Brain Cannabinoid CB1 Receptor Signaling Regulates Reward Response and Inhibitory Control

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Abstract

Despite centuries of cannabis use, its precise effects on cognition remain ambiguous. The central cannabinoid system, specifically in vivo CB1 receptor signaling, presents a promising target for treating eating disorders, yet its role in appetite control is still unresolved. In this study, we investigated key aspects of appetite regulation, including anticipatory food reward response and inhibitory control, in 41 healthy male participants. Functional magnetic resonance imaging was used to measure those brain cognitive responses, and CB1 receptor availability was quantified via [18F]FMPEP-d2 Positron Emission Tomography to assess its predictive value on reward response and cognitive control. Our findings revealed that individuals with higher CB1 receptor availability showed a stronger reward response and reduced inhibitory control. The findings underscore a distinct role for CB1 signaling in brain cognitive functions accounting for appetite regulation.

Key words: cannabinoid, CB1 receptor, reward, appetite, inhibition, feeding

Introduction

Overeating and obesity are significant global health concerns. Obesity is associated with an imbalance in brain systems governing appetite control, in that the reward circuit it is overactive to reward anticipation and inhibitory networks may fail to engage control of the reward circuit (1). The interaction between food reward responses and inhibitory control is crucial in understanding appetite regulation, since aberrant function of these systems may lead to overeating and weight gain (2). The molecular mechanisms underlying appetite control are not fully understood, but various neurotransmitter pathways, such as the dopamine and opioid signaling, are central to feeding (3, 4). Accumulating evidence also points to a key role for the endocannabinoid system in regulating appetite (5). This is underscored by the initial success of the CB1 antagonist rimonabant in managing weight (6), although its clinical use was discontinued due to psychiatric side effects (7). Marijuana use may stimulate appetite (8), but its long-term effects seem to lower the likelihood of overweight in users (9, 10). In our recent study involving generally healthy individuals, we further showed that family risk factors for obesity, exercise habits, and body mass indices are all potential modulators of central and peripheral CB1 signaling (11). However, the impact of cannabinoid signaling on brain function and eating behavior is complex, and its exact role in brain cognitive functions, especially in those relevant for appetite control, still remains unresolved.

The complex role of cannabinoid CB1 receptor signaling in regulating eating behaviors presents both therapeutic potential and challenges, especially for developing clinical interventions targeting eating disorders (5, 12). Elevated levels of the endocannabinoid 2-arachidonoyl glycerol (2-AG) in obesity correlate with higher body fat and fasting insulin levels, indicating a link between the endocannabinoid system and metabolic dysregulation (13). Preclinical studies have found that CB1 receptor activation promotes eating, supporting that CB1 antagonists could help curb overeating (6, 14). However, understanding CB1 signaling in appetite control is difficult due to its interactions with other neurotransmitter systems, such as the dopamine and opioid pathways (15). For example, activation of CB1 receptors affects the mesolimbic dopamine system, which governs reward and reinforcement behaviors, positioning CB1 as potentially substitutive for food intake by triggering dopamine-related satiation effects. This intricate receptor interaction contributes to the current ambiguity surrounding CB1's role in food reward responses. Despite some evidence suggesting cannabis use may protect against obesity, findings remain mixed, with discussions on acute versus long-term effects (9, 10). Advances in differentiating the roles of CB1, dopamine, and opioid receptors could yield new insights into managing eating behaviors and disorders through targeted pharmacological pathways.

In the current study, we investigated the specific role of central CB1 receptor signaling and its impact on appetite control, specifically the reward response and inhibitory control. CB1 receptor availability was quantified using positron emission tomography (PET) and radioligand [18F]FMPEP-d2 which binds selectively to CB1 receptors (16, 17). Acute responses to anticipatory food reward as well as inhibitory control were measured using task-based fMRI. We hypothesize that higher CB1 availability is associated with enhanced appetite, as is to be illustrated by increased anticipatory food-reward responses and reduced inhibitory control.

Methods

Participants

Healthy male participants with age of 20–35 years and BMI of 18.5–30 kg/m2 were involved in studies with fMRI (n = 41) and PET (37 out of 41) measures. None of the participants had detectable levels of 11-Nor-9-carboxy-delta9-tetrahydrocannabinol in their blood (a marker of

cannabis consumption). Exclusion criteria include smoking or use of nicotine products, abusive use of alcohol, use of illicit drugs, any chronic disease or medication that could affect glucose metabolism or neurotransmission, neurological or psychiatric disease, eating disorder, any contraindication to magnetic resonance imaging (MRI) and prior participation in PET studies or other significant exposure to radiation. More details of the participants can be found in our previous study (11).

PET data acquisition

Participants fasted for 6–12 hours before the [18F]FMPEP-d2 scans and were instructed to avoid physical exercise on the day of the PET scan as well as the day before. PET images were obtained using a PET/CT scanner (GE Discovery VCT, GE Healthcare). The tracer was administered via a catheter inserted into the antecubital vein. To prevent excessive head movement, the participants' heads were secured to the scan table. CT scans were performed prior to the PET scans for attenuation correction. Throughout the scanning process, participants were monitored by a physician. Plasma radioactivity was assessed at regular intervals using arterialized blood samples, measured with an automatic gamma counter (Wizard 1480 3", Wallac, Turku, Finland). T1-weighted anatomical MR images (TR: 8.1 ms; TE: 3.7 ms; flip angle: 7°; scan duration: 263 s; voxel size: 1 mm^3 isotropic) were acquired with a PET/MR scanner (Ingenuity TF PET/MR, Philips) for anatomical normalization and reference.

PET data modelling

The PET data was processed using the automated tool Magia (18). The processing pipeline started with motion correction of the PET scans, followed by co-registration of the PET and MR images. Before generating parametric images, the data was smoothed with a Gaussian kernel (FWHM = 6 mm) to improve the signal-to-noise ratio for model fitting. Finally, parametric images were spatially normalized to MNI space and smoothed again using a Gaussian kernel (FWHM = 6 mm). CB1 receptor availability was quantified as [18F]FMPEP-d2 volume of distribution (VT) using graphical analysis (Logan) (19), where the starting point of 36 min was used and plasma activities were corrected for metabolites (11, 20).

fMRI data acquisition

MRI data were collected using the Phillips Ingenuity TF PET/MR 3T whole-body scanner. High-resolution structural brain images (1 mm^3) were obtained using a T1-weighted sequence. Functional MRI (fMRI) data were acquired with a T2*-weighted echo-planar imaging sequence (TR = 2600 ms, TE = 30 ms, 75° flip angle, 240 mm field of view, 80×80 reconstruction matrix, 62.5 kHz bandwidth, 3.0 mm slice thickness, 45 interleaved slices acquired in ascending order without gaps). For the inhibitory control task, 145 functional volumes were collected, and 165 volumes for the food-reward task.

Behavioral measures

Anticipatory food reward experiment. We employed a previously established task (4, 21) to induce anticipatory reward response by presenting participants with images of palatable foods (e.g., chocolate, pizza, cakes) and bland foods (e.g., lentils, cereal, eggs), **Fig. 1A**. This task mimics real-life situations where appetite is stimulated by visual food cues, such as those found in advertisements. During the task, participants viewed alternating 16.2-second blocks displaying either palatable or bland food images. Each block contained nine images from one category, interspersed with fixation crosses. The food images were shown on either the left or right side of the screen, and participants were instructed to indicate the location by pressing corresponding buttons, ensuring they paid attention to the stimuli. Behavioral tasks were administered using Presentation software (Neurobehavioral System, Inc., Berkeley, CA, USA).

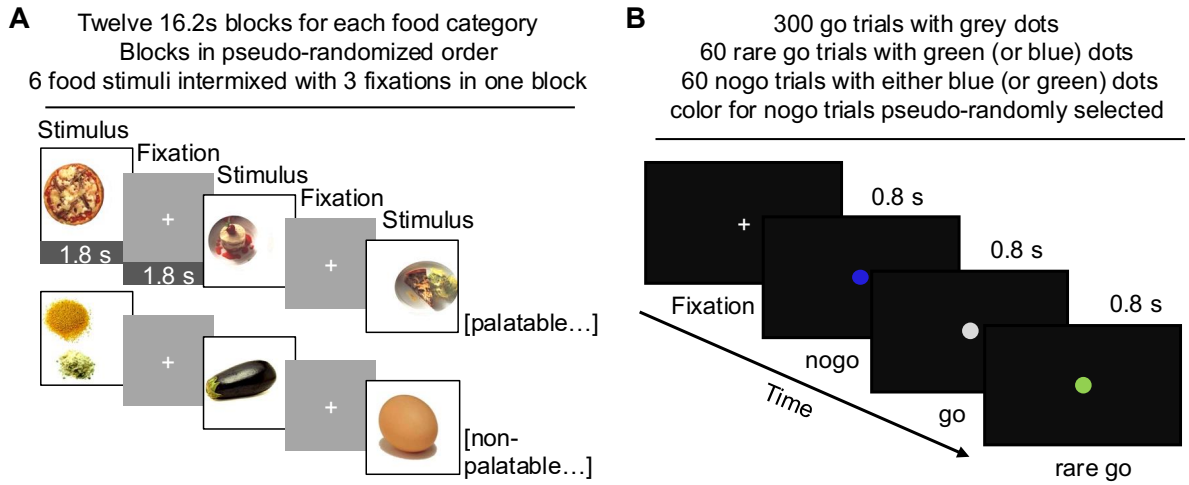

Figure 1. Behavioural tasks. **A)** Design for the anticipatory food-reward experiment. **B)** Design for the response inhibition task.

Inhibitory control task. Participants were instructed to press a button with their left hand in response to a "go" signal and to refrain from pressing the button during a "no-go" signal, **Fig. 1B**. Small dots were displayed sequentially in the center of the computer screen at 0.8-second intervals. The dots appeared in three colors: gray (70% of trials), green (15%), and blue (15%). Gray dots always signaled "go," requiring participants to press the button. Green and blue dots were randomly assigned as either rare "go" or "no-go" signals for each participant. The statistical contrast for inhibitory activation was based on equal probability of the green and blue dots serving as signals.

fMRI data processing

MRI data were processed using fMRIPrep version 1.3.0.2 (22). Structural T1 images underwent correction for intensity non-uniformity, skull stripping, brain surface reconstruction, and spatial normalization to the ICBM 152 Nonlinear Asymmetrical template version 2009c through nonlinear registration using antsRegistration (ANTs 2.2.0) and brain tissue segmentation. Functional MRI data were processed through a series of steps: co-registration with the T1 reference image, slice-time correction, spatial smoothing with a 6 mm Gaussian kernel, and automatic removal of motion artifacts using ICA-AROMA. The data were then resampled to the MNI152NLin2009cAsym standard space. The quality of the images was visually inspected to ensure whole-brain field of view coverage, proper alignment with the anatomical images, and absence of signal artifacts, and this was further verified through visual reports generated by fMRIPrep. All functional data were included in the present study.

Statistical analysis

Behavioral data. Reaction times for the go trials were analyzed, with outlier values below 100 ms or above 800 ms removed, as previously (23). Reaction times were analyzed separately using a mixed-effects linear model, with mean whole-brain GM CB1 Availability, Age and BMI as fixed factors and Subject as a random factor. Accuracy rates were calculated as the percentage of “no response” in all no-go trials, and they were analyzed using linear regression model with GM CB1 Availability, Age and BMI as factors. All analyses were conducted using R statistical software. Button responses in the food reward task were only acquired to ensure attention to the stimuli and were consequently not analyzed.

fMRI data. The full-volume fMRI data were analyzed in SPM12. The whole-brain random effects model was applied using a two-stage process with separate first and second levels. For each subject, first-level GLM was used to predict regional effects of task parameters on BOLD indices of activation. These parameters are in the response inhibition task: no-go vs. go signals; go signals include both "go" and "rare go" signals; in the food-reward experiment, palatable vs. bland food pictures. First-level contrast images were then subjective to second-level analysis. Statistical threshold was set at $p < 0.05$ with FDR correction at cluster level.

PET-fMRI fusion analysis. To map the association between cerebral CB1 receptor and anticipatory reward and inhibition responses, we used PET-fMRI fusion analyses where hemodynamic responses to the i) palatable vs. bland food images and ii) inhibitory responses (nogo vs. go trials). Because high regional autocorrelation of CB1R availability ($r > 0.9$, **Supplementary Figure S1**) mean grey matter CB1 availability (rather than regional availabilities) was used to predict task-specific response in the fMRI data, while controlling for Age and BMI. Statistical threshold was set at $p < 0.05$ with FDR correction at cluster level.

Regions of interest analysis. To validate the findings of full-volume analysis, brain regional BOLD and CB1 receptor levels were analyzed with Pearson correlation analysis. Six regions of interest (ROIs) were selected including the anterior cingulate cortex (ACC), amygdala, caudate, middle frontal cortex (MFC), insula and thalamus. Selection of ROIs were also justified by findings related to brain regions involved in reward and feeding behavior (23, 24).

Results

Brain CB1 receptor availability

Mean distribution of brain CB1 receptors is shown in **Fig. 2**.

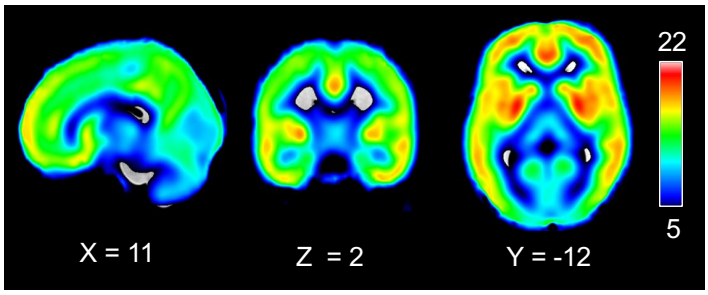

Figure 2. Mean distribution of brain CB1 receptor availability of the participants.

CB1 Receptor Availability and Brain Food-Reward Responses

In the anticipatory food-reward task, haemodynamic responses were elevated to palatable food pictures in regions such as the paracentral area (ParaC) and lingual gyrus (LG) (**Fig. 3A**). In contrast, decreased neural responses were observed in larger brain clusters including the caudate, thalamus, insula, precentral cortex (PreC), precuneus (PreCu), cingulate cortex (CC), and middle frontal cortex (MFC).

In the PET-fMRI fusion analysis higher CB1 availability was positively associated with increased haemodynamic responses in large brain clusters spanning the caudate, thalamus, amygdala, insula, MFC, CC, PreCu, PCC, mid-temporal gyrus, and LG (**Fig. 3B**). No negative associations were found between CB1 availability and these reward responses.

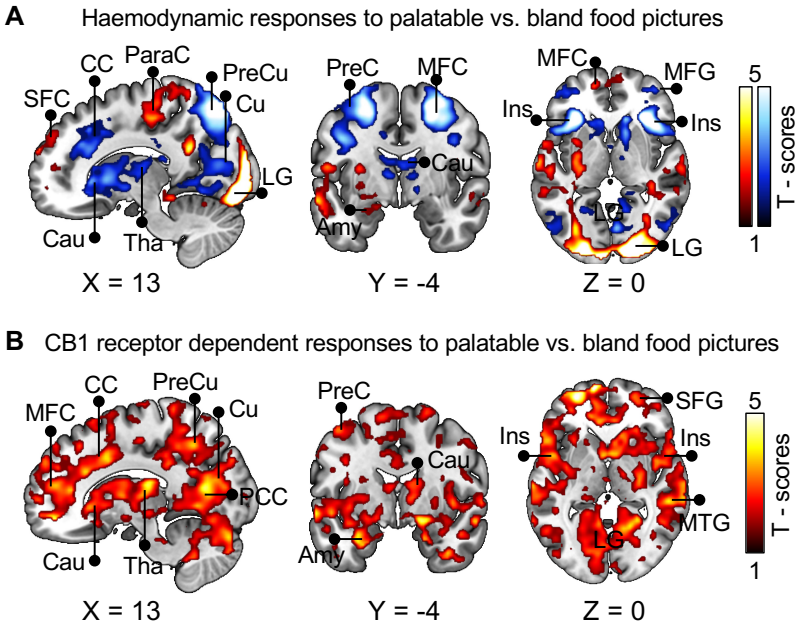

Figure 3. *Haemodynamic responses to palatable food images and their dependency on CB1 availability. (A) Haemodynamic BOLD responses to palatable versus bland food pictures. Hot colors indicate increased BOLD signals, while cold colors indicate reduced BOLD signals. (B) Increased CB1 receptor availability is associated with enhanced brain food-reward responses. Data are FDR-corrected at $p < 0.05$. Amy = amygdala, Cau = caudate, CC = cingulate cortex, Cu = cuneus, Ins = insula, LG = lingual gyrus, MFC = middle frontal cortex, MTG = middle temporal gyrus, ParaC = paracentral cortex, PCC = posterior cingulate cortex, PreCu = precuneus, SFC = superior frontal cortex, Tha = thalamus.*

Aligning with full-volume analysis, ROI-level PET-fMRI fusion analysis was further conducted. Data showed that brain CB1 receptor availability was significantly correlated with BOLD responses to palatable versus bland food images (**Fig. 4**).

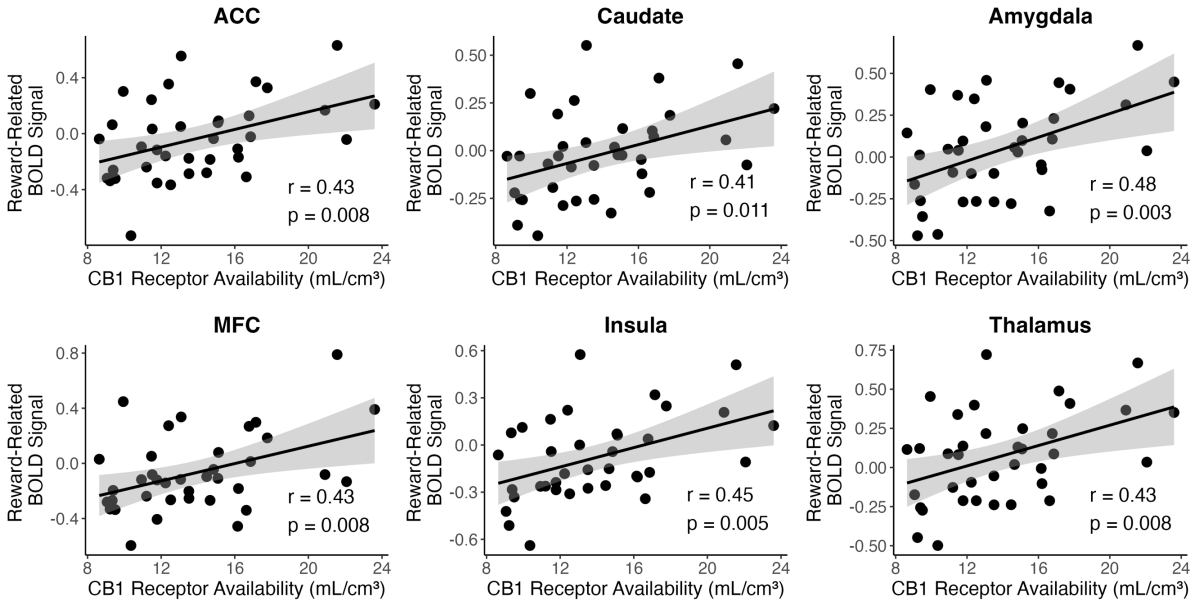

Figure 4. *ROI-level correlations between grey matter CB1 availability and BOLD responses to palatable versus bland food images. ACC = anterior cingulate cortex; MFC = middle frontal cortex.*

CB1 receptor availability and inhibitory control

Haemodynamic responses were larger during nogo trials compared to go trials in large clusters encompassing the primary and secondary motor cortical areas (including the precentral cortex [PreC], postcentral cortex [PostC], and paracentral area [ParaC]), insula, caudate, thalamus, substantia nigra (SN), middle frontal cortex (MFC), precuneus, inferior parietal lobe, superior temporal gyrus (STG), mid-temporal gyrus (MTG), and mid-occipital gyrus (**Fig. 5A**). Reduced responses were also observed in regions such as the superior frontal gyrus (SFG) and the posterior cingulate cortex (PCC).

PET-fMRI fusion analysis indicated that increased CB1 receptor availability was associated with heightened activation in the primary and secondary motor areas, cuneus, thalamus, insula, precuneus, STG, and SN (**Fig. 5B**). No negative associations were found between CB1 availability and BOLD responses during the inhibition task. These associations were however not manifested in the behavioral response data. CB1 availability had no statistically significant effects on reaction times either when "rare go" trails were included (β = -0.042, 95% CI [-0.097, 0.012]) or when they were excluded (β = -0.043, 95% CI [-0.097, 0.012]). Brain CB1 availability also had no impact on accuracy rate in the response inhibition performance (β = -0.011, 95% CI [-0.032, 0.010]). Also, age and BMI did not have statistically significant impact on either reaction times or accuracy rate.

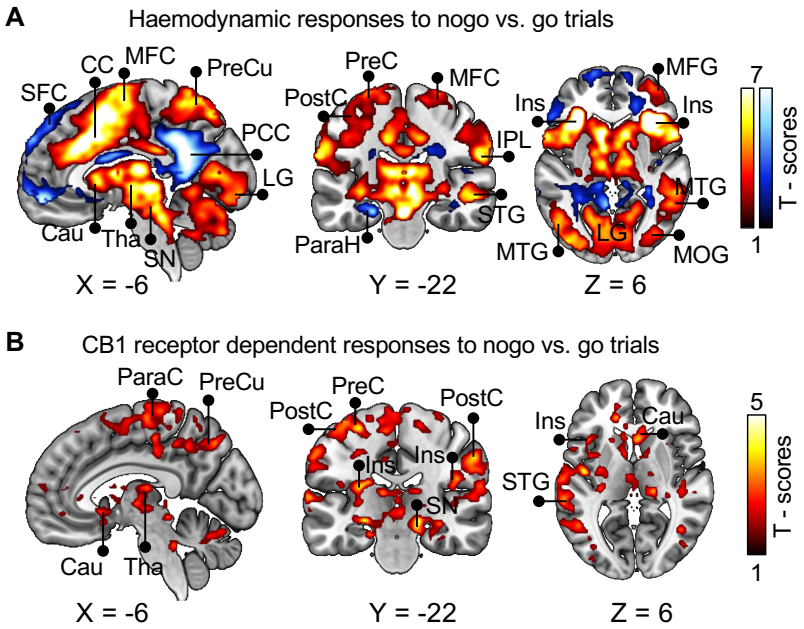

Figure 5. *Haemodynamic responses to inhibition and their dependency on CB1 availability. (A) Increased (hot color) and decreased (cold color) haemodynamic responses during nogo versus go trials. (B) Increased CB1 receptor availability is associated with greater effort in inhibitory control. Data are FDR-corrected at p < 0.05. Cau = caudate, CC = cingulate cortex, Ins = insula, IPL = inferior parietabl lobe, LG = lingual gyrus, MFC = middle frontal cortex, MOG = middle occipital gyrus, MTG = middle temporal gyrus, ParaC = paracentral cortex, ParaH = parahippocampus, PCC = posterior cingulate cortex, PreC = precentral cortex, PreCu = precuneus, SFC = superior frontal cortex, SN = substanti nirgra, STG = superior temporal gyrus, Tha = thalamus.*

Discussion

Our key finding is that the CB1 system is closely linked to brain reward responses and inhibitory control, highlighting its modulatory effect on appetite. Unlike traditional pharmaceutical studies, where a specific drug is often used to stimulate the cannabinoid CB1 system to disclose its potential functions, the current study leverages the *in vivo* nature of PET imaging, leaving the targeted system with trivial disturb. Cannabinoid receptor signaling is highly intertwined with the dopamine and opioid systems, making traditional studies insufficient in isolating the specific role of the cannabinoid CB1 receptor in brain functions. This study therefore bears merits in providing a clearer understanding of the purified role of this system. These findings align with previous studies showing that deactivating this pathway can reduce food intake (6), while activation promotes weight gain (25). Collectively, this evidence supports therapeutic strategies targeting the endogenous cannabinoid system for treating eating disorders.

Normal-weight individuals exhibit widely diverse responses to palatable versus bland food images. Contrary to our previous findings showing dominant BOLD signal activation in response to palatable food images (4, 23), participants in the current study displayed large-cluster suppression in reward circuits, including the caudate. This may suggest, at the sample level, a preference for bland light-tasting over high-caloric (assumed to be palatable) food images. Interestingly, the up- or down-regulated preference of high-caloric food is genuinely explained by the individual levels of cannabinoid CB1 receptor availability. Higher CB1 receptor signaling is consistently associated with stronger responses to high-caloric food pictures, affecting neural activity in major reward circuits.

Our data also show that individuals with higher CB1 receptor levels have aberrant inhibitory control. This is demonstrated with added effort in performing the task of inhibition, i.e., increased BOLD signals in key brain nodes, while the behavioral outcomes remain at a similar level. The inhibitory control task is highly engaging, requiring high attentional concentration, accurate and rapid responses. This task has been found to be sensitive toward endocrinological challenges, where infusion of a satiation-inducing hormone reduces brain reward responses and enhances inhibitory control (23). Therefore, together with increased food-reward responses, the aberrant cognitive control further supports an enhanced appetite in participants with higher brain cannabinoid CB1 receptor availability.

Clinically, these findings may have significant implications for understanding and managing eating disorders and obesity. Therapeutic strategies that modulate CB1 receptor activity could offer a targeted approach to restore balance between reward sensitivity and inhibitory control, as to be monitored via behavioral approaches. For instance, pharmacological interventions that blocks CB1 receptor signaling should efficiently attenuate the hyper-responsiveness to external food cues. Similarly, personalized treatments could consider individual variations in CB1 receptor availability to optimize behavioral or pharmacological interventions for weight management. These insights also emphasize the importance of integrating neuroimaging biomarkers into clinical research, enabling precise identification of individuals who might benefit from cannabinoid-based treatments. Overall, targeting the endogenous cannabinoid system offers a promising avenue for addressing the growing public health challenge posed by eating disorders and obesity.

Traditional studies on CB1 signaling have tightly linked its function with those of the dopamine and opioid signaling pathways. For example, activating CB1 receptor leads to increased release of dopamine in the brain limbic regions (15), and also activating dopamine D2 receptors promote release of anandamide, a endocannabinoid (26). Pharmaceutical effects are largely

enhanced when targeting both receptor signaling pathways simultaneously (27), with findings showing that these two receptors form heterodimers in co-expressed subcortical regions (28). The CB1 receptors also form heterodimer complex with the MORs in specific brain regions (29), with functional overlap including modulating pain pathway and reward (30). This linkage between MORs and CB1Rs receptors challenges traditional pharmaceutical studies applying drug modulation of the neurotransmission system, making the specific role of CB1 receptor signaling ambiguous. In contrast, the current study highlighting a specific role of the cannabinoid systems bears neuroscientific merits.

Limitations

The current study included only non-obese males, limiting the potential generalizability of the findings to females or individuals with eating disorders. Additionally, this study focuses on acute brain responses to appetite-inducing images and inhibitory control, thus it does not reveal how CB1 receptors would regulate responses to actual feeding or long-term-feeding behavior in general. Technically, while [18F]FMPEP-d2 binding in baseline condition is proportional to cannabinoid C1 receptor density, the exact contributions of receptor density, receptor affinity, and baseline occupancy by endogenous cannabinoid cannot be assessed in a single measurement, and these components cannot be differentiated in a single scan.

Conclusions

The present study underscores the critical role of brain cannabinoid CB1 receptor availability in modulating reward responses and inhibitory control, key neural systems involved in appetite regulation. The findings suggest that individuals with elevated CB1 receptor availability may require increased engagement of inhibitory control mechanisms to counteract reward-driven responses triggered by external cues, as opposed to enhanced internal satiety signals. These insights have potential implications for developing therapeutic strategies targeting the endogenous cannabinoid system to address eating disorders.

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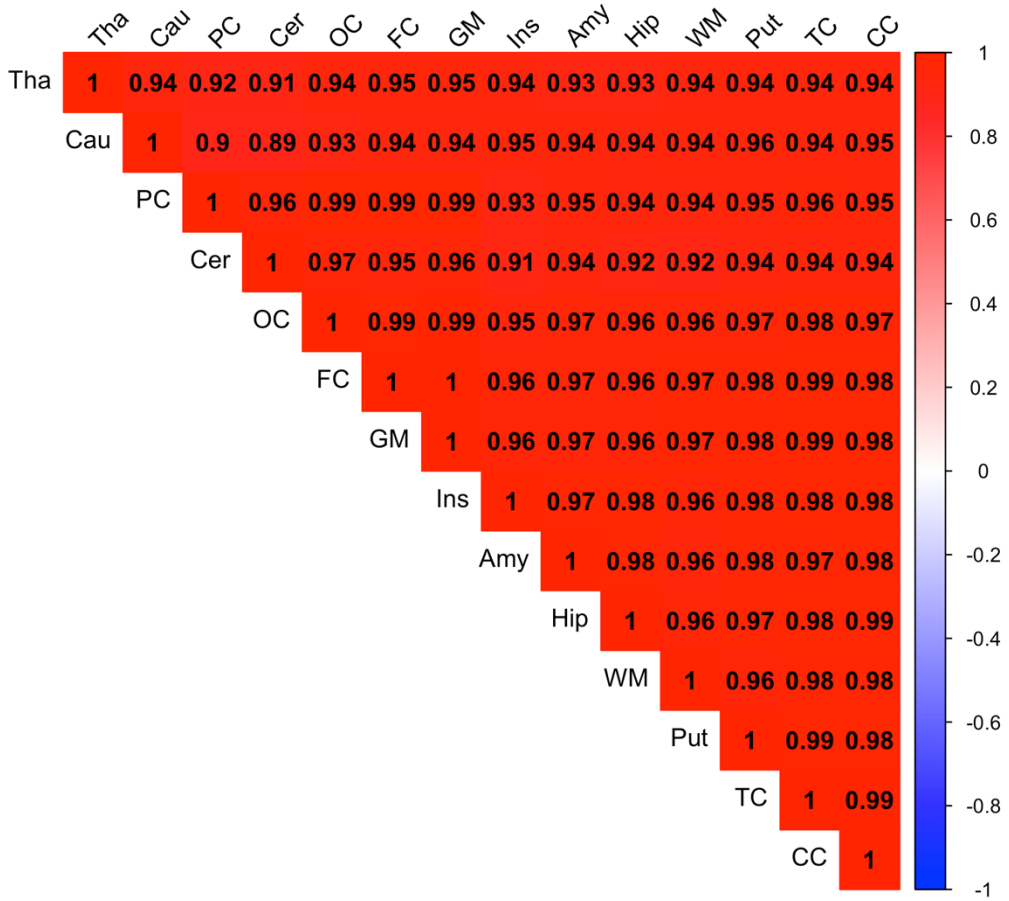
Supplementary Data



Supplementary Figure S1. Correlation between regional cannabinoid CB1 receptor availabilities. Amy = amygdala, Cau = caudate, CC = cingulate cortex, Cer = Cerebellum, FC = frontal cortex, Hip = hippocampus, GM = grey matter, Ins = insula, OC = occipital cortex, PC = parietal cortex, Put = putamen, TC = temperal cortex, Tha = thalamus, WM = white matter.