial/lateral orbitofrontal cortex but not somatosensory cortex. Orbitofrontal cortex and superior temporal cortex activation during hand massage was associated with the amount of money subjects were willing to pay and between orbitofrontal cortex activation and autism scores. Thus, hand-administered massage can potently increase oxytocin release and activity in brain regions involved in social cognition and reward but not sensory aspects of affective touch. Massage by hand induced changes in both oxytocin concentrations and neural circuits involved in processing social affective trust may have therapeutic potential in the context of autism.

## 1. Introduction

The neuropeptide oxytocin (OXT) plays an important role in influencing both social bonds and a number of different aspects of social cognition in a variety of different species, including humans (Kendrick et al., 2017). There is increasing evidence across cultures that basal plasma OXT concentrations are reduced in disorders with social dysfunction, such as autism, and by early life social neglect which can also lead to social dysfunction (Green et al., 2001; Oztan et al., 2018; Parker et al., 2014; Zhang et al., 2016). Importantly, reduced OXT concentrations correlate with autistic symptom severity in terms of social dysfunction in clinical and healthy populations in Caucasian (Parker et al., 2014) and Asian (Zhang et al., 2016) samples. In the context of depression, high intent suicide attempters also have reduced cerebrospinal fluid OXT concentrations (Jokinen et al., 2012). Furthermore, there is substantial evidence from both animal models and human

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https://doi.org/10.1016/j.psyneuen.2018.11.016
Received 13 August 2018; Received in revised form 29 September 2018; Accepted 12 November 2018
0306-4530/ 

studies that OXT administration can produce anxiolytic effects (Naja and Aoun, 2017; Neumann and Slattery, 2016). This has resulted in an increasing number of studies and clinical trials which are assessing the potential therapeutic benefit of attempting to increase endogenous OXT concentrations using administration of intranasal OXT either acutely or chronically (Kendrick et al., 2017). Several studies have shown some therapeutic efficacy of such endogenous OXT treatments in anxiety, autism and schizophrenia (Gordon et al., 2013; Guastella and Hickie, 2016; Kendrick et al., 2017; Naja and Aoun, 2017; Parker et al., 2017) although far more research is clearly required. In this context it is also important to explore whether there are alternative, non-invasive and non-pharmacological strategies which might be effective in increasing endogenous OXT concentrations. One such strategy may be through the use of tactile stimulation.

Social affective touch and/or massage treatments have been shown by several studies to reduce anxiety, stress, heart rate, blood pressure and pain (Diego et al., 2004; Diego and Field, 2009; Field, 2014, 2016; Wilhelm et al., 2001) and to be helpful in relation to a number of clinical conditions, most notably cancer (Kinkead et al., 2018; Lee et al., 2015; Wyatt et al., 2017). In the context of the current paper massage treatment has been shown to improve some symptoms of autism spectrum disorder (ASD), such as increased tolerance of touch and social cooperation and reduced anxiety and repetitive behavior (Escalona et al., 2001; Silva et al., 2015; Walaszek et al., 2017) as well as having positive effects in other psychiatric disorders (Rapaport et al., 2018).

Some of the beneficial effects of affective touch and massage may be due to it increasing OXT release where animal studies have consistently demonstrated effects associated with tactile stimulation (see Uvnäs-Moberg et al., 2014). A number of studies have reported that blood, saliva or urine OXT concentrations are increased in response to social affective touch in both chimpanzees (Crockford et al., 2013) and humans (Holt-Lunstad et al., 2008; Light et al., 2005; Morhenn et al., 2008, 2012; Odendaal and Meintjes, 2003). In human couples increased blood concentrations of OXT during the early stage of relationships are also correlated positively with levels of affective touching (Scheiderman et al., 2012). On the other hand, the OXT assays performed have sometimes not used the recommended extraction step (McCullough et al., 2013) and a number of studies have reported no effect (Heinrichs et al., 2003; Grewen et al., 2005; Ditzen et al., 2007), including one clinical trial on the effects of gentle touch in intensive care patients (Henricson et al., 2008). Findings in humans therefore currently need to be treated with some caution and more evidence is required

While receiving warm social affective touch is of great importance for social development and interactions (Bjornsdotter et al., 2014; Brauer et al., 2016) responses are clearly sensitive to who is doing the touching, context and duration (Ellingsen et al., 2014, 2016; Gazzola et al., 2012; McCabe et al., 2008; Scheele et al., 2014). Massage on the other hand is potentially much easier to employ therapeutically, and shoulder and neck massage (Bello et al., 2008; Turner et al., 1999) and back massage (Morhenn et al., 2012) can increase plasma OXT concentrations and correspondingly reduce adrenocorticotropin (ACTH), suggestive of an anxiolytic action (Morhenn et al., 2012). However, one study has reported no significant effect of back and neck massage (Wikstrom et al., 2003). Machine-administered massage (massage seat) can also increase endogenous OXT concentrations in saliva in men and these were associated with greater sensitivity to infant signals, although less effectively in individuals who had experienced childhood emotional maltreatment (Riem et al., 2017). One small study has reported that autistic children receiving the gentle massage from their mothers exhibited higher oxytocin concentrations during massage period compared to the non-massage period (Tsuji et al., 2015), although the study did not report any effects on symptoms. Thus massage administered either manually or via a mechanical device can increase OXT concentrations in either blood or saliva although their relative potency and modulatory effects of autistic traits and sensitivity to social touch have not been explored. In the current study we therefore compared the effects of hand (Chinese style) or mechanically delivered foot massage on OXT release. Both of these massages administer rhythmic pressure to the whole foot, with no stroking and such light pressure foot massage should activate both C-tactile (CT) and non-C-type fibers, the former being of particular importance for conveying the effects of social touch (Gordon et al., 2011; Olausson et al., 2010; Vallbo et al., 1993). In the study subjects were also asked to self-rate the pleasure, arousal and intensity of the massage and a physiological measure of arousal was also taken (skin conductance response). While we hypothesized that subjects should rate the pleasure of the manual massage highest our aim was that both kinds of massage would be similar in terms of their intensity and arousal since the latter could present potential non-specific confounders for making comparisons between manual and machine-based massage.

Although the respective efficacy of manual and machine massage for eliciting OXT release is a key component for their potential use in a therapeutic context for disorders with social dysfunction such as autism, an important secondary and related component is the extent to which these different types of massage can additionally activate neural circuitry involved in processing affective touch. Furthermore, the relationships between massage-evoked OXT release and neural activation changes associated with affective touch have yet to be established in humans, although it has been reported that intranasal OXT increased activation in these regions in response to social touch (Scheele et al., 2014). Social affective touch targeting CT-afferents particularly activates brain regions involved in social cognition (amygdala, medial prefrontal cortex, superior temporal sulcus – STS) and reward (orbitofrontal cortex – OFC) and regions involved in interoception and salience processing, such as the insula, as well as the somatosensory cortex (S1) (Bennett et al., 2014; Gordon et al., 2011; Olausson et al., 2010; Perini et al., 2015). Importantly, the response to social touch is also reduced in ASD in all of these regions (Kaiser et al., 2015) and in the OFC and STS in healthy individuals with higher autistic traits (Voos et al., 2013). Neural responses to massage-type stimuli are more varied, but generally have been shown to engage at least some components of the affective touch networks (Golaszewski et al., 2006; Ouchi et al., 2006). Notably, massage of the sole of the foot activates the STS, insula, thalamus and caudate as well as S1 (Golaszewski et al., 2006).

In the present study we have therefore investigated the respective effects of light pressure foot massage either administered by hand or by machine on both OXT release and activation of brain regions associated with affective touch. Neural activation was recorded using functional near infrared spectroscopy (fNIRS) which is an increasing used, optical neuroimaging method for monitoring haemodynamic responses in the brain with neural activation being measured via changes in the concentration of oxygenated haemoglobin (Oxy-Hb). An important advantage of the technique compared with functional MRI is that subjects can be recorded from in a more relaxed and normal environment with less constrictions on movement and for the present experiment it also allowed the use of mechanical massage devices which are not MRI compatible (Plichta et al., 2006). A previous fNIRS study has already demonstrated increased STS activity in response to affective touch (Bennett et al., 2014). Thus, we used fNIRS to measure cortical activation patterns the key cortical regions responding to affective touch (OFC, STS and S1) during hand and machine massage and correlated them with OXT release and the pleasure evoked by the massages. Given the focus of our study on possible therapeutic application of massage-evoked changes in OXT and activation of brain regions involved in social touch in relation to autism we additionally employed established questionnaires for quantifying autistic symptoms in both healthy and clinical populations (Autism Spectrum Questionnaire – AQ; Baron-Cohen et al., 2001; Ruzich et al., 2015) and reduced comfort and preference for social touch which autistic individuals also score high on (social touch questionnaire - STQ; Wilhelm et al., 2001).

Based on the previous findings summarized above we hypothesized that massage by hand would be rated more pleasurable, but not more arousing, than equal intensity machine massage. We additionally hypothesized that hand massage would be more effective at releasing OXT and increasing responses in brain regions responsive to processing cognitive and reward effects of social touch (OFC and STS) but not in those responding primarily to sensory and intensity aspects of touch (S1). Finally, we hypothesized that basal and/or evoked OXT release and neural responses to hand massage would be positively associated with pleasure/reward ratings and negatively associated with autistic traits and dislike of social touch but not with other personality traits.

## 2. Methods and materials

### 2.1. Participants

A total of 40 male heterosexual healthy Chinese University students (mean age ± sem = 21.78 ± 0.40) participated in the study. All subjects were reported being free of medical or psychiatric disorders, current or regular medication in an initial interview and did not consume any alcohol, caffeine or nicotine on the day of the experiment. To reduce novelty, all subjects were required to have had at least two or more previous experiences of receiving Chinese foot massage. The study had full approval from the local ethics committee of the University of Electronic Science and Technology of China and procedures were in accordance with the latest revision of the declaration of Helsinki. All subjects provided written informed consent.

### 2.2. Experimental design

Before the experimental session, each subject completed a number of questionnaires on personality, mood, traits and sensitivity to touch and reward. Chinese versions of the State-Trait Inventory (STAI; Spielberg et al., 1970), Beck's Depression Inventory II (BDI; Beck et al., 1996) and Cheek and Buss Shyness Scale (CBSS; Cheek, 1983) were administered to confirm that all subjects had scores on anxiety, depression and shyness/social anxiety within the normal healthy range. Chinese versions of: NEO-Five Factor Inventory (NEO-FFI; Costa and McCrae, 1992), Empathy Quotient (EQ; Baron-Cohen and Wheelwright, 2004), Behavioral Inhibition System and Behavioral Activation System Scales (BIS/BAS; Carver and White, 1994) and the Sensitivity to Punishment and Sensitivity to Reward Questionnaire (SPSRQ; Torrubia et al., 2001) were administered in order to assess the specificity of associations with the two specific scales of interest, the AQ and STQ which were also completed. For both the AQ and STQ higher scores indicate greater autistic traits/greater discomfort with social touch respectively. The AQ comprises 50 questions (e.g. "I enjoy social occasions") and is a widely used and established instrument for quantifying the continuum of autistic symptoms across the range from normality to pathology (Ruzich et al., 2015). The internal consistency (Cronbach's α) of the Chinese version used in the current study was good (0.73) and similar to that we have reported recently in a large scale genetics study (Montag et al., 2017). Individual scores ranged from 0 to 50 (M = 20.2, SE = 0.98). The STQ comprises 20 questions (e.g. "I get nervous when an acquaintance keeps holding my hand after a handshake") associated with feelings and attitudes towards social touch. The internal consistency (Cronbach's α) of the Chinese version of the questionnaire was also good (0.70). Individual scores ranged from 0 to 80 (M = 41.45, SE = 1.26). Additionally, the Positive and Negative Affect Schedule (PANAS; Watson et al., 1988) was administered after each type of massage as a measure of their respective impact on mood.

After completing the questionnaires, subjects were asked to wash their feet before they received the foot massage. Next they were asked to lean back on a comfortable reclining chair with their feet supported. A cap containing the fNIRS optodes was put on their head and two Ag–AgCl electrodes, attached to the index and middle fingers and connected to a Biopac Systems module for electrodermal activity recording for measurement of skin conductance responses (SCR). A catheter for blood sampling was then inserted into an arm vein by a qualified nurse. All participants were then blindfolded so that they could not see either the professional masseur or the machine massage devices and both the temperature and illumination in the experimental room was controlled to ensure comfort. All subjects were instructed to close their eyes and to focus on the massage. The study included two blocks, one of which was a Chinese foot massage given by a professional masseur and the other one was a machine-based massage applied using a commercial massage machine (Panasonic – EW-NA84). The Chinese foot massage is a pressure type massage (i.e. no stroking) and the machine used also provided a pressure type massage to match it as far as possible (although the machine can massage the lower leg as well we only used the foot component). The massage boots applied heat to maintain temperature at around 37 °C (low temperature setting on the device to simulate normal body temperature) to match that of the hand massage. All hand massages were performed by the same male masseur although subjects were unable to see who was massaging them. In each period of massage subjects received either hand massage or machine massage for 20 s and then had a rest for 10 s (i.e. no massage) and this was repeated 20 times (i.e. a total of 10 min). The right and left feet were massaged simultaneously and the order of the two massage types was counterbalanced. Blood samples (6 ml) were collected immediately before and after each of the two massages (i.e. 4 samples in all). Massaging both feet simultaneously controlled for any subject preference for left or right and, importantly, allowed us to use bilateral neural activation data. The time interval between the two massage periods was 15 min. Following each type of massage, subjects were asked to complete the PANAS and to rate three questions about the massage on a scale of 1–9 (1 = low, 9 = high): (1) How much did the massage make you feel pleasure? (2) How much did the massage arouse you? (3) How strong was the massage? (i.e. how intense). Additionally, subjects were asked how much they would be willing to pay for the massage (1–100 RMB). Finally, subjects were asked to guess whether the massage by hand was administered by a male or female professional masseur to control for possible sex-dependent effects.

Before and during the massages, SCR was used to measure sympathetic arousal and neural activity was recorded using fNIRS.

### 2.3. Data acquisition

#### 2.3.1. fNIRS

Preceding data collection, a 3D digitizer system (Polhemus, VT, USA) was used to localize the placement of each optode in relation to reference points on the subject's head (nasion, inion, left and right ears, top and back of the head) to assess variability in head size and shape. Measurements of neural activation were taken using a non-invasive near-infrared diffuse optical tomography instrument (CW6, Techen, Inc., Milford, MA, USA) with 27 optodes (15 detectors and 12 sources). Each adjacent source detector pair defined a single measurement channel with a 3.0 cm spatial separation between detectors and sources. This design allowed coverage of three main interest regions divded into six regions of interest (ROIs): bilateral orbitofrontal cortex (OFC), divided into lateral (lOFC), mediolateral (mlOFC) and medial (mOFC) (3 separate OFC ROIs were used due to the well established functional heterogeneity of this region), bilateral primary somatosensory cortex (medial S1 area representing foot and leg) and bilateral anterior and posterior superior temporal sulcus (aSTS and pSTS). Previous research suggests that STS changes in response to touch should be primarily in the posterior region (Davidovic et at., 2016). The instrument generated two wavelengths of near-infrared light (690 and 830 nm) and measured the changes in oxyhemoglobin (oxy-Hb) and deoxyhemoglobin (deoxy-Hb). The optodes were positioned according to international 10–20 coordinates (see Fig. 1). Hair was manually parted under the optodes to improve signal detection.

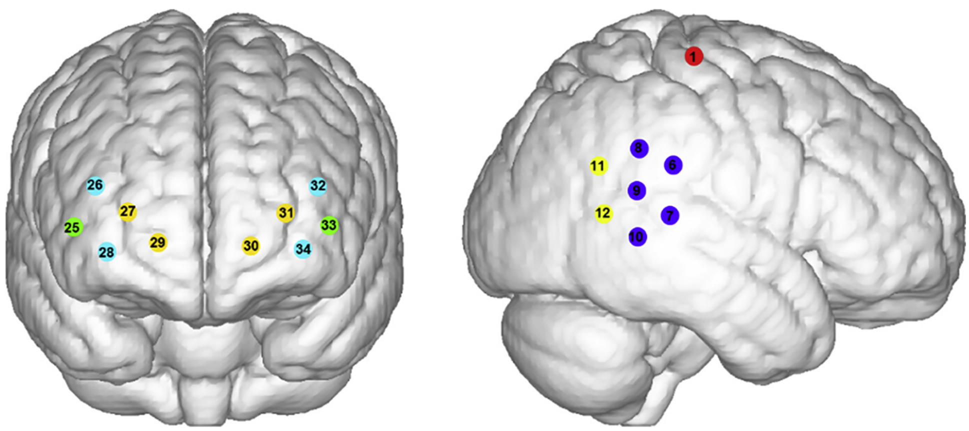


**Fig. 1.** Localization of fNIRS optodes over the 6 ROIs. These ROIs included somatosensory cortex (S1, channel 1 and 13, red), anterior superior temporal sulcus (aSTS, channels 6–10 and channels 18–22, purple), posterior superior temporal sulcus (pSTS, channels 11–12 and channels 23–24, yellow), medial orbitofrontal cortex (mOFC, channels 27,29,30,31, orange), medial-lateral orbitofrontal cortex (mlOFC, channels 26, 28, 32, 34, light blue), and lateral orbitofrontal cortex (lOFC, channels 25, 33, green) (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

#### *2.3.2. Blood sampling and oxytocin measurement*

Venous blood was collected into 6 ml EDTA tubes which were immediately kept chilled in ice and centrifuged at 1600 g for 15 min at 4 °C within half an hour of collection. Plasma was immediately aliquoted into chilled Eppendorf tubes and stored at −80 °C until OXT analysis. All samples were analyzed within 6 months of collection. Oxytocin concentrations in 1 ml plasma samples were measured in triplicate using a commercial ELISA assay (Cayman Chemical, Ann Arbor, Michigan USA Kit 500440). A standard prior extraction step was performed in accordance with the manufacturers recommended protocol and spiked samples (with 100 pg/ml OXT added) were included with every assay to calculate extraction efficiency which was 96.6%. The extraction step incorporated a 2-fold concentration of samples using a vacuum concentrator (Concentrator plus, Eppendorf, Germany) resulting in a detection sensitivity of 3 pg/ml. The majority of samples had detectable concentrations (> 98%) and those which did not were assigned the minimum detection value. The intra- and inter-assay coefficients of variation were 5.97 and 7.25% respectively. The manufacturer's reported cross-reactivity of the antibody with related neuropeptides, such as vasopressin and vasotocin, is < 0.01%.

### *2.4. Data analysis*

#### *2.4.1. Behavioral rating and SCR data analyses*

Paired t-tests with Bonferroni correction for multiple comparisons were used to analyze statistical differences in pleasure, arousal and intensity ratings and amount of money subjects were prepared to pay for the massage for the hand massage vs. machine massage conditions. SCR waveforms were analyzed offline, using AcqKnowledge 4.2 software (BIOPAC Systems Inc.). SCR amplitudes to hand and machine massage represented the dependent measures. The level of SCR response was determined by taking the mean base-to-peak difference for the first waveform (in microsiemens, μs) in the10 s window after massage onset or rest onset. Paired *t* tests were conducted between each type of massage and rest as well as between hand and machine massage.

#### *2.4.2. Plasma OXT concentration analysis*

We conducted paired t-tests to analyze whether mean concentrations of plasma OXT were increased following each type of massage compared to their respective baseline samples taken just prior to the massage. In order to compare the difference between the magnitudes of OXT increase following each massage, mean percent differences from baseline were calculated and paired t-tests used to analyze the difference between hand and machine massage. Correlation analysis was used to explore the relationship between OXT concentrations (averaged baseline and absolute increase in OXT after massage) and behavioral ratings including questionnaires (i.e. AQ and STQ), SCR and neural activation changes. Differences in correlation coefficients during the two types of massage were tested for by bootstrap analysis (Baguley, 2012; Wilcox, 2016).

#### *2.4.3. fNIRS data analysis*

Data from fNIRS optodes was analyzed using NIRS-SPM version 4.1 (Jang, 2008; Ye et al., 2009; Tak et al., 2011; Muthalib et al., 2015), with non-specific global trends due to breathing, cardiac, vaso-motion or other experimental errors being effectively removed by a Wavelet-MDL de-trending algorithm. For general linear model (GLM) analyses, 20-s blocks of hand massage and machine massage and 10-s blocks of rest after each massage were modeled separately with boxcar functions. We then performed single-subject GLM analyses by convolving four task events (hand massage, machine massage, rest after hand massage, rest after machine massage) with a hemodynamic response curve to model the hypothesized oxy-Hb response during each experimental condition. In line with many other studies initial analyses were assessed at an uncorrected statistical threshold of $P < 0.05$ (Bennett et al., 2014; Byun et al., 2014; Ehlis et al., 2008; Muthalib et al., 2015; Suzuki et al., 2008). We implemented a ROI-based analysis focusing on an average of oxy-Hb signals across all recording channels within the 6 specific ROIs. In each case we calculated activation differences between period of massage and periods of rest across the 10 min block for each type of massage. We conducted paired *t*-test [hand vs rest; machine vs. rest; hand vs machine] and Bonferroni-correction was applied to correct for the multiple ROIs. Correlations between regional oxy-Hb changes and behavioral ratings as well as questionnaire scores during hand massage and machine massage were also calculated and differences tested for using bootstrap analysis. In addition, we examined the mediation effect of STS on the relationship between S1 and OFC by using a bootstrap procedure (Preacher and Hayes, 2008). Four subjects were excluded due to technical problems with fNIRS acquisition leaving 36 subjects in the final analysis.

An additional exploratory analysis was conducted to investigate whether the perceived gender of the masseur would influence the neural responses, behavioral ratings, SCR and OXT release (independent *t*-test).

## 3. Results

### *3.1. Behavioral ratings and SCR results*

Table 1 shows that positive mood (PANAS) was higher after hand massage compared with machine massage ($t = 3.05$, $p_{\text{Bonferroni}} = 0.03$) but not negative mood ($t = 0.72$, $p_{\text{Bonferroni}} = 1.00$). Most importantly, pleasure ratings were significantly higher following hand massage relative to machine massage ($t = 7.18$, $p_{\text{Bonferroni}} < 0.001$). No differential effects on arousal or intensity ratings were found ($t < 2.62$, $ps_{\text{Bonferroni}} > 0.13$), confirming the specificity of the effects. Subjects were willing to pay significantly more for hand compared with machine massage ($t = 7.32$, $p_{\text{Bonferroni}} < 0.001$). The subjects could not

**Table 1**
Behavioral ratings and questionnaire scores for study subjects following two types of foot massage (mean ± sem).

| Measurements (40 subjects) | Machine massage | Hand massage | *t*-value | *p*-value with Bonferroni correction |
|---|---|---|---|---|
| Positive and Negative Affective Scale (PANAS)-Positive | 22.50 ± 1.35 | 24.45 ± 1.35 | 3.05 | 0.03 |
| Positive and Negative Affective Scale (PANAS)-Negative | 10.80 ± 0.54 | 11.18 ± 0.61 | 0.72 | 1.00 |
| Pleasure ratings | 5.90 ± 0.22 | 7.25 ± 0.13 | 7.18 | 0.001 |
| Arousal ratings | 5.13 ± 0.28 | 6.00 ± 0.26 | 2.62 | 0.10 |
| Intensity ratings | 5.94 ± 0.30 | 5.17 ± 0.24 | 2.22 | 0.26 |
| Payment (RMB) | 31.58 ± 3.73 | 55.18 ± 3.72 | 7.32 | 0.001 |
| Skin conductance (SCR) | 0.69 ± 0.11 | 0.86 ± 0.14 | 1.36 | 1.00 |

accurately recognize the gender of the professional masseur (17 thought was a male and 23 thought was a female - $\chi^2 = 0.90$, $p = 0.34$). For the SCR analysis 6 subjects were excluded due to low-quality data and so SCR data from 34 subjects were included in the final analysis. Results showed that there was no significant difference in SCR between hand and machine massage ($t = 1.36$, $p_{\text{Bonferroni}} = 1.00$, see Table 1). However, we found significant SCR increases during each type of massage compared to rest (hand massage: $p < 0.001$; machine massage: $p = 0.003$).

### 3.2. Plasma OXT concentrations

There was no difference between baseline OXT concentrations in samples taken prior to each type of massage (T1, $t = 1.17$, $p = 0.25$). More importantly, plasma OXT levels increased significantly after both hand (+7.13 pg/ml – $t = 5.71$, $p < 0.001$) and machine (+ 2.36 pg/ml, $t = 2.47$, $p = 0.02$) massage, but more potently after hand massage (+ 51.8% vs. + 18.2%, $p = 0.008$, see Fig. 2). In addition, there was a significant negative correlation between the averaged baseline OXT concentrations and AQ score [$r = -0.55$, $p < 0.001$- ($p_{\text{Bonferroni}} = 0.002$)](see Fig. 3a). Moreover, we found a significant negative correlation between the averaged baseline OXT concentrations and STQ score [$r = -0.38$, $p = 0.017$- ($p_{\text{Bonferroni}} = 0.03$)] (see Fig. 3b). There was also a significant negative correlation between the magnitude of the increase in OXT after hand massage for both AQ and STQ scores but not for machine massage (AQ: hand massage $r = -0.33$, $p = 0.04$, machine massage $r = 0.14$, $p = 0.38$; STQ: hand massage $r = -0.32$, $p = 0.04$, machine massage $r = 0.20$, $p = 0.22$) (see Fig. 3c and d). There were also significant differences between these coefficients (AQ: $p = 0.05$, bootstrap = 10,000; STQ: $p = 0.04$, bootstrap = 10,000 – i.e. using the method described by Baguley (2012) and Wilcox (2016) for non-independent samples). No significant correlations were found between either basal or massage-evoked increases of OXT and ratings of the massage experience or with SCR ($ps > 0.17$).

In view of the negative association between OXT release evoked by hand-administered foot massage and both AQ and STQ scores, we carried out an additional exploratory analysis to demonstrate that massage was nevertheless effective in producing significant OXT release in both individuals with lower and higher traits. We therefore

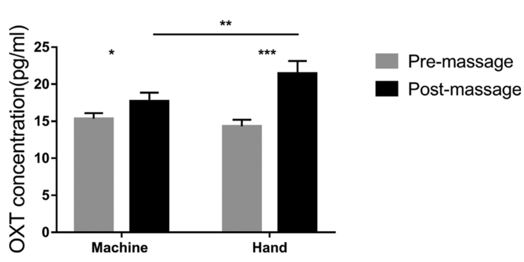


**Fig. 2.** Changes of oxytocin plasma concentrations. Histograms show mean ± SEM plasma concentrations of oxytocin (OXT) in 40 male subjects immediately before and immediately after a 10 min foot massage applied either by a machine or by hand. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

performed a median split analysis on subjects based on their AQ and STQ scores and carried out paired t-tests to analyze whether both groups showed significantly increased plasma OXT in response to the massage. This analysis confirmed that both sub-groups with lower and higher AQ scores showed robust increased OXT concentrations in response to massage (AQ scores: high – scores: 21–32, mean OXT increase = 5.76 pg/ml, $n = 20$, $t_{(19)} = 4.16$, $p = 0.001$; low – scores: 10–20, mean OXT increase = 8.5 pg/ml $n = 20$, $t_{(19)} = 4.11$, $p = 0.001$) and the same was also true for STQ scores (STQ: high – scores: 43–56, mean OXT increase = 8.44 pg/ml, $n = 19$, $t_{(18)} = 3.96$, $p = 0.001$; low – scores: 24–42, mean OXT increase = 5.69 pg/ml, n = 21, $t_{(20)} = 4.25$, $p < 0.001$).

Confirming the specificity of observed associations with the AQ and STQ no significant correlations were found between basal or massage-evoked OXT and other questionnaire scales (i.e. NEO-FFI, EQ, BIS/BAS and SPSRQ - all $ps > 0.1$).

### 3.3. fNIRS ROI analysis

To specify the differences between massage and rest periods and between the two types of massage in the 6 bilateral ROIs (S1, aSTS, pSTS, mOFC, mlOFC and lOFC), we performed paired *t*-test with *p* value Bonferroni correction. In comparison with periods of rest (i.e. no massage), hand massage evoked significant increased oxy-Hb in the pSTS ($p_{\text{Bonferroni}} = 0.01$) and mlOFC ($p_{\text{Bonferroni}} = 0.02$) although increased activity was also seen in S1 this failed to reach significance after correction. For the machine massage there was a significant decrease in oxy-Hb in the mlOFC ($p_{\text{Bonferroni}} = 0.01$), increased activity in S1 again failed to reach significance after correction (see Table 2 & Fig. 4). We found that oxy-Hb in the pSTS ($t = 3.49$, $p_{\text{Bonferroni}} = 0.006$, see Fig. 4b) and mlOFC ($t = 3.62$, $p_{\text{Bonferroni}} = 0.005$, see Fig. 4c) was significantly higher after hand massage compared to machine massage, but not for other regions ($t < 1.76$, $ps_{\text{Bonferroni}} > 0.52$).

In addition, we conducted correlation analyses between regional oxy-Hb changes and ratings of the massage experience and also with AQ and STQ scores. For rating scores significant associations were only found for pleasure and how much subjects were willing to pay for the massage. Massage-evoked activation of the mlOFC was positively correlated with the amount subjects were prepared to pay during hand compared to machine massage (hand massage- $r = 0.34$, $p = 0.04$; machine- $r = -0.23$, $p = 0.18$) but there was no significant difference between the coefficients ($p = 0.09$; $p = 0.07$, bootstrap = 10,000). Activation of pSTS was also positively correlated with how much subjects were prepared to pay for the hand massage ($r = 0.36$, $p = 0.03$) and rated their pleasure ($r = 0.42$, $p = 0.01$, see Fig. 5a) but not for machine massage (money: $r = 0.01$, $p = 0.96$; pleasure $r = -0.03$, $p = 0.87$). Only the coefficient with pleasure was significantly different between the two massage conditions (money: $p = 0.15$, pleasure: $p = 0.03$; bootstrap = 10,000). A positive correlation with AQ score was found for mlOFC activation after hand compared to machine massage (hand massage- $r = 0.42$, $p = 0.01$, machine massage - $r = -0.17$, $p = 0.33$), and the difference between coefficients was significant ($p = 0.03$, bootstrap = 10,000 – see Fig. 5b). No correlations were found with STQ scores or other personality traits.

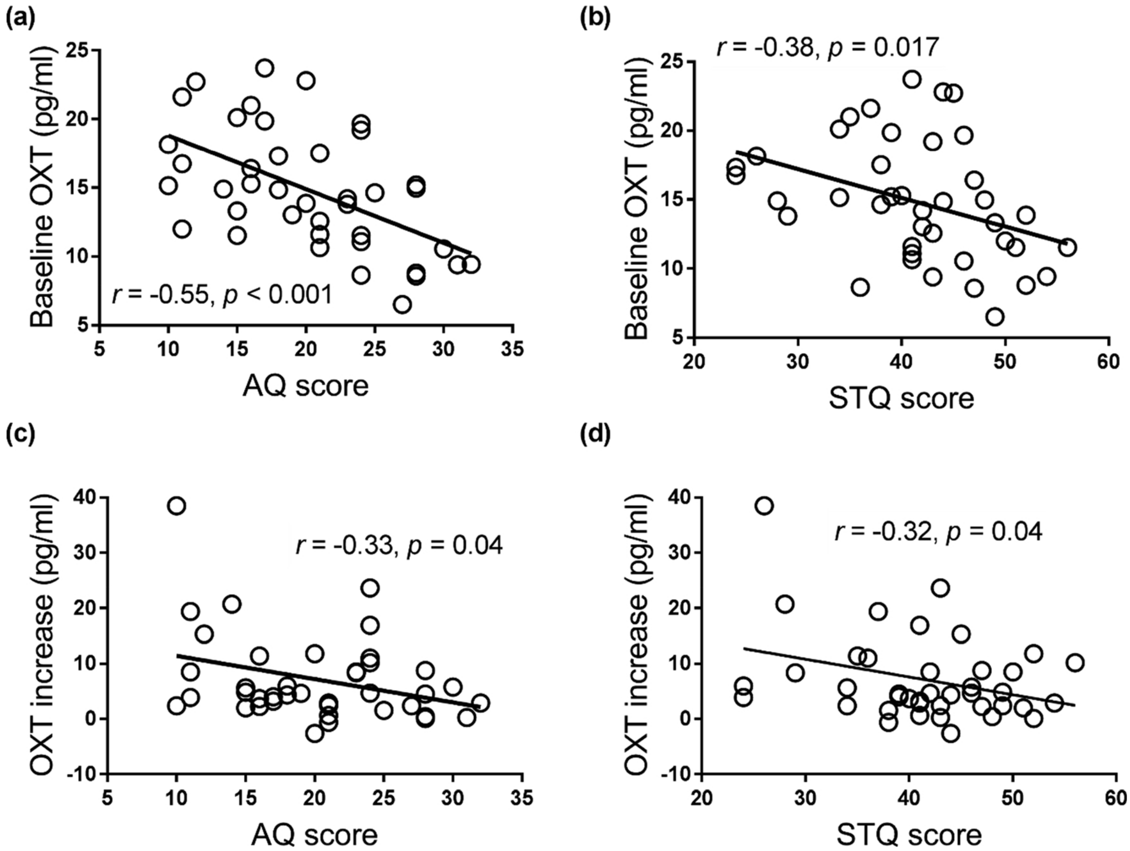


**Fig. 3.** Correlation analysis between concentrations of oxytocin and questionnaire scores. Regression graphs show significant correlations between baseline concentrations of oxytocin (OXT) and (a) autism spectrum quotient scores (AQ) and (b) social touch questionnaire (STQ) scores. They also show correlations between hand-massage evoked changes in OXT concentrations and (c) AQ and (d) STQ scores (n = 40 male subjects).

**Table 2**
Neural activation (oxy-Hb changes) in the 6 ROIs during the two types of massage (mean ± sem).

| Brain region | Machine massage | Hand massage | *t*-value | *p*-value with Bonferroni correction |
|---|---|---|---|---|
| S1 | 0.80 ± 0.54 | 0.64 ± 0.34 | 0.25 | 1.00 |
| Posterior STS | −1.16 ± 0.53 | 1.35 ± 0.38* | 3.49 | 0.006 |
| Anterior STS | −0.49 ± 0.49 | 0.34 ± 0.23 | 1.38 | 1.00 |
| Medial OFC | −0.53 ± 0.39 | 0.68 ± 0.36 | 1.76 | 0.52 |
| Medial-lateral OFC | −1.63 ± 0.52* | 1.31 ± 0.41* | 3.62 | 0.005 |
| Lateral OFC | −0.89 ± 0.53 | 0.26 ± 0.38 | 1.43 | 0.97 |

* $p < 0.05$ Bonferroni corrected vs rest.

A mediation analysis was conducted using a bootstrapping method (Preacher and Hayes, 2008) to investigate the relationship between S1, pSTS and mlOFC. The changes in S1 were significantly associated with the changes in pSTS (path a = 0.47) and the changes in mlOFC (path c = 0.41). When the changes in STS were included as the predictor, they were significantly associated with the changes in OFC (path b = 0.43) and the correlation between the changes in S1 and mlOFC was attenuated (path c' = 0.20). These results indicated partial mediation and using a bootstrap analysis the mediation was significant (indirect effect = 0.20, 95% CI = [0.03, 0.49], bootstrap = 1000, see Fig. 6). Results therefore confirmed that the oxy-Hb changes in S1 mediated changes in mlOFC through increasing pSTS activation.

### 3.4. Perceived gender of the masseur

In view of the fact that a number of studies have reported perceived gender of the individual giving social touch to a subject can influence both pleasure experience and neural responses to it (Gazzola et al., 2012; Scheele et al., 2014), including in the context of OXT administration (Scheele et al., 2014), we additionally performed an exploratory analysis investigating this in relation to our hand massage results. The perceived gender of the masseur had no significant effect on behavioral ratings of the massage or OXT release or SCR (all *ps* > 0.25). For the neural responses there was no difference in S1, pSTS or mlOFC activation in subjects who perceived the masseur to be male as opposed to female that could survive Bonferroni correction.

## 4. Discussion

The current study investigated whether hand- or machine-administered foot massage are effective in evoking endogenous OXT release and activating both cognitive and reward components of the neural system responding to social affective touch. Our results show clearly that the hand administered massage can evoke a large increase in plasma OXT (51.8%) and also activates regions processing reward aspects of social touch (mlOFC) and social cognition aspects (pSTS). By comparison machine-administered massage evoked smaller increases in OXT (18.2%) but did not produce significant changes in pSTS activation and reduced activity in mlOFC. Furthermore, hand massage was rated as more pleasurable and rewarding than machine massage despite being rated as of equal intensity and evoking similar levels of increased arousal. Both basal OXT concentrations and increases evoked by hand massage were negatively associated with AQ and STQ scores, although a median-split analysis showed that subjects with both higher and lower scores had significantly increased concentrations after massage. Additionally, pSTS and mlOFC activation were positively associated with pleasure ratings and/or how much subjects were willing to pay for

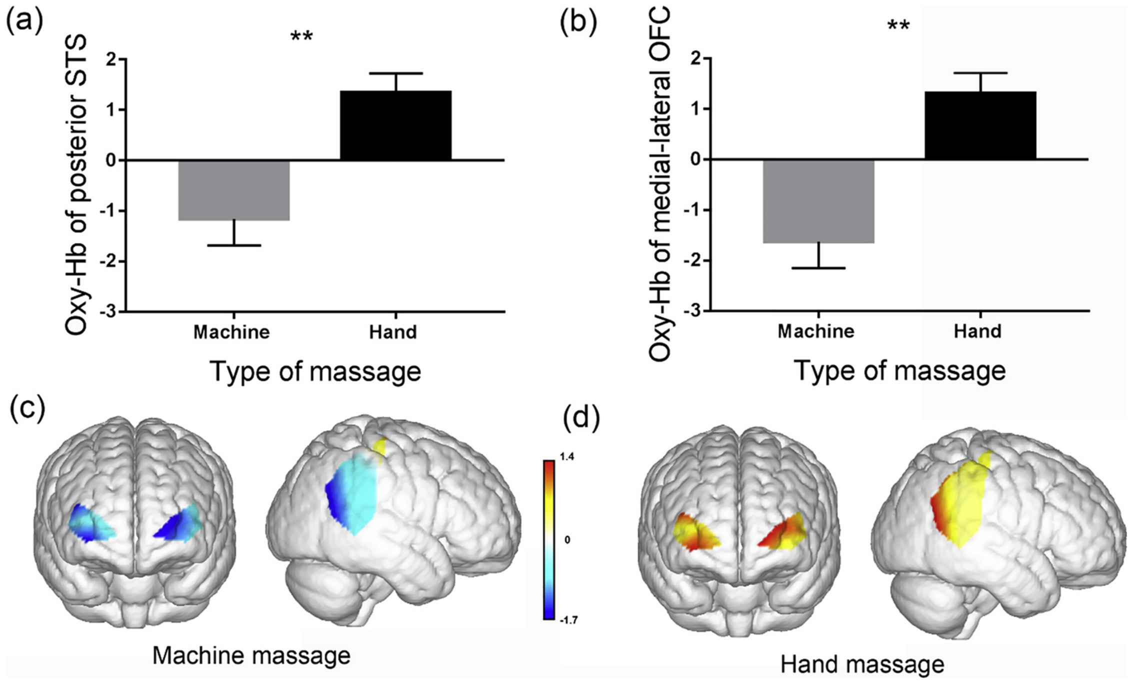


**Fig. 4.** Activation maps during hand and machine massage. Histograms show mean ± SEM activity changes in the posterior STS (a) and medial-lateral OFC (b) for hand vs machine massage. ** $p < 0.01$ Bonferroni corrected. The maps also show fNIRS activation during machine (c) and hand (d) massage in the orbitofrontal cortex (OFC), superior temporal sulcus (STS) and primary somatosensory cortex (S1)(see Fig. 1 for specific optode localizations).

the hand massage, and mlOFC activation was also associated positively with AQ scores. Thus overall, our findings demonstrate that foot massage administered by hand is effective both at increasing OXT concentrations and evoking increased activation in key brain regions involved in social affective touch processing. This supports its potential for therapeutic use in ASD.

Foot massage administered by hand was very effective in increasing plasma OXT concentrations, while machine-administered massage was significantly less potent despite being given similar intensity ratings and evoking similar increased arousal.While the baseline OXT concentrations we observed are slightly higher than those reported in some other studies using different commercial ELISA kits or radio-immunoassays (Gossen et al., 2012; Striepens et al., 2013), we did include a standard extraction procedure, post-extraction recovery was high and also results from samples "spiked" with known additional OXT concentrations were accurate. Our basal OXT concentrations are also very similar to those reported in saliva samples in Caucasian men given mechanical massage (Riem et al., 2017) and in blood samples from Caucasian and Asian typically developing controls and autism subjects (Oztan et al., 2018; Zhang et al., 2016). Hand massage-evoked changes in plasma OXT concentrations were comparable to or greater than those reported in response to affective touch (Holt-Lunstad et al., 2008; Light et al., 2005; Morhenn et al., 2008) and proportionately around a quarter of those evoked by 24–26 IU intranasal OXT after 15–45 min, although similar in terms of absolute magnitude (Gossen et al., 2012; Striepens et al., 2013). The 15-minute massage also only increased OXT concentrations for a short duration since they had returned to baseline within 15 min of the end of the massage period, whereas following intranasal OXT two studies have reported that concentrations only remain elevated for around 45 min (Gossen et al., 2012; Striepens et al., 2013). One study has claimed that OXT levels in saliva remain elevated for up to 7 h after administration (Van IJzendoorn et al., 2012) although this is out of line with blood-based analyses and may reflect the large concentrations of OXT applied to the nasal cavity permeating the throat and specifically influencing saliva concentrations over a long period. In comparison, the machine-administered foot massage only evoked small increases in plasma OXT. It is possible that other kinds of machine-delivered massage could be more effective, although a recent

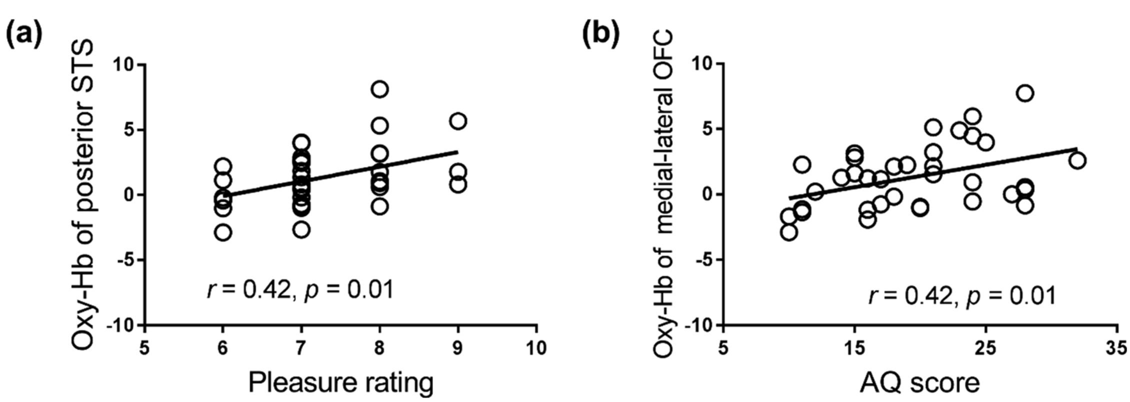


**Fig. 5.** Correlation analysis between behavioral ratings and brain activity. Regression graphs show significant correlations between: (a) pleasure rating and posterior STS activation to the hand massage (b) AQ scores and medial-lateral OFC activation in response to hand massage (n = 36 subjects).

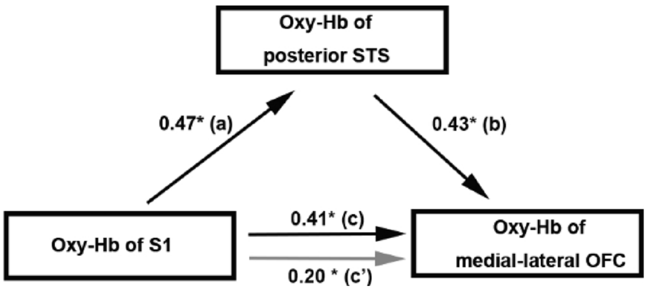


**Fig. 6.** Mediation analysis between the three key brain regions. Mediation analysis between activities of S1, posterior STS and medial-lateral OFC (path $a = 0.47$, $p = 0.01$; path $b = 0.43$, $p = 0.01$; path $c = 0.41$, $p = 0.03$; path $c' = 0.20$, $p = 0.03$).

study using a seat vibratory massage system reported similar small increases in saliva (Riem et al., 2017). While the subjects rated the strength of the hand and machine massages in our current study as equivalent, and both elicited similar levels of increased arousal, the pleasure ratings and positive mood scores (PANAS) for the hand massage were significantly higher as was the amount of money subjects were prepared to pay. This difference between the pleasure of touch administered by hand as opposed to machine is in agreement with a previous study (Ellingsen et al., 2014). Thus, it seems likely that the greater ability of hand massage to evoke OXT release may have been due to the greater feelings of pleasure it produced. Whether the greater pleasure was the result of the massage being administered by a person or some aspect of the quality of the massage itself (other than temperature and strength) cannot be determined with the protocol we used.

Both basal and hand massage-evoked increases in OXT concentrations were negatively associated with autism traits, as measured by the AQ, and touch sensitivity (STQ – where high scores indicate dislike of being touched). This is in agreement with previous studies reporting lower basal OXT and altered sensitivity to touch in ASD (Cascio et al., 2008). Healthy subjects with higher autism traits also exhibit altered sensitivity to touch (Robertson and Simmons, 2013). However, importantly an additional exploratory analysis revealed that hand massage significantly increased plasma OXT concentrations in a sub-group of subjects with higher scores on the AQ and STQ as well as in those with lower scores. Thus, hand massage may be a potential therapeutic strategy for increasing basal OXT concentrations in the context of ASD, although possibly greater frequencies or durations of massage might be required to achieve optimum outcomes.

Hand-administered foot massage produced a robust activation of the pSTS, but not the aSTS, whereas machine-administered massage did not influence either region. The STS is an important region for social cognition and both previous fMRI and fNIRS studies have consistently shown that the pSTS is activated during affective touch (Bennett et al., 2014; Davidovic et al., 2016; Gordon et al., 2013) as well as vocal emotion, faces and visual body motion (Deen et al., 2015; Schirmer and Adolphs, 2017). In young children the frequency of being touched by their mothers is also positively associated with pSTS activity and functional connectivity (Brauer et al., 2016). Thus, hand-administered foot massage is effective in influencing neural circuitry involved in affective touch processing as well as OXT release. Furthermore, pSTS responses were positively associated both with pleasure ratings given by subjects and how much they were prepared to pay for the massage. This is in agreement with a previous finding that pSTS responses are predictive of the pleasantness of stroking the skin (Monika et al., 2016) and that tactile stimulation which does not involve actual touch by another person (i.e. administered using some kind of device) appears not to routinely activate the pSTS (Perini et al., 2015; Sliz et al., 2012). In the context of visual and auditory stimuli the pSTS shows a degree of people/social specificity (Watson et al., 2014) and may therefore play a key role in the integration of multimodal social stimuli. Interestingly, the pleasure of social touch can be enhanced by its combination with pictures of a happy faces, and this effect is enhanced by intranasal oxytocin (Ellingsen et al., 2014). It is possible therefore that OXT may be producing this latter effect via the pSTS. The pSTS shows impaired responsivity to affective touch in ASD (Kaiser et al., 2015) and for healthy individuals with higher trait autism (Bennett et al., 2014; Voos et al., 2013). However, we did not find any association between AQ or STQ scores and pSTS responses.

Hand administered foot massage evoked significant activation in mlOFC, but not in mOFC or lOFC. The greater mlOFC activation observed during hand- compared to machine-administered massage may also reflect the greater pleasure and reward experienced since it was positively associated with the amount of money subjects were prepared to pay for the hand massage. Indeed, a recent study where OFC recordings were made using intracranial electrodes in humans has reported that the region we are defining as mlOFC is most associated with responses to experienced reward (Li et al., 2016). Since machine massage actually evoked a significant deactivation in the mlOFC this might possibly reflect the fact that it was significantly less rewarding than hand massage, although deactivation in this region has also been associated with increased reward seeking (Haber and Knutson, 2010) and so perhaps the machine massage might have promoted a greater motivation to have a hand massage instead. The OFC is again a key region involved in the processing of social affective touch (Gordon et al., 2013), and although we found no association between its activation and evoked OXT release a recent study has shown that intranasal OXT increased both OFC activation and pleasure ratings in response to social touch (Scheele et al., 2014). Several studies have reported decreased OFC activation in ASD subjects in response to affective touch (Kaiser et al., 2015), as well as in healthy subjects with higher trait autism (Voos et al., 2013), however in the current study we found that OFC activation in response to hand massage was actually positively correlated with AQ scores. This might suggest that individuals with higher autistic traits actually derived the most pleasure from the massage given mlOFC activation was also positively correlated with how much subjects valued it. However, there was no association between AQ scores and either pleasure ratings or the amount subjects were willing to pay. Possibly individuals with higher AQ scores might have found the pleasurable experience of the massage more novel, and this may have increased mlOFC activation without necessarily being associated with increased subjective ratings of pleasure/value. While mlOFC activation in response to social touch in male Caucasian subjects is also influenced by the perceived gender of the person administering the touch (Scheele et al., 2014) we did not observe this in the current study for OFC responses to hand administered massage.

Activation of the S1 region during massage compared to rest did not quite achieve significance which might reflect some habituation to the stimulation or carry over or activation from the massage periods to the rest ones. However, most importantly there was no evidence for differential activation of the S1 region responding to touching the feet during hand vs machine massage. This confirms the behavioral observation that the intensities of the two kinds of massage were similar and that differential changes in OFC and STS regions are therefore unlikely to have been due to differential sensory activation *per se*. There is some evidence that S1 activation can also be influenced by perception of who is administering social affective touch (Gazzola et al., 2012) but we found no evidence for this in the context of foot massage. Individuals with ASD show altered responsivity to sensory aspects of touch in terms of both increased and decreased sensitivity (Cascio et al., 2008) and high autistic traits are similarly associated with sensory sensitivity problems. There are also abnormalities in S1 functional connectivity in ASD (Khan et al., 2015) but we found no evidence for correlations between S1 activity and AQ scores in our current study.

We carried out a mediation analysis to investigate the neural circuit involved in response to hand massage and this demonstrated that activation of S1 primarily influences increased activation in OFC via the

STS rather than directly. Thus hand massage of this kind does appear to be effective in activating this specific circuitry involved in social cognition and reward aspects of social affective touch and our findings therefore demonstrate that its sensitivity extends to soft touch administered by a human which is not specifically affective in nature.

There are some limitations in the current study. Firstly, to avoid possible menstrual cycle-dependent effects in females we only included male subjects and it is possible that there may be some sex-differences in behavioral, OXT and neural responses to massage. Secondly, while our behavioral feedback from subjects revealed that they did not perceive the intensities of the hand- and machine-administered massages as different we did not have an objective measure of this. Thus, we cannot rule out the possible contribution of differential massage intensity to differences between the observed effects of hand and machine massage. Thirdly, it was not possible to administer the machine vs hand massage in a manner where the subject could be blinded since the two types of massage are obviously different, however the analyses of results were performed blind such that the experimenter was not aware which massage type was administered. Fourthly, we only measured blood concentrations of OXT as a marker for parallel changes in the brain. The relationship between basal blood and cerebrospinal fluid concentrations of OXT is not always consistent although importantly stimulus-evoked changes in blood and cerebrospinal fluid do show greater agreement (Valstad et al., 2017). A recent study directly comparing basal concentrations in blood and cerebrospinal fluid reported good correlations between them using ELISA protocols, although agreement between different types of assay was not so good (Lefevre et al., 2017). However, we cannot totally exclude the possibility that the massage did not alter OXT changes in the brain, although clearly it did increase activity in brain regions processing affective touch. Fifth, Chinese subjects were recruited in the current study who are used to massages being administered by both male and female masseurs and so we cannot exclude the possibility that for subjects from other cultures there might be more marked effects of the perceived sex of the masseur. Finally, while fNIRS technology has become increasingly established there is still a need for more work on providing better automated procedures for localization of functional brain activity (Pinti et al., 2018).

In summary, our findings demonstrate that light pressure foot massage administered by hand is more effective in promoting both increased endogenous blood concentrations of OXT and neural responses in key regions involved in cognitive (STS) and reward (OFC) of social touch compared to massage by machine. While the OXT effects of hand massage were reduced in individuals with higher autistic traits they were still significant and therefore our results support the possibility that massage could be considered as a non-invasive therapeutic method for increasing OXT concentrations and additionally for promoting both cognitive and rewarding aspects of social touch in ASD.

## Conflicts of interest

The authors report no conflict of interest.

## Acknowledgments

KMK was supported by a National Natural Science Foundation of China grant [NSFC grant number 31530032] and also by the CNS Program of the University of Electronic Science and Technology of China.

## References

Baguley, T., 2012. Serious Stats: A Guide to Advanced Statistics for the Behavioral Sciences. Macmillan International Higher Education. Palgrave, Basingstoke.

Baron-Cohen, S., Wheelwright, S., Skinner, R., et al., 2001. The autism-spectrum quotient (AQ): evidence from asperger syndrome/high-functioning autism, males and females, scientists and mathematicians. J. Autism Dev. Disord. 31 (1), 5–17. https://doi.org/10.1023/A:1005653411471.

Baron-Cohen, S., Wheelwright, S., 2004. The empathy quotient: an investigation of adults with Asperger syndrome or high functioning autism, and normal sex differences. J. Autism Dev. Disord. 34 (2), 163–175.

Beck, A.T., Steer, R.A., Brown, G.K., 1996. Beck depression inventory-II. San Antonio 78 (2), 490–498.

Bello, D., White-Traut, R., Schwertz, D., Pournajafi-Nazaraloo, H., Carter, S., 2008. An exploratory study of neurohormonal responses of healthy men to massage. J. Altern. Complement. Med. 14 (4), 387–394. https://doi.org/10.1089/acm.2007.0660.

Bennett, R.H., Bolling, D.Z., Anderson, L.C., Pelphrey, K.A., Kaiser, M.D., 2014. fNIRS detects temporal lobe response to affective touch. Soc. Cogn. Affect. Neurosci. 9, 470–476. https://doi.org/10.1093/scan/nst008.

Bjornsdotter, M., Gordon, I., Pelphrey, K.A., Olausson, H., Kaiser, M.D., 2014. Development of brain mechanisms for processing affective touch. Front. Behav. Neurosci. 8, 24. https://doi.org/10.3389/fnbeh.2014.00024.

Brauer, J., Xiao, Y., Poulain, T., Friederici, A.D., Schirmer, A., 2016. Frequency of maternal touch predicts resting state activity and connectivity of the developing social brain. Cereb. Cortex 26 (8), 3544–3552. https://doi.org/10.1093/cercor/bhw137.

Byun, K., Hyodo, K., Suwabe, K., Ochi, G., Sakairi, Y., Kato, M., et al., 2014. Positive effect of acute mild exercise on executive function via arousal-related prefrontal activations: an fNIRS study. Neuroimage 98, 336–345. https://doi.org/10.1016/j.neuroimage.2014.04.067.

Carver, C.S., White, T.L., 1994. Behavioral inhibition, behavioral activation, and affective responses to impending reward and punishment: the BIS/BAS Scales. J. Pers. Soc. Psychol. 67 (2), 319–333.

Cascio, C., McGone, F., Folger, S., Tannan, V., Baranek, G., Pelphrey, K.A., Essick, G., 2008. Tactile perception in adults with autism: a multidimensional psychophysical study. J. Autism Dev. Disord. 38 (1), 127–137. https://doi.org/10.1007/s10803-007-0370-8.

Cheek, J.M., 1983. The Revised Cheek and Buss Shyness Scale. Unpublished manuscript. Wellesley College, Wellesley, MA 2181.

Costa, P.T., McCrae, R.R., 1992. Revised NEO Personality Inventory(NEO PIR) and NEO Five Factor Inventory (NEO-FFI) Professional Manual. Psychological Assessment Resources, Odessa, FL.

Crockford, C., Wittig, R.M., Langergraber, K., Ziegler, T.E., Zuberbuhler, K., Deschner, T., 2013. Urinary oxytocin and social bonding in related and unrelated wild chimpanzees. Proc. Biol. Sci. 280 (1755), 20122765. https://doi.org/10.1098/rspb.2012.2765.

Davidovic, M., Jönsson, E.H., Olausson, H., Björnsdotter, M., 2016. Posterior superior temporal sulcus responses predict perceived pleasantness of skin stroking. Front. Hum. Neurosci. 10, 432. https://doi.org/10.3389/fnhum.2016.00432.

Deen, B., Koldewyn, K., Kanwisher, N., Saxe, R., 2015. Functional organization of social perception and cognition in the superior temporal sulcus. Cereb. Cortex 25 (11), 4596–4609. https://doi.org/10.1093/cercor/bhv111.

Diego, M.L., Field, T., Sanders, C., Hernandez-Rief, M., 2004. Massage therapy of moderate and light pressure and vibrator effects on EEG and heart rate. Int. J. Neurosci. 114, 31–45. https://doi.org/10.1080/00207450490249446.

Diego, M.L., Field, T., 2009. Moderate pressure massage elicits a parasympathetic nervous system response. Int. J. Neurosci. 119, 630–638. https://doi.org/10.1080/00207450802329605.

Ditzen, B., Neumann, I.D., Bodenmann, G., von Dawans, B., Turner, R.A., Ehlert, U., et al., 2007. Effects of different kinds of couple interaction on cortisol and heart rate responses to stress in women. Psychoneuroendocrinology 32, 565–574. https://doi.org/10.1016/j.psyneuen.2007.03.011.

Ehlis, A.C., Bähne, C.G., Jacob, C.P., Herrmann, M.J., Fallgatter, A.J., 2008. Reduced lateral prefrontal activation in adult patients with attention-deficit/hyperactivity disorder (ADHD) during a working memory task: a functional near-infrared spectroscopy (fNIRS) study. J. Psychiatr. Res. 42 (13), 1060–1067. https://doi.org/10.1016/j.jpsychires.2007.11.011.

Ellingsen, D.M., Leknes, S., Løseth, G., Wessberg, J., Olausson, H., 2016. The neurobiology shaping affective touch: expectation, motivation and meaning in the multisensory context. Front. Psychol. 6, 1986. https://doi.org/10.3389/psyg.2015.01986.

Ellingsen, D.M., Wessberg, J., Chelnokova, O., Olausson, H., Laeng, B., Leknes, S., 2014. In touch with your emotions: oxytocin and touch change social impressions while others' facial expressions can alter touch. Psychoneuroendocrinology 39, 11–20. https://doi.org/10.1016/j.psyneuen.2013.09.017.

Escalona, A., Field, T., Singer-Strunck, R., Cullen, C., Hartshorn, K., 2001. Brief report: improvements in the behavior of children with autism following massage therapy. J. Autism Dev. Disord. 1, 513–516. https://doi.org/10.1023/A:1012273110194.

Field, T., 2014. Massage therapy research review. Complement. Ther. Clin. Pract. 20, 224–229. https://doi.org/10.1016/j.ctcp.2014.07.002.

Field, T., 2016. Massage therapy research review. Complement. Ther. Clin. Pract. 24, 19–31. https://doi.org/10.1016/j.ctcp.2016.04.005.

Gazzola, V., Spezio, M.L., Etzel, J.A., Castelli, F., Adolphs, R., Keysers, C., 2012. Primary somatosensory cortex discriminates affective significance in social touch. Proc. Natl. Acad. Sci. U. S. A. E1657–E1666. https://doi.org/10.1073/pnas.1113211109.

Golaszewski, S.M., Siedentopf, C.M., Koppelstaetter, F., Fend, M., Ischeback, A., Gonzalez-Felipe, V., Haala, I., Struhal, W., et al., 2006. Human brain structures related to plantar vibrotactile stimulation: a functional magnetic imaging study. Neuroimage 29, 923–929. https://doi.org/10.1016/j.neuroimage.2005.08.052.

Gordon, I., Voos, A.C., Bennett, R.H., Bolling, D.Z., Pelphrey, K.A., Kaiser, M.D., 2011. Brain mechanisms for processing affective touch. Hum. Brain Mapp. 34 (4), 914–922. https://doi.org/10.1002/hbm.21480.

Gordon, I., Vander Wyk, B.C., Bennett, R.H., Cordeaux, C., Lucas, M.V., Eilbott, J.A., et al., 2013. Oxytocin enhances brain function in children with autism. Proc. Natl.

Acad. Sci. U. S. A. 110, 20953–20958. https://doi.org/10.1073/pnas.1312857110.
Gossen, A., Hahn, A., Westphal, L., Prinz, S., Schultz, R.T., Gründer, G., Spreckelmeyer, K.M., 2012. Oxytocin plasma concentrations after single intranasal oxytocin – a study in healthy men. Neuropeptides 46, 211–215. https://doi.org/10.1016/j.npep.2012.07.001.
Green, L.A., Fein, D., Modahl, C., Feinstein, C., Waterhouse, L., et al., 2001. Oxytocin and autistic disorder: alterations in peptide forms. Biol. Psychiatry 50, 609–613.
Grewen, K.M., Girdler, S.S., Amico, J., Light, K.C., 2005. Effects of partner support on resting oxytocin, cortisol, norepinephrine, and blood pressure before and after warm partner contact. Psychosom. Med. 67 (4), 531–538. https://doi.org/10.1097/01.psy.0000170341.88395.47.
Guastella, A.J., Hickie, I.B., 2016. Oxytocin treatment, circuitry, and autism: a critical review of the literature placing oxytocin into the autism context. Biol. Psychiatry 79 (3), 234–242. https://doi.org/10.1016/j.biopsych.2015.06.028.
Haber, S.N., Knutson, B., 2010. The reward circuit: linking primate anatomy and human imaging. Neuropsychopharmacology 35 (1), 4–26. https://doi.org/10.1038/npp.2009.129.
Heinrichs, M., Baumgartner, T., Kirschbaum, C., Ehlert, U., 2003. Social support and oxytocin interact to suppress cortisol and subjective responses to psychosocial stress. Biol. Psychiatry 54, 1389–1398. https://doi.org/10.1016/S0006- 3223(03)00465-7.
Henricson, M., Berglund, A.-L., Määttä, S., Ekman, R., Segesta, K., 2008. The outcome of tactile touch on oxytocin in intesnsive care patients: a randomized control trial. J. Clin. Nurs. 17, 2624–2633. https://doi.org/10.1111/j.1365-2702.2008.02324.x.
Holt-Lunstad, J., Birmingham, W.A., Light, K.C., 2008. Influence of a "warm touch" support enhancement intervention among married couples on ambulatory blood pressure, oxytocin, alpha amylase, and cortisol. Psychosom. Med. 70, 976–985. https://doi.org/10.1097/PSY.0b013e318187aef7.
Jang, K.E., 2008. Wavelet-MDL detrending for near infrared spectroscopy (NIRS). J. Biomed. Opt. 14 (3), 1–13. https://doi.org/10.1117/12.764141.
Jokinen, J., Chatzittofis, A., Hellström, C., Nordström, P., Uvnäs-Moberg, K., Åsberg, M., 2012. Low CSF oxytocin reflects high intent in suicide attempters. Psychoneuroendocrinology 37, 482–490. https://doi.org/10.1016/j.psyneuen.2011.07.016.
Kaiser, M.D., Yang, D.Y., Voos, A.C., Bennett, R.H., Gordon, I., Pretzsch, C., et al., 2015. Brain mechanisms for processing affective (and Nonaffective) touch are atypical in Autism. Cereb. Cortex 26, 2705–2714. https://doi.org/10.1093/cercor/bhv125.
Kendrick, K.M., Guastella, A., Becker, B., 2017. Overview of human oxytocin research. In: In: Hurlemann, R., Grinevich, V. (Eds.), Current Topics in Behavioral Neuroscience, vol. 35 Springer, Cham. https://doi.org/10.1017/7854_2017_19.
Khan, S., Michmizos, K., Tommerdahl, M., et al., 2015. Somatosensory cortex functional connectivity abnormalities in autism show opposite trends, depending on direction and spatial scale. Brain 138 (5), 1394–1409. https://doi.org/10.1093/brain/awv043.
Kinkead, B., Schettler, P.J., Larson, E.R., Carroll, D., Sharenko, M., Nettles, J., et al., 2018. Massage therapy decreases cancer-related fatigue: results from a randomized early phase trial. Cancer 124 (3), 546–554. https://doi.org/10.1002/cncr.31064.
Lee, S.H., Kim, J.Y., Yeo, S., Kim, S.H., Lim, S., 2015. Meta-analysis of massage therapy on cancer pain. Integr. Cancer Ther. 14 (4), 297–304. https://doi.org/10.1177/1534735415572885.
Lefevre, A., Mottolese, R., Dirheimer, M., et al., 2017. A comparison of methods to measure central and peripheral oxytocin concentrations in human and non-human primates. Sci. Rep. 7 (1), 17222. https://doi.org/10.1038/s41598-017-17674-7.
Light, K.C., Grewen, K.M., Amico, J.A., 2005. More frequent partner hugs and higher oxytocin levels are linked to lower blood pressure and heart rate in premenopausal women. Biol. Psychol. 69, 5–21. https://doi.org/10.1016/j.biopsycho.2004.11.002.
Li, Y., Vanni-Mercier, G., Isnard, J., Mauguière, F., Dreher, J., 2016. The neural dynamics of reward value and risk coding in the human orbitofrontal cortex. Brain 139 (4), 1295–1309. https://doi.org/10.1093/brain/awv409.
McCabe, C., Rolls, E.T., Bilderbeck, A., McGlone, F., 2008. Cognitive influences on the affective representation of touch and the sight of touch in the human brain. Soc. Cogn. Affect. Neurosci. 3 (2), 97–108. https://doi.org/10.1093/scan/nsn005.
McCullough, M.E., Churchland, P.S., Mendez, A.J., 2013. Problems with measuring peripheral oxytocin: can the data on oxytocin and human behavior be trusted? Neurosci. Biobehav. Rev. 37, 1485–1492. https://doi.org/10.1016/j.neubiorev.2013.04.018.
Monika, D., Jönsson, E.H., Håkan, O., Malin, B., 2016. Posterior superior temporal sulcus responses predict perceived pleasantness of skin stroking. Front. Hum. Neurosci. 10 (24), 432. https://doi.org/10.3389/fnhum.2016.00432.
Montag, C., Sindermann, C., Melchers, M., Jung, S., Luo, R., Becker, B., Xie, J., Xu, W., Guastella, A., Kendrick, K.M., 2017. A functional polymorphism of the OXTR gene is associated with autistic traits in Caucasian and Asian populations. Am. J. Med. Genet. B: Neuropsychiatr. Genet. 174, 808–816. https://doi.org/10.1002/ajmg.b.32596.
Morhenn, V., Beaven, L.F., Zak, P.J., 2012. Massage increases oxytocin and reduced adrenocorticotropin hormone in humans. Altern. Ther. Health Med. 18, 11–18.
Morhenn, V.B., Park, J.-W., Piper, E., Zak, P.J., 2008. Monetary sacrifice among strangers is mediated by endogenous oxytocin release after physical contact. Evol. Hum. Behav. 29, 375–383. https://doi.org/10.1016/j.evolhumbehav.2008.04.004.
Muthalib, M., Re, R., Zucchelli, L., Perrey, S., Contini, D., Caffini, M., et al., 2015. Effects of increasing neuromuscular electrical stimulation current intensity on cortical sensorimotor network activation: a time domain fNIRS study. PLoS One 10 (7), e0131951. https://doi.org/10.1371/journal.pone.0131951.
Naja, W., Aoun, M.P., 2017. Oxytocin and anxiety disorders: translational and therapeutic aspects. Curr. Psychiatry Rep. 19, 67. https://doi.org/10.1007/s11920-017-0819-1.
Neumann, I.D., Slattery, D.A., 2016. Oxytocin in general anxiety and social fear: a translational approach. Biol. Psychiatry 79 (3), 213–221. https://doi.org/10.1016/j.biopsych.2015.06.004.
Odendaal, J.S.J., Meintjes, R.A., 2003. Neurophysiological correlates of affiliative behavior between humans and dogs. Vet. J. 165 (3), 296–301. https://doi.org/10.1016/S1090-0233(02)00237-X.
Olausson, H., Wessberg, J., Morrison, I., McGlone, F., Vallbo, Å., 2010. The neurophysiology of unmyelinated tactile afferents. Neurosci. Biobehav. Rev. 34 (2), 185–191. https://doi.org/10.1016/j.neubiorev.2008.09.011.
Ouchi, Y., Kanno, T., Okada, H., Yoshikawa, E., Shinke, T., Nagasawa, S., et al., 2006. Changes in cerebral blood flow under the prone condition with and without massage. Neurosci. Lett. 407 (2), 131–135. https://doi.org/10.1016/j.neulet.2006.08.037.
Oztan, O., Jackson, L.P., Libove, R.A., Sumiyoshi, R.D., Phillips, J.M., Garner, J.P., Hardan, A.Y., Parker, K.J., 2018. Biomarker discovery for disease status and symptom severity in children with autism. Psychoneuroendocrinology 89, 39–45. https://doi.org/10.1016/j.psyneuen.2017.12.022.
Parker, K.J., Joseph, P., Garner, J.P., Robin, A., Libove, R.A., Hyde, S.A., Hornbeak, K.B., Carson, D.S., Liao, C.-P., Phillips, J.M., Hallmayer, J.F., Hardan, A.Y., 2014. Plasma oxytocin concentrations and OXTR polymorphisms predict social impairments in children with and without autism spectrum disorder. Proc. Natl. Acad. Sci. U. S. A. 111 (33), 12258–12263. https://doi.org/10.1073/pnas.1402236111.
Parker, K.J., Oztan, O., Libove, R.A., Sumiyoshi, R.D., Jackson, L.P., Karhson, D.S., et al., 2017. Intranasal oxytocin treatment for social deficits and biomarkers of response in children with autism. Proc. Natl. Acad. Sci. U. S. A. 114 (30), 8119–8124. https://doi.org/10.1073/pnas.1705521114.
Perini, I., Olausson, H., Morrison, I., 2015. Seeking pleasant touch: neural correlates of behavioral preferences for skin stroking. Front. Behav. Neurosci. 9, 8. https://doi.org/10.3389/fnbeh.2015.00008.
Pinti, P., Tachtsidis, I., Hamilton, A., et al., 2018. The present and future use of functional near-infrared spectroscopy (fNIRS) for cognitive neuroscience. Ann. N. Y. Acad. Sci. 40, 1–25. https://doi.org/10.1111/nyas.13948.
Plichta, M.M., Herrmann, M.J., Baehne, C.G., Ehlis, A.C., Richter, M.M., Pauli, P., Fallgatter, A.J., 2006. Event-related functional near-infrared spectroscopy (fNIRS): are the measurements reliable? Neuroimage 31 (1), 116–124. https://doi.org/10.1016/j.neuroimage.2005.12.008.
Preacher, K.J., Hayes, A.F., 2008. Asymptotic and resampling strategies for assessing and comparing indirect effects in multiple mediator models. Behav. Res. Methods 40 (3), 879–891.
Rapaport, M.H., Schettler, P.J., Larson, E.R., Carroll, D., Sharenko, M., Nettles, J., Kinkead, B., 2018. Massage therapy for psychiatric disorders. Focus 16, 24–31. https://doi.org/10.1176/appi.focus.20170043.
Riem, M.M.E., De Carli, P., van IJzendoorn, Linting, M., Grewen, K.M., Bakermans-Kranenburg, M.J., 2017. Emotional maltreatment is associated with atypical responding to stimulation of endogenous oxytocin release through mechanically-delivered massage in males. Psychoneuroendrocrinology 85, 115–122. https://doi.org/10.1016/j.psyneuen.2017.08.017.
Robertson, A.E., Simmons, D.R., 2013. The relationship between sensory sensitivity and autistic traits in the general population. J. Autism Dev. Disord. 43, 775–784. https://doi.org/10.1007/s10803-012-1608-7.
Ruzich, E., Allison, C., Smith, P., Watson, P., Auyeung, B., Ring, H., Baron-Cohen, S., 2015. Measuring autistic traits in the general population: a systematic review of the Autism-Spectrum Quotient (AQ) in a nonclinical population sample of 6,900 typical adult males and females. Mol. Autism 6 (2). https://doi.org/10.1186/2040-2392-6-2.
Scheele, D., Kendrick, K.M., Khouri, C., Kretzer, E., Schlapfer, T.E., StoffelWagner, B., et al., 2014. An oxytocin-induced facilitation of neural and emotional responses to social touch correlates inversely with autism traits. Neuropsychopharmacology 39, 2078–2085. https://doi.org/10.1038/npp.2014.78.
Scheiderman, I., Zagoory-Sharon, O., Leckman, J.F., Feldman, Rm, 2012. Oxytocin during the initial stages of romantic attachment: relations to couples' interactive reciprocity. Psychoneuroendocrinology 37 (8), 1277–1285. https://doi.org/10.1016/j.psyneuen.2011.12.021.
Schirmer, A., Adolphs, R., 2017. Emotion perception from face, voice, and touch: comparisons and convergence. Trends Cogn. Sci. 21 (3), 216–228. https://doi.org/10.1016/j.tics.2017.01.001.
Silva, L.M.T., Shalock, M., Gabrielsen, R., Budden, S.S., Buenrostro, M., Horton, R., 2015. Early intervention with a parent-delivered massage protocol directed at tactile abnormalities decreases severity of autism and improves child-to-parent interactions: a replication study. Autism Res. Treat. 904585. https://doi.org/10.1155/2015/904585.
Spielberg, C.D., Gorsuch, R.L., Lushene, R.E., 1970. STAI Manual for the State-Trait Anxiety Inventory. Consulting Psychologists Press, Palo Alto, CA.
Sliz, D., Smith, A., Wiebking, C., Northoff, G., Hayley, S., 2012. Neural correlates of a single session massage treatment. Brain Imaging Behav. 6, 77–87. https://doi.org/10.1007/s11682-011-9146-z.
Striepens, N., Kendrick, K.M., Hanking, V., Landgraf, R., Wüllner, U., Maier, W., Hurlemann, R., 2013. Elevated cerebrospinal fluid and blood concentrations of oxytocin following its intranasal administration in humans. Sci. Rep. 3, 3440. https://doi.org/10.1038/srep03440.
Suzuki, M., Miyai, I., Ono, T., Kubota, K., 2008. Activities in the frontal cortex and gait performance are modulated by preparation. An fNIRS study. Neuroimage 39 (2), 600–607. https://doi.org/10.1016/j.neuroimage.2007.08.044.
Tak, S., Yoon, S.J., Jang, J., Yoo, K., Jeong, Y., Ye, J.C., 2011. Quantitative analysis of hemodynamic and metabolic changes in subcortical vascular dementia using simultaneous near-infrared spectroscopy and fMRI measurements. Neuroimage 55 (1), 176–184. https://doi.org/10.1016/j.neuroimage.2010.11.046.
Torrubia, R., Ávila, C., Moltó, J., Caseras, X., 2001. The Sensitivity to Punishment and Sensitivity to reward Questionnaire (SPSRQ) as a measure of Gray's anxiety and impulsivity dimensions. Pers. Indiv. Differ. 31 (6), 837–862. https://doi.org/10.1016/S0191-8869(00)00183-5.
Tsuji, S., Yuhi, T., Furuhara, K., Ohta, S., Shimizu, Y., Higashida, H., 2015. Salivary oxytocin concentrations in seven boys with autism spectrum disorder received

massage from their mothers. Front. Psychiatry 6, 58. https://doi.org/10.3389/fpsyt.2015.00058.

Turner, R.A., Altemus, M., Enos, T., Cooper, B., McGuinness, T., 1999. Preliminary research on plasma oxytocin in normal cycling women: investigating emotion and interpersonal distress. Psychiatry 62 (2), 97–113. https://doi.org/10.1080/00332747.1999.11024859.

Uvnäs-Moberg, K., Handlin, L., Petersson, M., 2014. Self-soothing behaviors with particular reference to oxytocin release induced by non-noxious sensory stimulation. Front. Psychol. 5, 1529. https://doi.org/10.3389/fpsyg.2014.01529.

Valstad, M., Alvares, G.A., Egknud, M., Matziorinis, A.M., Andreassen, O.A., Westlye, T., Quintana, D.S., 2017. The correlation between central and peripheral oxytocin concentrations: a systematic review and meta-analysis. Neurosci. Biobehav. Rev. 78, 117–124. https://doi.org/10.1016/j.neubiorev2017.04.017.

Vallbo, A., Olausson, H., Wessberg, J., Norrsell, U., 1993. A system of unmyelinated afferents for innocuous mechanoreception in the human skin. Brain Res. 628, 301–304. https://doi.org/10.1016/0006-8993(93)90968-S.

Van IJzendoorn, M.H., Bhandari, R., Van der Veen, R., Grewen, K., Bakermans-Kranenburg, M.J., 2012. Elevated salivary levels of oxytocin persist more than 7 h after intranasal administration. Front. Neurosci. 6, 174. https://doi.org/10.3389/fnins.2012.00174.

Voos, A.C., Pelphrey, K.A., Kaiser, M.D., 2013. Autistic traits are associated with diminished neural response to affective touch. Soc. Cogn. Affect. Neurosci. 8, 378–386. https://doi.org/10.1093/scan/nss009.

Walaszek, R., Maśnik, R., Marszalek, A., Walaszek, K., Burdacki, M., 2017. Massage efficacy in the treatment of autistic children—a literature review. Int. J. Dev. Disabil. 1–5. https://doi.org/10.1080/20473869.2017.1305139.

Watson, D., Clark, L.A., Tellegen, A., 1988. Development and validation of brief measures of positive and negative affect: the PANAS scales. J. Pers. Soc. Psychol. 54 (6), 1063–1070.

Watson, R., Latinus, M., Charest, I., Crabbe, F., Belin, P., 2014. People-selectivity, audiovisual integration and heteromodality in the superior temporal sulcus. Cortex 50, 125–135. https://doi.org/10.1016/j.cortex.2013.07.011.

Wikstrom, S., Gunnarsson, T., Nordin, C., 2003. Tactile stimulus and neurohormonal response: a pilot study. Int. J. Neurosci. 113, 787–793. https://doi.org/10.1080/00207450390200954.

Wilcox, R.R., 2016. Comparing dependent robust correlations. Br. J. Math. Stat. Psychol. 69 (3), 215–224. https://doi.org/10.1111/bmsp.12069.

Wilhelm, F.H., Kochar, A.S., Roth, W.T., Gross, J.J., 2001. Social anxiety and response to touch: incongruence between self-evaluative and physiological reactions. Biol. Psychol. 58, 181–202. https://doi.org/10.1016/S0301-0511(01)00113-2.

Wyatt, G., Sikorskii, A., Tesnjak, I., Frambes, D., Holmstrom, A., Luo, Z., et al., 2017. A randomized clinical trial of caregiver-delivered reflexology for symptom management during breast cancer treatment. J. Pain Symptom Manage. 54 (5), 670–679. https://doi.org/10.1016/j.jpainsymman.2017.07.037.

Ye, J.C., Tak, S., Jang, K.E., Jung, J., Jang, J., 2009. NIRS-SPM: statistical parametric mapping for near-infrared spectroscopy. Neuroimage 44 (2), 428–447. https://doi.org/10.1016/j.neuroimage.2008.08.036.

Zhang, H.F., Dai, Y.C., Wu, J., Jia, M.X., Zhang, J.S., Shou, X.J., Han, S.P., Zhang, R., Han, J.S., 2016. Plasma oxytocin and arginine-vasopressin levels in children with autism spectrum disorder in China: associations with symptoms. Neurosci. Bull. 32 (5), 423–432. https://doi.org/10.1007/s12264-016-0046-5.