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Social touch modulates endogenous μ-opioid system activity in humans

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ABSTRACT

In non-human primates, opioid-receptor blockade increases social grooming, and the endogenous opioid system has therefore been hypothesized to support maintenance of long-term relationships in humans as well. Here we tested whether social touch modulates opioidergic activation in humans using in vivo positron emission tomography (PET). Eighteen male participants underwent two PET scans with [11C]carfentanil, a ligand specific to μ-opioid receptors (MOR). During the social touch scan, the participants lay in the scanner while their partners caressed their bodies in a non-sexual fashion. In the baseline scan, participants lay alone in the scanner. Social touch triggered pleasurable sensations and increased MOR availability in the thalamus, striatum, and frontal, cingulate, and insular cortices. Modulation of activity of the opioid system by social touching might provide a neurochemical mechanism reinforcing social bonds between humans.

Introduction

Large social network size (Holt-Lunstad et al. 2010) and availability of social support (Broadhead et al. 1983) are associated with beneficial effects for somatic health and psychological well being, yet little is known about the molecular mechanisms supporting establishment and maintenance of social bonds in humans. Touching is one of the most intimate means for bonding and showing affection towards others. A firm embrace upon meeting an old friend elevates the spirits and triggers warm and pleasant feelings, whereas a gentle caress from one's lover might literally send shivers down the spine. Abundant evidence suggests that both humans (Jones and Yarbrough 1985; Suvilehto et al. 2015; Willis and Briggs 1992) and non-human primates use touching or social grooming for reinforcing social structures (Dunbar 2010). Because blockade of opioid receptors stimulates grooming and social behaviour in non-human primates (Fabre-Nys et al. 1982; Keverne et al. 1989; Meller et al. 1980), it has been hypothesized that touching and consequent modulation of endogenous opioid-system activity could support maintenance and establishment of long-term relationships in humans (Machin and Dunbar 2011). However, this hypothesis currently lacks direct experimental support from in vivo human studies.

The μ-opioid receptors (MORs) mediate the effects of endogenous β-endorphins and of various exogenous opioid agonists and antagonists, and the endogenous mesolimbic opioid system contributes to the rewarding effects of, for example, food and drugs (Henriksen and Willoch 2008) but also of different types of social rewards (Trezza et al. 2011). Specifically, several observations in animals suggest that the opioid system may be involved in social bonding. Endogenous opiates modulate prosocial behaviour in polygamous rodents (Panksepp et al. 1980), and MOR-gene-knockout mice pups display deficits in attachment behaviour (Moles et al. 2004). In line with these findings, opioid agonists increase social play and approach behaviour towards contact calls in rats (Manduca et al. 2014; Wohr and Schwarting 2009). Activation of the endogenous striatal MOR is also essential for bonding in adult monogamous prairie voles (Burkett et al. 2011) suggesting the involvement of MOR in long-term social bonds. Rhesus infants carrying a gain-of-function OPRM1 77G allele experience increased reward from maternal contact and display increased measures of attachment (Barr et al. 2008), and the A118G polymorphism of the OPRM1 is associated with enhanced dispositional and neural sensitivity to social rejection in humans (Way et al. 2009).

In primates opioid receptor antagonists increase the frequency of both grooming (Fabre-Nys et al. 1982; Graves et al. 2002) and grooming solicitations (Keverne et al. 1989), implying that low endogenous opioid tone is associated with affiliative behaviour, and that the MOR system may underlie social bonding. In line with this, cerebral MOR availability in the limbic system and frontal cortex is negatively associated with avoidant attachment behaviour in humans (Nummenmaa et al. 2015).

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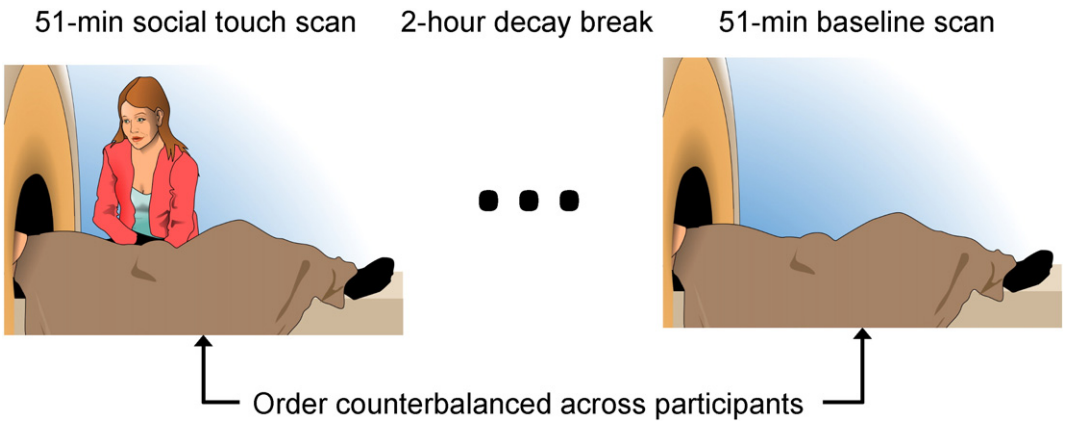

Fig 1. Experimental setup. Participants were scanned twice with the l MOR-specific ligand [11C]carfentanil. In the social touch condition (left) participants' partner touched them all over the body in a pleasurable, non-sexual fashion. In the neutral baseline condition participants lay alone in the PET camera in the absence of sensory stimulation. The conditions were separated by 2-h break allowing tracer decay.

Indirect evidence also comes from behavioural studies that have shown that pain threshold (a proxy of endogenous β-endorphin release) is modulated by social activities promoting intragroup bonding (Dunbar et al. 2012).

Here we tested whether social touch—the human analogue of social grooming—influences MOR system activity in humans, as quantified with in vivo positron emission tomography (PET). Measures of MOR availability were acquired with the MOR-specific ligand [11C]carfentanil during two separate sessions (Fig. 1): social touch and a neutral baseline condition. Under this experimental design, deactivation of the endogenous opioid system would be manifested as higher radioligand binding in the social touch condition versus baseline condition, and vice versa (Kennedy et al. 2006; Zubieta et al. 2001).

Methods and materials

Participants

The study protocol was approved by the ethics board of the Southwestern Finland hospital district, and the study was conducted in accordance with the Declaration of Helsinki. Eighteen healthy male adults (age range 20–26, $M_{age} = 22$ years, $SD_{age} = 1.8$) volunteered for the study and their female partners served as confederates. Romantic relationship was chosen as the candidate model for social bonding, as romantic partners have strongest social bonds and largest 'touching allowances' with each other (Suvilehto et al. 2015). Only young males were scanned, because age and sex influence both MOR concentrations and the capacity to activate the MOR system (Gabilondo et al. 1995; Zubieta et al. 2002; Zubieta et al. 1999). Exclusion criteria (in addition to standard PET and MRI exclusion criteria) were poor compliance, smoking, excessive alcohol consumption (>8 U/week), use of illicit drugs, current medication affecting the central nervous system, or a history of or current neurological or psychiatric disease confirmed using the structured clinical interview for DSM-IV, medical history and blood tests. All subjects were compensated for their time and travel costs, and they signed ethics-committee-approved informed consent forms. The participating couples had been together in a committed romantic relationship from 1 to 4.50 years ($M = 2.85$, $SD = 2.24$), with regular sexual contact and with mean self-reported relationship quality of 4.22 ($SD = 0.49$) as reported by males and 4.46 ($SD = 0.45$) as reported by females on a scale ranging from 1 = very poor to 5 = very good (Hendrick et al. 1998). The male and female estimates of relationship quality correlated significantly with each other ($r = 0.48$, $p < 0.05$).

Self-reports and laboratory measurements

Participants reported their sensations of pleasure, pain, arousal, tension, and sleepiness using a visual analogue scale (VAS; 0–100) at the beginning, midpoint and end of each PET scan. Because some studies have shown that interpersonal touching alleviates stress as indexed by cortisol levels (Ditzen et al. 2007), cortisol levels were estimated from venous blood samples drawn at the beginning and at the midpoint of each scan to evaluate stress levels during the scans. The self-report and cortisol data were analyzed using measurement × condition fully within-subjects ANOVAs.

Social touching task

During PET acquisition, the participant was lying in the PET scanner wearing only his underpants and covered with light blankets. The lights in the scanner room were dimmed. In the *social touch* challenge condition the participant's partner was sitting on a MRI-compatible bed next to the participant (Fig. 1), and was instructed to touch the participant everywhere on the body in a pleasurable way constantly throughout the scanning session. Touching on genitals and speaking were not allowed. They were instructed to start touching approximately 1 min before tracer injection to avoid movement due to onset of touching, and to keep on touching until the experimenter declared the end of the scan to ensure constant touch-dependent MOR response throughout the experiment. In the control condition, the participant was prepared similarly but lay in the scanner alone throughout the scan. The conditions were separated by a two-hour break to allow for tracer decay, and the order of conditions was counterbalanced across participants.[1]

Behavioural assessment of touch-triggered pleasure

After the PET scan, participants evaluated the sensory pleasantness of being touched with a hand by their partner or a stranger: They were blindfolded in the bore of the scanner and their partner touched repeatedly their leg. However, the participants were led to believe than on half of the occasions they were touched by a male stranger (MD supervising the study) and on other half their partner. This arrangement ensured comparable tactile kinematics throughout the

[1] The most comprehensive design would have involved a second control with non-social touching manipulation. We opted against this design to minimize the effective dose of radiation, because we are not aware of any data suggesting that non-social touching would lead to significant experience of pleasure or bondedness or subsequent modulation of the MOR system.

testing while manipulating the context-dependent interpretation (i.e. who is touching) of the touch. Male stranger was chosen as the control person as our recent large-scale behavioural study showed that male strangers have weakest social bonds with and smallest 'touching allowances' on male subjects (Suvilehto et al. 2015). Consequently, they provided the most clear-cut control condition for the relationship-dependent effects of social touching.

PET data acquisition and analysis

Data were acquired with the Philips Ingenuity PET-MR scanner at Turku PET Centre. After intravenous 250 MBq radioligand (mean injected mass 0.32 μg) bolus-injection, radioactivity in the brain was measured with the PET camera for 51 min with in-plane resolution of 3.75 mm. The subjects were lying in a supine position throughout the studies. Arterial blood samples for radioactivity measurements were not necessary for this radioligand. Data were corrected for dead-time, decay, and measured photon attenuation. Dynamic PET-scans were reconstructed with MRP reconstruction method (Alenius and Ruotsalainen 1997). High-resolution (1 mm^3) anatomical MR reference images were acquired using a T1-weighted sequence (TR 25 ms, TE 4.6 ms, flip angle 30°, scan time 376 s).

To correct for head motion, dynamic PET images were first realigned frame-to-frame. The individual T1-weighted MR images were coregistered to the summation images calculated from the realigned frames. Reference regions were drawn manually on MRI images using PMOD 3.4 software (PMOD Technologies Ltd., Zurich, Switzerland). Receptor availability was expressed in terms of BP_{ND}, which is the ratio of specific to non-displaceable binding in the brain using the occipital cortex as the reference region, which is known to be practically devoid of MOR (Hiller and Fan 1996). BPND was calculated for each voxel using the simplified reference tissue model (SRTM) with reference-tissue time activity curves (TACs) as input data (Gunn et al. 1997). This outcome measure is not confounded by blood flow or tracer transport (Sander et al. 2014). The subject-wise parametric BP_{ND} images were normalized to the MNI space using the T1-weighted MR images, and smoothed with a Gaussian kernel of 8-mm FWHM.

The effects of social touch on MOR availability were then assessed in SPM8 (http://www.fil.ion.ucl.ac.uk/spm/) using a repeated measures *t* test. Statistical threshold was set at $p < 0.05$, FDR corrected at cluster level. In a complementary approach, anatomical regions of interest (ROIs) were generated in the key MOR-rich components of the human emotion circuit (Karlsson et al. 2015; Saarimäki et al. 2015) in the thalamus, ventral striatum, dorsal caudate, putamen, amygdala, insula, orbitofrontal cortex, anterior, medial and posterior cingulate cortices, primary (SI) and secondary (SII) somatosensory cortices, and cerebellum using the AAL (Tzourio-Mazoyer et al. 2002) and Anatomy (Eickhoff et al., 2005) toolboxes. Subject-wise regional BP_{ND}s were then analysed using a fully within-subjects ROI (13) × condition (2: social touching vs. baseline) ANOVA. To rule out the effects of baseline affective state contributing to MOR availability, corresponding VAS scores were used to predict the baseline BP_{ND}.

Results

Self-reports (Fig. 2) revealed that participants experienced more pleasure during social touch than baseline scan, but not before or after the scans, $F(2,34) = 5.07$, $p = 0.01$, $\eta_p^2 = 0.23$ (contrast for during scan conditions: $p = 0.008$, for before and after conditions $ps > 0.17$). Pain ratings were in general low (<15 units) and lower during touch than baseline condition, $F(1,17) = 4.91$, $p = 0.041$, $\eta_p^2 = 0.22$, and increased slightly throughout the scans, $F(2,34) = 5.62$, $p = 0.008$, $\eta_p^2 = 0.2$. Participants experienced less tension during touch than baseline condition, $F(1,18) = 7.30$, $p = 0.015$, $\eta_p^2 = 0.30$. Sleepiness increased, $F(2,34) = 10.84$, $p < 0.001$, $\eta_p^2 = 0.39$, and arousal decreased, $F(2,34) = 6.12$, $p = 0.005$, $\eta_p^2 = 0.35$, during scanning, but there were

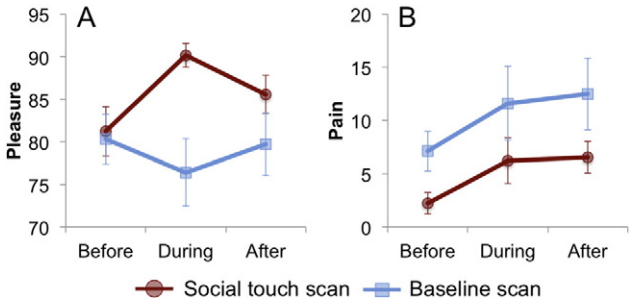

Fig 2. Means and standard errors of mean for self-reported experience of pleasure (A) and pain (B) during the social touch and baseline conditions show that experience of pleasure increased only in the social touch scan. Pain ratings increased negligibly but consistently in both conditions.

neither main effects of condition nor an interaction between condition and timepoint. Cortisol levels were higher before than after both scans, $F(1,15) = 72.385$, $p < 0.001$, $\eta_p^2 = 0.83$, with no differences between conditions. In the post-experimental test participants rated the touch by their partner as significantly more pleasant than the touch by a stranger, $t(15) = 6.00$, $p < 0.001$.

Whole-brain analysis of the PET data ($p < 0.05$, FDR corrected) revealed that the MOR availability was significantly higher during touch than baseline condition in ventral striatum, amygdala and medial prefrontal cortices (Fig. 3). Additional clusters were observed in orbital, medial and cingulate cortices, as well as in insular and parietal cortices. More stringent statistical thresholding ($p < 0.005$, FDR corrected) pinpointed the maximum effect in ventral striatum and in frontal, prefrontal and orbitofrontal cortices. Region of interest (ROI) analysis confirmed that MOR availability was higher during touch than baseline condition, $F(1,17) = 8.62$, $p = 0.009$, $\eta p^2 = 0.34$, and availability varied across ROIs, $F(1,12) = 200.66$, $p < 0.001$, $\eta p^2 = 0.92$ (Table 1). However, there was no interaction between condition and ROI ($p = 0.19$). To test for possible order effects, we also used GLM to address the effect of counterbalancing order (touch first versus baseline first) on the BP_{ND} changes. Counterbalancing was not found to influence the observed BP_{ND} changes. Self-reported pleasure, pain, arousal, tension and sleepiness scores were not associated with baseline receptor availability or changes in BP_{ND}.

To test whether blood flow changes could account for the findings, we compared k2 images between the conditions. This analysis however revealed no significant differences.

Discussion

These results demonstrate that social touch deactivates the endogenous μ-opioid system in human adults. Modulation of endogenous opioid release was observed in large, global clusters, peaking in the reward circuitry but also in the ventromedial prefrontal cortices involved in subfunctions such as emotions and theory of mind that are critical for social interaction (Amodio and Frith 2006). Furthermore, MOR system engagement was observed in the amygdala, which is known to support a wide array of social and emotional functions (Zald 2003). We thus propose that the opioid system may modulate the social aspects of touch, and consequently underlie the maintenance of interpersonal bonds.

Our data show that social touching modulates μ-system activity and triggers pleasurable sensations. Touching in human relationships may thus share functional and neurobiological similarities with grooming in other primates, including establishing and maintaining social structures (Dunbar 2010), as well as reducing tension and anxiety-related behaviours (Graves et al. 2002). Indeed, behavioural work in humans suggests that postnatal skin-to-skin contact promotes mother-infant bonding, and in couples the quality and quantity of social touching is

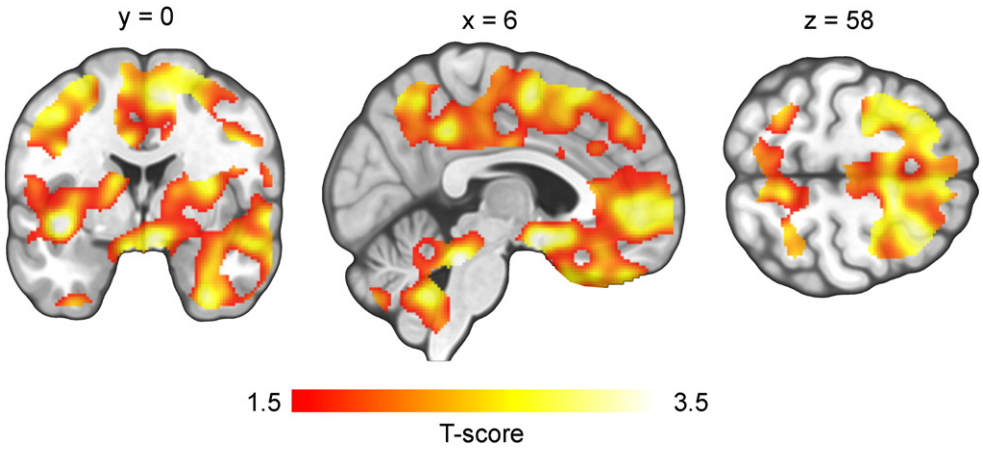

Fig 3. Brain regions showing increased BP_{ND} during social touch versus baseline scan. The data are thresholded at $p < 0.05$, FDR corrected at cluster level.

positively correlated with relationship satisfaction (Hertenstein et al. 2006).

We however observed higher pleasure coupled with lower opioid release levels in the social touch condition. This effect was unexpected and in contrast with prior evidence from PET studies suggesting that pleasant affect is associated with increase rather than decrease of endogenous opioids (Boecker et al. 2008; Koepp et al. 2009). Pharmacological studies in primates have also found that downregulation of the MOR system by exogenous opioid antagonist injection increases grooming and grooming solicitations in monkeys (Fabre-Nys et al. 1982; Keverne et al. 1989; Meller et al. 1980). The present study however addresses the causal link between social touching and endogenous opioid levels from the opposite direction (i.e. measuring opioid activity triggered by touching, rather than measuring touching triggered by opioid injections), and suggests that when social touching actually occurs, it has a causal role in lowering endogenous opioid system activity in humans.

The role of the endogenous opioid system in social touching and also in social bonding may be more complex and variable across mammalian species and bonding conditions than previously thought. For example, in rodents opioid agonists increase and antagonists decrease social motivation, whereas the opposite is true for non-human primates (see review in Loseth et al. 2014). Ultimately, however, the current findings are important because they establish in vivo a causal relationship between bonding-related touching behaviour and opioidergic activity in humans.

Table 1
Means, standard errors of mean (SEM), and effect sizes (r) for BP_{ND} in the social touch and baseline conditions. *Note*: OFC = orbitofrontal cortex, ACC = anterior cingulate cortex, MCC = middle cingulate cortex, PCC = posterior cingulate cortex, SI = primary somatosensory cortex, SII = secondary somatosensory cortex.

	Social touch BP_{ND}		Baseline BP_{ND}		
	Mean	SEM	Mean	SEM	r
Thalamus	1.43	0.07	1.39	0.07	0.32
Ventral striatum	1.69	0.09	1.61	0.09	0.54
Dorsal caudate	0.84	0.07	0.79	0.07	0.49
Putamen	1.28	0.08	1.20	0.07	0.53
Amygdala	1.33	0.07	1.28	0.07	0.39
Insula	0.94	0.06	0.88	0.06	0.58
OFC	1.02	0.07	0.94	0.06	0.61
ACC	1.09	0.06	1.03	0.06	0.58
MCC	0.91	0.07	0.85	0.06	0.58
PCC	0.50	0.04	0.47	0.04	0.52
SI	0.33	0.03	0.39	0.04	0.66
SII	0.56	0.05	0.62	0.05	0.67
Cerebellum	0.58	0.05	0.62	0.05	0.54

However the present results do not uniformly confirm whether the presently observed MOR response would be specific to bonding-related social touching. Future studies are needed to investigate whether the MOR system responds differently to various social-bonding behaviours, or whether interactions of different neurotransmitter systems (Tuominen et al. 2014) could govern bonding behaviour in different contexts.

Subset of the regions where MOR system activity decreased during social touch (ACC, aINS, thalamus) contribute to the experience of pain, possibly via an analgesic effect (Singer et al. 2004), and they show increased opioid peptide release during nociceptive stimulation (Zubieta et al. 2001) and social rejection (Hsu et al. 2013). Touching by the participant's partner in turn triggered decreases in endogenous opioid release accompanied by increased pleasurable and decreased painful sensations, essentially an opposite neural and behavioural effect to that observed during nociceptive stimulation. This finding fits with the view that similar visceral and negative affective responses may be engaged during physical pain and social distress (Eisenberger et al. 2003; Hsu et al. 2013), which would here be disengaged during affiliation. Social touching reduces stress (Ditzen et al. 2007) and it could be expected to downregulate the opioidergic components of the physical pain and social distress circuitries, thus leading to decreased tonic opioid neurotransmitter release as is observed here. Theoretically, this reduction in the basal state of the MOR system might promote more effective coding of the pleasurable sensations associated with the social touching.

The effects of social touch could be mediated by the unmyelinated C-tactile fibres (CTFs) that respond selectively to slow pleasurable stroking. Stimulating these fibers activates insular but not somatosensory cortices and possibly provides the sensory pathway for emotional and affiliative touching (Loken et al. 2009; Olausson et al. 2002). In line with this argument, significant changes in opioid receptor availability during social touch were observed in the insular cortex. Given the proposed lateralization of affective processing and anterior–posterior organization of emotional versus somatosensory and interoceptive processing in the insula (Duerden et al. 2013; Naqvi and Bechara 2009), we also analyzed the insular responses using hemisphere-specific anterior and posterior insular ROIs. The touching-dependent MOR response was however found to be equivalent across hemispheres and anterior/posterior regions ($Fs < 1$, $ps > 0.35$). The primary and secondary somatosensory cortices also contain MOR even though to a lesser extent than adjacent cortical regions (Jones et al. 1991). In line with this, significant clusters in the SPM analysis were observed only sparsely in SI and SII. However, complementary region-of-interest analysis revealed significant

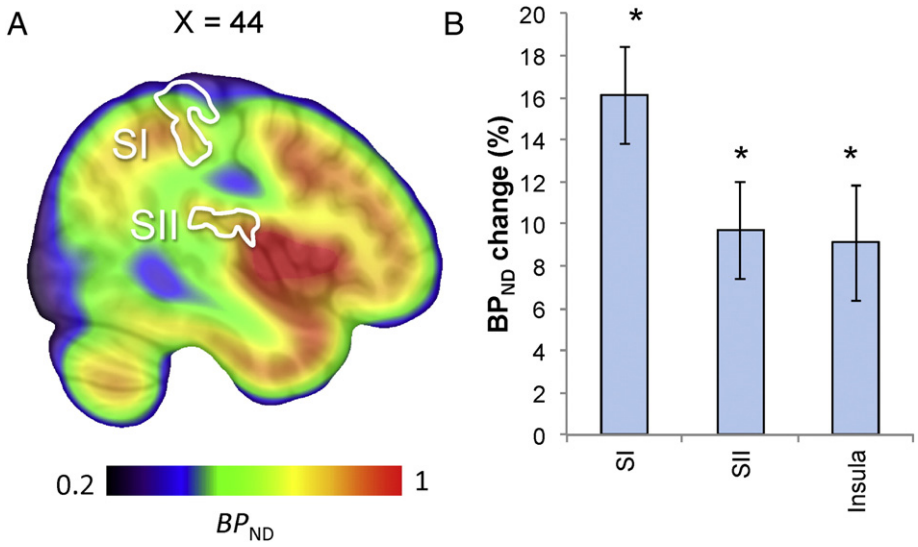

Fig 4. The [11-C]carfentanil binds significantly to primary (SI) and secondary (SII) somatosensory cortices (A). Region-of-interest analyses revealed that social touching increased BP_{ND} significantly both in SI, SII and the insular cortex (B). Asterisks denote significant differences from zero.

effects also in SI and SII (Fig. 4), suggesting that both the fast-conducting myelinated afferents and CTFs may contribute to the μ-opioid system downregulation via social touching.

The size of social networks (Holt-Lunstad et al. 2010) and, more generally, the availability of social support (Broadhead et al. 1983), is associated with a wide variety of beneficial effects for somatic health. Thus, the effectiveness of engaging the neurochemical pathways supporting social bonding with conspecifics via, for example, touching, may contribute significantly to an individual's wellbeing. Conversely, such opioidergic involvement in intimate social interaction also accords with clinical data on patients with substance abuse. Disruption of the endogenous opioid system by opiate addiction is associated with antisocial behaviour (Ross et al. 2005) and chronic opiate addiction leading to opioid tolerance (Koch and Hollt 2008) may thus render MOR-dependent pain and social distress circuitries unresponsive to social interaction. This accords well with prior work showing that frontocortical MOR availability is positively associated with intimacy of social relationships (Nummenmaa et al. 2015); volume of this MOR-rich region is also positively associated with social network size in adults (Lewis et al. 2011).

In humans, social touch is regulated by society norms and the social relationships between individuals, and intimate touch is typically restricted to the closest relationships (Jones and Yarbrough 1985; Willis and Briggs 1992), and the area allowed for social touching depends linearly on the emotional bond between the dyad (Suvilehto et al. 2015). Even though our participants experienced higher levels of pleasure during social touch than during the baseline condition, it is unlikely that the effect of touching on the opioid system would reflect mere pleasurable sensations during touch of any type. Indeed, participants rated the touch by a stranger significantly less pleasurable than the touch by their partner. Here we studied the effects of social touching on the μ-opioid system in an already established, romantic and prospectively reproductive social bond. However, it is possible that similar repeated exposures to social touch or other types of prosocial behaviour could tune the responsiveness of the μ-opioid system, thus promoting establishment of social bond or dependency towards social interaction with the partner.

Because the size of human social networks significantly exceeds the network that can be maintained by social grooming or touching (Dunbar 2012), humans do not maintain these types of relationships solely via touching. Instead, other means, such as conversation or social laughter allow engagement of the bonding mechanism *among all members* of an interacting group and they could play a critical role in enabling humans to live in exceptionally large social networks (Dunbar 2012; Dunbar et al. 2012). However, it remains to be tested whether such means of interpersonal bonding, and bonding in relationships other than reproductive ones, are supported by the same opioidergic mechanism as is observed in the present study. Also, in this study we specifically quantified the neurochemical consequences of social touching in a prospectively reproductive relationship, thus the social touching might also involve a sexually arousing component. Importantly, the lack of any social touching dependent arousal effects suggests that this effect is not primarily driven by sexual and potentially reproductive nature of touching. It is thus possible that this effect also scales down to touching in non-intimate relationships such as friendships and kinships (Machin and Dunbar 2011). Yet, this needs to be established in future work.

Limitations

The observed BPND changes may reflect receptor internalization or altered conformation rather than occupancy by endogenous neurotransmitter. Our outcome measure cannot directly specify which interpretation is most appropriate. In principle the changes in PB_{ND} could also reflect increase in receptor synthesis, even though this is extremely unlikely in the time-scale of the experiment. Our study sample also only comprised males. It is well established that the effects of neuropeptides, such as oxytocin and vasopressin, have gender-specific roles in social functioning (see review in Dunbar 2010), and thus caution is warranted when generalizing our findings to female subjects. Finally, we acknowledge that we cannot completely rule out the possibility that any type of touching would influence the MOR system, as our study did not include a non-social control condition. However, given that monkey studies showing specifically social (rather than non-social) modulation in touching behaviour (Fabre-Nys et al. 1982; Graves et al. 2002; Keverne et al. 1989) and behavioural data suggesting that particularly interpersonal touching is modulated by social bonds (Suvilehto et al. 2015) we find this possibility unlikely.

Conclusions

We conclude that social touching modulates μ-opioid system activity. Altogether with pharmacological studies in primates, this suggests that social touching and concomitant modulation of MOR activity might underlie the neurochemical mechanism reinforcing and maintaining social bonds between humans. Even though the role of

language-based mechanisms is often emphasized in human communication, our data highlight the central role played by touching and somatosensation in modulating human social interaction and interpersonal bonds.

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