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Adult Attachment System Links With Brain Mu Opioid Receptor Availability In Vivo

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ABSTRACT

BACKGROUND: Secure attachment is important in maintaining an individual's health and well-being. Attachment disturbances increase the risk for developing psychiatric disorders such as affective disorders. Yet, the neurobiological correlates of human attachment are poorly understood at the neurotransmitter level. We investigated whether adult attachment style is linked to functioning of the opioid and serotonergic systems in the human brain.

METHODS: We used positron emission tomography with radioligands [^{11}C]carfentanil and [^{11}C]MADAM to quantify mu opioid receptor (n = 39) and serotonin transporter (n = 37) availability in volunteers with no current psychiatric disorders. Attachment style was determined according to the Dynamic-Maturational Model of Attachment and Adaptation with the structured Adult Attachment Interview.

RESULTS: Secure attachment was associated with higher mu opioid receptor availability in the hippocampus, amygdala, thalamus, and prefrontal cortex when compared with insecure (i.e., avoidant or ambivalent groups combined) attachment. In contrast, attachment style was not associated with serotonin transporter availability.

CONCLUSIONS: Our results provide preliminary in vivo evidence that the opioid system may be involved in the neurocircuits associated with individual differences in adult attachment behavior. The results suggest that variation in mu opioid receptor availability may be linked with the individuals' social relationships and psychosocial well-being and thus contributes to risk for psychiatric morbidity.

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Mammals, including humans, are equipped with an innate bonding system that maintains infants' closeness to caretakers during threats and regulates support-seeking behavior (1). Such need to form and maintain close interpersonal relationships is fundamental to human life (2). Attachment style develops in a dynamic interaction between early interactive experiences with caregivers, environmental circumstances, and individuals' psychobiological qualities such as temperament (3). In childhood, attachment emerges as behavioral patterns in relation to primary caregivers. The attachment style can be divided into secure, avoidant, and ambivalent attachment styles. Avoidant and ambivalent attachment can be further grouped together as insecure attachment style. Secure attachment is manifested in intrinsic reliance on others' good intentions and trust in others in distressing situations. Avoidant attachment describes a disposition to deny or hide one's negative emotions in threatening situations, have excessive self-reliance, and be unable to seek comfort from others. Finally, ambivalent attachment refers to one's uncertainty about others' support, leading to alertness across situations, fears of becoming rejected, and sensitivity to display negative emotions [P. Crittenden, Ph.D., unpublished data, 1999; (4)]. These attachment styles generalize to attachment-based strategies in romantic and other close relationships, and they contribute to coping, emotion regulation, and social behavior in general (3). Further, the prototype of attachment style remains moderately stable from childhood to adulthood, although changes can occur with maturation and because of abuse, stressful life events, or severe conflicts in social relationships (5,6).

Accumulating evidence also demonstrates that attachment style is important for mental health (7). For instance, insecure attachment is linked to a variety of psychiatric disorders, such as anxiety (8), depression (9), eating disorders (10), substance abuse (11), and psychosis (12), with some differences in the vulnerabilities between avoidant and ambivalent attachment styles. Accordingly, the World Health Organization has postulated that attachment should be one crucial target in early prevention of mental disorders. Attachment is also one of the National Institute of Mental Health's Research Domain Criteria domains for research purposes (13). Hence, investigating the neurobiological basis of the attachment system could substantially advance our understanding about the etiological mechanisms of psychiatric disorders.

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Neuropeptides oxytocin and vasopressin are involved in the formation of attachment relationships (14,15), and recent studies have also elucidated the contribution of the dopamine system in social motivation (16,17). However, the role of the serotonergic and opioid systems in human attachment has remained poorly understood. The role of endogenous opioids in modulating attachment was first suggested following the observation that exogenous opioid agonists alleviate separation distress of rat pups (18). Subsequently, it has been argued that experiences of interpersonal warmth and social euphoria result in endogenous opioid release, and decline in endogenous opioid levels following social isolation drives the individual to search for interpersonal contacts (19). Previously, social touch was found to increase the mu opioid receptor availability (20). Animal studies have indeed suggested that social attachment is linked to mu opioid receptors in both prairie voles (21) and rhesus macaques (22). Further, genetic studies have found that attachment behavior is related to mu opioid receptor genes in rhesus monkeys (23) and mice (24). In humans, opioid receptor density correlates with the frequency of prosocial behavior such as social laughter (25), and one study suggested that high avoidance in attachment correlates with lower mu opioid receptor availability in limbic emotion circuits and the frontal cortex (26). Human studies on the opioidergic basis of attachment have, however, relied on self-report questionnaires. Self-report questionnaires may cause bias for several reasons: questionnaires may cause anxiety and activate psychological defenses, responses to questionnaires may be affected by current affective states and be less stable over long time periods, and the items are commonly summed together (without emphasizing some theoretically relevant issues over others) (27,28). Therefore, additional work based on objective, interview-based external measurements of attachment behavior are needed to elucidate how the endogenous opioid system contributes to human attachment style differences.

Childhood abuse, which is known to severely disrupt formation of secure attachment, is related to lower serotonin transporter availability in subjects with major depressive disorder (29). The serotonergic system is also linked with several subcomponents of attachment behavior, such as social cognition and emotion regulation (30). Studies in rhesus monkeys have found that social subordination stress (31) and early maternal deprivation predict the level of serotonin transporter availability (32). Similarly, pharmacological studies in humans have suggested that modulation of the serotonin function changes the appraisal of close relationships. For instance, on the one hand, both tryptophan depletion (33) and serotonin receptor blockade with citalopram (34) have been shown to result in lower ratings of relationship intimacy and quality. On the other hand, MDMA leads to feelings of closeness with others and has been shown to enhance pleasantness of social touch (35) and increase prosocial behavior, possibly via serotonergic mechanisms (36,37). In summary, converging evidence suggests that the serotonin system and serotonin transporter in particular are important molecular mechanisms supporting close relationships. However, to our knowledge, no study has investigated directly whether human attachment style as such is related to the serotonin transporter availability.

In this study, we investigated whether attachment type is linked to functional alterations in opioid and serotonergic systems in vivo in the brain. We used positron emission tomography (PET) with radiotracers [^{11}C]carfentanil and [^{11}C]MADAM to measure mu opioid receptor and serotonin transporter availability, respectively. A sample of 39 volunteers with no current psychiatric disorders was recruited. Attachment styles were evaluated using the Adult Attachment Interview (AAI) (C. George, Ph.D., *et al.*, unpublished data, 1996) that was further analyzed with the Dynamic-Maturational Model of Attachment and Adaptation (DMM) [P. Crittenden, Ph.D., unpublished data, 1999; (4)]. Hence, attachment type assessment was based on a reliable psychiatric interview that captures also unconscious representations about close interpersonal relationships. Based on previous indirect evidence, the starting hypotheses were that secure (vs. insecure) attachment would be associated with higher mu opioid receptor availability and higher serotonin transporter availability in brain regions associated with social-emotional processing. We used both a whole-brain approach and, as additional analysis, a region of interest (ROI)–based approach (including the amygdala, hippocampus, ventral striatum, dorsal caudate, thalamus, insula, orbitofrontal cortex, anterior cingulate cortex, middle cingulate cortex, and posterior cingulate cortex).

METHODS AND MATERIALS

This study is a part of a larger "Neurobiology of Personality" project at the University of Turku and University of Helsinki and a substudy of a population-based, still ongoing nationwide Cardiovascular Risk in Young Finns Study (YFS), a prospective cohort study that started in 1980 with preexisting somatic health and psychological data. Participants (Table 1) were selected from the YFS sample on the basis of their harm avoidance (HA) scores (a scale of the Temperament and Character Inventory). The recruited subject groups with high versus low HA were matched with regard to age, sex, and educational level. We invited all the participants with low/high HA who could be matched with each other with regard to age, sex, and educational level. Two such subsamples (with high and low HA) were collected: in the first sample, past or present psychiatric disorders were excluded (n = 22) (38); in the second sample, subjects (who had not participated in previous published studies) were allowed to have past but not current psychiatric disorders, making the whole study group less selected. A more detailed description of the recruitment is available elsewhere (38–40).

The current study protocol was approved by the Joint Ethical Committee of the University of Turku and the Turku University Central Hospital. After the nature of the procedures had been fully explained in written form, all the participants gave written consent that was approved by the Ethical Committee. The study was conducted in accordance with the ethical guidelines of the Declaration of Helsinki.

All participants were healthy, as confirmed by medical examination and interview, blood and urine screening, electrocardiogram, and magnetic resonance imaging examination. Regular smoking was an exclusion criterion because smoking influences the binding potential for [^{11}C]carfentanil. Structured

Table 1. Demographics of the Study Population (*N* = 39)

	Subjects With Secure Attachment (*n* =15)	Subjects With Insecure Attachment (*n* = 24)
Age, Years	37.0 ± 4.9	37.6 ± 4.8
Female	12 (80.0)	7 (29.2)
Educational Level in Adulthood (2001)		
Comprehensive school	0 (0.0)	1 (4.2)
High school or occupational school	8 (53.3)	14 (58.3)
Academic level	7 (46.7)	9 (37.5)
Parents' Educational Level in Childhood (1980)		
Comprehensive school (Grades 1–9)	4 (26.7)	6 (25.0)
High school or occupational school	9 (60.0)	9 (37.5)
Academic level (Bachelor's or Master's degree)	2 (13.3)	9 (37.5)
Stressful Life Events in Childhood (1980)[a]	1 (6.7)	3 (15.0)

Values are mean ± SD or *n* (%).
[a]Stressful life events included parental death, parental hospitalization, parental divorce, change of school, and home movement.

Clinical Interview for DSM-IV was used to exclude any current DSM-IV Axis I diagnosis. Depressive symptoms were also assessed using the Hamilton Depression Rating Scale (all subjects had scores <10). None of the subjects had current psychiatric medication. In order to increase the representativeness of the sample, previous mild/moderate depressive episodes or mild/moderate anxiety symptomatology (in 6 subjects) were not regarded as exclusion criteria. All the subjects were ethnic Finns. There was no difference in HA between subjects with secure versus insecure attachment (p = .14).

Attachment Style Measurement

Attachment style was determined by conducting the AAI (C. George, Ph.D., *et al.*, unpublished data, 1996) that was then coded with the DMM coding scheme [P. Crittenden, Ph.D., unpublished data, 1999; (4)]. The AAI exposes the subject to memories of threats to important attachments and is a procedure for assessing adults' strategies for identifying, preventing, and protecting the self from perceived dangers, particularly dangers tied to intimate relationships. It investigates how the subject is able to recall and narrate the events, persons, and feelings linked to the threat. The AAI is thus used as a tool to stimulate the attachment strategies, which can then be analyzed according to the DMM model. For more information, see the Supplement. The DMM has been widely used previously (41–43). The DMM coding has good construct validity (42) and has been validated in samples with various psychiatric disorders such as personality disorders, depression, and posttraumatic stress disorder (44–47).

In this study, AAI was conducted shortly after the PET session within the same day. Subjects were classified as having secure (n = 16), avoidant (n = 14), and ambivalent (n = 9) attachment types. Classifications were made by an experienced AAI interpreter (A.H.) with training qualifications on DMM and AAI. Owing to a limited sample size, our primary analysis was focused on the comparison between the securely versus insecurely (avoidantly or ambivalently) attached subjects, even though full three-category attachment style classification was used and corresponding three-class analyses were also run. The grouping of avoidant and ambivalent attachment styles of the DMM has been utilized in previous reports but is clearly not the ideal solution (42). An independent-samples t test showed that different attachment type groups did not differ significantly with regard to age. However, the χ^2 test showed that men were more likely to have insecure (avoidant or ambivalent) attachment and that women were more likely to have secure attachment ($p < .05$). There were no differences between securely versus insecurely attached subjects in age, parents' educational level, subjects' educational level in adulthood, or number of stressful life events in childhood.

PET Imaging

A brain-dedicated high-resolution PET scanner (ECAT HRRT; Siemens Medical Solutions, Erlangen, Germany) was used for PET imaging. Prior to emission scan, Cesium-137 point source transmission was used to obtain tissue attenuation maps by forward projection. These maps were then used for attenuation correction. Data were gathered in list mode and reconstructed into 1.22 × 1.22 × 1.22 mm^3 voxel size images with speed-optimized Ordinary Poisson OSEM in full 3-dimensional reconstruction (48). During the PET scans, the head of the subject was fixed using an individually molded thermoplastic mask. A T1-weighted magnetic resonance imaging scan with 1 × 1 × 1 mm^3 resolution voxel size was obtained from each subject using Philips Gyroscan Intera 1.5T CV Nova Dual magnetic resonance imaging scanner (Philips Healthcare, Best, the Netherlands) to exclude structural abnormalities and for anatomical reference.

All subjects underwent a PET scan with serotonin transporter tracer [^{11}C]MADAM followed by a PET scan with mu opioid receptor tracer [^{11}C]carfentanil during the same day using identical head positioning as described in Tuominen *et al.* (39) (Figure 1). Radiochemistry procedures of the tracers have been described in detail elsewhere (38,39). Tracers were injected as intravenous bolus injections and flushed with saline. The injected doses and masses were 484.5 ± 49.9 MBq and 0.59 ± 0.42 μg for [^{11}C]MADAM (n = 37) and 423.6 ± 73.9 MBq and 1.08 ± 0.84 μg for [^{11}C]carfentanil (n = 39), respectively. Radioactivity of [^{11}C]MADAM was measured for 75 minutes using 17 frames (3 × 1 min, 4 × 3 min, and 10 × 6 min) and radioactivity of [^{11}C]carfentanil for 69 minutes using 16 frames (3 × 1 min, 4 × 3 min, and 9 × 6 min).

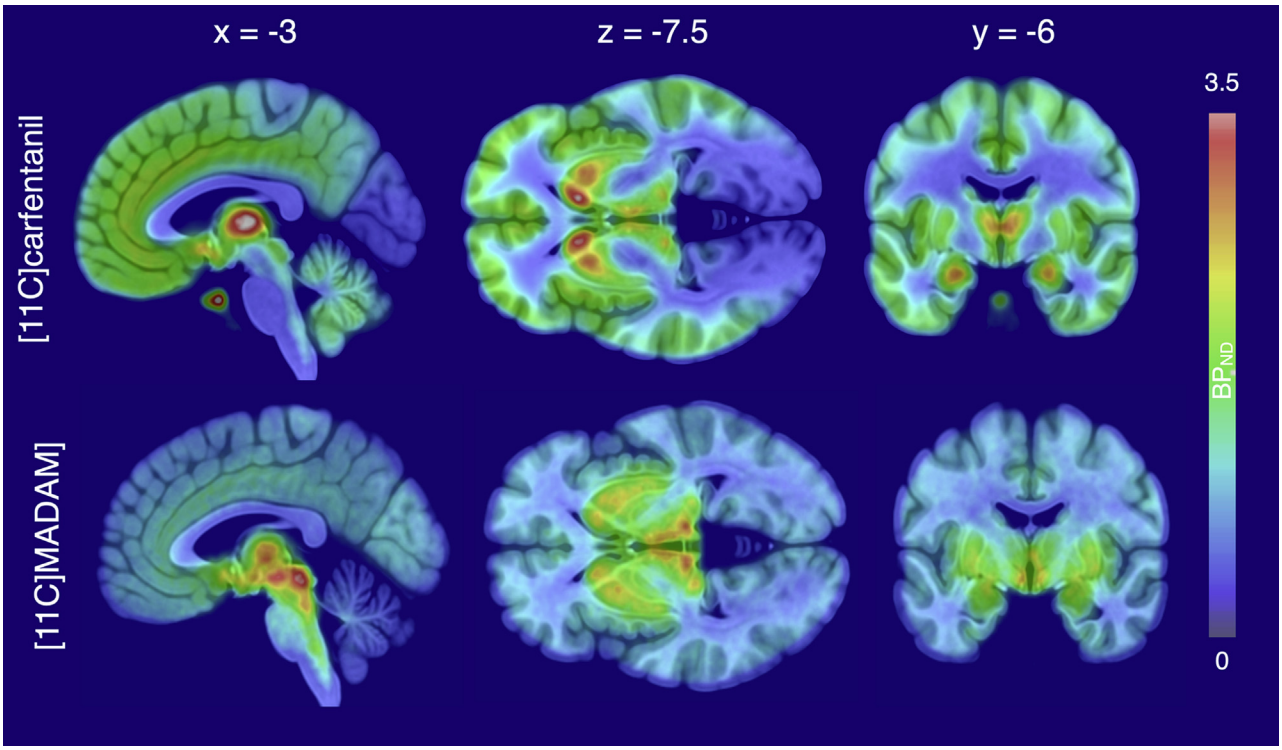

Figure 1. Mean binding potential maps for [^{11}C]carfentanil and [^{11}C]MADAM.

PET Image Processing

PET images were preprocessed using the automated PET data processing pipeline Magia (49) (https://github.com/tkkarjal/magia) running on MATLAB (The MathWorks, Inc., Natick, MA). PET data were first corrected for motion by realigning the frames of each scan. Radiotracer binding was quantified using nondisplaceable binding potential (BP_{ND}), which is the ratio of specific binding to nondisplaceable binding in the tissue (50). This outcome measure is not confounded by differences in peripheral distribution or radiotracer metabolism. The BP_{ND} is taken here as an estimate for number of target receptors/transporters available for tracer binding (receptor availability). Binding potential was calculated applying basis function method for each voxel using the simplified reference tissue model (51), with occipital cortex ([^{11}C]carfentanil) or cerebellar gray matter ([^{11}C]MADAM) serving as the reference regions. The parametric images were spatially normalized to Montreal Neurological Institute space via segmentation and normalization of T1-weighted anatomical images and were finally smoothed with an 8-mm full width at half maximum Gaussian kernel.

Statistical Analysis

The population-level full volume statistical analysis was done using SPM12. The normalized and smoothed BP_{ND} images were entered into general linear model, in which BP_{ND} was predicted with attachment style (using a three-class variable of attachment styles and also a two-class variable by collapsing subjects into securely vs. insecurely attached groups), separately for mu opioid receptor and serotonin transporter. The statistical threshold was set at $p < .025$, false discovery rate corrected at cluster level. In a complementary methodological approach, the data were analyzed by averaging BP_{ND}s within ROIs. Atlas-based ROIs were generated in the mu opioid receptor–rich regions in the brain (amygdala, hippocampus, ventral striatum, dorsal caudate, thalamus, insula, orbitofrontal cortex, anterior cingulate cortex, middle cingulate cortex, and posterior cingulate cortex) using the AAL (52) and Anatomy (53) toolboxes. Mean regional [^{11}C]carfentanil and [^{11}C]MADAM BP_{ND}s were extracted for each region. Data were analyzed with R statistical software (R Foundation for Statistical Computing, Vienna, Austria; https://cran.r-project.org) using analysis of variance. Because age may affect [^{11}C]carfentanil and [^{11}C]MADAM BP_{ND}, analyses were run separately with and without age as a covariate. In addition, because attachment was affected by sex in this sample, we ran additional analyses with sex as a covariate.

RESULTS

First, we compared the mu opioid receptor availability and serotonin transporter availability between securely and insecurely attached subjects in a voxelwise manner. This analysis revealed that mu opioid receptor availability was significantly higher in the securely attached subjects bilaterally in the amygdala, hippocampus, and thalamus, and also in the right lateral prefrontal cortex (Figure 2) (thresholded at $p < .025$, false discovery rate corrected). Three-way analysis of variance in SPM between all the attachment style groups yielded

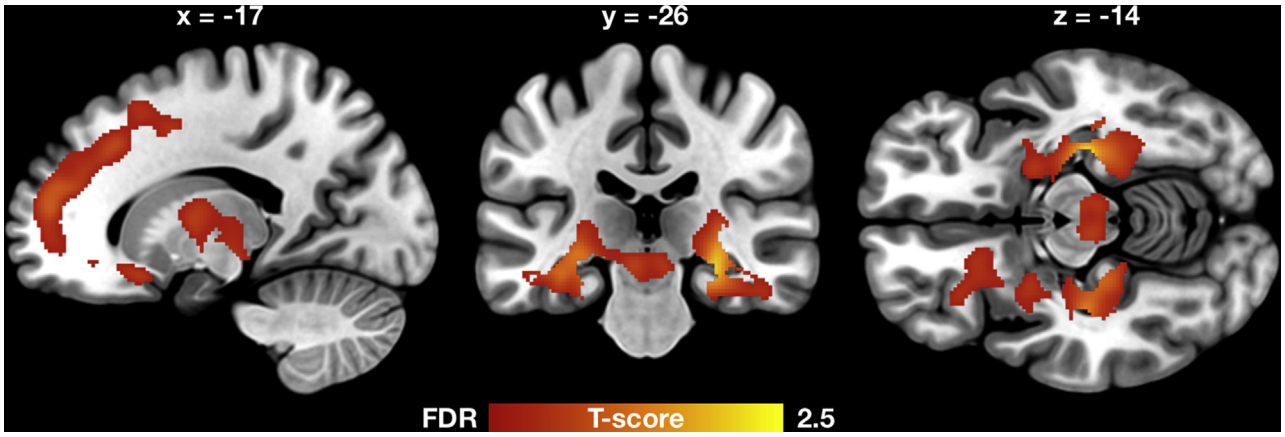

Figure 2. Brain regions in which the level of [^{11}C]carfentanil was higher in participants with secure vs. insecure (i.e., ambivalent or avoidant) attachment. The data are thresholded at $p < .025$, false discovery rate (FDR) corrected.

corroborating findings, revealing significant differences in the amygdala-hippocampal complex. No statistically significant effects were observed for serotonin transporter availability between subjects with different attachment styles.

Second, we investigated whether there are differences in mu opioid receptor availability and serotonin transporter availability in the ROIs that are previously found to associate with socio-emotional processing (i.e., amygdala, hippocampus, ventral striatum, dorsal caudate, thalamus, insula, orbitofrontal cortex, anterior cingulate cortex, middle cingulate cortex, and posterior cingulate cortex). The ROI analysis mainly confirmed the results of the full-volume analysis (Table 2 and Figure 3). Specifically, subjects with secure attachment had higher binding potential for [^{11}C]carfentanil in the hippocampus ($p = .001$), amygdala ($p = .010$), and thalamus ($p = .042$) but not in the other ROIs when compared with participants with insecure attachment. Further, we obtained no differences in [^{11}C]MADAM between securely and insecurely attached subjects in any of the ROIs. These findings were obtained without covariates. All the associations remained significant after adjusting for age: subjects with secure attachment had higher binding potential for [^{11}C]carfentanil in the hippocampus ($p = .001$), amygdala ($p = .012$), and thalamus ($p = .046$) but not in the other ROIs when compared with participants with insecure attachment.

In addition, an exploratory analysis with both age and sex as covariates confirmed a significant secure attachment–opiate receptor association in the hippocampus but not in the other ROIs (Figure S1). Owing to the comparatively small sample sizes and categorical outcome variable, we did not run the analyses separately among male and female subjects.

As a complementary analysis, we also investigated the differences in binding potentials for [^{11}C]carfentanil and [^{11}C]MADAM in the ROIs between participants with a three-class variable of attachment type (secure, avoidant, or ambivalent). The variance analyses showed that there were group differences in [^{11}C]carfentanil BP_{ND} in the hippocampus and amygdala but not in the other ROIs. Post hoc tests (Tukey's tests) showed that participants with ambivalent attachment had lower [^{11}C]carfentanil BP_{ND} in the hippocampus ($p < .001$) and amygdala ($p = .004$) when compared with participants with secure attachment. Post hoc tests showed no other between-group differences in [^{11}C]carfentanil BP_{ND} (i.e., no differences between avoidant vs. secure attachment or between avoidant vs. ambivalent attachment).

DISCUSSION

Our findings suggest that secure attachment is associated with higher mu opioid receptor availability in the hippocampus, amygdala, thalamus, and prefrontal cortex, whereas the attachment style is not associated with serotonin transporter availability in analyses using age as a covariate. The association of secure attachment with higher mu opioid receptor availability in the hippocampus remained significant also after adding sex as a covariate in the model, as sex unexpectedly associated with attachment style. Although literature on sex differences in mu opioid receptor availability is not consistent [see (54)], we cannot fully exclude the effect of sex or hormonal factors on the association between attachment and mu opioid receptor availability in the hippocampus/amygdala-thalamus-prefrontal cortex circuitry. The attachment type was evaluated with a structured objective psychiatric interview evaluated by a trained rater [P. Crittenden, Ph.D., unpublished data, 1999; (4)]. This method also captures less consciously accessible representations about close relationships with others and is a more comprehensive way of describing adult attachment styles that is not synonymous with early childhood attachment. Rather, childhood attachment patterns continue to function as a working model for relationships in adulthood. The presently observed results are in line with prior PET studies indicating a crucial role of the mu opioid system for attachment and sociability in humans (25,26,55-57) and suggest that there are similar parallels in the opioid basis of the attachment system across primates and other mammals (1,19).

High mu opioid receptor availability measured with binding potential for [^{11}C]carfentanil can be interpreted as increased density of the mu opioid receptor agonist sites available for tracer binding. However, there is evidence that binding

Table 2. The Results of Variance Analyses, When Investigating the Differences Between Participants With Secure and Insecure Attachment (Avoidant or Ambivalent Attachment) in Binding Potentials for [^{11}C]Carfentanil and [^{11}C]MADAM in the Regions of Interest

	Analysis Without Covariates		Analysis While Adjusting for Age	
	F	*p*	*F*	*p*
[^{11}C]Carfentanil (*n* = 39)				
Anterior cingulate cortex	1.10	.300	1.27	.267
Medial cingulate cortex	0.60	.445	0.64	.428
Orbitofrontal cortex	0.20	.658	0.32	.574
Posterior cingulate cortex	0.49	.489	0.60	.444
Amygdala	7.41	.010[a]	7.04	.012[a]
Hippocampus	14.59	.001[a]	14.48	.001[a]
Dorsal caudate	0.59	.446	0.68	.416
Insula	0.68	.414	0.80	.378
Putamen	2.07	.158	2.45	.127
Thalamus	4.44	.042[a]	4.27	.046[a]
Ventral striatum	1.39	.246	1.35	.253
[^{11}C]MADAM (*n* = 37)				
Anterior cingulate cortex	0.03	.863	0.03	.875
Medial cingulate cortex	0.03	.874	0.03	.865
Orbitofrontal cortex	0.01	.931	0.10	.756
Posterior cingulate cortex	0.23	.633	0.08	.775
Amygdala	1.75	.195	1.48	.232
Hippocampus	2.59	.116	2.24	.144
Dorsal caudate	0.09	.770	0.22	.645
Insula	0.00	.962	0.12	.730
Putamen	0.89	.352	0.58	.452
Thalamus	0.00	.954	0.22	.646
Ventral striatum	0.05	.422	0.00	.946

[a]Statistically significant difference.

potential for [^{11}C]carfentanil can be modulated by synaptic concentrations of endogenous opioids (such as β-endorphin or encephalins) via direct binding competition or potentially via long-term changes in endogenous opioid concentrations causing compensatory changes in receptor binding dynamics (such as receptor internalization) (58-60). Thus, the link between higher binding potential for [^{11}C]carfentanil and secure attachment could be explained by either increased receptor availability or altered endogenous opioid release, or a combination of both. Specific pharmacological challenge studies using the [^{11}C]carfentanil binding paradigm would be needed to distinguish between these mechanisms.

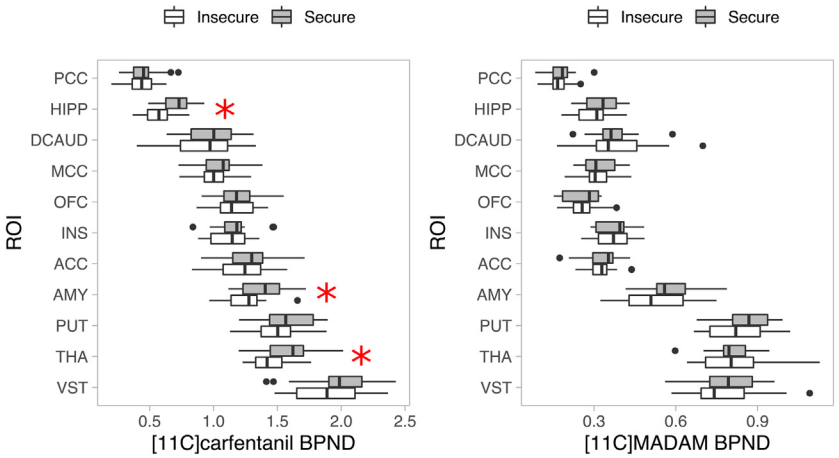

Figure 3. Boxplots of distributions of regional binding potentials for [^{11}C]carfentanil (left) and [^{11}C]MADAM (right) for the securely and insecurely (avoidantly or ambivalently) attached subjects. Dots show outliers (>1.5 times the interquartile range). Significant between-group differences are marked with asterisks. ACC, anterior cingulate cortex; AMY, amygdala; BPND, nondisplaceable binding potential; DCAUD, dorsal caudate; HIPP, hippocampus; INS, insula; MCC, medial cingulate cortex; OFC, orbitofrontal cortex; PCC, posterior cingulate cortex; PUT, putamen; ROI, region of interest; THA, thalamus; VST, ventral striatum.

The Opioid System and Neurocircuits Related to Human Attachment

In this study, the participants were not exposed to any attachment-related stimuli during PET imaging. Hence, this study investigated the stable differences in the endogenous opioid system. Our results together with other results (26) indicate that secure attachment is related to higher mu opioid receptor availability. Previous studies, in turn, indicate that both exposure to social rejection and acceptance are related to increased endogenous opioid release (i.e., lower mu opioid receptor availability) in some brain regions (55,56). Interestingly, increased endogenous opioid release correlates with decreased negative affect during rejection and with greater social motivation during acceptance (55,56). Hence, increased endogenous opioid release appears to make an individual more sensitive to changes (whether positive or negative) in social interaction. Future studies could investigate whether secure versus insecure attachment is related to different reactivity of the endogenous opioid system in response to changes in social situations (e.g., acceptance or rejection).

Most prominent attachment style–dependent variations in mu opioid receptor availability were observed in the amygdala and hippocampus, regions that have high mu opioid receptor density and that also contribute centrally to human socioemotional functions (61,62). These results are consistent with those observed in previous molecular imaging studies using questionnaire-based measures of adult romantic attachment, suggesting concordance between the brain basis for romantic and other types of attachment (26). Our findings are also consistent with genetic studies on the linkage between the mu opioid receptor and attachment behavior in animals. Mu opioid receptor knockout mice also express deficient maternal attachment (24), and conversely, monkey infants with gain-of-function *OPRM1 77G* allele display enhanced maternal attachment (23).

The present results suggest that insecure attachment is related to changes in opioid transmission in wide brain networks responsible for socioemotional processing, ranging from primary emotional appraisal to more sophisticated sociocognitive processing. Previously, it has been shown that the activity level and gray matter volume of the amygdala and hippocampus are related to social appraisal (63), processing attachment-related social stimuli (64), and experiencing separation anxiety (65). Temporal regions, in turn, are involved in face recognition and theory-of-mind processing (66). Further, frontal regions are related to social control and emotional decision making (67). Functional imaging studies have also found that individuals with ambivalent attachment respond to thoughts of loss with increased activity of emotion-related brain areas (e.g., anterior temporal lobe) and reduced activity of the frontal regions responsible for emotion regulation (68). Moreover, insecure attachment style is related to altered activity patterns in the amygdala and striatum in response to facial expressions of emotions, indicating neurobiological changes in sensitivity to social reward and social punishment (63). Thus, attachment styles might be related to differences in the evaluation of safety versus threat in social interactions and the fact that this process takes place in a brain network including regions such as the amygdala, hippocampus, and medial prefrontal cortex (69). It is possible that the opioid system might also contribute to the management of both actual and anticipated safety- and threat-related episodes in social relationships. This is because the opioid system acts as a buffer against psychological stressors (60,70) and because *OPRM1* is found to influence the self-experienced security during a romantic partner's quarrelsome behavior (71). This view is supported by pharmacological studies in primates, which have found that opioid antagonist administration increases social grooming in monkeys (72,73), whereas opioid agonists alleviate separation distress in pups (18). Finally, pharmacological studies in humans have shown that naltrexone alters the response of the ventral striatum when exposed to images of close others and also reduces feelings of social connection to the close others (74,75).

The brain opioid theory of social attachment proposes that feelings of interpersonal warmth and social euphoria are related to endogenous opioid release and, conversely, that social isolation results in a lower level of endogenous opioids (19). Our data show that secure attachment is related to a higher mu opioid receptor availability when compared with avoidant or ambivalent attachment. In numerous psychiatric disorders, the core symptomatology refers to disturbances in social interaction, especially in threatening or distressing situations. For example, patients with major depressive disorder exhibit altered endogenous opioid release in response to others' rejection and acceptance (44). Typically, the disturbances in social interaction derive from early experiences with attachment figures. For example, major depressive disorder typically includes experiencing shame and worthlessness in relation to others, anxiety disorders contain hostile interpretation biases of others' behavior, paranoid disorder refers to beliefs about others' vicious intentions toward the self, and schizophrenia commonly includes a strong tendency to social isolation. Against this background, our findings may provide new neurobiological insights as to why individuals with psychopathologies may experience social contacts as less rewarding, or even threatening and hostile, and why their sociocognitive processing may be more biased toward negative affect.

The opioid system, however, works in tandem with numerous other neurotransmitter systems when governing social behavior. It has been suggested that opioids help to maintain secure relationships in adulthood by making social contacts more rewarding, whereas oxytocin and vasopressin may increase parental nurturing and facilitate the formation of secure parent–child relationship (14,15). It has been found that the opioid system is involved in the regulation of oxytocin secretion, so that opioid release has an inhibitory influence on oxytocin release, possibly inhibiting nurturing behavior (76). Hence, it is possible that the opioid system modulates parent–child attachment, yet this hypothesis currently lacks direct empirical support.

In contrast to the opioid system, the associations between attachment style and the serotonin transporter in this sample of healthy subjects were not statistically significant. Converging lines of evidence have suggested that the

serotonin system could be related to attachment styles. For instance, insecure attachment style may convey the risk for depression (8), which suggests that that similar serotonergic abnormalities could be seen in depression and insecure attachment. This is true especially because other known risk factors for depression, such as personality trait neuroticism, have been associated with altered serotonin transporter density (77). Although there is high variability between individual studies (78), a meta-analysis suggested lower serotonin transporter density in major depression (79). Therefore, we hypothesized that we would find lower serotonin system function in people who have insecure attachment, but we did not find evidence for this hypothesis. It is feasible that neuroticism is mainly an indicator of a higher genetic predisposition to depression, whereas attachment style may be influenced more by the environment. Finally, the serotonin transporter is only one component in the serotonin system, and other components of the serotonin system such as serotonin receptor subtype expression may explain variability in the attachment style.

Limitations

First, although the sample size in this study (n = 39) was relatively large for a PET investigation, the study includes a limited amount of statistical power and increased risk for false negative or false positive findings. The serotonin transporter availability (the binding potential for [^{11}C]MADAM) in the secure attachment group was 12% higher in the hippocampus and 8% higher in the amygdala than in the insecure attachment group. These associations, however, were not statistically significant, and it was not possible to completely rule out a false negative finding. Second, owing to the small group sizes, we combined the participants with avoidant or ambivalent attachment into one study group. Optimally, avoidant and ambivalent attachment styles should be investigated separately because they may be differently related to some aspects of neurotransmitter systems. Third, owing to our small sample size, it was not reasonable to run analyses separately among male and female subjects. Hence, we cannot fully exclude the possibility that sex differences or hormonal effects may partly explain the association between attachment and mu opioid receptor availability. Fourth, there were 6 participants with past but not current affective psychiatric disorders in our sample. However, because the serotonin transporter availability does not differ between patients who have recovered from major depressive disorder and individuals who have never been depressed (79), it is unlikely that including these participants would explain the lack of associations between the serotonin transporter and the attachment style.

Conclusions

This study showed that the secure attachment is related to higher mu opioid receptor availability in the amygdala and hippocampus when compared with avoidant or ambivalent attachment. However, there was no link between attachment style and serotonin transporter availability. Our findings provide new insights into the neurobiological mechanisms between disturbances in attachment and related psychiatric morbidity.

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JH, LK-J, and OR designed the study, recruited the subjects, and wrote the manuscript. LT recruited the study subjects, collected the data, analyzed the data, and wrote the manuscript. LN, AS, and R-LA analyzed the data and wrote the manuscript. OT contributed to the clinical evaluations and wrote the manuscript. MT, AH, and HL wrote the manuscript.

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