Adult Attachment Style is Associated With Cerebral μ-Opioid Receptor Availability in Humans

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Abstract: Human attachment behavior mediates establishment and maintenance of social relationships. Adult attachment characteristically varies on anxiety and avoidance dimensions, reflecting the tendencies to worry about the partner breaking the social bond (anxiety) and feeling uncomfortable about depending on others (avoidance). In primates and other mammals, the endogenous μ-opioid system is linked to long-term social bonding, but evidence of its role in human adult attachment remains more limited. We used in vivo positron emission tomography to reveal how variability in μ-opioid receptor (MOR) availability is associated with adult attachment in humans. We scanned 49 healthy subjects using a MOR-specific ligand [^{11}C]carfentanil and measured their attachment avoidance and anxiety with the Experiences in Close Relationships-Revised scale. The avoidance dimension of attachment correlated negatively with MOR availability in the thalamus and anterior cingulate cortex, as well as the frontal cortex, amygdala, and insula. No associations were observed between MOR availability and the anxiety dimension of attachment. Our results suggest that the endogenous opioid system may underlie interindividual differences in avoidant attachment style in human adults, and that differences in MOR availability are associated with the individuals' social relationships and psychosocial well-being. *Hum Brain Mapp 00:000–000, 2015.*

Key words: attachment; emotion; opioids; neurotransmitters; social interaction; positron emission tomography

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INTRODUCTION

Human adults have enduring affective relationships with each other in all areas of life, yet they differ markedly in the way they establish and maintain such social bonds. Attachment theory [Bowlby, 1982] posits an innate bonding system—presumably analogous with the attachment circuitry in other mammals—whose function is to maintain infants' proximity to significant others in the presence of threats and to regulate seeking for support when needed [Nelson and Panksepp, 1998]. In human adulthood, this attachment mechanism continues to modulate social interactions in close relationships [Hazan and Shaver, 1987].

Adult attachment behavior characteristically varies on two dimensions—anxiety and avoidance. These dimensions reflect the tendencies to worry about the partner breaking the social bond (anxiety) and feeling uncomfortable about depending on others (avoidance), with low scores on both dimensions reflecting attachment security [Brennan et al., 1998; Fraley et al., 2000]. Avoidantly attached individuals experience less pleasure from social interactions and avoid intimate interpersonal exchanges with potential of social rejection, thus leading to preference for being alone [Bartholomew, 1990]. Because large social network size [Holt-Lunstad et al., 2010] and the availability of social support [Broadhead et al., 1983] are associated with beneficial effects for somatic health and psychological well-being, it is not surprising that individual differences in adult attachment influence psychosocial and somatic well-being. Specifically, insecure attachment has been associated with psychological adjustment problems, substance abuse, and psychopathology [Brennan and Shaver, 1995; Griffin and Bartholomew, 1994; Mikulincer and Shaver, 2007].

Individual differences in adult attachment modulate activation of the corticolimbic circuits that encode social and affective information [see review in Vrticka and Vuilleumier, 2012]. At subjective level, avoidant attachment is associated with lowered experience of pleasantness when viewing positive social scenes, whereas anxious attachment is associated with heightened experience of arousal when viewing negative social scenes [Vrticka et al., 2012]. In line with these findings, haemodynamic responses in the striatal reward circuit to signals conveying positive emotional signals are negatively associated with attachment avoidance [Vrticka et al., 2008], whereas amygdala responses to negative emotional signals have been positively associated with both attachment avoidance [Norman et al., 2015] and anxiety [Vrticka et al., 2008]. Finally, the putative human social distress circuit (dorsal anterior cingulate cortex [dACC] and insula) is more responsive to social rejection in anxiously attached and less responsive in avoidantly attached individuals [DeWall et al., 2012]. In sum, attachment anxiety seems to increase responsiveness to negative social signals, whereas attachment avoidance lowers responsivity of brain circuits involved in socioemotional processing.

The neurochemical basis of human attachment is less well understood. Oxytocin and vasopressin systems contribute significantly to attachment behavior [Johnson and Young, 2015; Young et al., 2001], yet animal studies suggest that the endogenous opioid system could be another candidate neurochemical pathway for human attachment circuit. The opioidergic system modulates reward functions, drives motivated behaviors [Van Ree et al., 2000] and endogenous opiates widely modulate social behavior in rodents [Panksepp et al., 1980]. Exogenous opioid agonists alleviate separation distress in puppies [Panksepp et al., 1978], whereas μ-opioid receptor (MOR) gene knockout mice pups display deficit maternal attachment behavior [Moles et al., 2004]. The A118G polymorphism of the MOR gene OPRM1 is associated with enhanced dispositional and neural sensitivity to social rejection in humans [Way et al., 2009], whereas rhesus infants carrying a gain-of-function OPRM1 77G allele experience increased reward from maternal contact [Barr et al., 2008].

Pharmacological manipulations in primates further show that opioid receptor antagonists increase the frequency of both social grooming [Fabre-Nys et al., 1982; Graves et al., 2002] and grooming solicitations [Keverne et al., 1989], suggesting that endogenous opioid tone modulates attachment behavior. Furthermore, activation of the endogenous MORs is essential for bonding in monogamous adult voles [Burkett et al., 2011; Resendez et al., 2013], suggesting the role of MOR in long-term adult social bonds. In line with this, genetic studies in human adults suggest that the minor allele (G) of the OPRM1 A118G polymorphism is associated self-reported avoidant attachment [Troisi et al., 2011]. Finally, human behavioral studies provide indirect evidence for the role of MOR system in bonding, by showing that pain threshold—a proxy of endogenous opioid release—is increased by social behavior promoting intragroup affiliation [Dunbar et al., 2012].

These converging lines of evidence suggest that the MOR-mediated neurotransmission could underlie individual differences in human adult attachment. However, this hypothesis currently lacks empirical support. Here, we use positron emission tomography (PET) coupled with behavioral attachment-style measures to show that avoidant but not anxious attachment style is negatively associated with cerebral MOR availability.

MATERIALS AND METHODS

Participants

The study protocol was approved by the ethics board of the South-western Finland hospital district, and the study was conducted in accordance with the Declaration of Helsinki. A priori power analysis based on effect sizes in previous PET studies on associations between personality trait variables and MOR availability suggested that sample

sizes exceeding $n = 45$ would have power higher than 0.95 for detecting statistically significant effects. Consequently, the final sample size was set at 50. Altogether, 50 healthy adults (20 females, ages 19–58, mean age 32 years, SD 6.4 years) volunteered for the study. Exclusion criteria (in addition to standard PET and MRI exclusion criteria) were poor compliance, smoking, excessive alcohol consumption (over 8 weekly doses), substance abuse determined by interview and blood tests, a history of or current neurological or psychiatric disease, and current medication affecting the central nervous system. All subjects were compensated for their time and travel costs, and they signed ethics-committee-approved, informed consent forms. One participant was removed from the sample because their MRI revealed previously nondiagnosed neurological disease.

Questionnaires

The participants completed the Experiences in Close Relationships-Revised (ECR-R) questionnaire addressing adult attachment style [Fraley et al., 2000]. The questionnaire consists of 36 Likert-scale questions and has been psychometrically validated to capture anxiety and avoidance dimensions of adult attachment style. As endogenous opioid systems is associated with both mood and anxiety related processes [Colasanti et al., 2011; Lutz and Kieffer, 2013], participants complete the Beck Depression Inventory II [Beck et al., 1988] and State-Trait-Anxiety Inventory [Spielberger et al., 1983] to rule out anxious and depressive symptoms and their potential association with MOR availability.

PET Imaging and Analysis

Data were acquired with the Philips Ingenuity PET-MR and GE Heatlhcare Discovery TM 690 PET/CT scanners in Turku PET Centre. After intravenous radioligand injection (targeted 250 MBq; mean 251 MBq, SD = 11 MBq), 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. Data were corrected for dead-time, decay, and measured photon attenuation and dynamic PET-scans were reconstructed with vendor provided standard MRAC and MRP methods [Alenius and Ruotsalainen, 1997]. High-resolution anatomical MR reference images (1 mm^3 resolution) 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. Occipital cortex was delineated manually on MRI images with PMOD 3.4 software (PMOD Technologies, Zurich, Switzerland) and used as reference region Receptor binding was expressed in terms of BP_{ND}, which is the ratio of specific to nondisplaceable binding in brain using the occipital cortex as the reference region. BP_{ND} was calculated for each voxel using the simplified reference tissue model with reference tissue time activity curves as input data [Gunn et al., 1997]. 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 anxious and avoidant attachment styles on MOR availability were then assessed in SPM8 (http://www.fil.ion.ucl.ac.uk/spm/) using linear regression model. Statistical threshold was set at $P < 0.05$, FDR corrected at cluster level.

In addition to its putative role in social bonding, the endogenous opioid system is intimately involved in processing both rewards and nociceptive information [Van Ree et al., 2000; Zubieta et al., 2001], and both mechanisms have been proposed to contribute to the maintenance of social ties [Eisenberger, 2012]. To specify the role of these circuits in adult attachment, anatomical regions of interest (ROIs) were drawn around components of the reward (ventral striatum, dorsal striatum, amygdala, and orbitofrontal cortex [OFC]) and pain circuits (ACC, insula, and thalamus). This functional division is obviously not exclusive, as most of these regions subserve a multitude of functions related to social, emotional, and nociceptive processing. The ROIs were defined using the AAL [Tzourio-Mazoyer et al., 2002] and Anatomy [Eickhoff et al., 2005]. Subsequently, associations between regional BP_{ND} and attachment avoidance and anxiety were analyzed in each ROI. In a complementary methodological approach, linear regression analysis with attachment avoidance (or anxiety) as the dependent variable and backward elimination of ROI-wise BP_{ND} predictors was used to pinpoint regions whose BP_{ND}'s had the strongest associations with attachment anxiety and avoidance.

RESULTS

Figure 1 shows the mean [11C]carfentanil binding distribution in the brain. Avoidance scores correlated negatively ($P < 0.05$ FDR corrected) with MOR availability in the thalamus, anterior (ACC), middle (MCC) and posterior (PCC) cingulate cortices, and medial (mPFC) and lateral prefrontal cortex (Figs. 2 and 3). Additional associations were observed in regions spanning ventral striatum, amygdala, and insula. There was no association between MOR availability and anxiety scores. The effect of attachment avoidance (or anxiety) on MOR availability did not differ across males and females; accordigly avoidance and anxiety scores did not differ between males and females, ts$(47) < 1.67$, Ps > 0.11 and were not correlated with each other ($r = 0.08$, n.s.) Finally, neither depression nor anxiety scores were associated with MOR availability.

ROI analysis paralleled the overall pattern of the results from whole-brain GLM in a subset of the tested

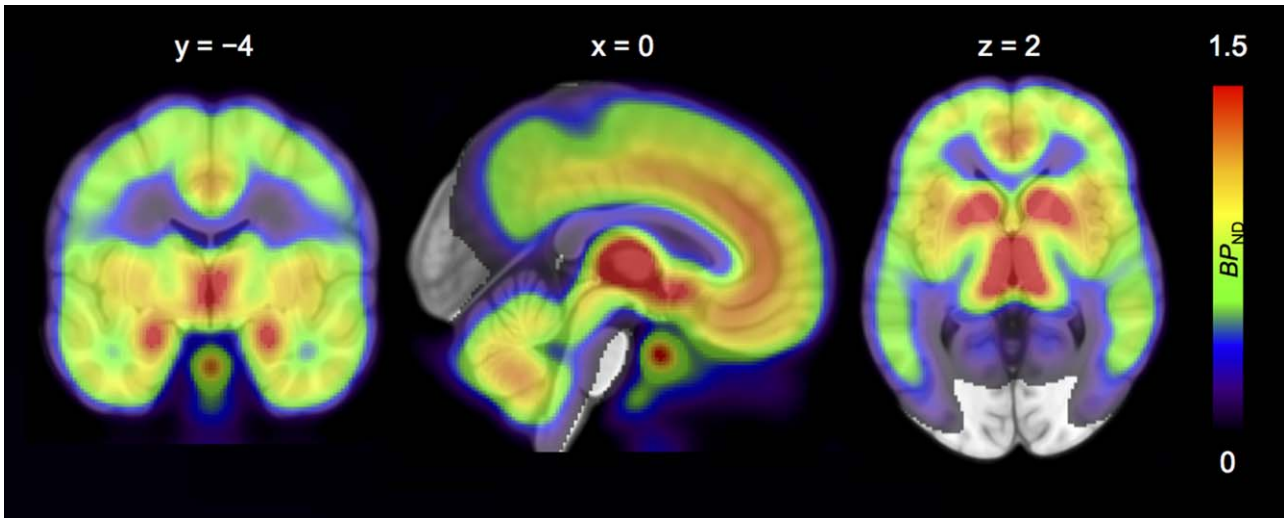

Figure 1.
Mean [11C]carfentanil BP_{ND} distribution in the brain.

ROIs: Attachment avoidance (but not anxiety) was negatively associated with BP_{ND} in OFC, amygdala, dorsal striatum, and thalamus ($Ps < 0.05$ in one-tailed test). However, associations were not significant in insula, ACC, ventral, and dorsal striatum ($Ps > 0.05$). Finally, linear regression analysis revealed that [11C]carfentanil BP_{ND} in the OFC emerged as the sole predictor for attachment avoidance ($\beta = -0.89$, $t = -2.02$, $P < 0.05$), with no significant predictors observed for attachment anxiety.

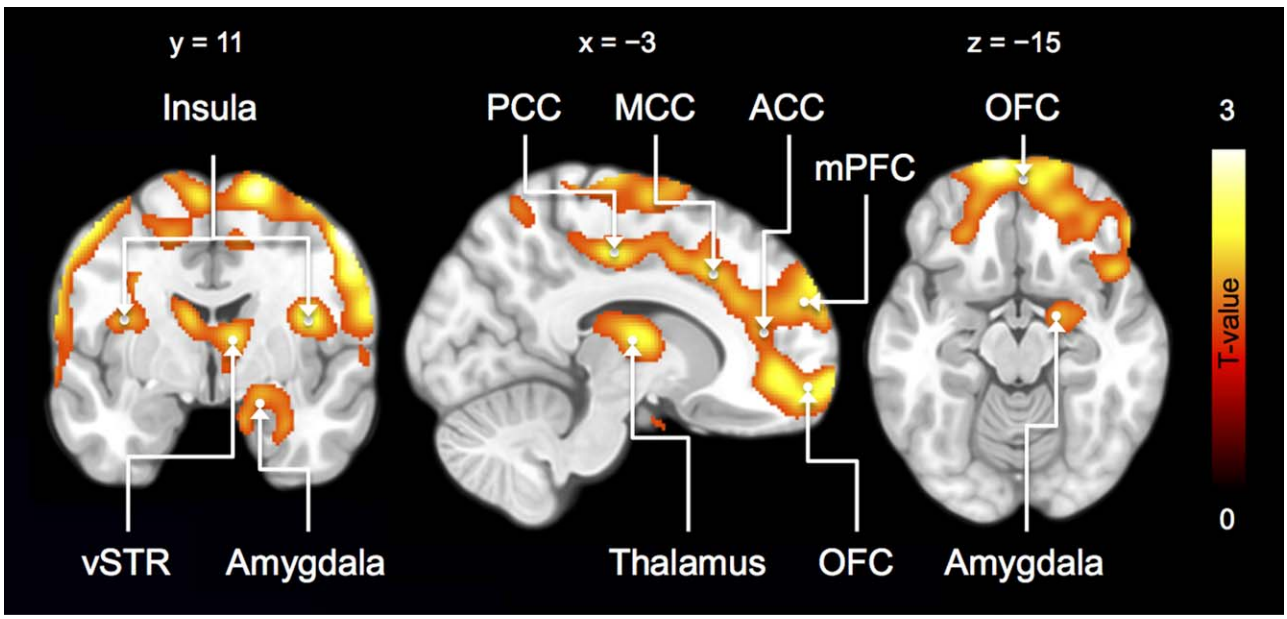

Figure 2.
Brain regions showing a statistically significant association between avoidant attachment and MOR availability. The data are thresholded at $P < 0.05$, FDR corrected. ACC = anterior cingulate cortex, MCC = Middle cingulate cortex, mPFC = medial prefrontal cortex, OFC = orbitofrontal cortex, PCC = Posterior cingulate cortex, vSTR = ventral striatum.

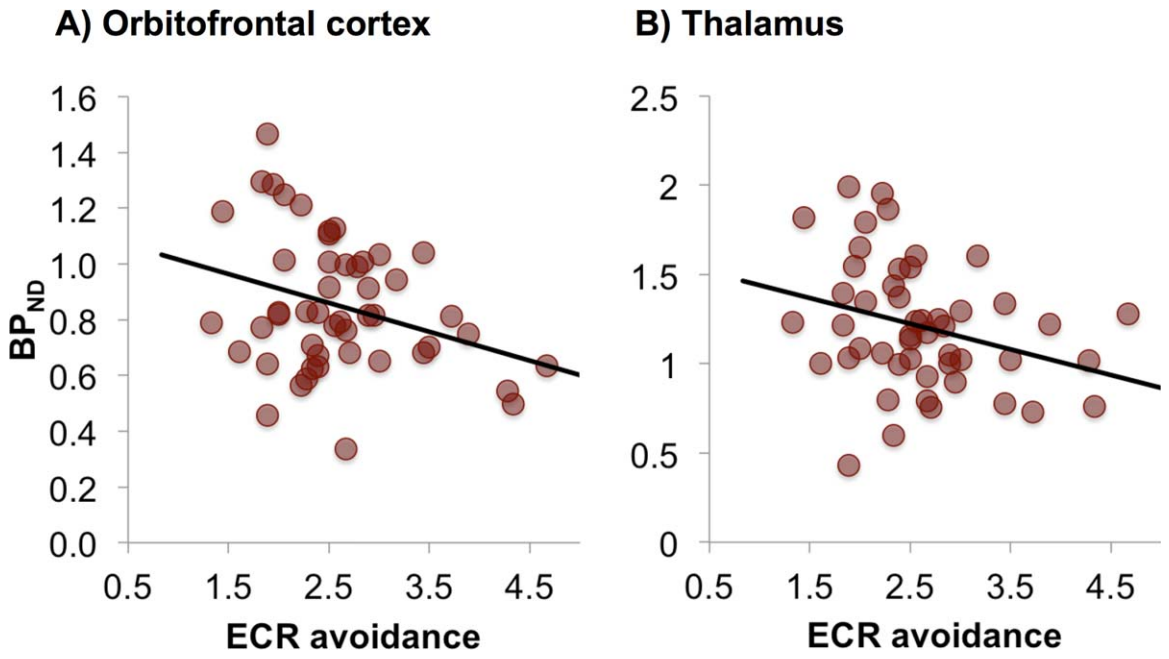

Figure 3.

Association between avoidant attachment style and MOR availability in orbitofrontal cortex (**A**) and thalamus (**B**). Note: The scatterplots are for visualization only and the statistical reasoning is based on the full-volume SPM analysis. Cook's distance for all observations is <1 suggesting that no single data point or their removal significantly biases the correlation.

DISCUSSION

We show for the first time that individual differences in the attachment style of human adults is associated with baseline MOR availability, with high attachment avoidance being associated with low MOR availability both in regions belonging to the putative social distress circuit [ACC and thalamus; Panksepp, 2003] and in the medial frontocortical regions that support functions such as emotions and theory-of-mind that are critical for social interaction [mPFC, OFC; Amodio and Frith, 2006]. Subset of the regions showing attachment-dependent MOR availability also overlap with the fronto-insular saliency network [Seeley et al., 2007], possibly highlighting the role of the this system in subserving alert functions during intimate interpersonal situations. Our finding accords with primate work showing that the opioid system modulates pair bonding and attachment in primates and other mammals [Machin and Dunbar, 2011; Nelson and Panksepp, 1998], in addition to the well-known oxytocin and vasopressin systems [Young et al., 2001].

These findings suggest that variation in focal MOR availability may provide an important neurochemical mechanism explaining individual differences in avoidant adult attachment behavior. Our results emphasize that this is a quantitative relationship with receptor density, and animal studies have indeed linked endogenous MOR availability with attachment behavior. Preclinical experiments and postmortem work in humans suggest OPRM1-modulated MOR expression [Mague et al., 2009; Zhang et al., 2005], also confirmed by human PET studies [Pecina et al., 2015; Weerts et al., 2013]. Whereas low endogenous MOR availability seen in gene knock-out mice leads to a deficit in maternal attachment in mice [Moles et al., 2004], monkey infants with gain-of-function OPRM1 77G allele express enhanced maternal attachment [Barr et al., 2008]. In human adults, the minor allele (G) of the OPRM1 A118G polymorphism also predicts self-reported avoidant attachment [Troisi et al., 2011]. In line with these studies, prior PET work in humans shows that MOR activity increases in the amygdala and anterior insula during social acceptance [Hsu et al., 2013], whereas MOR-mediated neurotransmission is decreased when individuals recall past events involving termination of social bonds [Zubieta et al., 2003]. Together with these findings, our data suggest that the MOR system is intimately involved in maintenance of social connections with significant others.

Pharmacological studies further corroborate the role of MOR in attachment behavior by showing that exogenous opioid antagonists increase social grooming in monkeys [Fabre-Nys et al., 1982; Keverne et al., 1989], whereas opioid agonists alleviate separation distress in puppies [Panksepp et al., 1978]. These effects may reflect the well-known role the opioid system plays in reward and pain processing

[Van Ree et al., 2000; Zubieta et al., 2001]. Low availability of endogenous MORs may dilute the calming effects of endogenously released opioid peptides acting on the MOR during social interaction, thus inhibiting establishment and reinforcement of safe attachment bonds [see e.g. Nelson and Panksepp, 1998]. This also accords with findings from functional imaging studies showing that attachment avoidance is associated with lowered responses to particularly positive social signals [see review in Vrticka and Vuilleumier, 2012]. However, even though the anxiety-alleviating effects of exogenous opioid agonists are well-known [Colasanti et al., 2011], individual differences in attachment anxiety or trait anxiety within the subclinical range were not mediated by endogenous MOR availability in our dataset. These findings suggest that distinct neuromolecular pathways support avoidant and anxious attachment behavior, and also imply that individual differences in subclinical trait anxiety are not manifested in MOR availability.

Prior functional magnetic resonance imaging (fMRI) work demonstrates that avoidant attachment is associated with lowered responsiveness in the brain's reward circuit during social encounters [Vrticka et al., 2008]. Our ROI analyses support these findings by showing that MOR availability was significantly associated with avoidant attachment in ROIs belonging to the reward circuit (dorsal striatum, amygdala, and OFC). Regression analysis further highlighted that MOR availability in the OFC was the best predictor for avoidant attachment. Even though significant in full-volume analysis, associations between BPND and attachment avoidance in regions involved in pain processing (insula, anterior cingulate cortex) failed to reach significance in the ROI analyses. However, whether individual differences in avoidant attachment are more strongly mediated by MOR-dependent brain circuits encoding the rewarding rather than punishing value of social encounters needs to be qualified in studies using active challenge paradigms [see DeWall et al., 2012 for related fMRI work; Vrticka et al., 2008].

The observed linkage between MOR availability and avoidant attachment also accords with clinical data on patients with substance abuse. Disruption of the endogenous opioid system by opiate addiction is associated with antisocial behavior [Ross et al., 2005]. Chronic opiate addiction leading to opioid tolerance [Koch and Hollt, 2008] may thus render MOR-dependent attachment circuitries unresponsive to social interaction. Importantly, insecure maternal—offspring attachment is associated with higher likelihood of opioid use [Cerdá et al., 2014; Schindler et al., 2005], while, critically, abuse of heroin (but not drugs that do not influence the opioidergic system, such as ecstasy or cannabis) is associated with avoidant adult attachment [Schindler et al., 2009]. Together with animal work showing how opioid agonists alleviate separation distress [Panksepp et al., 1978], these data suggest that exogenous opiates may be used as a chemical substitutes of secure attachment in avoidantly attached human individuals, further highlighting the specific role of the opioid system in governing human avoidant attachment behavior.

Secure adult attachment style is an important protective psychosocial factor [Griffin and Bartholomew, 1994]. While secure attachment leads to relationship satisfaction, insecure and avoidant attachment is associated with psychological adjustment problems including loneliness and substance abuse [Brennan and Shaver, 1995; Kassel et al., 2007]. Moreover, avoidant attachment is associated with avoidance of intimate interpersonal exchanges that may make them vulnerable to social rejection, ultimately leading to preference for being alone [Bartholomew, 1990]. The orbitofrontal and medial prefrontal regions that show negative association between MOR availability and attachment avoidance are also crucially involved in the maintenance of human social networks [Lewis et al., 2011; Powell et al., 2012]. Insecure attachment is also associated with smaller social networks [Fiori et al., 2011], and both large social network size [Holt-Lunstad et al., 2010] and the availability of social support [Broadhead et al., 1983] are associated with beneficial effects for somatic health. Accordingly, the reciprocal links between MOR availability, attachment avoidance, and social networks could in part explain the beneficial psychosocial effects of secure attachment.

Our cross-sectional study cannot, however, establish a causal link between MOR system and attachment behavior. Although it is biologically plausible to assume that genetically determined individual differences in opioidergic neurotransmission influence social behavior [Barr et al., 2008; Moles et al., 2004; Way et al., 2009] and attachment [Troisi et al., 2010], it is also possible that individual differences in engaging with different types of social relationships could trigger neuroplastic changes in the opioid system during development. Perpetual overstimulation of the MOR system may lead to its downregulation [Karlsson et al., 2015], and similarly recurrent presence of threats and consequent support seeking could downregulate the attachment-related components of the MOR system. Even though the well-established stability of attachment security from infancy to early adulthood [Fraley, 2002] suggests that MOR availability may causally influence attachment behavior, longitudinal studies will be needed to resolve this relationship and to assess the specific contributions of genetically determined MOR neurotransmission versus experience-dependent plasticity of infant and adult attachment systems.

Ultimately, however, these findings are important because they demonstrate a direct quantitative relationship between psychological attachment style and the opioidergic system. Such a relationship might be expected to generalize across primates as a function of species differences in the intensity of the bonding system [Dunbar and Shultz, 2010] and perhaps other mammalian taxa [Shultz and Dunbar, 2010]. Differences in the degree of "bondedness" between different species or orders may be correlated with the density of the μ-receptor system and the underlying genetics.

Finally, we stress that our study was strictly focused on the individual differences in attachment and baseline receptor availability. In future studies, it would be important to use challenge paradigms where acute changes in MOR availability are measured when the attachment system is activated. Such an approach would help elucidating how individual differences in attachment styles translate to task-dependent activation of the MOR system.

CONCLUSIONS

We show that low endogenous MOR levels are associated with avoidant attachment style in human adults, suggesting that the endogenous opioid system is an important candidate for the neuromolecular mechanism underlying individual differences in attachment. Endogenous opioids may significantly contribute to human attachment behavior, in addition to the well-known effects of oxytocin and vasopressin systems [Young et al., 2001]. Yet future studies are needed to delineate the causal link between MOR expression and attachment behavior. Altogether, our findings suggest that individual differences in MOR availability could have a profound impact on the social relationships individuals establish, thus potentially having a strong impact on psychological well-being.

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