**Supplementary Material**

**Methods**

*Preprocessing of fMRI data*.

Resting state data were preprocessed in our laboratory. As described in Ang et al. (2020), preprocessing of the data was performed in SPM12 and included realignment, slice-timing correction, normalization to Montreal Neurological Institute (MNI) space, and smoothing with a 6-mm kernel. SPM12 was used to evaluate head motion by translation and rotation in *x*, *y*, *z* directions. Next, Artifact Detection Tools (ART, [www.nitrc.org/projects/artifact\_detect/](http://www.nitrc.org/projects/artifact_detect/)) were used to calculate outlier time points of head motion (>0.5mm from previous frame) or spikes in the magnetic field (global mean intensity higher than 3 standard deviations from mean intensity across functional scans). Similar to Ang et al. (2020), only participants with <15% outlier volumes of the resting state scan series were included in analyses; for these participants, outlier time points were included as covariates in all fMRI analyses. (Of note, groups did not differ with respect to the number of motion outliers (*p* value = 0.336). Further, framewise displacement showed no significant difference between groups overall (omnibus *p* = 0.196) or for *post hoc* pairwise comparisons (see Supplemental Table 2). Additionally, framewise displacement was not significantly associated with body mass index (BMI) (*r* = 0.084, *p* = 0.23).) To reduce physiological artifacts, a denoising process was employed by estimating and regressing out physiological noise from white matter and cerebrospinal fluid for each participant using the CompCor method (Behzadi, Restom, Liau, & Liu, 2007). A first-level general linear model included three translation plus three rotation parameters along with one composite motion parameter indexing maximum scan-to-scan motion, as well as modeling of outlier images and CompCor corrections. Then, in order to remove frequency related to cardiac and respiratory activity, a temporal band-pass filter of 0.009-0.10 Hz was applied to the time series.

*Statistical analyses of demographic and clinical measures*

For most non-categorical measures (e.g., clinical symptom measures, age, BMI), we used one-way analysis of variance (ANOVA) to compare mean values across groups. When applicable, Tukey’s Test was used to perform post-hoc comparisons. For non-categorical measures that were substantially skewed (e.g., the length of current MDD episode), we used a Kruskal-Wallis Rank Sum Test to compare median values across groups. A Fisher’s exact test was used to compare groups on categorical measures (e.g., sex, race). Significance was set at *p* ≤ 0.05 for omnibus tests.

*Region of interest definition*

In the mask-restricted analyses, the NAcc, caudate, putamen, and ventral pallidum were defined using masks from the California Institute of Technology (CIT168) probabilistic atlas (Pauli, Nili, & Tyszka, 2018) using a probability threshold of 0.5. Masks of the hypothalamus, anterior insula, and OFC were anatomically defined and obtained from Makris (Makris et al., 2006; Makris et al., 2016; Makris et al., 2013). See Supplemental Figure 1 for details. Given inadequate coverage of the OFC due to signal dropout, we created a conjunction mask derived from all participants’ data and only examined voxels within the OFC that were present in all participants; these voxels were located in the lateral OFC, and the medial OFC was not included due to signal dropout. For the seed-based connectivity analyses, the mask for the NAcc and masks resulting from the fALFF group comparisons were used as seeds.

*Preregistration*

Hypotheses and data analysis plans were pre-registered on Open Science Framework (see <https://osf.io/fxqdp>), with the following exceptions. Resting state analyses using the fALFF seeds, as well as sensitivity analyses using QIDS appetite and weight change scores, were included following preregistration in response to co-author (and reviewer) feedback on further elucidating initial results. Likewise, supplemental analyses focused on BMI were included following preregistration in response to reviewer feedback. Also, analyses exploring moderation by sex were included following preregistration at the suggestion of a reviewer. Additionally, one sensitivity analysis proposed in the preregistration was not performed since BMI status matching was not possible, and another (i.e., adjustment for depression scores) was not performed because there were no differences between MDD groups. Finally, the actual sample size (*n* = 223) was smaller than the preregistration sample size due to the removal of one additional participant without relevant fMRI data.

*Sensitivity Analyses with Appetite and Weight Change Scores*

 Pearson’s correlations were used to examine the bivariate relationships between beta values from each significant fALFF and RSFC finding (fALFF in the right anterior insula, fALFF in the right lateral OFC, RSFC between right lateral OFC and left anterior insula, and RSFC between right OFC and left precentral gyrus) on the one hand and the QIDS appetite (or weight) change scores on the other hand, as well as for beta values and BMI. Results are presented in Supplemental Figure 2.

Multiple regression analysis was used to examine whether beta values from all four significant fALFF and RSFC findings predicted QIDS appetite change scores, or (separately) QIDS weight change scores. Results are presented in Supplemental Tables 3 and 4 below. To assess for possible multicollinearity within our multiple regression model, we also calculated the variance inflation factor (VIF) using the *car* package in R. Results (see Supplemental Table 5) indicated low correlations between the variables included as predictors.

*Analyses of fALFF and RSFC for BMI*

In response to a reviewer’s comment, we used CONN to conduct supplementary analyses focused on BMI. Specifically, we investigated how fALFF and RSFC (for the NAcc) correlated with BMI, controlling for *Sex* and *Site*. We performed the analyses for the regions within our mask, as well as the whole brain. All details of analyses and reporting are the same as for our primary analyses.

**Results**

*Sample characteristics*

*Demographics*. There was a significant difference in sex frequencies across groups (*p* = 0.038), with the hyperphagic MDD group having more female participants than the other MDD groups. Groups also differed on BMI (*p* < 0.001), with the hyperphagic MDD group having higher BMI than all other groups. No significant differences were found across groups for age (*p* = 0.486), education (*p* = 0.952), race (*p* = 0.607), or Hispanic or Latino ethnicity (*p* = 0.088). See Table 1 for details.

*Clinical Measures*. With regards to the clinical measures, the healthy comparison group showed significantly lower scores compared to all MDD groups (all *p*-values < 0.001) on the MASQ subscales for general distress, anhedonic depression, and anxious arousal, and the SHAPS score.

There were no significant differences among MDD groups for MDD severity (*p* = 0.408), number of episodes (*p* = 0.054), age at MDD onset (*p* = 0.274), QIDS scores (*p* = 0.111), or the MASQ subscales (all *p* values > 0.05). For the SHAPS, the hypophagic MDD group had significantly higher scores (*p* = 0.025), indicating greater anhedonia, when compared to the euphagic MDD group. Lastly, all MDD groups differed significantly from each other with respect to the appetite and weight change scores calculated from QIDS, in the expected directions (all *p* values < 0.001). No other significant differences were found among the other group comparisons.

*Analyses of fALFF and RSFC for BMI*

Findings for BMI (see Supplemental Tables 6 and 7, which report significant clusters for fALFF and NAcc seed-based connectivity, respectively) were generally different than those found for the appetite/weight phenotype groups. For BMI, there were no significant findings for the mask-restricted fALFF analyses, although numerous regions emerged as significant in the whole brain fALFF analyses. Also, several regions emerged as significant in the mask-restricted and whole brain NAcc seed-based connectivity analyses.

**References**

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Supplemental Table 1. Image acquisition parameters for the four research sites: Columbia University (CU), Massachusetts General Hospital (MGH), University of Texas Southwestern Medical Center (TX) and University of Michigan (UM).

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **CU** | **MGH** | **TX** | **UM** |
| Scanner  | General Electric 3T | Siemens Tim Trio 3T | Phillips 3T | Phillips 3T |
|  |  |  |  |  |
| T1  | FSPGTR = 6.0 msTE = 2.4 msTI = 900 msSlices = 178Slice thickness = 1 mmFOV = 256x256 mmMatrix = 256x256Flip angle = 9º | MPRAGETR = 2300 msTE = 2.54 msTI = 900 msSlices = 176Slice thickness = 1 mmFOV = 256x256 mmMatrix = 256x256Flip angle = 9º | Turbo Field EchoTR = 8.2 msTE = 3.7 msTI = 1100 msSlices = 178Slice thickness = 1 mmFOV = 256x256 mmMatrix = 256x256Flip angle = 12º | MPRAGETR = 2100 msTE = 3.7 msTI = 1100 msSlices = 178Slice thickness = 1 mmFOV = 256x256 mmMatrix = 256x256Flip angle = 12º |
|  |  |  |  |  |
| T2\*  | TR = 2000 msTE = 28 msSlice thickness = 3.1 mmFOV = 205x205 mmMatrix = 64x64Flip angle = 90ºScan time = 6 min | TR = 2000 msTE = 28 msSlice thickness = 3.1 mmFOV = 205x205 mmMatrix = 64x64Flip angle = 90ºScan time = 6 min | TR = 2000 msTE = 28 msSlice thickness = 3.1 mmFOV = 205x205 mmMatrix = 64x64Flip angle = 90ºScan time = 6 min | TR = 2000 msTE = 28 msSlice thickness = 3.1 mmFOV = 205x205 mmMatrix = 64x64Flip angle = 90º Scan time = 6 min |

Supplemental Table 2. Head motion using framewise displacement, by group

|  |  |
| --- | --- |
|  | **Framewise Displacement** |
| **Group** | **Mean** | **Standard Deviation** | **Contrast** | ***p* value** |
| Healthy Comparison | 2.67 | 1.16 | Euphagic MDD | 0.9033 |
|  |  |  | Hypophagic MDD | 0.3968 |
|  |  |  | Hyperphagic MDD | 0.1907 |
| Euphagic MDD | 2.94 | 1.44 | Hypophagic MDD | 0.8321 |
|  |  |  | Hyperphagic MDD | 0.5827 |
| Hypophagic MDD | 3.23 | 1.68 | Hyperphagic MDD | 0.9682 |
| Hyperphagic MDD | 3.37 | 2.16 |  |  |

Abbreviations: MDD = major depressive disorder

Supplemental Table 3. Results from multiple regression of QIDS appetite changes scores on beta values for significant fALFF and RSFC findings

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Predictors** | **Estimate** | **Standard Error** | ***t* value** | ***p* value** |
| Intercept | -0.1430 | 0.2245 | -0.637 | 0.5252 |
| fALFF R Anterior Insula  | -0.4016 | 0.2058 | -1.951 | 0.0530 |
| fALFF R Lateral OFC | 0.5296 | 0.2705 | 1.958 | 0.0522 |
| RSFC R Lateral OFC and L Anterior Insula | -0.2095 | 1.0569 | -0.198 | 0.8432 |
| RSFC R Lateral OFC and L PreCG | 2.1707 | 0.9269 | 2.342 | 0.0206 |

Abbreviations: fALFF = fractional amplitude of low-frequency fluctuations; L = left; OFC = orbitofrontal cortex; PreCG = precentral gyrus; QIDS = Quick Inventory of Depressive Symptomatology; R = right; RSFC = resting state functional connectivity

Supplemental Table 4. Results from multiple regression of QIDS weight changes scores on beta values for significant fALFF and RSFC findings

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Predictors** | **Estimate** | **Standard Error** | ***t* value** | ***p* value** |
| Intercept | -0.25175 | 0.22367 | -1.126 | 0.26227 |
| fALFF R Anterior Insula  | -0.23477 | 0.20503 | -1.145 | 0.25411 |
| fALFF R Lateral OFC | 0.61870 | 0.26949 | 2.296 | 0.02315 |
| RSFC R Lateral OFC and L Anterior Insula | -0.07377 | 1.05288 | -0.070 | 0.94424 |
| RSFC R Lateral OFC and L PreCG | 3.07992 | 0.92342 | 3.335 | 0.00109 |

Abbreviations: fALFF = fractional amplitude of low-frequency fluctuations; L = left; OFC = orbitofrontal cortex; PreCG = precentral gyrus; QIDS = Quick Inventory of Depressive Symptomatology; R = right; RSFC = resting state functional connectivity

Supplemental Table 5. Variance inflation factors for predictors included in the multiple regression models

|  |  |
| --- | --- |
| **Predictors** | **VIF**a |
| fALFF R Anterior Insula  | 1.0 |
| fALFF R Lateral OFC | 1.2 |
| RSFC R Lateral OFC and L Anterior Insula | 1.3 |
| RSFC R Lateral OFC and L PreCG | 1.1 |

Abbreviations: fALFF = fractional amplitude of low-frequency fluctuations; L = left; OFC = orbitofrontal cortex; PreCG = precentral gyrus; R = right; RSFC = resting state functional connectivity; VIF = variance inflation factor

a VIF above 5 indicates high collinearity between predictors (James, Witten, Hastie, & Tibshirani, 2017)

Supplemental Table 6. Clusters exhibiting significant findings for BMI in whole brain analyses of fractional amplitude of low-frequency fluctuations (fALFF). Models included adjustment for *Sex* and *Site*.

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Regiona** | **Clusterb****(x, y, z)c** | **Size** | **Peaks** | **Cluster****t** | **TFCE** | **Peak** **p-FWE** | **Peak** **p-unc** | **Type** |
| L and R Occipital Pole | -08 | -102 | -16 | 9741 | 306 | -13.06 | 1217.43 | 0.000000 | 0.000000 | WB |
| L Lateral Occipital Cortex | -50 | -78 | +24 | 609 | 26 | -5.81 | 544.32 | 0.003000 | 0.000001 | WB |
| L PHG | -12 | -02 | -22 | 198 | 5 | -6.72 | 500.72 | 0.005000 | 0.000007 | WB |
| L Temporal Pole | -50 | +10 | -18 | 62 | 1 | -5.62 | 499.15 | 0.005000 | 0.000007 | WB |
| L Cerebellum VIII | +12 | -72 | -56 | 295 | 40 | 7.19 | 481.91 | 0.008000 | 0.000012 | WB |
| R Frontal Pole | +34 | +40 | +04 | 133 | 7 | 8.13 | 481.39 | 0.008000 | 0.000012 | WB |
| R Cerebellum Crus II | +34 | -86 | -42 | 253 | 19 | -4.62 | 461.70 | 0.014000 | 0.000018 | WB |
| R Temporal Pole | +46 | +04 | -30 | 28 | 2 | 5.74 | 436.68 | 0.025000 | 0.000031 | WB |
| R Cerebellum Crus I | +56 | -50 | -34 | 43 | 2 | -4.16 | 436.29 | 0.025000 | 0.000031 | WB |
| R Frontal Pole | +34 | +58 | -08 | 73 | 8 | 5.65 | 434.37 | 0.026000 | 0.000032 | WB |
| R Cerebellum Crus I | +60 | -60 | -22 | 74 | 6 | -4.44 | 434.03 | 0.026000 | 0.000032 | WB |
| L Frontal Pole | -34 | +52 | -06 | 25 | 1 | 4.68 | 433.69 | 0.026000 | 0.000032 | WB |
| L Temporal Pole | -48 | +02 | -12 | 46 | 2 | -4.57 | 432.46 | 0.028000 | 0.000033 | WB |
| Brainstem | +06 | -46 | -60 | 61 | 9 | 5.45 | 428.92 | 0.030000 | 0.000036 | WB |
| L MTG | -60 | -02 | -16 | 59 | 6 | -6.17 | 424.91 | 0.032000 | 0.000038 | WB |
| L MTG | -68 | -20 | -22 | 25 | 1 | -4.22 | 419.04 | 0.034000 | 0.000042 | WB |
| R Cerebellum VI | +38 | -68 | -24 | 33 | 1 | -3.32 | 418.05 | 0.035000 | 0.000043 | WB |
| R TFC | +28 | -08 | -40 | 39 | 3 | 6.23 | 413.80 | 0.037000 | 0.000048 | WB |
| L Planum Polare | -42 | -6 | -10 | 58 | 1 | -3.96 | 400.05 | 0.048000 | 0.000071 | WB |
| L Superior Parietal Lobe | -30 | -50 | +46 | 27 | 1 | 3.94 | 399.59 | 0.048000 | 0.000072 | WB |

Abbreviations: FWE = family-wise error; L = left; MR = mask-restricted; MTG = middle temporal gyrus; PHG = parahippocampal gyrus; OFC = orbitofrontal cortex; R = Right; TFC = temporal fusiform cortex; TFCE = threshold-free cluster enhancement; unc = uncorrected; WB = whole brain

a Region with the most voxels within the relevant cluster

b Only clusters with more than 20 voxels are reported

c Montreal Neurological Institute (MNI)

Supplemental Table 7. Clusters exhibiting significant findings for BMI in mask-restricted or whole brain analyses of seed-based connectivity (with the nucleus accumbens as the seed). Models included adjustment for sex and site.

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Regiona** | **Clusterb****(x, y, z)c** | **Size** | **Peaks** | **Cluster****t** | **TFCE** | **Peak** **p-FWE** | **Peak** **p-unc** | **Type** |
| L Frontal Pole | -32 | +30 | -22 | 198 | 4 | -5.22 | 367.67 | 0.001000 | 0.000029 | MR |
| R OFC | +32 | +34 | -20 | 96 | 4 | -5.28 | 264.55 | 0.003000 | 0.000042 | MR |
| L Frontal Pole | -32 | +30 | -22 | 341 | 5 | -5.82 | 944.81 | 0.006000 | 0.000068 | WB |
| R OFC | +34 | +32 | -22 | 472 | 8 | -7.41 | 939.56 | 0.006000 | 0.000069 | WB |
| L OFC | -14 | +12 | -26 | 38 | 1 | -4.38 | 665.58 | 0.042000 | 0.000437 | WB |
| L PHG | -14 | -02 | -24 | 24 | 2 | -4.04 | 647.04 | 0.046000 | 0.000522 | WB |

Abbreviations: FWE = family-wise error; L = left; MR = mask-restricted; PHG = parahippocampal gyrus; OFC = orbitofrontal cortex; R = right; TFCE = threshold-free cluster enhancement; unc = uncorrected; WB = whole brain

a Region with the most voxels within the relevant cluster

b Only clusters with more than 20 voxels are reported

c Montreal Neurological Institute (MNI)

**Figure Caption**

***Supplemental Figure 1.* Regions of interest masks.** Masks for the nucleus accumbens, caudate, putamen, and ventral pallidum were extracted from the California Institute of Technology (CIT168) probabilistic atlas (Pauli et al., 2018). Masks of the hypothalamus, anterior insula, and lateral OFC were anatomically defined and obtained from Makris (Makris et al., 2006; Makris et al., 2016; Makris et al., 2013).

(Abbreviations: OFC = Orbitofrontal cortex; ROI = Region of interest)

***Supplemental Figure 2.* Scatterplot of the correlation between beta values from significant between-group findings and appetite or weight change scores or body mass index (BMI).** Beta values extracted from each significant region from group comparisons were correlated with the appetite change score, the weight change score, or BMI. The appetite change score combined Quick Inventory of Depressive Symptomatology (QIDS) items indicating appetite increase (represented by positive values) and appetite decrease (represented by negative values); the same procedure was used to create the weight change score. Scatterplots for appetite and weight changes scores include participants with major depressive disorder who correctly followed instructions for completing the QIDS appetite and weight change items (*n* = 147), and scatterplots for BMI include participants with major depressive disorder and healthy comparison participants with BMI available (*n*  = 201). Jitter was added to the plotted points to aid in visualization. With the exception of fractional amplitude of low-frequency fluctuations in the anterior insula and weight change and functional connectivity between the lateral orbitofrontal cortex seed and the anterior insula, beta values were mostly significantly correlated with the appetite and weight change items. Finally, no significant correlation was found between beta values and BMI. (Abbreviations: fALFF = fractional amplitude of low-frequency fluctuations; OFC = orbitofrontal cortex; QIDS = Quick Inventory of Depressive Symptomatology; RSFC = resting state functional connectivity)