Endogenous μ-opioid receptor system modulates sex drive in human males

Lauri Nummenmaa[1,2], Patrick Jern[3], Tuulia Malén[1], Tatu Kantonen[1,4], Laura Pekkarinen[1], Lasse Lukkarinen[1], Lihua Sun[1], Pirjo Nuutila[1], Vesa Putkinen[1,5]

[1]Turku Pet Centre and Turku University Hospital, Turku, Finland
[2]Department of Psychology, University of Turku, Finland
[3]Department of Psychology, Åbo Akademi University, Finland
[4]Departmen of Clinical Neurosciences, Turku University Hospital, Finland

Address correspondence to
Lauri Nummenmaa
Turku PET Centre and
Turku University Hospital
FI-20520 Turku, Finland
Tel: +358 50 574 7933
Email: latanu@utu.fi

Abstract

The endogenous mu-opioid receptor (MOR) system modulates a multitude of social and reward-related functions, and exogenous opiates also influence sex drive in humans and animals. However, there is no *in vivo* evidence for the contribution of MOR system on human sex drive. Here we measured healthy male subjects' (n=52) brain's MOR availability with positron emission tomography (PET) using an agonist radioligand, [^{11}C]carfentanil, that has high affinity for MORs. Sex drive was measured using self-reports of engaging in sexual behaviour (sex with partner and masturbating). Bayesian hierarchical regression analysis revealed that sex drive was positively associated with MOR availability in cortical and subcortical areas, notably in caudate nucleus, hippocampus, and cingulate cortices. These results were replicated in full-volume GLM analysis. Complementary voxel-based morphometry analysis (n=108) provided limited evidence for association between sex drive and cortical density in the midcingulate cortex. We conclude that MOR system modulates individual differences in sex drive in human males.

Keywords: Opioids, sex drive, neurotransmission, PET, VBM
Word count: 5680

Introduction

Endogenous opioids modulate a range of behaviors ranging from analgesia to socioemotional processes and pleasure (Nummenmaa & Tuominen, 2018). Although dopamine is the principal neurotransmitter responsible for reward processing, opioids produce reward independent of dopamine (Hnasko et al., 2005). In animals, μ opioid receptor (MOR) stimulation of the nucleus accumbens increases both incentive motivation and consummatory rewards (Berridge et al., 2010; DiFeliceantonio & Berridge, 2016; Peciña & Berridge, 2013), and injection of μ-opioids into the mesolimbic reward system induces reward (Bozarth & Wise, 1981). Human sex drive varies both between sexes as well as between and within individuals (Baumeister et al., 2001; Twenge et al., 2017), and multiple lines of evidence suggest that the MOR system could be involved in maintenance of human sex drive (Pfaus & Gorzalka, 1987).

Opioid receptors (OR) are widely expressed in the complex neurocircuitry that underlies sexual behavior (Le Merrer et al., 2009). In a fashion similar to that of having sex, opioid agonists may increase pleasure and liking, and the euphoric sensations following opioid administration in drug addicts has sometimes been called "pharmacogenic orgasm" (Chessick, 1960). The predominant action of μ-opioids in the nervous system is inhibitory, and opioid system is activated during sexual inhibition thus blunting the ability of excitatory systems to be activated (Pfaus, 2009). Administration of opioid agonist heroin results in acute suppression of lutenizing hormone, and subsequently lowered plasma testosterone levels (Mirin et al., 1980). Animal studies suggest that hypothalamic administration of OR agonists and antagonists inhibit and excite sexual behavior in mice, whereas striatal administration yields less consistent outcomes (see review in Le Merrer et al., 2009).

In humans, both short- and long-term use of μ opioid receptor agonists decreases sexual desire and pleasure (Argiolas & Melis, 2013; Birke et al., 2019). Over 50% of patients on methadone maintenance treatment suffer from sexual dysfunction (SD), most commonly due to decreased desire and libido (Yee et al., 2014). Comparable rates of SDs are reported for heroin and buprenorphine maintenance, and prevalence of SDs exceeds 90% for those on naltrexone maintenance (Grover et al., 2014). Finally, there is also some evidence on the role of long-term opioid therapy on chronic pain being associated with SD (Chou et al., 2015). This may be due to opioids' effects on testosterone and oxytocin levels, or more speculatively, saturation of the brain's reward centres (Argiolas & Melis, 2013). Animal studies have confirmed the inhibitory role of endogenous opioids on male sex drive and showed that administration of opioid antagonists shortens ejaculation latency while increasing copulation rate (Rodríguez-Manzo & Fernández-Guasti, 1995).

The current study

Taken together, there is ample evidence suggesting that ORs may modulate sexual behaviour in humans, but direct in vivo evidence regarding this question is lacking. Here, using a cross-sectional design, we hypothesized that human sex drive is associated with endogenous MOR availability. We used positron emission tomography (PET) with radioligand [^{11}C]carfentanil that has high affinity for MOR, and measured MOR availability in 52 healthy males. Because there is evidence on the relationship between sex drive and cerebral grey matter density in certain patient populations (Bloemers et al., 2014; Schmidt et al., 2017; Takeuchi et al., 2015) but limited data on healthy subjects (Takeuchi et al., 2015), we also addressed this issue as a secondary research question. To that end, we tested whether sex drive links with regionally specific alterations in cortical density using the voxel-based morphometry (VBM) approach of T1-weighted magnetic resonance imaging scans in a partially overlapping sample of 108 males. Sex drive was determined by self-reports. We show that frequency of engaging in sexual behavior (both masturbating and partnered sex) is positively associated with MOR availability in striatum,

cingulum, and hippocampus, while there was only limited evidence for sex-drive dependent alterations in cortical density.

Materials and Methods

Subjects

The study protocol was approved by the Turku University Hospital Clinical Research Services Board, and the study was conducted in accordance with the declaration of Helsinki. The PET sample consisted of 52 healthy males (**Table 1**) studied with high-affinity agonist radioligand [^{11}C]carfentanil (Frost et al., 1985), retrieved from the AIVO (http://aivo.utu.fi) database of *in vivo* PET images hosted at the Turku PET Centre. All subjects provided written informed consent. Brain imaging data were acquired using a GE Healthcare Discovery 690 PET/CT scanner. All PET subjects and an additional sample of 56 male subjects (a total of 108 males) were scanned with Phillips Ingenuity TF PET/MR 3-T whole-body scanner using T1-weighted sequence (TR 9.8 ms, TE 4.6 ms, f lip angle 7◦, 250 mm FOV, 256 × 256 reconstruction matrix). Again, all subjects gave written informed consent and completed the questionnaires as a part of the corresponding experimental protocols.

Sex drive was measured with self-reported frequency of engaging in masturbation, sexual fantasies and various sexual behaviours (kissing and caressing, oral, anal, and vaginal sex) with partner (Derogatis, 1978). Each item was rated on a nine-step scale ranging from "not at all" to "more than once per day" and averaged to yield total sex drive score. To rule out potential effects of anxiety and depression on MOR and GM density (Nummenmaa et al., 2020) all subjects also completed the Beck Depression Inventory II (BDI-II; (Beck et al., 1988) and the trait anxiety scale from the state-trait anxiety inventory (STAI-X; Spielberger et al., 1970). Power analysis on prior molecular imaging studies on personality and [^{11}C]carfentanil binding (Karjalainen et al., 2016; Nummenmaa et al., 2020; Nummenmaa et al., 2015; Tuominen et al., 2012) suggested that an expected effect size of r=0.45, a sample size of 45 subjects would be sufficient for establishing the predicted effects at power of 0.95.

Table 1. *Subject characteristics (means and standard deviations).*

	PET and MRI sample (n = 52)	MRI only sample (n = 56)
Age	25.7 (0.71)	30.1(8.66)
Sex drive	4.01 (1.13)	3.60(1.05)
BDI-II score	3.73 (4.37)	8.11(7.22)
STAI-X score	33.57 (7.86)	41.34(9.66)

PET and MR image preprocessing

PET images were preprocessed using the automated PET data processing pipeline Magia (Kantonen et al., 2020; Karjalainen et al., 2020) (https://github.com/tkkarjal/magia) running on MATLAB (The MathWorks, Inc., Natick, Massachusetts, United States). Radiotracer binding was quantified using nondisplaceable binding potential (BP_{ND}), which is the ratio of specific binding to non-displaceable binding in the tissue (Innis et al., 2007). This outcome measure is not confounded by differences in peripheral distribution or radiotracer metabolism. BP_{ND} is traditionally interpreted by target molecule density (B_{max}), even though [^{11}C]carfentanil is also sensitive to endogenous neurotransmitter activation (Zubieta et al., 2001). Accordingly, the BP_{ND} for the tracer should be interpreted as density of the receptors unoccupied by endogenous ligands (i.e., receptor availability). Binding potential was calculated by applying basis function method (Gunn et al., 1997) for each voxel using the simplified reference tissue model (Lammertsma & Hume, 1996), with occipital cortex serving as the reference region (Frost et al.,

1989). The parametric images were spatially normalized to MNI-space via segmentation and normalization of T1-weighted anatomical images, and finally smoothed with an 8-mm FWHM Gaussian kernel.

To assess the link between cerebral density and sex drive, we performed a complementary voxel-based morphometry (VBM) analysis of the T1 images. VBM was done with SPM12 (https://www.fil.ion.ucl.ac.uk/spm/software/spm12/), which enables automated spatial normalization, tissue classification and radio-frequency bias correction to be combined with the segmentation step. Cut-off of spatial normalization was 25 mm and medium affine regularization 0.01 was used. Following normalization and segmentation into GM and WM, a modulation step was incorporated to take into account volume changes caused by spatial normalization and to correct for the differences in total brain size across subjects. Finally, the segmented, normalized, and modulated GM images were smoothed using 8-mm FWHM Gaussian kernel.

Data analysis

Regional effects were estimated using Bayesian hierarchical modeling using the R package BRMS (Bürkner, 2017), which uses the efficient Markov chain Monte Carlo sampling tools of RStan (https://mc-stan.org/users/interfaces/rstan). Atlas-based ROIs were generated in the MOR-rich regions in the brain (amygdala, hippocampus, ventral striatum, dorsal caudate, thalamus, insula, orbitofrontal cortex (OFC), anterior cingulate cortex (ACC), middle cingulate cortex (MCC), and posterior cingulate cortex (PCC) using AAL (Tzourio-Mazoyer et al., 2002) and Anatomy (Eickhoff et al., 2005) toolboxes. The ROI data were analysed with R statistical software (https://cran.r-project.org). Mean regional [^{11}C]carfentanil BP_{ND} and GM densities from VBM were extracted for each region.

We used weakly informative priors: For intercepts, we used the default of BRMS (i.e., Student's t-distribution with scale 3 and 10 degrees of freedom). For predictors, a Gaussian distribution with standard deviation of 1 was used to provide weak regularization. The BRMS default prior half Student's t-distribution with 3 degrees of freedom was used for standard deviations of group-level effects; BRMS automatically selects the scale parameter to improve convergence and sampling efficiency. The BRMS default prior LKJ(1) was used for correlations of group-level random effects. The ROI-level models were estimated using five chains, each of which had 1000 warmup samples and 3000 post-warmup samples, thus totaling 15000 post-warmup samples. The sampling parameters were slightly modified to facilitate convergence (*adapt_delta* = 0.99 *max_treedepth* = 20). The sampling produced no divergent iterations and the Rhats were all 1.0, suggesting that the chains converged successfully. Before model estimation, predictors were standardized to have zero mean and unit variance, thus making the regression coefficients comparable across the predictors. Binding potentials were log-transformed because posterior predictive checking (Gabry et al., 2019; Gelman et al., 2013) indicated that log-transformation significantly improves model fit. The log-transformation essentially switches the model from additive to multiplicative; it also helps in model fitting because the assumption of linear additivity works poorly when the dependent variable is restricted to positive values (Gelman & Hill, 2006).

Complementary full volume statistical analysis was performed using SPM12. The normalized and smoothed BP_{ND} images and GM segments were entered into separate general linear models, where they were predicted with sex drive. Age was entered into the models as nuisance covariate because aging influences both MOR availability and sex drive (Kantonen et al., 2020; Twenge et al., 2017). Statistical threshold was set at $p < 0.05$, FDR-corrected at cluster level. In a complementary methodological approach, the data were analyzed by averaging voxelwise BP_{ND} / GM density within the ROIs.

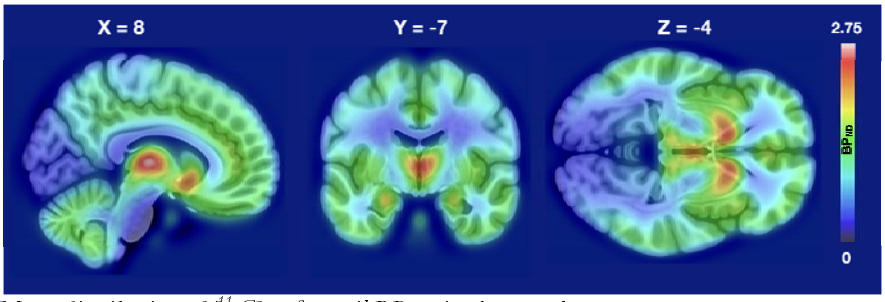

Figure 1. *Mean distribution of [^{11}C]carfentanil BP_{ND} in the sample.*

Results

Sex drive was independent of the depression and anxiety scorers as well as age (rs < 0.2, ps > 0.05); depression and anxiety scores however correlated significantly as expected (r = 0.62, p < 0.001). Mean distribution of MORs is shown in **Figure 1**. Regional Bayesian analysis revealed that sex drive was in general positively associated with MOR availability (**Figure 2**). The 95% posterior intervals did not overlap zero in middle and posterior cingulate cortices, hippocampus and dorsal caudate nucleus. The 80% posterior intervals did not overlap with zero in any of the tested regions. For VBM, there was only limited evidence for sex drive dependent differences in cortical density. All the 80% posterior intervals overlapped with zero and only in MCC was there was a weak association between sex drive dependent GM density increase.

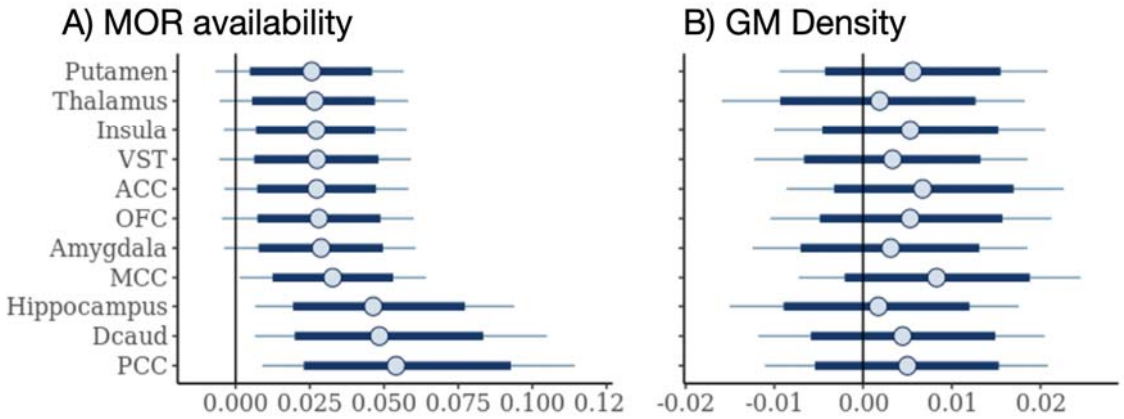

Figure 2. Posterior distributions of the regression coefficients for sex drive dependent variability in MOR availability (A) and cortical density (B). *Thick lines show 80% and thin lines 95% posterior intervals. ACC = anterior cingulate cortex, Dcaud = Dorsal caudate nucleus, MCC = middle cingulate cortex, PFC = orbitofrontal cortex, PCC = posterior cingulate cortex, VST = ventral striatum.*

The complementary full-volume SPM analysis yielded corroborating findings (**Figure 3**). Significant positive associations between sex drive and MOR availability were found in amygdala, hippocampus, cingulate cortex and ventral and dorsal striatum. Additional effects were observed in thalamus, medial and lateral frontal cortex as well as primary somatosensory and motor cortices. Again, the effects were consistently positive and when a stricter statistical threshold (p < .01, FDR corrected) was used, activations remained significant in the cingulate and left lateral frontal cortices.

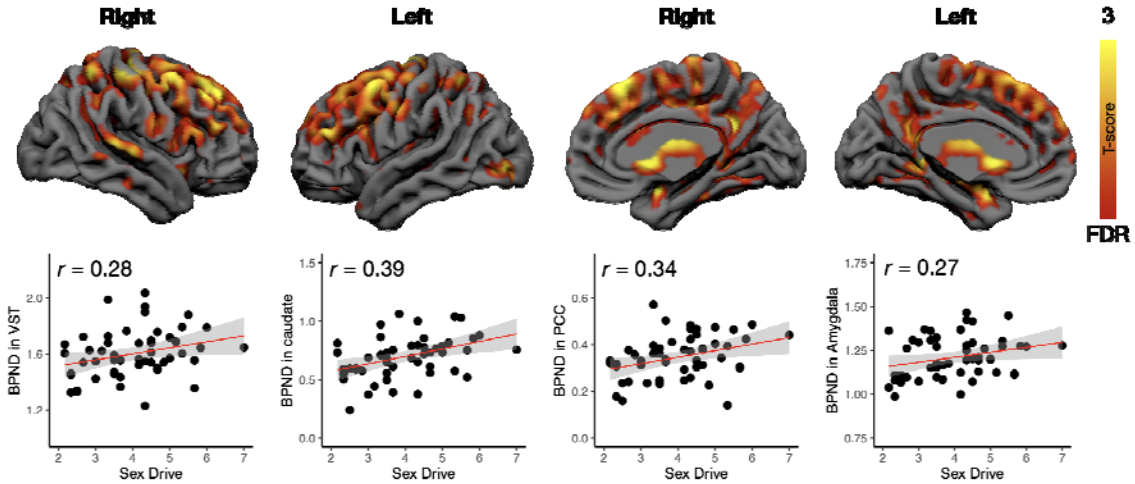

Figure 3. Brain regions where MOR availability was associated with sex drive. The data were thresholded at $p < .05$, FDR corrected. Scatterplots show least-squares-regression lines with 95% confidence intervals in representative regions. PCC = posterior cingulate cortex, VST = ventral striatum.

Finally, we performed full-volume GLM analysis for the GM segments. We found that sex drive was associated with increased cortical density in the anterior, middle and posterior cingulate cortex, supplementary motor cortex and primary somatosensory cortex (SI). No effects were found in extrastriatal areas (**Figure 4**). The effects in the cingulate cortex overlapped with those where sex drive dependent MOR upregulation was observed (see **Figure 3**). When stricter statistical thresholding ($p < .01$, FDR corrected) was applied, no effects remained significant.

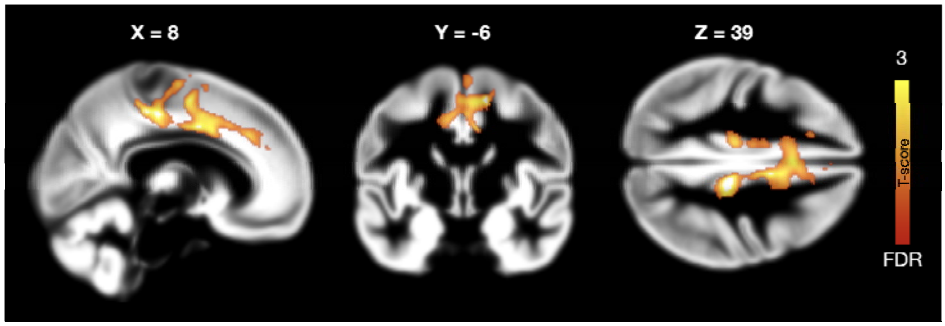

Figure 4. Brain regions where cortical density was associated with sex drive. *The data are thresholded at $p < 0.05$, FDR corrected.*

Discussion

Our main finding was that male sex drive is positively associated with central opioidergic tone. The more frequently the subjects reported in engaging in sexual activities, the more μ-opioid receptors they had in the striatum, thalamus, amygdala and middle cingulate cortex. In the cingulate cortex, this effect was paralleled by increased grey matter tissue density. Our study thus demonstrates, for the first time, that individual differences in male sex drive are associated with availability of μ-opioid receptors, suggesting that central opioidergic mechanisms modulate not only affiliative bonding but also sexual behavior in the human male.

Opioidergic modulation of sex drive

Sex drive had a consistent positive association with MOR availability in hippocampus, dorsal caudate and midcingulate cortices. Although the 95% posterior intervals overlapped with zero in

the other tested ROI:s, the effects were systematically positive. Complementary whole-brain analysis supported sex drive dependent MOR expression in amygdala, thalamus, frontal cortex as well as primary somatosensory and motor cortices. This general widespread effect likely reflects the high autocorrelation in MOR expression as quantified with PET (Tuominen et al., 2014). The regions in which MOR availability was associated with sex drive are known to modulate variety of socioemotional functions (Amodio & Frith, 2006; Saarimäki et al., 2016), and they also contribute to modulating sexual behavior. While ventral and dorsal striatum modulate sexual motivation (Calabrò et al., 2019), the cingulate cortex is particularly associated with modulation of sexual drive, and meta-analyses show that anterior and middle cingulate cortices are consistently activated during sexual stimulation in humans (see review in Stoléru et al., 2012). Moreover, direct stimulation of the ACC elicits masturbation-like genital touching in the macaque (Robinson & Mishkin, 1968). Finally, the whole-brain analysis revealed sex drive dependent variability of MOR in the somatosensory cortices. Touching is a powerful way of triggering sexual arousal (Steers, 2000), and individual differences in the brevity of the sexually receptive fields of the body ("erogenous zones") is associated with sexual drive and sexual interest (Nummenmaa et al., 2016a). It is thus possible that such individual differences in the capacity for tactile sexual stimulation are dependent on MOR availability.

To our knowledge, this is the first *in vivo* imaging study of sexual function and MOR in humans, and the present findings suggest that variation in focal MOR availability may provide an important neurochemical mechanism explaining individual differences in sex drive. Our results emphasise that this is a quantitative relationship with receptor density. It is nevertheless remarkable that MOR availability was positively rather than negatively associated with sex drive. This is a surprising observation given the general inhibitory role of OR agonist administration on sexual behaviour (see review in Le Merrer et al., 2009; Pfaus, 2009). However, comparable pattern (i.e. downregulation by agonists and positive trait correlation with MOR availability) has also been established in the closely related phenomena of romantic and affiliative bonding, which are also modulated by MORs. Pharmacological studies in non-human primates have established that opioid antagonists promote social bonding behaviour in monkeys (Fabre-Nys et al., 1982; Graves et al., 2002; Keverne et al., 1989); conversely opioid agonists alleviate separation distress in puppies (Panksepp et al., 1978). Similarly as for sex drive, exogenous opioid use is associated with lower affiliative social motivation in humans (Ross et al., 2005; Schindler et al., 2009). Paralleling the pharmacological and clinical studies, molecular imaging experiments have consistently shown that MOR expression is consistently and positively associated with secure romantic and affiliative bonding (Manninen et al., 2017; Nummenmaa et al., 2015; Nummenmaa et al., 2016b; Turtonen et al., 2021). It has also been established that the more OR individuals have in the striatum, the higher pain threshold they have (Hagelberg et al., 2012). In similar vein, it is possible that individuals with high MOR availability are more tolerant to the MOR agonist driven sexual inhibition. Alternatively, it is possible that the individuals with high MOR levels simply derive more hedonic enjoyment from sexual behaviours, potentiating sex drive. Accordingly, PET imaging studies have established that MOR availability is associated with behavioural activation system tone, which in turn is linked with appetitive motivation in general (Karjalainen et al., 2016). Finally, it must be noted that both alcohol and cocaine dependence are associated with increased rather than decreased MOR availability, possibly due to reduction in endogenous opioids or upregulation of MORs (Gorelick et al., 2005; Weerts et al., 2011). It is thus possible that frequent sexual contact might similarly upregulated MOR or downregulate endogenous opioids, thus explaining the present findings.

Sex drive and cortical density

The complementary voxel-based morphometric analysis revealed that grey matter density across the cingulate, primary somatosensory and supplementary motor cortex was negatively associated

with sex drive. Although 80% posterior intervals overlapped with zero in the primary regional analysis, the overall effect of sex drive on GM density was consistently positive. The sex drive dependent effects in MOR availability and GM density overlapped in the cingulate cortex. This possibly reflects the fact that GM density estimates derived from VBM are influenced by the voxel-wise neuroreceptor densities (Manninen et al., 2021), thus the present VBM and PET data in the cingulum provide corroborative evidence on the sex drive dependent alterations in MOR expression. There is currently limited evidence on the cortical density changes associated with sexual function in healthy subjects. In one study healthy subjects' sexual permissiveness (i.e., how acceptable people consider sexual activities in general) is negatively associated with grey matter density in amygdala in a mixed-sex sample (Takeuchi et al., 2015). Patient studies have found increased amygdala density in mixed-sex sample of subjects with compulsive sexual behavior (Schmidt et al., 2017), whereas women with hypoactive sexual desire disorder, as compared with controls, had reduced GM volume in the insula, anterior temporo-occipital and frontal cortex, as well as ACC (Bloemers et al., 2014).

Limitations

Sex drive was based on self-reported sexual activity. These may not be perfectly accurate, as subjects may not remember their sexual activity accurately or may be reluctant to disclose their sexual behavior. However, prior studies confirm that this kind of self-reports yield reasonably reliable results – for example partners' retrospective reports of marital intercourse frequency are consistent (Clark & Wallin, 1964; Upchurch et al., 1991). Our study only included young male subjects, thus the results do not necessarily generalize to older men or women due to differences in the sex-specific reproductive biology as well as sex differences in sex drive and erotic plasticity (Baumeister, 2000; Baumeister et al., 2001). Sex drive levels were in general moderately high in the sample and we did not observe associations between sex drive and age, likely due to the limited age range of the subjects. Our data cannot thus reveal whether aging and accompanying altered MOR signaling (Kantonen et al., 2020) underlies lowered sexual drive towards the old age (Lindau et al., 2007). Finally, as the data were cross-sectional, we cannot conclude whether the links between MOR availability / cerebral integrity and sex drive reflect i) genetically determined individual differences in MOR availability / cortical structure (Weerts et al., 2013) contributing to increased motivation for sexual behaviour; or ii) upregulation of MOR neurotransmission and cortical density resulting from frequent sexual behaviour.

Conclusions

Central opioidergic system modulates sex drive in human males. Striatal and limbic OR availability is positively associated with sex drive, and with the exception of midcingulate cortices this effect was not related to cerebral grey matter density. Although opioid system acutely suppresses sex drive (Pfaus, 2009), our study suggests that central opioidergic mechanisms modulate not only affiliative bonding but also long-term sexual behaviour in the human male.

Declaration of interest statement This study was supported by the Academy of Finland (grant #294897 to LN) Sigrid Juselius foundation (LN) and Päivikki and Sakari Sohlberg Foundation (to TM). The authors declare no conflict of interest.

Authors contributions:

Acquired the data: TK, VP, LS, LL, LP
Analyzed the data: LN, VP, TM
Designed the study: LN
Wrote the manuscript: all authors

References

Amodio, D. M., & Frith, C. D. (2006). Meeting of minds: the medial frontal cortex and social cognition. *Nature Reviews Neuroscience, 7*(4), 268-277. doi:10.1038/nrn1884

Argiolas, A., & Melis, M. R. (2013). Neuropeptides and central control of sexual behaviour from the past to the present: a review. *Prog Neurobiol, 108*, 80-107. doi:10.1016/j.pneurobio.2013.06.006

Baumeister, R. F. (2000). Gender differences in erotic plasticity: The female sex drive as socially flexible and responsive. *Psychological Bulletin, 126*(3), 347-374. doi:10.1037//0033-2909.126.3.347

Baumeister, R. F., Catanese, K. R., & Vohs, K. D. (2001). Is there a gender difference in strength of sex drive? Theoretical views, conceptual distinctions, and a review of relevant evidence. *Personality and Social Psychology Review, 5*(3), 242-273. doi:10.1207/s15327957pspr0503_5

Beck, A. T., Steer, R. A., & Garbin, M. G. (1988). Psychometric properties of the Beck depression inventory: twenty-five years of evaluation. *Clinical Psychology Review, 8*, 77-100.

Berridge, K. C., Ho, C.-Y., Richard, J. M., & DiFeliceantonio, A. G. (2010). The tempted brain eats: Pleasure and desire circuits in obesity and eating disorders. *Brain Research, 1350*, 43-64. Retrieved from http://www.sciencedirect.com/science/article/B6SYR-4YTV7YB-1/2/11316cad076e46922e57ef92db6e3085

Birke, H., Ekholm, O., Højsted, J., Sjøgren, P., & Kurita, G. P. (2019). Chronic Pain, Opioid Therapy, Sexual Desire, and Satisfaction in Sexual Life: A Population-Based Survey. *Pain Medicine, 20*(6), 1132-1140. doi:10.1093/pm/pny122

Bloemers, J., Scholte, H. S., van Rooij, K., Goldstein, I., Gerritsen, J., Olivier, B., & Tuiten, A. (2014). Reduced Gray Matter Volume and Increased White Matter Fractional Anisotropy in Women with Hypoactive Sexual Desire Disorder. *The Journal of Sexual Medicine, 11*(3), 753-767. doi:https://doi.org/10.1111/jsm.12410

Bozarth, M. A., & Wise, R. A. (1981). Intra-Cranical Self-Administration of Morphine into the Ventral Tegmental Area in Rats. *Life Sciences, 28*(5), 551-555. Retrieved from <Go to ISI>://A1981LA46700011

Bürkner, P.-C. (2017). brms: An R package for Bayesian multilevel models using Stan. *Journal of Statistical Software, 80*(1), 1-28.

Calabrò, R. S., Cacciola, A., Bruschetta, D., Milardi, D., Quattrini, F., Sciarrone, F., . . . Anastasi, G. (2019). Neuroanatomy and function of human sexual behavior: A neglected or unknown issue? *Brain and Behavior, 9*(12), e01389. doi:https://doi.org/10.1002/brb3.1389

Chessick, R. D. (1960). THE PHARMACOGENIC ORGASM IN THE DRUG-ADDICT. *Archives of General Psychiatry, 3*(5), 545-556. Retrieved from <Go to ISI>://WOS:A1960WF14600010

Chou, R., Turner, J. A., Devine, E. B., Hansen, R. N., Sullivan, S. D., Blazina, I., . . . Deyo, R. A. (2015). The Effectiveness and Risks of Long-Term Opioid Therapy for Chronic Pain: A Systematic Review for a National Institutes of Health Pathways to Prevention Workshop. *Annals of Internal Medicine, 162*(4), 276-286. doi:10.7326/M14-2559

Clark, A. L., & Wallin, P. (1964). The accuracy of husbands' and wives' reports of the frequency of marital coitus. *Population Studies, 18*(2), 165-173. doi:10.1080/00324728.1964.10405517

Derogatis, L. R. (1978). The DSFI: A multidimensional measure of sexual functioning. *Jourrnal of Sex & Martial Therapy, 5*(244-281).

DiFeliceantonio, A. G., & Berridge, K. C. (2016). Dorsolateral neostriatum contribution to incentive salience: opioid or dopamine stimulation makes one reward cue more motivationally attractive than another. *European Journal of Neuroscience, 43*(9), 1203-1218. doi:https://doi.org/10.1111/ejn.13220

Eickhoff, S. B., Stephan, K. E., Mohlberg, H., Grefkes, C., Fink, G. R., Amunts, K., & Zilles, K. (2005). A new SPM toolbox for combining probabilistic cytoarchitectonic maps and functional imaging data. *Neuroimage, 25*(4), 1325-1335. doi:10.1016/j.neuroimage.2004.12.034

Fabre-Nys, C., Meller, R. E., & Keverne, E. B. (1982). Opiate antagonists stimulate affiliative behaviour in monkeys. *Pharmacology Biochemistry and Behavior, 16*(4), 653-659. doi:http://dx.doi.org/10.1016/0091-3057(82)90432-4

Frost, J. J., Douglass, K. H., Mayberg, H. S., Dannals, R. F., Links, J. M., & Wilson, A. A. (1989). Multicompartmental analysis of [11C]-carfentanil binding to opiate receptors in humans measured by positron emission tomography. *Journal of Cerebral Blood Flow and Metabolism, 9*, 398–409.

Frost, J. J., Wagner, H. N., Jr., Dannals, R. F., Ravert, H. T., Links, J. M., Wilson, A. A., . . . et al. (1985). Imaging opiate receptors in the human brain by positron tomography. *J Comput Assist Tomogr, 9*(2), 231-236.

Gabry, J., Simpson, D., Vehtari, A., Betancourt, M., & Gelman, A. (2019). Visualization in Bayesian workflow. *Journal of the Royal Statistical Society: Series A (Statistics in Society), 182*(2), 389-402. doi:10.1111/rssa.12378

Gelman, A., Carlin, J. B., Stern, H. S., Dunson, D. B., Vehtari, A., & Rubin, D. B. (2013). *Bayesian data analysis*: Chapman and Hall/CRC.

Gelman, A., & Hill, J. (2006). *Data analysis using regression and multilevel/hierarchical models*: Cambridge university press.

Gorelick, D. A., Kim, Y. K., Bencherif, B., Boyd, S. J., Nelson, R., Copersino, M., . . . Frost, J. J. (2005). Imaging brain mu-opioid receptors in abstinent cocaine users: time course and relation to cocaine craving. *Biol Psychiatry, 57*(12), 1573-1582. doi:10.1016/j.biopsych.2005.02.026

Graves, F. C., Wallen, K., & Maestripieri, D. (2002). Opioids and attachment in rhesus macaque (Macaca mulatta) abusive mothers. *Behavioral Neuroscience, 116*(3), 489-493. doi:10.1037//0735-7044.116.3.489

Grover, S., Mattoo, S. K., Pendharkar, S., & Kandappan, V. (2014). Sexual dysfunction in patients with alcohol and opioid dependence. *Indian journal of psychological medicine, 36*(4), 355-365. doi:10.4103/0253-7176.140699

Gunn, R. N., Lammertsma, A. A., Hume, S. P., & Cunningham, V. J. (1997). Parametric Imaging of Ligand-Receptor Binding in PET Using a Simplified Reference Region Model. *Neuroimage, 6*(4), 279–287. doi:10.1006/nimg.1997.0303

Hagelberg, N., Aalto, S., Tuominen, L., Pesonen, U., Någren, K., Hietala, J., . . . Martikainen, I. K. (2012). Striatal μ-opioid receptor availability predicts cold pressor pain threshold in healthy human subjects. *Neuroscience Letters, 521*(1), 11-14. doi:https://doi.org/10.1016/j.neulet.2012.05.042

Hnasko, T. S., Sotak, B. N., & Palmiter, R. D. (2005). Morphine reward in dopamine-deficient mice. *Nature, 438*(7069), 854-857. doi:10.1038/nature04172

Innis, R. B., Cunningham, V. J., Delforge, J., Fujita, M., Giedde, A., Gunn, R. N., . . . Carson, R. E. (2007). Consensus nomenclature for in vivo imaging of reversibly binding radioligands. *Journal of Cerebral Blood Flow and Metabolism, 27*(9), 1533-1539. doi:10.1038/sj.jcbfm.9600493

Kantonen, T., Karjalainen, T., Isojärvi, J., Nuutila, P., Tuisku, J., Rinne, J., . . . Nummenmaa, L. (2020). Interindividual variability and lateralization of μ-opioid receptors in the human brain. *Neuroimage*. doi:10.1101/821223

Karjalainen, T., Santavirta, S., Kantonen, T., Tuisku, J., Tuominen, L., Hirvonen, J., . . . Nummenmaa, L. (2020). Magia: Robust automated modeling and image processing toolbox for PET neuroinformatics. *Frontiers in Neuroinformatics*, 604835. doi:10.1101/604835

Karjalainen, T., Tuominen, L., Manninen, S., Kalliokoski, K., Nuutila, P., Jääskeläinen, I. P., . . . Nummenmaa, L. (2016). Behavioural activation system sensitivity is associated with cerebral μ-opioid receptor availability. *Social Cognitive and Affective Neuroscience, 11*, 1310-1316.

Keverne, E. B., Martensz, N. D., & Tuite, B. (1989). Beta-endorphin concentrations in cerebrospinal-fluid of monkeys are influenced by grooming relationships. *Psychoneuroendocrinology, 14*(1-2), 155-161. doi:10.1016/0306-4530(89)90065-6

Lammertsma, A. A., & Hume, S. P. (1996). Simplified reference tissue model for PET receptor studies. *Neuroimage, 4*(3), 153–158. doi:10.1006/nimg.1996.0066

Le Merrer, J., Becker, J. A. J., Befort, K., & Kieffer, B. L. (2009). Reward Processing by the Opioid System in the Brain. *Physiological Reviews, 89*(4), 1379-1412. doi:10.1152/physrev.00005.2009

Lindau, S. T., Schumm, L. P., Laumann, E. O., Levinson, W., O'Muircheartaigh, C. A., & Waite, L. J. (2007). A study of sexuality and health among older adults in the United States. *New England Journal of Medicine, 357*(8), 762-774. doi:10.1056/NEJMoa067423

Manninen, S., Karjalainen, T., Tuominen, L. J., Hietala, J., Kaasinen, V., Joutsa, J., . . . Nummenmaa, L. (2021). Cerebral grey matter density is associated with neuroreceptor and neurotransporter availability: A combined PET and MRI study. *Neuroimage* , 2020.2001.2029.924530. doi:10.1101/2020.01.29.924530

Manninen, S., Tuominen, L., Dunbar, R. I. M., Karjalainen, T., Hirvonen, J., Arponen, E., . . . Nummenmaa, L. (2017). Social laughter triggers endogenous opioid release in humans. *The Journal of Neuroscience, 37*, 6125-6131.

Mirin, S. M., Meyer, R. E., Mendelson, J. H., & Ellingboe, J. (1980). OPIATE USE AND SEXUAL FUNCTION. *American Journal of Psychiatry, 137*(8), 909-915. Retrieved from <Go to ISI>://WOS:A1980KC80200005

Nummenmaa, L., Karjalainen, T., Isojärvi, J., Kantonen, T., Tuisku, J., Kaasinen, V., . . . Rinne, J. (2020). Lowered endogenous mu-opioid receptor availability in subclinical depression and anxiety. *Neuropsychopharmacology*. doi:10.1038/s41386-020-0725-9

Nummenmaa, L., Manninen, S., Tuominen, L., Hirvonen, J., Kalliokoski, K. K., Nuutila, P., . . . Sams, M. (2015). Adult attachment style Is associated with cerebral μ-opioid receptor availability in humans. *Human brain mapping, 36*, 3621-3628.

Nummenmaa, L., Suvilehto, J. M., Glerean, E., Santtila, P., & Hietanen, J. K. (2016a). Topography of human erogenous zones. *Archives of Sexual Behavior*.

Nummenmaa, L., Tuominen, L., Dunbar, R., Hirvonen, J., Manninen, S., Arponen, E., . . . Sams, M. (2016b). Social touch modulates endogenous μ-opioid system activity in humans. *Neuroimage, 138*, 242-247.

Nummenmaa, L., & Tuominen, L. J. (2018). Opioid system and human emotions. *British Journal of Pharmacology, 175*, 2737-2749. doi:doi: 10.1111/bph.13812

Panksepp, J., Herman, B., Conner, R., Bishop, P., & Scott, J. P. (1978). Biology of social attachments - Opiates alleviate separation distress. *Biol Psychiatry, 13*(5), 607-618. Retrieved from <Go to ISI>://WOS:A1978FU56200011

Peciña, S., & Berridge, K. C. (2013). Dopamine or opioid stimulation of nucleus accumbens similarly amplify cue-triggered 'wanting' for reward: entire core and medial shell mapped as substrates for PIT enhancement. *European Journal of Neuroscience, 37*(9), 1529-1540. doi:https://doi.org/10.1111/ejn.12174

Pfaus, J. G. (2009). Pathways of Sexual Desire. *Journal of Sexual Medicine, 6*(6), 1506-1533. doi:10.1111/j.1743-6109.2009.01309.x

Pfaus, J. G., & Gorzalka, B. B. (1987). OPIOIDS AND SEXUAL-BEHAVIOR. *Neuroscience and Biobehavioral Reviews, 11*(1), 1-34. doi:10.1016/s0149-7634(87)80002-7

Robinson, B. W., & Mishkin, M. (1968). Penile Erection Evoked From Forebrain Structures in Macaca mulatta. *Archives of Neurology, 19*(2), 184-198. doi:10.1001/archneur.1968.00480020070007

Rodríguez-Manzo, G., & Fernández-Guasti, A. (1995). Opioid antagonists and the sexual satiation phenomenon. *Psychopharmacology (Berl), 122*(2), 131-136. doi:10.1007/BF02246087

Ross, J., Teesson, M., Darke, S., Lynskey, M., Ali, R., Ritter, A., & Cooke, R. (2005). The characteristics of heroin users entering treatment: findings from the Australian Treatment Outcome Study (ATOS). *Drug and Alcohol Review, 24*(5), 411-418. doi:https://doi.org/10.1080/09595230500286039

Saarimäki, H., Gotsopoulos, A., Jääskeläinen, I. P., Lampinen, J., Vuilleumier, P., Hari, R., . . . Nummenmaa, L. (2016). Discrete Neural Signatures of Basic Emotions. *Cerebral Cortex, 6*, 2563-2573. doi:10.1093/cercor/bhv086

Schindler, A., Thomasius, R., Petersen, K., & Sack, P.-M. (2009). Heroin as an attachment substitute? Differences in attachment representations between opioid, ecstasy and cannabis abusers. *Attachment & Human Development, 11*(3), 307-330. doi:10.1080/14616730902815009

Schmidt, C., Morris, L. S., Kvamme, T. L., Hall, P., Birchard, T., & Voon, V. (2017). Compulsive sexual behavior: Prefrontal and limbic volume and interactions. *Human brain mapping, 38*(3), 1182-1190. doi:https://doi.org/10.1002/hbm.23447

Spielberger, C. D., Gorsuch, R. L., & Lushene, R. E. (1970). *Manual for the State-Trait Anxiety Inventory*. Palo Alto, CA Consulting Psychologists Press.

Steers, W. D. (2000). Neural pathways and central sites involved in penile erection neuroanatomy and clinical implications. *Neuroscience and Biobehavioral Reviews, 24*(5), 507-516. doi:10.1016/s0149-7634(00)00019-1

Stoléru, S., Fonteille, V., Cornélis, C., Joyal, C., & Moulier, V. (2012). Functional neuroimaging studies of sexual arousal and orgasm in healthy men and women: A review and meta-analysis. *Neuroscience & Biobehavioral Reviews, 36*(6), 1481-1509. doi:https://doi.org/10.1016/j.neubiorev.2012.03.006

Takeuchi, H., Taki, Y., Nouchi, R., Hashizume, H., Sekiguchi, A., Kotozaki, Y., . . . Kawashima, R. (2015). The structure of the amygdala associates with human sexual permissiveness: Evidence from voxel-based morphometry. *Human brain mapping, 36*(2), 440-448. doi:https://doi.org/10.1002/hbm.22638

Tuominen, L., Nummenmaa, L., Keltikangas-Jarvinen, L., Raitakari, O., & Hietala, J. (2014). Mapping neurotransmitter networks with PET: An example on serotonin and opioid systems. *Human brain mapping, 35*(5), 1875-1884. doi:10.1002/hbm.22298

Tuominen, L., Salo, J., Hirvonen, J., Nagren, K., Laine, P., Melartin, T., . . . Hietala, J. (2012). Temperament trait Harm Avoidance associates with mu-opioid receptor availability in frontal cortex: A PET study using C-11 carfentanil. *Neuroimage, 61*(3), 670-676. doi:10.1016/j.neuroimage.2012.03.063

Turtonen, O., Saarinen, A., Nummenmaa, L., Tuominen, L., Tikka, M., Armio, R.-L., . . . Hietala, J. (2021). Adult attachment system links with brain μ-opioid receptor availability in vivo. *Biol Psychiatry*.

Twenge, J. M., Sherman, R. A., & Wells, B. E. (2017). Declines in Sexual Frequency among American Adults, 1989–2014. *Archives of Sexual Behavior, 46*(8), 2389-2401. doi:10.1007/s10508-017-0953-1

Tzourio-Mazoyer, N., Landeau, B., Papathanassiou, D., Crivello, F., Etard, O., Delcroix, N., . . . Joliot, M. (2002). Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. *Neuroimage, 15*(1), 273-289. doi:10.1006/nimg.2001.0978

Upchurch, D. M., Weisman, C. S., Shepherd, M., Brookmeyer, R., Fox, R., Celentano, D. D., . . . Hook, E. W., III. (1991). Interpartner Reliability of Reporting of Recent Sexual Behaviors. *American Journal of Epidemiology, 134*(10), 1159-1166. doi:10.1093/oxfordjournals.aje.a116019

Weerts, E. M., McCaul, M. E., Kuwabara, H., Yang, X. J., Xu, X. Q., Dannals, R. F., . . . Wand, G. S. (2013). Influence of OPRM1 Asn(40)Asp variant (A118G) on C-11 carfentanil binding potential: preliminary findings in human subjects. *International Journal of Neuropsychopharmacology, 16*(1), 47-53. doi:10.1017/s146114571200017x

Weerts, E. M., Wand, G. S., Kuwabara, H., Munro, C. A., Dannals, R. F., Hilton, J., . . . McCaul, M. E. (2011). Positron emission tomography imaging of mu- and delta-opioid receptor binding in alcohol-dependent and healthy control subjects. *Alcohol Clin Exp Res, 35*(12), 2162-2173. doi:10.1111/j.1530-0277.2011.01565.x

Yee, A., Loh, H. S., Hisham Hashim, H. M., & Ng, C. G. (2014). The prevalence of sexual dysfunction among male patients on methadone and buprenorphine treatments: a meta-analysis study. *J Sex Med, 11*(1), 22-32. doi:10.1111/jsm.12352

Zubieta, J. K., Smith, Y. R., Bueller, J. A., Xu, Y., Kilbourn, M. R., Jewett, D. M., . . . Stohler, C. S. (2001). Regional mu opioid receptor regulation of sensory and affective dimensions of pain. *Science, 293*, 311–315. doi:10.1126/science.1060952