Effects of bariatric surger and weight loss on resting-state functional connectivity

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2 Introduction

/data/pt_02161/Analysis/Project2_resting_state/seed-based/Second_level /code_and_manuscript

Table 1: Distribution of data points at months after intervention

	BARS	NBARS
count: only 0	7	2
count: only 6	3	0
count: only 12	2	0
count: 0 and 6	4	4
count: 6 and 12	7	1
count: complete data	10	10
total number of subjects	33	17
total data points	64	42

3 Methods

3.1 Sample and study design

The ADIPOSITAS-Study conducted in the Charité Berlin is a observational, prospective and longitudinal design described in detail by Prehn et al. (2020). Data collection is still ongoing but only data available in April 2019 is used. The procedures followed were in accordance with the Helsinki Declaration. This study was registered at clinicaltrials.gov as NCT01554228 and described in more detailed in the preregistration under https://osf.io/mzyxv. Participants were recruited from the Center for Bariatric and Metabolic Surgery if they were between age 18 and 70 and fulfilled the inclusion criteria. These were, in accordance with BARS guidelines, a failure of conservative obesity treatment and either (1) a BMI > 40 km/m^2 or (2) a BMI > 35 kg/m^2 and at least one typical co-morbidity (e.g. type-2 diabetes, hypertension, non-alcoholic fatty liver disease)(Mechanick et al. 2013). Participants with a history of cancer, chronic inflammatory disease and addiction, other severe untreated diseases, brain pathologies identified in the MRI scan or cognitive impairments (MMSE score < 34) were excluded from the study. Measures were taken at baseline (BL), 6 (FU1) and 12 (FU2) months post-surgery or after the baseline appointment but not all participants have complete data for all time points (see Table 2). 20 participants had complete data, 16 provided data for two time points and 14 for only one time point. The current sample is the subsample of 69 subjects that were originally enrolled in the study entailing only subjects that have received MRI. Analyses were performed on all participants that provided at least one data point of fMRI data (detailed information on data availability in 1).

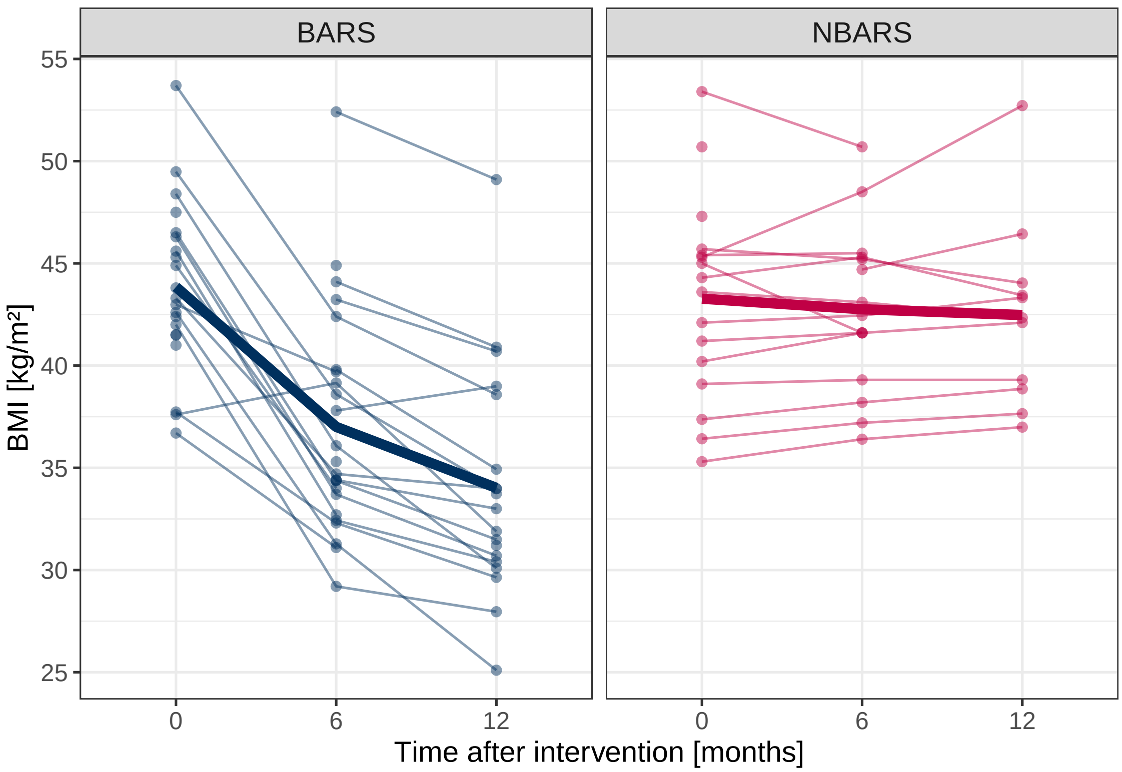
The final sample entailed morbidly obese individuals (n = 50, 37 female; ages 44.3 $\pm$ 11.64 SD years (range 21-68), that either underwent surgery (n = 17, 26 female) or were waiting list controls (n = 17, 11 female). The study design was quasi-experimental, as patient in the waiting control list had also been recommended to undergo bariatric surgery, but were still waiting for their health insurance's approval.

Histograms on baseline characteristics revealed, that patients in the control group did not differ notably from the intervention group regarding BMI and log mean FD, and only slightly in distribution of sex and age, the control group had a higher number of male participants (n = 6 vs. n = 10) and a higher mean age (47.25 vs. 39.33). As intervention, 0 participants received surgery that combines restrictive and malabsorptive mechanisms (RYGB) and 0 surgery purely restricting energy intake (VSG: n = 0, GB: n = 0).

Subjects arrived in the morning (between 07:00 and 12:00) after an overnight fast. They underwent medical assessments including an interview, blood draw and anthropometric measurements before having a one our break for STANDARDIZED?? breakfast. MRI scanning was done after further psychological tests (for details see Prehn et al. (2020)).

Table 2: BMI and mean FD of participants acquired in each condition and time point

predictor	tp	group	n	mean	sd
BMI	bl	IG	21	43.85	4.10
		KG	16	43.27	4.97
	fu	IG	24	37.00	5.44
		KG	15	42.76	4.04
	fu2	IG	19	34.02	5.58
		KG	11	42.47	4.49
logmFD	bl	IG	21	-0.65	0.28
		KG	16	-0.54	0.27
	fu	IG	24	-0.73	0.25
		KG	15	-0.49	0.29
	fu2	IG	19	-0.70	0.24
		KG	11	-0.52	0.27



3.2 fMRI acquisition

MRI images were retrieved with a 12-channel head coil of a 3 Tesla Siemens Trio system. T1-weighted anatomical images were acquired as described in Prehn et al. (2020) (with MPRAGE, TR = 1900 ms, TE = 2.52 ms, a = 9, voxel size = 1 x 1 x 1 mm^3, 192 sagital slices). Resting state gradient echo were acquired in 34 slices at an 90° flip angel with a repetition time (TR) of 2.3 s and echo time (TE) of 30 ms; image matrix = 64 x 64 voxel with in-plane resolution of 3 mm x 3 mm and a slice thickness of 4 mm, 150 volumes. The total acquisition time was 5:45 minutes. Field map or phase-encode reversed images were not acquired. Participants were instructed to close their eyes but to remain awake during scanning.

3.3 Pre-proceessing

Data preprocessing was conducted with FSL and Freesurfer using a nipype (version 14.0.2) workflow implemented in python 2.7. The preprocessing workflow included anatomical, functional and diffusion-weighted imaging preprocessing and wrapped modules from FSL version 6.0.1, Freesurfer version 6.0.0p1, ANTS . Details have been published on github https//:.???.com The T1-weighted image was segmented to remove non-brain tissue and together with the functional images normalized to a default brain template from the Monteal Neurological Institute (MNI) space. Functional images were smoothed with an 0 mm FWHM Gaussian kernel.

Preprocessing pipeline included removal of first four volumes and a transformation of the blood oxygen level dependent (BOLD) time series into the subject's anatomical space. This transform combines parameters from motion correction (FSL's MCFLIRT), fieldmap distortion correction (based on fieldmap and FSL's FUGUE) and coregistration to the subject's anatomical template space (using Freesurfer's bbregister and the transform from individual to longitudinal template space in Freesurfer's longitudinal processing stream).

Volumes were further preprocessed with ICA-AROMA and compCor (CC) and, optionally, with a subsequent global signal regression (GSR) (Ciric et al. 2017; Parkes et al. 2018) to reduce the effect of physiological noise and head motion on the connectivity estimates. As global signal regression is very efficient in removing the correlation of head motion and connectivity dependence, but is known to introduces spatial dependency and spurious correlations, we performed GSR after ICA-AROMA in a separate sensitivity analysis.

3.3.1 Seed region of interest (ROI)

Seed regions were . . . mm spheres in the precuneus (MNI: x,y,z = x,x,x) associated with the default mode network, and the Nucleus Accumbens (MNI: x,y,z = x,x,x) by averaging the time series across voxels.

3.3.2 Connectivity maps

Voxel-wise seed-based connectivity maps in the individual subject's space (which was coregistered to the Freesurfer longitudinally preprocessed timepoint (more details)) were calculated using Pearson's correlation between average seed time series from pre-defined ROIs within the reward network (Nucleus accumbens, NAcc) and the DMN (precuneus, PCC). Subsequently, r-to-z transform was applied to the correlation to obtain normally distributed functional connectivity (using nilearn, nipype and python). Then, we will transform the connectivity maps into MNI space with a non-linear warp derived from anatomical preprocessing of the longitudinally preprocessed timepoints (using ANTS).

3.3.3 Quality Assessment

Participants in which head motion artifacts affected the T1-weighted image preprocessing (e.g. caused Freesurfer to fail or perform very poorly, i.e. rated "Failed" according to Klapwijk et al. (2019)) were excluded because a subject's motion is highly similar across scans and we thus suspect the fMRI data to also suffer from motion artifacts in these subjects. As the expected average head motion is high (Hodgson et al. 2016), we did not exclude any other participants based on head motion estimates because it is difficult to determine a critical threshold in this sample. We therefore apply best-practice motion correction (ICA-AROMA and CC, plus optionally GSR) and monitor the reduction of motion-related artifact according to current recommendations (Ciric et al. 2018). As quality checks statistical analysis were performed on both with and without global signal regression, considering the controversial discussion about GSR introducing negative correlations and spatial bias into connectivity data (Ciric et al. 2017; Murphy and Fox 2017). Additionally, mean framewise displacement (FD) was extracted from 6 translational/rotational motion parameters of the whole time series according to Power et al. (2012), log-transformed and examined within and separate from the main models.

3.3.4 Outcomes

The main outcome measure was the aggregated functional connectivity (FC) values for the two ROI NAcc and PCC.

3.4 Analysis

Statistical analysis were performed in MATLAB using the sandwich estimator (SwE) toolbox 2.2.1 (Guillaume et al. 2014) as implemented in SPM12 and R version 3.6.1 (Team and others 2013). During analyses an implicit mask and an explicit mask were used. Therefore, the MNI ICBM 2009a Nonlinear Symmetric brain mask http://www.bic.mni.mcgill.ca/ServicesAtlases/ICBM152NLin2009 were re-sampled to 3 x 3 x 3 mm^3 and binarized at threshold 0.5.

Two theoretically derived models were set up. The first model was aimed at testing the interaction of time and group: $FC = group + time + group * time$. The second model on the influence of between-subject differences in average BMI and longitudinal within-subject change in BMI was specified as follows: $FC = between - subjectBMI + within - subjectBMI$. These were examined each for correlation maps of two different seed regions (NAcc / PCC), and for the purpose of comparison for correlation maps of two different preprocessing pipelines (only AROMA+CC / with GSR)), with two different covariate sets (with/ without mean FD), resulting in 16 a priori planned analyses. Initially, analyses were run with a brain mask but after post hoc considerations detailed below, models were re-run with a grey matter mask which reduced the number of tests (voxels of interest) from 52378 to 29451. As a result a total of 32 different analyses were performed. Computation with the grey matter mask were exploratory and deviate from the preregistration.

The marginal model implemented via the SwE toolbox implicitly accounts for random effects without the need to specify them through the error term. It therefore accommodates any repeated measurement covariance structures. We used a modified SwE assuming different covariance structures for the intervention and the control group because of their unbalanced sample size, so heteroscedasticity would be considered.

For the first model, time was introduced as factor because did not assume strict linearity for the increase in connectivity and sought to increase power to detect specific trends. The resulting flexible factorial design contained one regressor for each time point per group. For the second and third model, we calculated the centered mean BMI and log mean FD per subject and the intra-subject-centered BMI as proposed by Guillaume et al. (2014). With a model containing average BMI and longitudinal change per subject, we investigated potential effects .... on the complete sample and subsequently in a exploratory fashion for the intervention group only as the effect of longitudinal change in BMI was expected to be driven by this subsample. Age at baseline, sex, and log mean framewise displacement (FD) were entered into the first and second model as nuisance variables. Age and sex were between-subject covariates while FD is time-varying. Mean FD was log-transformed and age was demeaned by subtracting the overall mean across subjects and time points. As change in FD and change in BMI share variance (Beyer et al. 2019), the inclusion of log mean FD may be disputed and done optionally. For that reason, we performed each analysis separately one with mean FD and without. Differences in results will be reported. For a better understanding of the unique contribution of average and longitudinal change FD measures, we employed a third post hoc model to disentangle the effects: $FC = between - subjectFD + within - subjectFD$. These post-hoc analyses deviate from the preregistration and should be considered to be exploratory.

All parametric inferences on activation were drawn based on False Discovery Rate (FDR) adjusted p-values ≤ 0.05. To ensure robustness of our results, we computed estimates with non-parametric test using Wild bootstrap with an unrestricted SwE on all contrasts of interest for voxelwise inference, p-values were FDR-corrected for $\alpha = 5$. In contrast to the parametric estimation, Wild Bootstrap avoids any parametric distributional assumptions (e.g. random field theory), and is unlike permutation based framework appropriate for longitudinal data.

4 Results

4.1 Manipulation check

We ran separate one-sample t-test for network activation at baseline controlling for log mean FD, age, and sex for each time point to check whether the assumed reward and default mode network was at all identifiable.

4.2 Interaction effect of intervention and time

There was no interaction of group and time point regarding the resting state connectivity for neither the PCC nor the NAcc as was hypothesized. Nor was there a significant main effect for any of the covariates of interest (time, group) in voxelwise inference with FDR correction. Results obtained for parametric estimation and non-parametric wild bootstrap did not differ. When reducing the number of nuisance covariates by leaving out mean FD, connectivity was found between the PCC with one other voxel. In the connectivity maps only corrected with AROMA-CC co-activation of voxel $x, y, z = 18, 42, 30$ [mm] yielded $Z = 4.72$ ($q_{FDRcorr} = 0.040$). However, verification of the effect with non-parametric bootstrapping failed to yield significant ($p_{\mathrm{FWEcorr}} = 0.061$; $q_{FDRcorr} = 0.999$). There was no other significant co-activation for any other region of interest for neither of the preprocessing variants.

Parametric and non-parametric significance test for the model testing for group-time-interaction did not show any different results when using a grey matter mask. Again, parametric estimation and non-parametric estimation differed in regard to the group-time-interaction of PCC and voxel $(18, 42, 30)$ in the connectivity maps without GSR correction. While co-activation was significant in parametric estimation ($Z = 4.72$, $q_{FDRcorr} = 0.040$), it was non-significant when using wild bootstrap ($q_{FDRcorr} = 0.998$).

4.3 Effect of BMI

Next, we tested for significant effects of the average BMI and the individual change in BMI longitudinally across the three time points. There was no significant co-activation for neither the PCC nor the NAcc associated with average BMI nor change in BMI. Omitting mean FD as nuisance covariate did not change these results. Upon inclusion of only a subsample entailing participants from the intervention group but not the waiting control group, there was still no effect for average BMI, but a significant effect of change in BMI on co-activation between the seed region NAcc and a voxel $(-18, -42, -9$ [mm]$)$ with $Z = 4.64$ ($p_{FWEcorr} = 0.049$) (in GSR corrected connectivity maps). However the effect did not survive recalculation with Wild bootstrap ($p_{FWEcorr} = 0.426$). The effect also disappeared when running those tests without mean FD as nuisance covariate. Running the tests on a subsample of only two time points and omitting data from the third did not yield any significant co-activation with the regions of interest for neither of the preprocessing variants. Omitting mean FD did not change these results.

Results obtained from analyses with the grey matter masks were equal to those reported for the brain masks except test statistics for the above reported significant longitudinal effect for the NAcc in the intervention group differed only marginally ($q_{FDRcorr} = 0.048$) and did not survive recalculation with Wild bootstrap either ($q_{FDRcorr} = 0.552$). In regard to the exploratory expeditions on subsamples, consistent with previous results, no significant co-activation was found when using the grey matter mask.

4.4 Further investigation of the effect of FD

To investigate the unique contributions of the average value of and the longitudinal change in mean FD, we constructed a model that entailed both of the predictors as covariates of interest and only age and sex as nuisance covariates. Surprisingly, there was no significant effect neither for the total sample, nor for the intervention group only. Similarly, analysis with the grey matter mask did not reveal any findings either.

Unthresholded maps for the t-tests as well as contrasts of average BMI and change BMI of the main model, and post-hoc contrasts for average FD and change FD will be are published on NeuroVault.

5 Discussion

Utilizing resting-state functional MRI on morbidly obese individuals that either underwent or awaited bariatric surgery over the course of one year. Building on the evidence for post-surgery changes in functional activity, this study explored the longitudinal relationship between surgery-induced weight loss and functional integrity in target networks indicated by resting-state functional connectivity. Over the course of one year we collected neuroimaging and anthropometric data from 33 morbidly obese patients undergoing bariatric surgery and compared them to the longitudinal data of 17 patients on the waiting list. With the model on group-time-interaction, we primarily investigated whether changes in functional connectivity over time vary depending whether participants have received surgery or not, while controlling for individual variance in resting-state connectivity over time and at baseline. Beyond that, also main effects of the intervention and of the time were examined. The second model further investigates if changes in connectivity are a function of an average BMI (controlled for individual variance in BMI) and the longitudinal change in BMI.

To summarize, there were few significant co-activation that emerged from the marginal models. Co-activation was locally highly specific and (NOT???) in accordance with our hypothesis regarding network activity changes. Given the multiplicity of of models resulting from variations of inspected networks and sensitivity analysis for different preprocessing and correction approached, the obtained significant correlations between seed regions and voxels are likely to be false positive. Ventures to verify effects by re-calculating with non-parametric Wild bootstrap confirmed supported presumption as effects were not robust across estimation procedures.

Our results are not consistent with the present literature. Although there are few studies investigating the impact of bariatric surgery on functional connectivity at resting state, the present articles do significant changes in network activation [@;@;@].

However, hypotheses about the plasticity functional networks following bariatric surgery could not be validated. Due to the shortcomings of the inferential paradigm used, our null findings may either put conclusions drawn from previous research into question or may neither provide evidence for the presence nor the absence of the effect. A previous repeated measurement design with patients undergoing bariatric surgery and behavioral dietary intervention manipulating satiety showed a differential effect of satiety between intervention groups on the resting-state functional connectivity seeded in the precuneus. After the intervention, the functional connectivity was higher in bariatric patients. It decreased after a meal while dietary patients showed an increase (Lepping et al. 2015). prandrial state is a relevant factor when investigating spontaneous brain activity (Wiemerslage et al. 2016). putamine, insula

Common challenge in medical intervention studies is the difficulty to draw causal inference about the effect of interventions such as surgeries because randomization is often unethical or unfeasible as done in randomized control trials. To isolate the effect of the surgical intervention to a maximum possible extent, the intervention group has to be comparable to a control group in regard to predisposition. Studies comparing the sample of bariatric patients to lean individuals or behavioral dieters may have investigated risk or contributing factors to the condition or other dispositional difference between groups, e.g. in cognitive control, openness or responsiveness to behavioral interventions [@;@]. However, they provide insufficient evidence to directly evaluate impact of the surgical procedure. Prospective non-randomization trial study design are secondary to randomized control trials in regard to internal control. By establishing temporality, longitudinal measurements support the validity of conclusions about the effects of the surgery. Contrasting pre- and post-surgery measures change while controlling for individual variance. The waiting list control group equivalent in BMI, treatment history and treatment recommendation allows controlling for concurrent factors (Thiese 2014). Incorporating these consideration, our study aimed at a higher internal validity for conclusions about the effects of bariatric surgery on functional connectivity.

Size and composition of our sample did not allow separate analyses for the sexes. The disproportionate sex distribution is reflective prevalence differences and under-utilization of bariatric surgery by men (Fuchs et al. 2015; Chooi, Ding, and Magkos 2019).

Due to the limitation of the traditional ANOVA framework (with respect to the spherity assumption, handling missing data, handling continuous data), it is often recommended to use modern models such as mixed-effect models and marginal models (Chen et al. 2013; Guillaume et al. 2014; McFarquhar 2019). McFarquhar (2019) demonstrated that specifying complex multi-level models and deriving the correct contrast weights with standard neuroimaging software packages such as SPM and FSL can be quite tedious and complicated if done appropriately. However, for the purpose of comparison, we re-ran the analysis for the group-time-interaction with age and sex as nuisance covariates. An advantage of the group-time interaction in our model is that the F-ratio does not require partitioning the error and includes only factors and time-invariant nuisance convariates. The model was set up as flexible factorial design with factors "subject", "group", and "time" assuming unequal group variances. Differences could be attributed to different corrections for non-spherity and assumptions on voxel covariance structures. Detailed comparisons between SPM12, SwE, and other software packages have been described elsewhere (McFarquhar et al. 2016). Opposed to flexible factorial models, where each individual is modelled separately, models are parsimonious and preserve more degrees of freedom.

Based on concerns expressed in the literature [@], we tried to closely inspect and rigorously control for the influence of head motion. The presence of multicollinearity of our predictors has been established before. As described in Monti (2011) in the presence of multicollinearity, the unique contribution of the regressor for the prediction cannot be disentangled. Confidence in β estimates will suffers and estimates can behave erratic depending on which regressors included in the model.

6 Code availability

All code is available in the github repository https://github.com/hsx1/adi2_rsfmri. The code includes script for data preparation and analysis of different models.

7 Declaration of interest

8 Funding

9 Acknowledgments

10 Author Contributions

Stud conception and design Aqcuisiiton of data: Analysis andinterpretation of data: Frafting of manuscript: Ciritical revision:

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