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• **Supplementary File** •

Bariatric surgery induces alterations in effective connectivity between the orbitofrontal cortex and limbic regions in obese patients

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Appendix A Materials/Methods

Appendix A.1 Image Processing

All imaging data were preprocessed and analyzed using Statistical Parametric Mapping 12. The functional images first underwent slice-timing correction for within-scan time differences between slices. Framewise displacement (FD) was calculated to index the head movement from one volume to the next [1]. Next, we spatially normalized the realigned images to the standard EPI template and resampled them to a voxel size of 3 x 3 x 3 mm^3. Demeaning and detrending were performed and head motion parameters, white matter signals and cerebrospinal fluid signals were regressed out as nuisance covariates [2]. Root mean squared signal change (DVARS) which indicates the change in signal intensity from one volume to the next, and standard deviation (SD) were calculated respectively [2]. We compared the three parameters (i.e., FD, DVARS and SD) of each subject to the criteria proposed by Power and his colleague [1]. If any subject did not meet the requirements (FD value less than 0.5, and ΔBOLD of DVARS less than 0.5%) [1], we formed a temporal mask using the SD obtained from quality measures, performed a least-squares spectral decomposition of the good data (met the requirements) and this decomposition was used to reconstitute data at bad time points (did not meet the requirements) [2]. Thus, the good data defined the frequency characteristics of signals that then replaced the bad data [2]. A band-pass filter between 0.01 and 0.08 Hz was applied to the data to remove the effects of very low frequency drift and high frequency noise using the REST toolkit (http://resting-fmri.sourceforge.net). Spatial smoothing was not applied because this conventional preprocessing step could remove fine-grained spatial information potentially useful for GCA [3, 4], Global normalization was applied using the global scaling function of the SPM toolbox to remove global noise. Specifically, for each volume, the SPM function returned the mean counts integrated over the whole brain, and then the original value of each voxel was divided by this mean value. Although whether or how to remove the global noise is problemic-specific [5-9], we found that for our data the global normalization is helpful in reducing the common noise and making the BOLD time series more stationary [10, 11], which is required by Granger causality analysis.

Appendix A.2 ROI analysis

Slow fluctuations of brain activity are a fundamental feature of the resting brain, and their presence is vital to determine correlated activity between brain regions and to define resting state networks. The relative magnitude of these fluctuations can differ between brain regions and between subjects, and thus may act as a marker of individual differences or of dysfunction. ALFF [12] is a neuroimaging method that can be used to measure the spontaneous fluctuations in BOLD-fMRI signal intensity, and it has been investigated as part of a reliable biomarker for many neurological conditions such as attention-deficit hyperactivity disorder [12], schizophrenia [13], Alzheimers [14] and Parkinsons [15] diseases, anxiety [16], major depressive disorder [17, 18], obesity [19] and addiction [20]. The ALFF analysis was therefore carried out using the

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REST Toolkit (http://resting-fmri.sourceforge.net) to define the regions of interest (ROIs). The calculation procedure was the same as that reported in a previous study [12]. The filtered time series of each voxel was transformed to the frequency domain using a fast Fourier transform and the power spectrum was calculated accordingly. For each voxel, ALFF was calculated by averaging the square root of the power spectrum across 0.01-0.08 Hz [12]. For standardization, the ALFF of each voxel was further divided by the global mean ALFF values [12]. Then, the voxel-wise two-sample t-tests were employed to compare the differences in ALFF values between OB and NW groups (OB > NW). Paired t-test was used in the OB group for before and after surgery comparisons (PreBS > PostBS). The brain regions showing significant ALFF alterations related to the frontal-mesolimbic circuit were selected as ROIs ($P < 0.05$, cluster size > 100 voxels, False discovery rateFDR corrected).

Appendix A.3 Granger causality analysis

After obtaining the ROIs that showed significant ALFF differences of the two groups, GCA [21] was performed on the spatially normalized data. GCA is being increasingly applied to the analysis of functional neuroimaging data including electroencephalography (EEG) [22] and fMRI [11, 23-29]. Our group has successfully applied GCA methods to study cognitive and emotional processes [3, 4, 19, 30], and we have validated it using neural physiological data-based simulation [31].

In the current analysis, based on Bayesian information criterion [4, 24, 28, 32], the order of the vector auto regression (VAR) model was determined to be 2 [4, 24, 28]. Given any two ROIs time series x(t) and y(t), the following time domain pair-wise GCA components were evaluated based on an order-two VAR model: the causal influence from x(t) to y(t) ($F_{x\to y}$) and the causal influence from y(t) to x(t) ($F_{y\to x}$) were calculated. We used the individual voxel time series for each ROI pair after spatial normalization to calculate pair-wise GC values for all voxel pairs and then averaged the GC results of all voxel pairs between two ROIs to yield the mean GC values. We used this analysis strategy to avoid possible loss of temporal information when spatially averaging signals within an ROI [4]. Then, following a similar method used by Scridharan et al [33], we normalized the causal influence by using the following equation:

$$R_{x\to y} = (F_{x\to y} - F_{y\to x})/(F_{x\to y} + F_{y\to x})$$

where, $R_{x\to y}$ is the ratio that describes the relative strength and directionality of the causal influences between x and y. A positive $R_{x\to y}$ with a larger absolute value denotes stronger causal influence from x to y, while a negative $R_{x\to y}$ with a larger absolute value denotes stronger causal influence from y to x [33]. Finally, the alterations of $R_{x\to y}$ were calculated by computing the differences between the OB and NW, and in the OB group between before and after surgery, respectively.

Table 1 The brain regions showing differences in brain activity levels between OB and NW (OB vs. NW), and between pre- and post-surgery (PreBS vs. PostBS) in obese subjects

Contrast	ROI	Hem	MNI			t value	voxel	Contrast	ROI	Hem	MNI			t value	Voxel
			x	y	z						x	y	z		
OB>NW	OFC	L	-11	46	-27	3.38	27	PreBS>PostBS	OFC	L	-12	48	-27	3.55	51
		R	7	35	-24	4.42	189			R	15	42	-27	3.1	54
	AMY	L	-23	1	-16	4.31	1080		AMY	L	-21	-3	-18	3.92	81
		R	25	4	-19	3.29	513			R	21	-3	15	3.48	27
	HIPP	L	-32	-2	-25	3.42	135		HIPP	L	-24	-30	-15	3.16	216
		R	31	-2	-25	3.22	81			R	30	-18	-15	4.85	162
NW>OB	CAU	L	-8	22	0	3.4	162	PostBS>PreBS	CAU	L	-12	18	-6	3.3	27
		R	4	22	0	3.3	27			R	15	21	3	4.92	108
	THA	L	-2	-20	9	3.67	1188		THA	L	-6	-9	6	4.03	27
		R	1	-17	9	3.11	1053			R	6	-12	6	4.85	162

Table 2 Normalized ratios among ROIs demonstrate the alterations of directionality and strength of the effective connectivity. We arbitrarily designate the row index (Source) as i and the column index (Target) as j. If the (i,j) cell is red, it indicates the increased strength (normalized ratio) of casual influence from i to j in OB group compared to NW (OB vs. NW) and also in OB group before and after surgery (PostBS vs. PreBS), respectively; if the (i,j) cell is blue, it denotes the decreased strength (normalized ratio) of causal influence.

OB vs. NW

Source (X) \ Target (Y)	OFC	CAU	AMY	HIPP	THA
OFC		0.28	0.21	0.16	0.17
CAU					
AMY		0.03			0.03
HIPP		0.13			0.07
THA		0.08			

Normalized Ratio

PostBS vs. PreBS

Source (X) \ Target (Y)	OFC	CAU	AMY	HIPP	THA
OFC		0.19	0.06	0.07	0.12
CAU					
AMY		0.11			0.2
HIPP		0.12			0.03
THA		0.01			

Normalized Ratio

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