Cerebral μ-opioid and CB_1-receptor systems have distinct roles in human feeding behavior

Short title: Eating behavior and central MOR and CB_1R systems

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Abstract

Eating behavior varies greatly between healthy individuals, but the neurobiological basis of these trait-like differences in feeding remains unknown. Central μ-opioid receptors (MOR) and cannabinoid CB_1-receptors (CB_1R) regulate energy balance via multiple neural pathways, promoting food intake and reward. Because obesity and eating disorders have been associated with alterations in the brain's opioid and endocannabinoid signaling, the variation in MOR and CB_1R system function could potentially underlie distinct eating behavior phenotypes. In this retrospective positron emission tomography (PET) study, we analyzed [^{11}C]carfentanil PET scans of MORs from 92 healthy subjects (70 males and 22 females), and [^{18}F]FMPEP-d_2 scans of CB_1Rs from 35 subjects (all males, all also included in the [^{11}C]carfentanil sample). Eating styles were measured with the Dutch Eating Behavior Questionnaire (DEBQ). We found that lower cerebral MOR availability was associated with increased external eating – individuals with low MORs reported being more likely to eat in response to environment's palatable food cues. CB_1R availability was associated with multiple eating behavior traits. We conclude that although MORs and CB_1Rs overlap anatomically and functionally in the brain, they have distinct roles in mediating individual feeding patterns.

1. Introduction

Obesity is one of the leading public health issues, resulting from individuals' long-term excessive energy intake in relation to energy expenditure (Guyenet and Schwartz, 2012). Yet, humans vary greatly in their choices and habits related to food intake quantity and quality i.e. eating behavior (French et al., 2012; Larson and Story, 2009). Trait-like eating behaviors have been associated with multiple clinical eating disorders in addition to obesity (Baños et al., 2014; Barrada et al., 2016; Cebolla et al., 2014; Wardle, 1987), but also non-obese individuals vary in how they control their feeding (Yeomans et al., 2008). Interacting with peripheral hormones, central nervous system (CNS) integrates hunger and satiety signals with environmental stimuli to regulate food intake (Guyenet and Schwartz, 2012). Large-scale genome-wide association studies have identified limbic system, hippocampus and hypothalamus to be key regions in the CNS contributing to individual's body mass index (BMI) and eating behavior (Locke et al., 2015; Silventoinen and Konttinen, 2020). Central regulation of feeding is however constantly challenged by the modern environment characterized by abundance of palatable and energy-dense food products, promoting feeding independently of metabolic needs (Berthoud, 2012; Hill and Peters, 1998).

Palatability and hedonic properties of food are centrally mediated by μ-opioid receptor (MOR) system (Gosnell and Levine, 2009; Nummenmaa et al., 2018). Both endogenous and exogenous opioids stimulate feeding, especially via hedonic hotspots of nucleus accumbens, insula and frontal cortex (Castro and Berridge, 2017; Mena et al., 2011; Nogueiras et al., 2012; Smith and Berridge, 2007). Conversely, opioid antagonists reduce food intake and related hedonic responses in rodents (Nogueiras et al., 2012) and humans (Yeomans and Gray, 2002; Ziauddeen et al., 2013). Human positron emission tomography (PET) studies have revealed that obesity associates with decrease of MORs in appetite regulating brain areas (Burghardt et al., 2015; Karlsson et al., 2015), and insular MORs are lowered in patients with bulimia nervosa proportionally to fasting behavior (Bencherif et al., 2005). Central MOR system function varies considerably also in healthy humans (Kantonen et

al., 2020), and traits linked with feeding control such as impulsivity are associated with MOR availability (Love et al., 2009). Nevertheless, the association between the MOR system and specific patterns of eating behavior remains elusive.

Feeding is also regulated by brain's endocannabinoid system, which overlaps anatomically and functionally with the central MORs (Cota et al., 2006). The most abundant central cannabinoid receptors are the CB_1-receptors (CB_1Rs), which regulate food intake through circuits of ventral striatum, limbic system and hypothalamus (Bermudez-Silva et al., 2012; Mechoulam and Parker, 2013). Functional interplay between MOR and CB_1R systems is highlighted in animal studies, where CB_1R-antagonists and MOR-antagonists have synergistic effect on reducing food intake (Rowland et al., 2001), and CB_1R-antagonist can be used to block MOR-agonist induced food intake and vice versa (Solinas and Goldberg, 2005). MOR-agonists also directly increase endocannabinoid concentration and CB_1R-agonists increase opioid concentration in the brain, including nucleus accumbens (Solinas et al., 2004; Vigano et al., 2004). In humans, CB_1R-antagonist rimonabant showed promise as an anti-obesity drug, but was withdrawn due to psychiatric side effects (Di Marzo and Després, 2009). More nuanced understanding of CB_1R system and feeding is clearly required to enable further pharmacological advancement.

1.1. The current study

Accumulating evidence suggests that variation in central MOR and CB_1R function could be linked to feeding and pathological eating behavior traits in humans, but it remains unresolved what facets of feeding they govern in humans. Individual differences in eating patterns can be conceptualized based on the psychological mechanisms that contribute to or attenuate development of overweight. In such conceptualization, *emotional eating* refers to reactive overeating to distress or negative emotions, while *external eating* refers to tendency to overeat in response to attractive food-cues. Finally, *restrained eating* refers to the tendency to eat less than desired (Van Strien et al., 1986b; Van Strien et al., 2009; Van Strien et al., 2012a). The emotional and external overeating are based on

psychosomatic and externality theories of eating behavior, while restrained eating dimension centers around food intake self-inhibition (Van Strien et al., 1986a). Such consistent patterns contribute to differences in weight gain and maintenance (Van Strien et al., 2009; Van Strien et al., 2012b), and they can be measured using The Dutch Eating Behavior Questionnaire (DEBQ) (Van Strien et al., 1986a). Here we compiled 92 [^{11}C]carfentanil PET scans targeting the MOR system and 35 [^{18}F]FMPEP-d_2 PET scans of CB_1R system and corresponding DEBQ data in a retrospective PET database study. We tested whether the MOR and CB_1R availabilities in food-intake-regulating brain areas associate with individual eating behavior traits measured with DEBQ.

2. Materials and Methods

2.1. Subjects

The study subjects were historical controls retrieved from the AIVO neuroinformatics database (http://aivo.utu.fi), a large-scale molecular image database hosted by Turku PET Centre. We identified all the [^{11}C]carfentanil and [^{18}F]FMPEP-d_2 baseline PET studies accompanied with completed DEBQ form (Van Strien et al., 1986a). Exclusion criteria were neurologic and psychiatric disorders, current use of medications that could affect CNS or abuse of alcohol or illicit drugs. Subjects were not preselected on the basis of weight or eating habits. Final sample consisted of 92 subjects (70 males and 22 females) scanned with [^{11}C]carfentanil from five distinct projects with three different PET scanners. The [^{18}F]FMPEP-d_2 sample consisted of 35 males, all of which were also all included in the [^{11}C]carfentanil male sample. All subjects of the [^{18}F]FMPEP-d_2 subsample were nonsmoking males, while in the [^{11}C]carfentanil sample seven females smoked. All [^{18}F]FMPEP-d_2 scans were carried out with GE Discovery VCT PET/CT (GE Healthcare). The original data were acquired between 2011 and 2019. Characteristics of the study sample are summarized in **Table 1**, and the information of smoking status and PET scanners are detailed in **Supplementary Table 1**. The study was conducted in accordance with the Declaration of Helsinki and approved by the Turku University Hospital Clinical Research Services. The subjects had signed written informed consent forms and completed the DEBQ forms as a part of the original study protocols.

Table 1. Characteristics of the studied subjects.

	[^{11}C]carfentanil scans					
	Males (n = 70)			Females (n = 22)		
	mean	SD	range	mean	SD	range
Age (years)	27.4	7.5	19−58	47.7	10.0	20−59
BMI (kg/m^2)	24.5	2.8	19−31	23.7	3.1	18−31
Total DEBQ score	67.0	12.8	40−109	73.4	12.8	46−97
Emotional eating score	21.0	6.8	13−40	22.1	5.7	13−32
External eating score	24.7	6.5	10−43	25.0	5.4	13−34
Restrained eating score	21.3	5.5	11−39	26.2	5.5	10−33
Injected activity (MBq)	277.0	77.9	223−508	352.3	125.5	234−519

	[^{18}F]FMPEP-d_2 scans		
	Males (n = 35)		
	mean	SD	range
Age (years)	25.9	4.3	21−35
BMI (kg/m^2)	24.5	3.1	19−31
Total DEBQ score	68.6	14.5	43−109
Emotional eating score	20.7	7.4	13−40
External eating score	27.1	6.0	14−43
Restrained eating score	20.8	5.6	12−32
Injected activity (MBq)	187.9	12.8	147−215

2.2. Eating behavior assessment with the DEBQ

The Dutch Eating Behavior Questionnaire (DEBQ) (Van Strien et al., 1986a) was used to quantify eating behavior. The DEBQ is a 33-item questionnaire with Likert-type scoring in each item (response options ranging from 1−5, from "Never" to "Very often"). It is divided in three dimensions measuring different behavioral traits: Emotional eating, External eating and Restrained eating (Van Strien et al., 1986b; Van Strien et al., 2009; Van Strien et al., 2012a). The DEBQ subscales have been designed to measure independent dimensions of feeding behavior (Van Strien et al., 1995), and the subscales have good internal consistency, dimensional validity and test-retest reliability (Cebolla et al., 2014; Malesza and Kaczmarek, 2019; Van Strien et al., 1986a; Wardle, 1987).

2.3. Image processing and modeling

PET images were preprocessed similarly using automated processing pipeline Magia (Karjalainen et al., 2020). [^{11}C]carfentanil data preprocessing has been described previously (Kantonen et al., 2020). MOR availability was expressed as [^{11}C]carfentanil binding potential (BP_{ND}), which is the ratio of specifically bound radioligand to that of nondisplaceable radioligand in tissue (Innis et al., 2007). Occipital cortex served as the reference region (Frost et al., 1989). CB_1R availability was expressed as [^{18}F]FMPEP-d_2 volume of distribution (V_T), which was quantified using graphical analysis by Logan (Logan, 2000). The frames starting at 36 minutes and later since injection were used in the model fitting, since Logan plots became linear after 36 minutes (Logan, 2000). Plasma activities were corrected for plasma metabolites as described previously (Lahesmaa et al., 2018).

2.4. Statistical analysis

The study question was whether the DEBQ subscales (Emotional eating, External eating, Restrained eating) or Total DEBQ scores are associated with [^{11}C]carfentanil BP_{ND} or [^{18}F]FMPEP-d_2 V_T. We used Bayesian hierarchical modeling to analyze these effects in *a priori* regions of interest (ROIs). FreeSurfer (http://surfer.nmr.mgh.harvard.edu/) was used to extract 10 bilateral ROIs based on known regions with high density of MORs (Kantonen et al., 2020) and CB_1Rs (Terry et al., 2010): amygdala, caudatus, cerebellum, dorsal anterior cingulate cortex, insula, middle temporal cortex, nucleus accumbens, orbitofrontal cortex, putamen, and thalamus. The Bayesian models were estimated using the R package brms (https://cran.r-project.org/web/packages/brms/index.html) that utilizes the Markov chain Monte Carlo sampling of RStan (https://mc-stan.org/users/interfaces/rstan). Because age influences [^{11}C]carfentanil binding (Kantonen et al., 2020; Zubieta et al., 1999) and different PET scanners may yield slightly different BP_{ND} estimates (Nummenmaa et al., 2020), both age and PET scanner were controlled for in all [^{11}C]carfentanil models. Age was also controlled for

in all [^{18}F]FMPEP-d_2 V_T models (the scanner-adjustment was not needed since the [^{18}F]FMPEP-d_2 data were acquired using a single scanner). For both tracers, we created models separately for the Total DEBQ score as well as its subscales, adjusting for age. [^{11}C]carfentanil BP_{ND} and [^{18}F]FMPEP-d_2 V_T were log-transformed to improve model fit (Kantonen et al., 2020). For both tracers, we estimated varying (random) intercepts for the subjects and ROIs, and varying (random) slopes across ROIs for the predictor of interest (e.g. Total DEBQ score) and age. Compared to a model where the regionally specific effects would be estimated using interaction term for ROI, the hierarchical model produces results that are partially pooled towards each other, thus accounting for the multiple comparisons performed (Gelman et al., 2012). For both tracers, we also estimated regionally varying (random) residual variances. For [^{11}C]carfentanil data, we also estimated regionally varying (random) intercepts for the scanners. We used the standard normal distribution as a prior distribution for the regression coefficients of the predictors to provide regularization. The standard normal distribution was also used as the prior distribution for the standard deviation of the group-level (random) effects. Otherwise we used the default priors of brms. We used 1000 warmup samples, 1000 post-warmup samples and 10 chains, thus totaling 10 000 post-warmup samples. The sampling parameters were slightly modified to facilitate convergence (*adapt_delta* = 0.999; *max_treedepth* = 20). The samplings produced no divergent iterations and the Rhats were all 1.0, suggesting that the chains converged successfully.

To examine associations in the whole brain, we used nonparametric approach with SnPM13 (http://nisox.org/Software/SnPM13/) to create full-volume linear regression models for BP_{ND} and V_T values. We used $p < 0.01$ as the cluster-defining threshold, and only report clusters large enough to be statistically significant at FWE $p < 0.05$. 5000 permutations were used to estimate the null distribution. We created distinct models for Total DEBQ score and all the subscale scores, adjusting for age and also for PET scanner in [^{11}C]carfentanil models. To rule out the possible effects of sex, smoking and BMI, we replicated the [^{11}C]carfentanil full volume analysis with these additional

covariates. The [^{18}F]FMPEP-d_2 models were also replicated with BMI as additional covariate (there were no smokers or females in the [^{18}F]FMPEP-d_2 data).

3. Results

Mean distribution of MORs and CB_1Rs is shown in **Figure 1**. Correlations between the DEBQ subscales were positive but only modest, strongest being between Emotional and External eating (r = +0.33). BMI had a significant correlation only with Restrained eating (r = +0.27). Correlations with p-values are presented in **Supplementary Figure 1** and **Supplementary Table 2**.

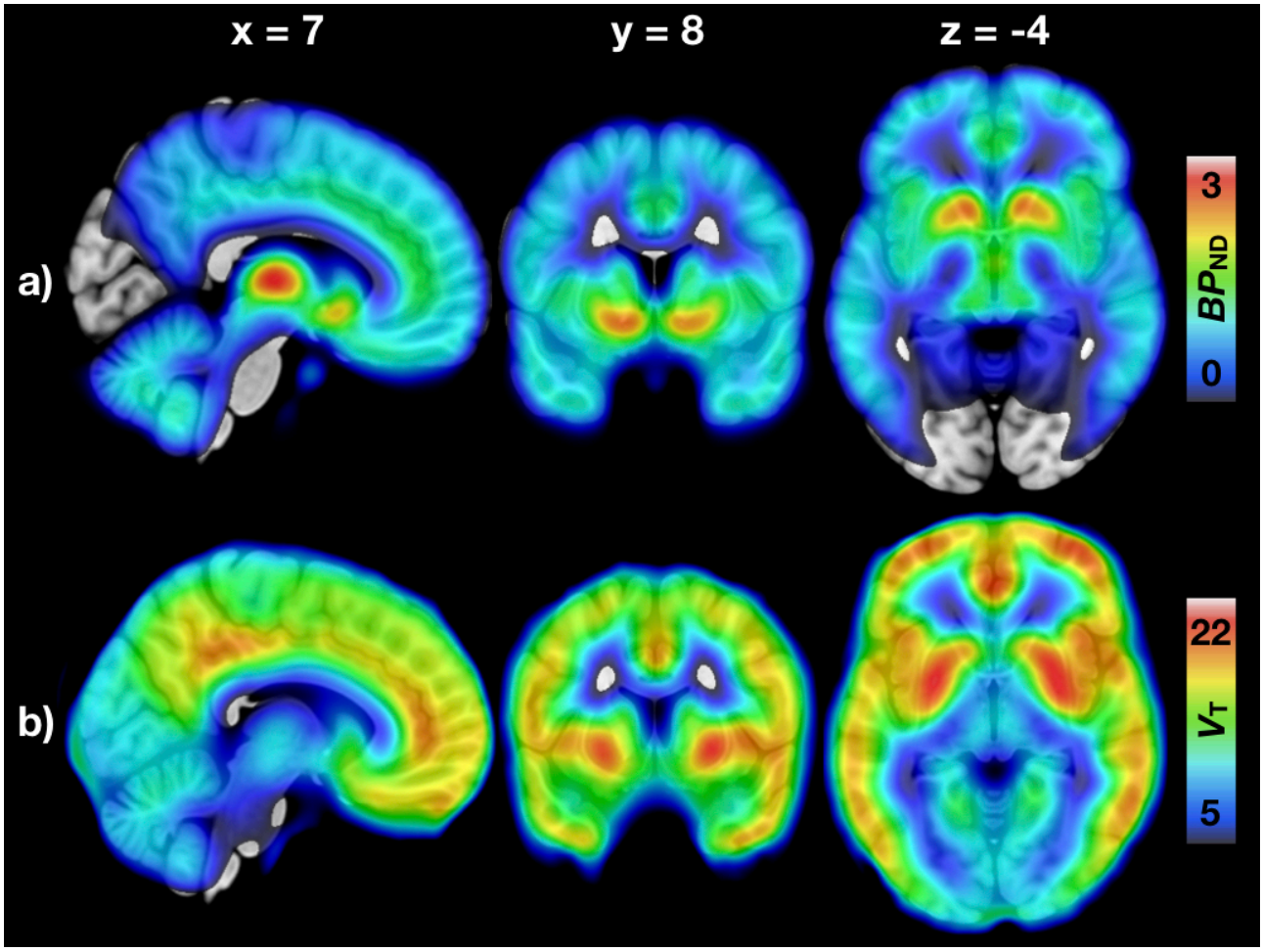

Figure 1. Mean distribution of central μ-opioid and CB_1-receptors. a) Mean binding potential (BP_{ND}) of the 92 subjects (70 males and 22 females) studied with [^{11}C]carfentanil. b) Mean volume of distribution (V_T) of the 35 males studied with [^{18}F]FMPEP-d_2.

3.1. Regional analysis of neuroreceptor availability and eating behavior

Higher External eating score was associated with lower [^{11}C]carfentanil BP_{ND} in all *a priori* ROIs (**Figure 2**). In the [^{11}C]carfentanil models with other DEBQ subscales and Total DEBQ, the 80%

confidence intervals overlapped with zero. For [^{18}F]FMPEP-d_2, higher Total DEBQ score was associated with lower V_T all examined ROIs (**Figure 2**). The association directions between V_T and all DEBQ subscales were negative, but the 95% confidence intervals overlapped with zero. Visualization of the regional relationships between DEBQ scores and neuroreceptor availability in representative ROIs is presented in **Figure 3**.

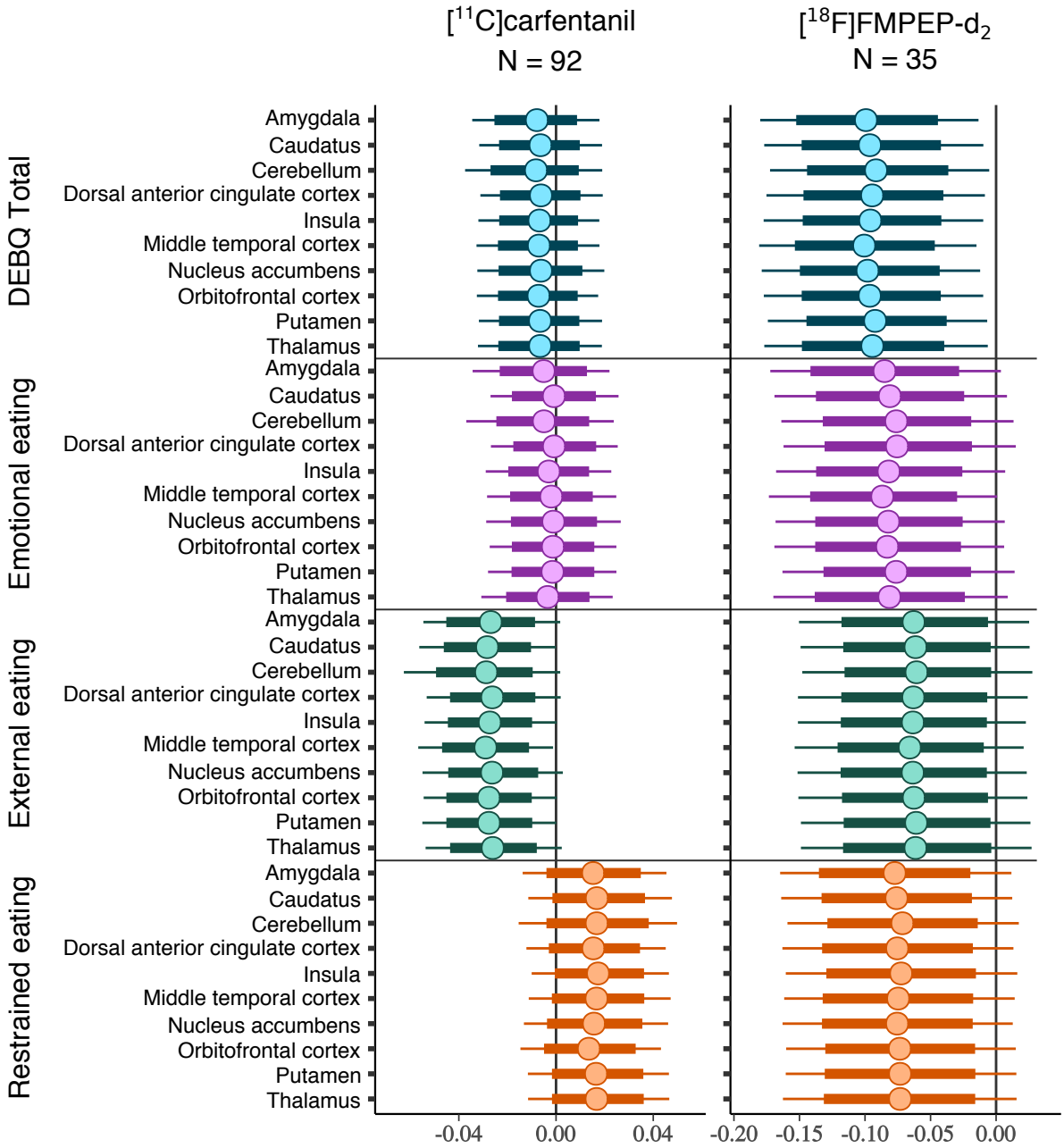

Figure 2. Regional associations of Total DEBQ and subscale scores with μ-opioid and CB_1-receptor availabilities. The figure shows posterior distributions of the regression coefficients for

Total DEBQ and subscale scores on log-transformed [^{11}C]carfentanil binding potential (BP_{ND}) and [^{18}F]FMPEP-d_2 volume of distribution (V_T) in 10 regions of interest. Age (and PET scanner for [^{11}C]carfentanil data) are controlled as covariates. The colored circles represent posterior means, the thick horizontal bars 80% posterior intervals, and the thin horizontal bars 95% posterior intervals.

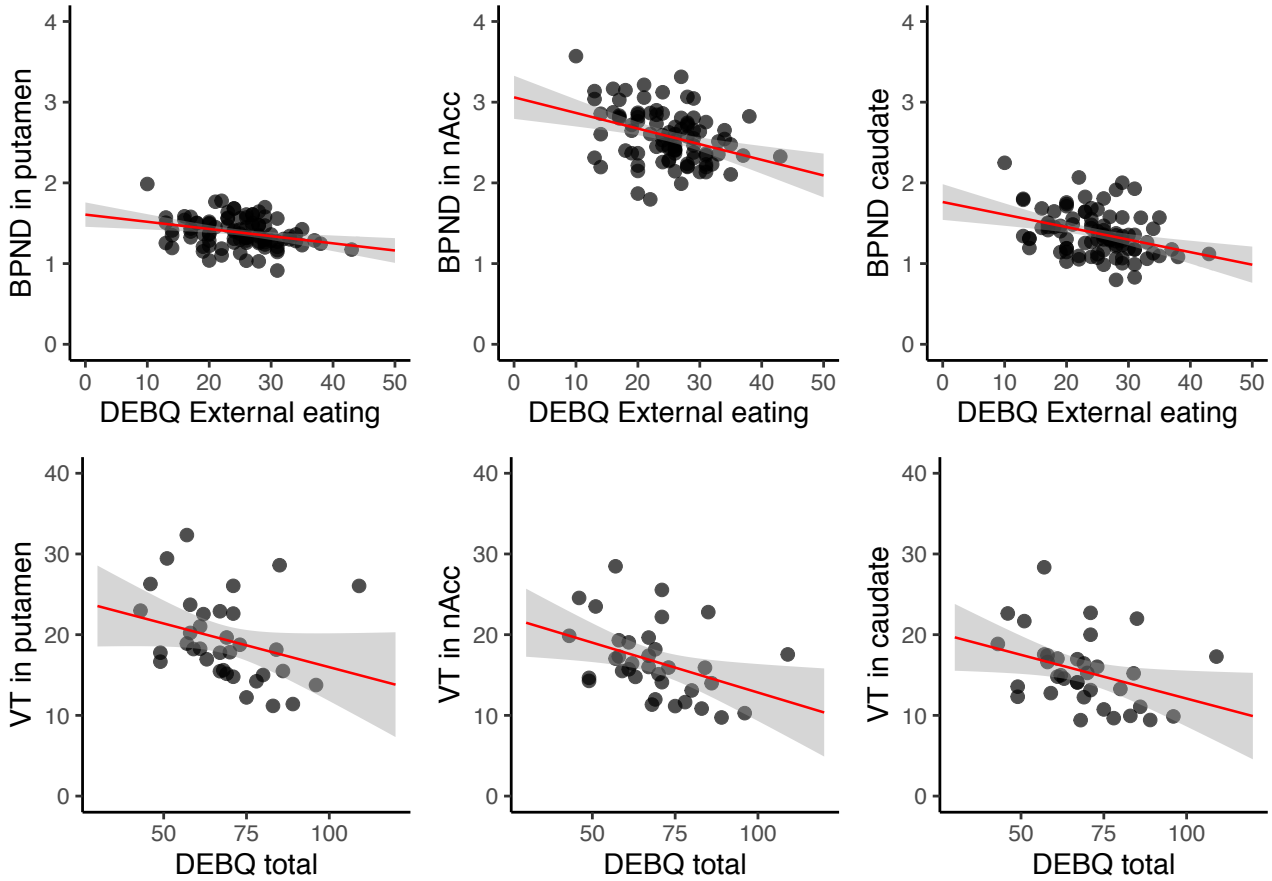

Figure 3. Visualization of regional associations in three representative regions of interest. Upper row: Scatterplots show the associations of External eating score and [^{11}C]carfentanil binding potential (BP_{ND}) in putamen, nucleus accumbens (nAcc) and caudate (92 subjects, LS-regression line with 95% CI). Lower row: Scatterplots show the associations of Total DEBQ score and [^{18}F]FMPEP-d_2 volume of distribution (V_T) in putamen, nucleus accumbens (nAcc) and caudate (35 subjects, LS-regression line with 95% CI).

3.2. Full volume analysis of central receptor availability and eating behavior

For both tracers, full volume results were consistent with the ROI models.

3.2.1. μ-opioid receptor availability and DEBQ

Higher External eating score was associated with lower [^{11}C]carfentanil BP_{ND} in multiple brain areas (**Figure 4**). Strongest cerebral associations were found in the right frontotemporal cortex and insula (peak voxel coordinates in **Supplementary Table 3**). Associations with Total DEBQ or other subscale scores were not statistically significant. Results were similar in the male subsample (n = 70, **Supplementary Figure 2**) and also when additionally controlling for sex, smoking and BMI, but significant only with more lenient threshold (cluster forming $p < 0.05$, FWE corrected). In the female subsample, there were no significant associations, likely due to limited statistical power.

3.2.2. CB_1-receptor availability and DEBQ

Higher Total DEBQ score was associated with lower [^{18}F]FMPEP-d_2 V_T bilaterally in multiple brain regions (**Figure 5**). Most prominent associations were found in parahippocampus, frontal striatum, insula, anterior cingulate and frontotemporal cortices (peak voxel coordinates in **Supplementary Table 3**). Full-volume associations with distinct DEBQ subscales and V_T were not statistically significant. Results were essentially the same when controlling for BMI.

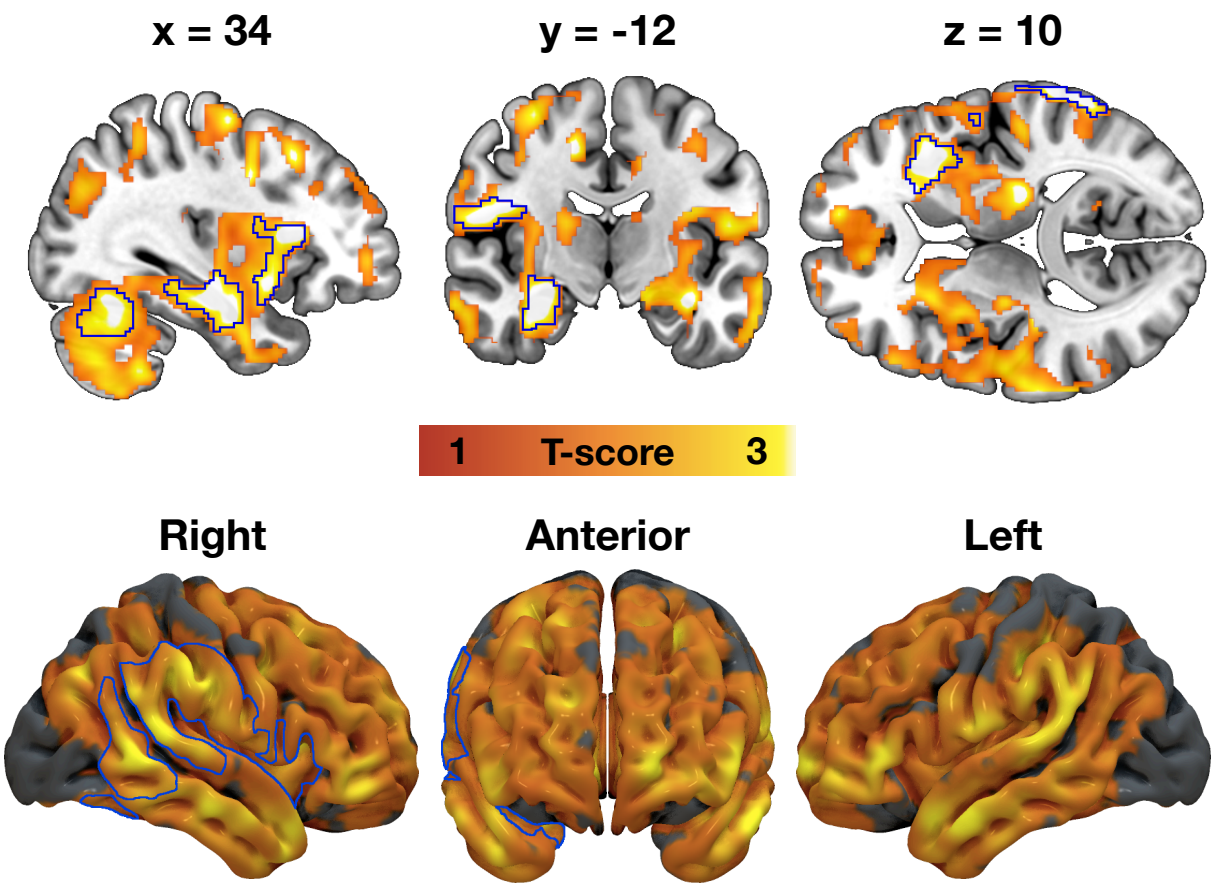

Figure 4. Association between External eating and decreased μ-opioid receptor availability. The blue outline marks brain regions where lower [^{11}C]carfentanil binding potential (BP_{ND}) associated with higher External eating score, age and PET scanner as nuisance covariates, cluster forming threshold $p < 0.01$, FWE corrected. In the red–yellow T-score scale shown are also additional bilateral associations significant with more lenient cluster-defining threshold ($p < 0.05$, FWE corrected) for visualization purposes.

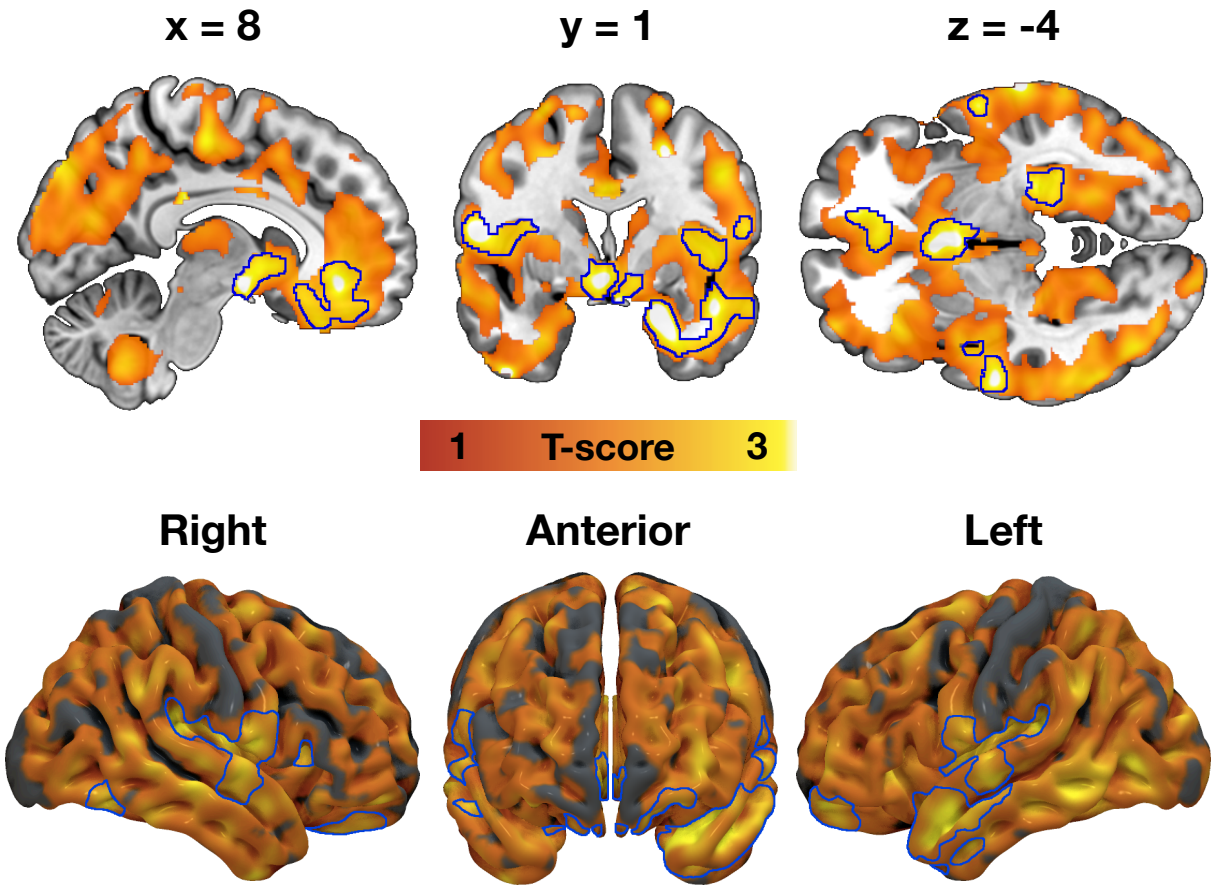

Figure 5. Total Dutch Eating Behavior Questionnaire (DEBQ) score associated with decreased CB_1-receptor availability. The blue outline marks brain regions where lower [^{18}F]FMPEP-d_2 volume of distribution (V_T) associated with higher Total DEBQ score, age as a nuisance covariate, cluster forming threshold $p < 0.01$, FWE corrected. In the red–yellow T-score scale shown are also additional associations significant with more lenient cluster-defining threshold ($p < 0.05$, FWE corrected) for visualization purposes.

4. Discussion

Our main finding was that higher DEBQ scores were associated with lower central availability of μ-opioid and CB_1-receptors in healthy, non-obese humans. MOR and CB_1R systems however showed distinct patterns of associations with specific dimensions of self-reported eating: While CB_1Rs were associated in general negatively with different DEBQ subscale scores (and most saliently with the Total DEBQ score), MORs were specifically and negatively associated with externally driven eating only. Our results support the view that variation in endogenous opioid and endocannabinoid systems explain interindividual variation in feeding, with distinct effects on eating behavior measured with DEBQ.

4.1. Central μ-opioid receptors and external eating behavior

External eating – the tendency to feed when encountering palatable food cues such as advertisements – was associated with lowered MOR availability in insula, cortico-limbic regions and striatum, which are major brain areas processing environmental food cues and mediating reward (Berthoud et al., 2017). A bulk of studies have shown that these regions are activated by mere perception of food cues or anticipation of feeding (Nummenmaa et al., 2012; Stice et al., 2008a; Stice et al., 2008b), and our recent work shows that lowered MOR availability is associated with amplified hemodynamic responses to food images in the same regions (Nummenmaa et al., 2018). Higher score on external eating is associated with increased food craving (Burton et al., 2007) and cue-induced palatable food intake (Anschutz et al., 2009; Van Strien et al., 2012a), and may also contribute to short-term weight gain (Van Strien et al., 2012b). Altogether these results suggest that central MOR system has an important role in modulating particularly this kind of impulsive feeding that may lead to overweight.

Previous PET studies have established that feeding triggers endogenous opioid release in humans (Burghardt et al., 2015; Tuulari et al., 2017). Binge eating disorder (BED) is accompanied with downregulated central MORs and high External and Emotional eating scores (Joutsa et al.,

2018). Morbid obesity is also associated with lowered central MOR availability (Burghardt et al., 2015; Karlsson et al., 2015), possibly reflecting receptor downregulation due to repeated overstimulation following feeding. In minipigs, already 12 days of high sucrose intake and following central endogenous neurotransmitter release downregulates MORs in cingulate and prefrontal cortices, nucleus accumbens and elsewhere in striatum (Winterdahl et al., 2019). The present findings extend the role of MORs in obesity and eating disorders to different feeding patterns in healthy subjects.

Healthy humans vary considerably in central MOR availability (Kantonen et al., 2020), and it is also possible that lowered MOR availability constitutes a genetically determined (Weerts et al., 2013) risk factor for externally driven eating behavior. In healthy humans, trait impulsivity is associated with central MOR availability (Love et al., 2009). Increased cue-reactivity is prevalent feature of behavioral addictions (Antons et al., 2020), and patients with BED and pathological gambling have reduced availability of central MORs as measured with *in vivo* PET (Majuri et al., 2017). It is thus possible that subjects with lower MOR availability are susceptible for increased external eating in modern environment where they are consistently bombarded with feeding cues in advertisements and food shelves in supermarkets (Berthoud, 2012). However, the present data are purely cross-sectional and longitudinal human studies are needed to further disentangle the causes and the effects between the decrease of MORs in relation to external eating.

4.2. Central CB_1-receptors and eating behavior

Higher Total DEBQ score associated with lower availability of central CB_1Rs, and ROI-level modeling suggested a consistent negative association with all DEBQ subscales. Compared with the [^{11}C]carfentanil model, wider posterior distributions reflect the uncertainty arising from smaller [^{18}F]FMPEP-d_2 sample size. Brain's endocannabinoid system is a major homeostatic signaling system, with CB_1Rs abundant in all known food intake regulating central regions (Bermudez-Silva

et al., 2010). In previous brain PET studies, lowered CB_1R availability has been associated with increased BMI (Hirvonen et al., 2012), while globally upregulated CB_1Rs have been found in anorexia nervosa (Gérard et al., 2011). These opposite phenotypes on body adiposity spectrum could potentially result from corresponding alterations from CB_1R-regulated food intake behaviors. Indeed, stimulation of CB_1Rs by pharmacological agonists or endocannabinoids promotes food intake and amplifies the rewarding properties of feeding (Richard et al., 2009). In contrast, antagonism of the CB_1Rs by rimonabant (withdrawn anti-obesity drug, Acomplia) effectively reduces food intake and increases energy expenditure, but in many patients also induces psychiatric symptoms (e.g. depressive mood, suicidality, anxiety) (Bermudez-Silva et al., 2010). Accordingly, the endocannabinoid system function has been connected to several other essential behavioral processes in addition to feeding (e.g. stress-coping, emotion regulation, pain perception) (Di Marzo, 2008; Lutz et al., 2015). Being this diverse and complex regulatory system, it may not be possible to pinpoint single distinct aspect of food intake behavior mediated by CB_1Rs. Rather, our results add support to central CB_1Rs role in regulation of multiple eating behavior traits, with implications on both homeostatic and hedonic feeding (Quarta et al., 2011).

4.3. Limitations and methodological considerations

The [^{11}C]carfentanil data were pooled from three PET scanners, which may produce minor variance in outcome measures (Nummenmaa et al., 2020). However, this was accounted for in the analyses by adding the PET scanner as a nuisance covariate to all full-volume and regional analyses. The sample studied with [^{11}C]carfentanil consisted predominantly of males, and our statistical power was compromised for detecting potential sex differences. Also all subjects of the [^{18}F]FMPEP-d_2 subsample were males, and thus conclusions regarding CB_1Rs might not be generalizable to females. Eating behavior was assessed by self-reports, rather than by direct observations. DEBQ has however been found to successfully identify clinically relevant eating styles (Baños et al., 2014; Wardle, 1987).

Our study had a cross-sectional design, and although we found evidence of eating behavior's association with MOR and CB_1R systems, whether these receptor systems' alterations directly promote future weight gain is to be examined in longitudinal studies. Finally, in a single PET scan it is not possible to determine the exact proportions for causal factors to the altered receptor availability, which could potentially be affected by changes in receptor density, affinity or endogenous ligand binding (Henriksen and Willoch, 2008).

5. Conclusions

Low cerebral MOR availability is associated with increased externally triggered eating behavior. Modern obesogenic environment may promote food consumption via engaging the opioidergic link of the reward circuit whose tone is linked with cue-reactive eating. Central CB_1Rs are in turn associated with multiple eating behavioral traits measured with DEBQ, consistent with endocannabinoid system's role as a major homeostatic regulatory system at the intersection of feeding, emotion and behavior.

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manuscript has been posted on preprint server bioRxiv (https://www.biorxiv.org/content/10.1101/2020.12.17.423284v1).

Data and code availability statement

The code for PET data processing pipeline (Magia) is available at https://github.com/tkkarjal/magia.

Author contributions

TaK: Corresponding and first author, study design, study coordination, data acquisition, data modeling, statistical analysis, interpretation of the results, tables and figures, main writer of the manuscript. ToK: Study design, data modeling, statistical analysis, interpretation of the results, figures, writing of the manuscript. LP: Data acquisition, interpretation of the results, writing of the manuscript. JI: Data acquisition, interpretation of the results, writing of the manuscript. KK: Interpretation of the results, writing of the manuscript. VK: Interpretation of the results, writing of the manuscript. JH: Data modeling, interpretation of the results, writing of the manuscript. PN: Study design, study coordination, interpretation of the results, writing of the manuscript. LN: Study design, study coordination, statistical analysis, interpretation of the results, figures, writing of the manuscript, supervision of the study.

Supplementary Material

Supplementary Material accompanies this paper.

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