Altered neural inhibition responses to food cues after Roux-en-Y Gastric Bypass

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Running title: RYGB modulates neural inhibition to food cues

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Abstract

Background: Roux-en-Y gastric bypass (RYGB) surgery is a highly effective weight-loss intervention that often reduces preference and intake of high-energy foods. Research into the neural mechanisms behind this shift has mainly focused on reward processing of food cues. However, the ability to successfully control food intake and thereby weight-loss also depends on inhibitory control capacity. We investigated whether RYGB leads to alterations in neural inhibitory control in response to food cues.

Methods: A food-specific go/no-go task with pictures of high-energy (desserts) and low-energy foods (vegetables), was used to assess neural inhibition responses before and after RYGB with functional magnetic resonance imaging. Data from 18 morbidly obese patients (15 females; age 41±11 years; BMI 42±4 kg/m^2 before; BMI 36±4 kg/m^2 after) were analysed. Pre- and post-RYGB BOLD fMRI responses were compared for response inhibition towards high- and low-energy foods. Participants were tested in a satiated state.

Results: Response inhibition to high-energy foods was associated with increased activation of the right lateral prefrontal cortex (PFC), right medial PFC, dorsolateral PFC, right middle cingulate cortex and the right inferior frontal operculum (involved in inhibitory control), after compared to before surgery. Response inhibition to low-energy foods elicited diminished post- compared to pre-surgery responses in the left superior temporal pole, right parahippocampal gyrus and right hypothalamus (involved in metabolic control).

Conclusion: Neural changes indicate improved response inhibition towards high-energy food cues, altered influence of metabolic control during response inhibition toward low-energy food cues and a more positive attitude to both high-energy and low-energy food after RYGB. Alterations in neural circuits involved in inhibitory control, satiety signalling and reward processing may contribute to effective weight-loss after RYGB.

Keywords

Bariatric surgery; weight-loss; go/no-go; food preferences; fMRI; impulsivity; inhibitory control

Introduction

Roux-en-Y gastric bypass (RYGB) patients frequently show decreased preferences and consumption of high-energy foods after surgery, which are associated with long-term weight reduction (Kenler, Brolin, & Cody, 1990; Laurenius et al., 2013; Ochner et al., 2011; Sjöström, 2013; Thirlby, Bahiraei, Randall, & Drewnoski, 2006). The underlying mechanism of this decreased preference for high-energy foods is yet unclear. Most studies to date focused on altered reward processing, but changes in inhibitory control may also play an important role. It has been suggested that people with low inhibitory control are more prone to overeating and hence to developing overweight or obesity (Guerrieri, Nederkoorn, & Jansen, 2008; C. Nederkoorn, Guerrieri, Havermans, Roefs, & Jansen, 2009; Weygandt et al., 2015). Suppression of automatic tendencies to choose highly rewarding energy-dense foods over low energy-dense foods could help to decrease caloric intake, which contributes to successful weight-loss.

How well we are able to control our impulses in part determines how much and what we consume. Decreased inhibitory control is assumed to increase the odds of eating in the absence of hunger, especially in a tempting and food-rich environment (Boutelle & Bouton, 2015; Meule, Lutz, Vögele, & Kübler, 2014; Volkow, Wang, & Baler, 2011), and could eventually lead to weight gain. Overeating and obesity have been associated with higher impulsivity, both in self-reported and behavioural measures (Bongers et al., 2015; Dykes, Brunner, Martikainen, & Wardle, 2004; Chantal Nederkoorn, Smulders, Havermans, Roefs, & Jansen, 2006; Rydén et al., 2003; Stoeckel, Cox, Cook, & Weller, 2007; Vainik, Dagher, Dubé, & Fellows, 2013). Furthermore, individuals that were unsuccessful in regulating their weight show decreased inhibitory control(Houben, Nederkoorn, & Jansen, 2012) while behavioural responses of successful weight-loss maintainers indicate better inhibition to high-energy foods (Phelan et al., 2011). The extent of inhibitory control seems to influence the ability to maintain weight-loss after intervention. RYGB surgery is widely viewed as the most effective method for long-term weight loss in morbidly obese individuals (Rubino et al., 2004). Previous studies into neural responsivity after RYGB or other types of weight loss surgery have mainly focused on (alterations in) reward processing during presentation of high-energy food cues (Bruce et al., 2012; Ochner et al., 2011; Ochner, Laferrère, et al., 2012). In order to better understand successful weight-loss regulation upon RYGB, it is important to consider changes in inhibitory control processes as well (Price, Higgs, & Lee, 2015).

Previous studies showed that people who were attempting to lose weight displayed increased activation of the inferior frontal gyrus and anterior insula/frontal operculum in response to pictures of high-energy foods (Smeets, Kroese, Evers, & De Ridder, 2013). These areas are involved in inhibitory control. Also, successful weight-loss maintainers show greater activation to food cues in prefrontal regions (superior-,

middle frontal gyrus) associated with inhibitory control (McCaffery et al., 2009). Batterink et al. (Batterink, Yokum, & Stice, 2010) have introduced a food-specific go/no-go task to assess neural measures of response inhibition to high-energy food items. In their study, a higher BMI was related to less activation during no-go trials in frontal inhibitory regions, including superior- and middle frontal gyrus, ventromedial- and medial prefrontal cortex, and orbitofrontal cortex. A higher BMI was also associated with more activation during no-go trials in the temporal operculum. Increased understanding of the (neuro)biological mechanisms involved in inhibitory control is necessary to improve the outcome of weight-loss interventions.

With this study we aimed to determine whether RYGB surgical intervention in morbidly obese patients results in altered neural activation underlying response inhibition, using a food specific go/no-go task. Participants were tested in a satiated state to better understand alterations in situations of overeating. We hypothesized that participants would be better able to suppress responses to high-energy items after RYGB surgery, as reflected in changes in neural responses related to inhibitory control, while behavioural and neural responses to low-energy items would remain similar.

Methods

Overall design

This study had a 2x2x2 within-subject design, including the factors time point (pre- and post-RYGB), stimulus (dessert/vegetable), and task-instruction (Go/No-Go).

Participants

Twenty morbidly obese individuals participated in the food-specific go/no-go task, pre- and post- RYGB surgery. All participants were enlisted to undergo RYGB surgery at Rijnstate hospital, Arnhem, the Netherlands. Requirements for the surgery were: Body Mass Index (BMI) of >40 kg/m^2 or >35 kg/m^2 with co-morbidity that was expected to improve after surgically-induced weight loss, long-lasting obesity (>5 years), proven failed attempts to lose weight in a conventional way, intention to adhere to a postoperative follow-up programme. Individuals were not considered for surgery when they were pregnant or lactating, had psychiatric disorders, alcohol or drug dependency, life threatening conditions or when they were dependent on the care of others. Patients were screened at Rijnstate hospital. All participants were right-handed, non-smoking, and did not have conditions that conflicted with MR safety or would cause artefacts in the MR images (*e.g.* claustrophobic, irremovable ferromagnetic objects in or on their body, pacemaker), had a normal sense of smell (scoring ≥10 on the identification part of the Sniffin' Sticks (Hummel, Kobal, Gudziol, & Mackay-Sim, 2007), were not vegetarian and did not have allergies or intolerances to the foods used in the study. Participants received financial compensation for

their contribution. All participants provided written informed consent before entering the study. The protocol was approved by the Medical Ethical Committee of Wageningen University (NL45837.081.13) and was executed in accordance with the ethical principles of the Declaration of Helsinki of 1975, as revised in 2013. The study was registered on clinicaltrials.gov as NCT02068001.

Experimental procedures

Participants visited the test facilities at three occasions. First, they were familiarized with the MRI test environment and the experimental task in a dummy MRI scanner at Wageningen University (training session). After the trainings session, actual measurements were performed in two identical test sessions. The first test session took place on average 3.3 (SD 1.8) weeks before, and the second test session took place on average 9.3 (range 8-12 weeks, SD 1.2) weeks after RYGB surgery. Participants were instructed to refrain from eating and drinking anything but water and weak tea in the three hours before the test sessions. Upon arrival at hospital Gelderse Vallei (Ede, the Netherlands), blood samples were taken for analysis of plasma levels of endocannabinoids and ghrelin (data reported elsewhere). Participants were tested in comfortably full state, to mimic a context of eating in the absence of hunger. We provided a standardized meal that was adapted to pre- or post-surgery conditions in order to match the hunger states of the participants before and after surgery. Participants first drank orange juice, and after a small break they consumed a standardized meal consisting of bread roll(s), cheese, ham and butter (see Supplementary Table 1). Following meal consumption, participants waited for 15 minutes. In order to assess changes in general inhibition participants filled in the 24-item BIS/BAS questionnaire (Carver & White, 1994). Measurements of brain reward responses to visual and olfactory food and non-food cues were collected (and reported elsewhere). At the end of this reward paradigm participants rated their appetite (hunger, fullness, prospective consumption, desire to eat, and thirst) on a 100-mm visual analogue scale (VAS). Then a structural MR image was collected. Finally, participants took part in two functional runs during which a food-specific go/no-go task was performed. At the end of the test session, olfactory performance was assessed using the Sniffin' Sticks (threshold, discrimination, identification; Hummel et al., 2007).

fMRI – Go/No-Go task

The food-specific go/no-go paradigm was adapted from Batterink et al. (Batterink et al., 2010). Participants were instructed to press a button as quickly and accurately as possible in response to go trials (75% occurrence) and to refrain from responding to no-go trials (25% occurrence). Two separate functional runs were performed, each consisting of 48 trials. One run contained go-vegetable items and

no-go dessert items, the other run contained go-dessert items and no-go vegetable items (see Figure 1). The order of the runs was counterbalanced between participants. During each trial a picture was presented for 500 ms, depicting either a low-energy vegetable (i.e. corn, peas, Brussels sprouts, radishes, carrot, broccoli, cauliflower, haricots, zucchini) or a high-energy dessert (i.e. ice cream, cake, frozen yogurt, pudding, chocolate mousse, chocolates, cookies). Participants had 2000 ms to respond from stimulus onset. Trials were presented in pseudo-randomized order. Between trials a fixation cross was presented for a duration of 7-19 seconds. No-go trials would appear after 1, 2, or 3 go-trials. Reaction times were measured from the beginning of trial onset and collected with a fiber-optic response box system. Stimuli were presented visually using the Presentation software package (Version 9, Neurobehavioral Systems, Davis, CA) and were displayed using a video projector that illuminated a rear projection screen located at the end of the magnet bore. Subjects viewed the stimuli through an adjustable mirror attached to the head coil.

<<Figure 1 Approximately here>>

(f)MRI measurements

Each participant was scanned at approximately the same time of day, between 14:00-17:00 at hospital Gelderse Vallei (Ede, the Netherlands). Images were acquired with a 3-Tesla Siemens Magnetom Verio MRI scanner in combination with a 32-channel head coil. A high-resolution T_1-weighted anatomical MRI scan was acquired (MPRAGE: repetition time = 1900 ms, echo time = 2.26 ms, 9° flip angle, field of view = 256 x 256 mm, 192 sagittal slices, voxel size = 0.5 x 0.5 x 1 mm). Subsequently, 176 T_2^*-weighted gradient echo images with BOLD contrast (repetition time = 2240 ms, echo time = 25 ms, 90° flip angle, field of view = 192 x 192 mm, 45 axial slices, ascending order, voxel size 3 x 3 x 3 mm) were acquired for each of the two functional runs during which participants performed a food Go/No-Go task. The imaging volume was tilted at an oblique angle of 30° to the anterior-posterior commissure line to reduce signal dropout in the orbitofrontal and ventral temporal lobes (Deichmann, Gottfried, Hutton, & Turner, 2003). Head movements were restricted by placing foam cushions next to the participants' head. In addition, adhesive tape was placed across the participants' forehead to provide feedback on head movements. Earplugs were provided for noise reduction.

Data analyses

Participant characteristics

Participant characteristics were analysed using SPSS in IBM SPSS Statistics for Windows, Version 22.0 (IBM Corp., Armonk, NY, USA). Paired-samples T-tests were used to test differences in weight, BMI, hunger ratings and BIS/BAS-scores pre- and post-surgery.

Behavioural data go/no-go

Behavioural data of the go/no-go task were also analysed using SPSS. Mean commission error rates of the go/no-go task were calculated by dividing the total number of incorrect responses to no-go trials by the total number of no-go trials. Mean omission error rates were calculated by dividing the total number of non-responses to go-items by the total number of go-trials. Mean reaction times (ms) of responses to each type of trial (go-dessert, go-vegetable, no-go dessert, no-go vegetable) were calculated for each participant. Response times below 200 ms and over 2000 ms were excluded. The low number of commission errors rendered the reaction time data for the no-go items unsuitable for statistical testing. Pre- to post-surgery differences in response time (ms) to go items were analysed by following a linear Mixed Effects Models procedure including stimulus type (go-dessert; go-vegetable) as fixed effects factor. Time point (pre- and post-gastric bypass surgery), stimulus (dessert/vegetable), and task-instruction (go/no-go) were included as repeated variables. A p-value of <0.05 was considered statistically significant.

<< Table 1 Approximately here >>

fMRI data go/no-go

Whole brain functional images were pre-processed and analysed using the SPM12 software package (Wellcome Department of Imaging Neuroscience, London, United Kfingdom) run within MATLAB 7.12.0 (R2011a, The Mathworks Inc). Functional images were slice timed, realigned and coregistered. The DARTEL framework was used to create a study-specific template and participant-specific deformation fields (Ashburner, 2007). The images were then spatially normalized to the Montreal Neurological Institute (MNI) standard brain using the study-specific DARTEL template and the participant-specific deformation fields. Smoothing was applied to the normalized images using an isotropic Gaussian kernel with a 6-mm full width at half maximum. Artefact Repair was applied using the ArtRepair toolbox in SPM12 (see: http://cibsr.stanford.edu/tools/human-brain-project/artrepair-software.html). Of the twenty datasets that were acquired, two datasets were excluded that contained movements more than 4 mm. Trials with commission errors (incorrect no-go trials) were not excluded from the analyses.

Subject level analyses: Each test session (pre-/post-surgery) was modelled separately. Four conditions were included per model: visual exposure to go dessert trials, no-go vegetable trials, go vegetable trials and no-go dessert trials. Motion-correction parameters were included in the model. For each subject four contrast images were calculated: nogo_dessert$_{pre}$ vs rest, nogo_dessert$_{post}$ vs rest, nogo_vegetable$_{pre}$ vs rest and nogo_vegetable$_{post}$ vs rest. Subsequently we subtracted the post-surgery contrast images from the pre-surgery contrast images using the SPM12 image calculation routine.

Group level analyses: Two one-sample T-tests were performed to test our hypotheses. In each test we looked at contrast images containing the difference between activations pre- and post-surgery (nogo_dessert$_{pre}$-nogo_dessert$_{post}$; nogo_vegetable$_{pre}$-nogo_vegetable$_{post}$). We report whole brain results, with a significance level of p=.001 (uncorrected) and a cluster extent threshold of k=8 contiguous voxels. The MarsBar toolbox (http://marsbar.sourceforge.net/) run in Matlab 7.12.0 (R2011a; The Mathworks Inc., Natick, MA) was used to extract mean beta values from all significant clusters. These values were subsequently correlated with pre- to post- surgery changes in BMI, changes in body weight, and changes in feelings of hunger, fullness, prospective consumption and desire to eat. Correlation analyses were performed in SPSS using Pearson's correlation coefficient.

Results

RYGB effects - weight loss

The mean weight of our study population decreased from 121±15 pre-RYGB to 105±16 kg post-RYGB (mean±SD), a mean weight loss of 17±3 kg (p<.001). This weight change led to a decrease in BMI from 42±4 to 36±4 kg/m^2 (p<.001), with a mean decrease of 6±1 kg/m^2.

Behavioural ratings

During the post-surgery test session, participants indicated less hunger before the go/no-go task (± 50 min after meal intake; p=.056), rated a higher fullness, a decreased prospective consumption and less desire to eat (all p<.01). Ratings for thirst were comparable between the two test sessions (p=.349; see Table 1). There were no changes in BIS/BAS scores, except for a slight increase in reward responsiveness pre- to post surgery (p = .045).

Behavioural data

No-go items

Commission errors (incorrect responses during the no-go items) for no-go dessert items occurred at a mean rate of 8.5% (±8.6) pre-surgery, and 8.8% (±10.9) post-surgery. Commission errors for no-go vegetable items occurred around 16.8% (±15.8) pre-surgery, and 14.8% (±14.7) post-surgery.

The go/no-go task included 12 no-go items per run. Commission errors to no-go dessert items occurred at 443±87 ms (mean±SD) pre-surgery and at 501±132 post-surgery. Commission errors in response to no-go vegetable items had a mean reaction time of 526±125 ms. After surgery, responses to no-go vegetable items occurred at 504±143.

Go items

For the go dessert items, the omission error rate (non-responses during the go-trials) changed from 0.9% (± 1.7) before surgery to 1.7% (±2.5) after surgery. The mean rate of omission errors for go vegetable items was 4.0% (±2.7) before surgery and 3.4% (±2.0) after surgery.

There were no significant differences between reaction times to go dessert items before (543±90 ms; mean±SD) versus after RYGB (567 ± 122 ms; p=.395), nor between reaction times to go vegetable items before (544 ± 138 ms) and after RYGB (538 ± 135 ms; p=.395).

Functional imaging data

No-go desserts

Comparisons between pre- and post-surgery fMRI BOLD responses for the no-go dessert trials revealed increased post-surgical activation of the right middle frontal gyrus (lateral part), the medial part of the right superior frontal gyrus, the right inferior frontal gyrus (pars triangularis), the right middle cingulum and the inferior frontal operculum (see Table 2 and Figure 2). There were no regions in which no-go activation was significantly decreased post- compared to pre-surgery.

There were no significant correlations between pre- to post-surgery changes in neural responses during no-go dessert trials and changes in BMI or body weight, changes in feelings of hunger, fullness, prospective consumption and desire to eat (all p >.05).

No-go vegetables

Pre-surgical neural activation to no-go vegetable items was significantly higher in the right hypothalamus, left superior temporal pole and right parahippocampal gyrus, relative to post-surgery (see

Table 2 and Figure 3). There were no regions in which activation was significantly increased post-compared to pre-surgery.

Pre- to post-surgery changes in activation of the right parahippocampal gyrus during no-go vegetable items were correlated with changes in ratings of fullness provided right before the go/no-go task ($r = -0.625$, $p = .007$). No significant correlations were found between pre- to post-surgery changes in neural responses during no-go vegetable trials and BMI or body weight, and changes in feelings of hunger, prospective consumption and desire to eat (all $p > .05$).

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Discussion

To our knowledge, this is the first study to investigate changes in neural inhibition to food cues after RYGB. We found pre- to post-surgery increases in neural response to no-go high-energy dense food items in regions involved in inhibitory control (middle, medial superior- and inferior frontal gyrus). Further, neural activation in response to no-go low-energy dense food items was less pronounced in regions related to satiation (hypothalamus, parahippocampal gyrus, superior temporal pole) after surgery. Alterations in reward related activation were found for both no-go dessert and no-go vegetable trials (inferior frontal gyrus, middle cingulate gyrus, inferior frontal operculum, parahippocampal gyrus, superior temporal pole).

As expected, neural activation to no-go vegetable items did not change after surgery in regions involved in inhibitory control. During response inhibition towards desserts, however, we observed increased involvement of prefrontal regions (middle-, medial superior- and inferior frontal gyrus) after surgery. Previous research has linked increased activation in these regions to greater exertion and success of inhibitory control (Chikazoe et al., 2009; Hutcherson, Plassmann, Gross, & Rangel, 2012; Kober et al., 2010; Li, Huang, Constable, & Sinha, 2006; Scharmüller, Übel, Ebner, & Schienle, 2012; Sebastian et al., 2012; Van der Meer, Groenewold, Nolen, Pijnenborg, & Aleman, 2011). This suggests that activation in these frontal regions can serve as an indicator for response inhibition capacity. Interestingly, Lapenta et al. found that it is possible to induce changes in response inhibition processes by transcranial direct current stimulation (tDCS) of the dorsolateral prefrontal cortex (dlPFC) (Lapenta, Di Sierve, De Macedo, Fregni, & Boggio, 2014). They showed that this type of neural stimulation leads to significant changes in

neural markers of inhibitory control, and also to reduced craving and food intake. In our study, increased prefrontal cortex activation post-surgery could indicate an increase in neural inhibitory control in response to appetizing food items. In contrast to Batterink et al. (Batterink et al., 2010) who found correlations between current BMI and prefrontal activation during inhibitory control, we did not find significant correlations between changes in prefrontal activation and changes in body weight or BMI. This is likely related to greater variation (from lean to obese) in current BMI in their study (Batterink et al., 2010), versus limited variation in within-subject changes in BMI in the current study. The observed changes in neural processing after RYGB support an improved response inhibition towards high-energy foods. Moreover, research on the effect of laparoscopic adjustable gastric banding, showed increased activity in similar frontal regions such as medial, middle, superior frontal gyrus, that was associated with weight loss (Ness et al., 2014). Together this highlights the role of neural circuitry implicated in reward and cognitive control in the success and maintenance of weight loss surgery.

Post-surgical reductions in parahippocampal gyrus, superior temporal pole, and also hypothalamus activation during low-energy no-go items, but not during high-energy no-go items, could relate to metabolic signals of satiety. In the current study, participants were equally satiated directly after meal intake in both test sessions (see Supplementary Table 2), but felt less hungry and more full post- compared to pre-surgery before starting the go/no-go task. This could be related to accelerated digestion and absorption of nutrients after RYGB (Bojsen-Moller et al., 2015). Moreover, a significant correlation was found between pre- to post-surgery changes in parahippocampal gyrus activation and changes in ratings of fullness. Previous studies found increased brain activation to high-energy food cues (visual, taste) in the parahippocampal gyrus and hypothalamus in a hungry compared to a satiated state (Haase, Cerf-Ducastel, & Murphy, 2009; LaBar et al., 2001; Leidy, Lepping, Savage, & Harris, 2011; Van der Laan, De Ridder, Viergever, & Smeets, 2011), and related this to an increased salience of energy-rich products during hunger (Mohanty, Gitelman, Small, & Mesulam, 2008; Van der Laan, De Ridder, Viergever, & Smeets, 2014). In light of this, the decrease in hypothalamic, parahippocampal and superior temporal pole activation during response inhibition after surgery suggests that the increase in feelings of fullness is related to a decrease in salience of low-energy products, but not high-energy products.

Besides increased activation in prefrontal regions of inhibitory control, we found increased activation in the inferior frontal gyrus, inferior frontal operculum and middle cingulate cortex during response inhibition towards high-energy food. Although, activation in these regions has been linked to selective attention and more effective response inhibition (Booth et al., 2003; Cojan, Waber, Carruzzo, & Vuilleumier, 2009; Hirose et al., 2009; Li et al., 2006), these regions are also implicated in processing of

reward value and taste evaluation in response to cue exposure during anticipation, consumption (Nummenmaa et al., 2012; Small, Zatorre, Dagher, Evans, & Jones-Gotman, 2001; Stice, Spoor, Bohon, Veldhuizen, & Small, 2008), and self-regulation (Hare, Malmaud, & Rangel, 2011; Vollm et al., 2006; Zotev et al., 2011). Our results thus suggest greater engagement of these reward-related areas during response inhibition for high-energy products after surgery. Decreased post-surgery activation of the parahippocampal gyrus and superior temporal pole during response inhibition for low-energy food products could also be associated with changes in reward processing. Increased activation in the parahippocampal gyrus during exposure to taste and smell of food was associated with decreasing reward value in healthy (Small et al., 2001) and obese subjects (Bragulat et al., 2010). The observed reduction in parahippocampal gyrus deactivation during response inhibition to low-energy food cues thus could imply a more positive attitude towards these cues. However, we have no ratings of liking or wanting ratings for the food stimuli, so we can only speculate about a link between the decrease in inhibitory activation and higher preference for low-energy products. Nevertheless, the relative increase in preference for low-energy food found in RYGB patients reported in previous studies (Kenler et al., 1990; Ochner, Stice, et al., 2012; Thirlby et al., 2006) and our own research (under review elsewhere), does support a more positive attitude towards vegetables after surgery.

As mentioned above, the regions in which we see increased activation in response to no-go dessert items after surgery have been linked to increased exertion of neural inhibitory control and also to more successful behavioural inhibition (Chikazoe et al., 2009; Hutcherson et al., 2012; Kober et al., 2010; Li et al., 2006; Scharmüller et al., 2012; Sebastian et al., 2012; Van der Meer et al., 2011). It would be interesting to link these neural data to actual behavioural changes. However, the limited amount of no-go trials (n=12) in the task we used, unfortunately rendered the behavioural data for this condition unsuitable for reliable statistical inferences about correlation to neural outcomes. Further, reaction times to go-dessert and go-vegetable items were not significantly different between the pre- and post-surgery test session. Thus, with the current data we cannot conclude whether the changes we find solely reflect increased exertion of neural inhibitory control or whether they have implications for actual behaviour. It is important to note though, that diminished activation assessed by means of fMRI BOLD response could imply more, as well as less efficient neural processing of stimuli. Future research including more extensive behavioural measures is needed to clarify the link between changes in neural and behavioural response inhibition in RYGB patients. However, the food specific go/no-go task does approach real-life decision-making processes better than the passive reward tasks that have been used in previous research (*e.g.* Ochner et al., 2011; Ochner, Stice, et al., 2012). Because of limited statistical power due to the relatively small sample size, we have used a relatively lenient threshold for the fMRI analyses. We

are aware that this increases the risk of false positive results. Nonetheless, this research provides unique additional insight in the mechanisms underlying the effectivity of RYGB surgery. The within-subject design provides a solid method for testing RYGB related changes. However, in order to rule out alternative mediating factors of the neural findings, besides surgery, future studies should preferably also include a control group of (morbidly) obese individuals, who will follow a dietary weight loss program, that includes the same psychological, and physical support that is offered in the bariatric surgery programme. Moreover, unlike most previous research, measurements in this study have been obtained in a satiated state, to better mimic a context of overeating that has a greater ecological relevance in obesity. Despite high effectiveness of RYGB on weight loss and promising results demonstrated in a 20 year follow-up study (Sjöström, 2013), weight regain after more than one year post-surgery is a recurring problem in a subset of patients (Himes et al., 2015). Perhaps additional (cognitive) treatment focused on improving and maintaining response inhibition skills can reduce weight-regain after RYGB surgery.

Conclusion

After RYGB surgery, patients showed increased activation during a food specific go/no-go task to high-energy food cues in prefrontal brain regions implicated in inhibition. These neural changes after surgery indicate improved response inhibition towards high-energy food cues and increased influence of metabolic control during processing of low-energy food cues. We found altered neural responses during response inhibition towards both high- and low-energy food cues in reward-related areas, which indicate a more positive attitude towards these cues after RYGB. It is plausible that changes in the (re)activity of neural circuits involved in inhibitory control, satiety and reward processing together underlie effective weight-loss by contributing to the shift in preference and intake from high- to low-energy dense foods observed after RYGB. Future research should aim to clarify the association between neural changes and actual measures of eating behaviour and put effort into improving effectivity of weight-loss treatment.

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363 Conflict of interest

364 The authors declare no conflict of interest.

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Figure legends

Figure 1. *The food-specific Go/No-Go paradigm. In block A. participants were instructed to press a button in response to vegetable items (36 items) and withhold their response to dessert items (12 items). In block B. the instruction was reversed, participants had to press the button in response to dessert items (36 items) and withhold their response to vegetable items (12 items). The block order was counterbalanced between participants.*

Figure 2. *Regions in which brain activation during response inhibition to dessert items was significantly different pre- and post RYGB surgery. Brain images were thresholded at p=.005 for visualisation.* ***Upper:*** *The right inferior frontal gyrus (Tri; MNI: 57 27 18) was more activated after compared to before surgery and the right inferior frontal operculum (MNI: 51 9 24) showed more activation after compared to before surgery.* ***Middle:*** *The right middle frontal gyrus (MNI: 45 54 6) was more activated after than before surgery and the right medial superior frontal gyrus (MNI: 12 60 27) showed deactivation before surgery and activation after surgery.* ***Lower:*** *The right middle cingulate cortex (MNI 3 -27 33) was more activated after surgery.*

Figure 3. *Regions in which brain activation during response inhibition to vegetable items was significantly reduced post- compared to pre-RYGB surgery. Brain images were thresholded at p=.005 for visualisation.* ***Left:*** *The right hypothalamus (MNI: 3 3 -12) was activated before surgery and deactivated after surgery.* ***Middle:*** *The right parahippocampal gyrus (MNI: 18 -15 -21) displayed activation before and deactivation after surgery.* ***Right:*** *The left superior temporal pole (MNI: -36 12 -27) showed activation before surgery and deactivation after surgery.*

Supplemental Table 1. Composition of the standardized meal.

	Men		Women	
	Pre	**Post**	**Pre**	**Post**
Bread Roll (*Wheat bread (±22 g/roll))*	4 pcs	2 pcs	3 pcs	1 pcs
Margarine (*Low-fat)*	30 g	15 g	15 g	15 g
Cheese (*Full-fat semi-cured)*	40 g	20 g	40 g	20 g
Ham	40 g	20 g	20 g	-
Orange Juice	150 g	75 g	100 g	50 g
kCal total meal	570	174	421	107

Supplemental Table 2. Hunger ratings provided after meal intake and around 50 minutes before the go/no-go task commenced, before and after RYGB surgery.

		Pre-surgery Mean ± SD	Post-surgery Mean ± SD	Sign. Difference
Hunger	*100-mm VAS*	11 ± 21	11 ± 24	$p = 0.954$
Fullness		74 ± 25	67 ± 35	$p = 0.335$
Prospective consumption		25 ± 26	8 ± 18	$p = 0.051$
Desire to eat		18 ± 19	12 ± 23	$p = 0.435$
Thirst		66 ± 27	53 ± 29	$p = 0.049$

Table 1. Weight, BMI, Hunger ratings provided right before the go/no-go task and BIS/BAS scores before and after RYGB surgery.

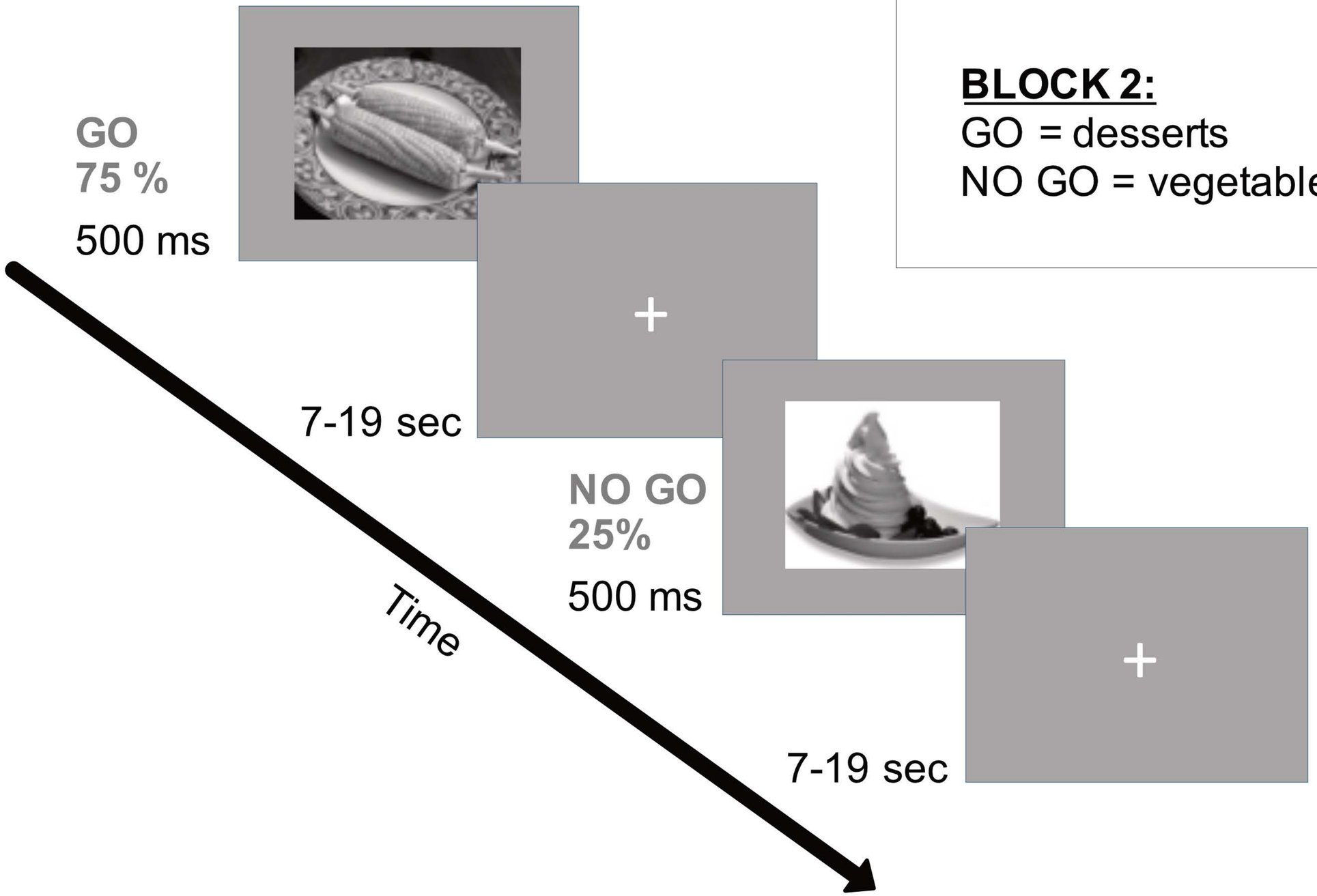
		Before surgery Mean ± SD	After surgery Mean ± SD	Sign. Difference
Weight (kg)		121 ± 15	105 ± 16	$p <$ 0.001
BMI (kg/m^2)		42 ± 4	36 ± 4	$p <$ 0.001
Hunger	*100-mm VAS*	27 ± 31	14 ± 24	$p =$ 0.056
Fullness		43 ± 29	72 ± 18	$p =$ 0.001
Prospective consumption		37 ± 27	17 ± 21	$p =$ 0.002
Desire to eat		44 ± 35	24 ± 26	$p =$ 0.009
Thirst		76 ± 26	70 ± 28	$p =$ 0.349
BAS Drive	*max 16*	11.6 ± 2.1	12.1 ± 2.2	$p =$ 0.132
BAS Fun Seeking	*max 16*	10.8 ± 2.1	11.3 ± 2.3	$p =$ 0.166
BAS Reward Responsiveness	*max 20*	17.8 ± 1.6	18.4 ± 1.6	$p =$ 0.045
BIS	*max 28*	20.3 ± 4.4	19.8 ± 3.6	$p =$ 0.366

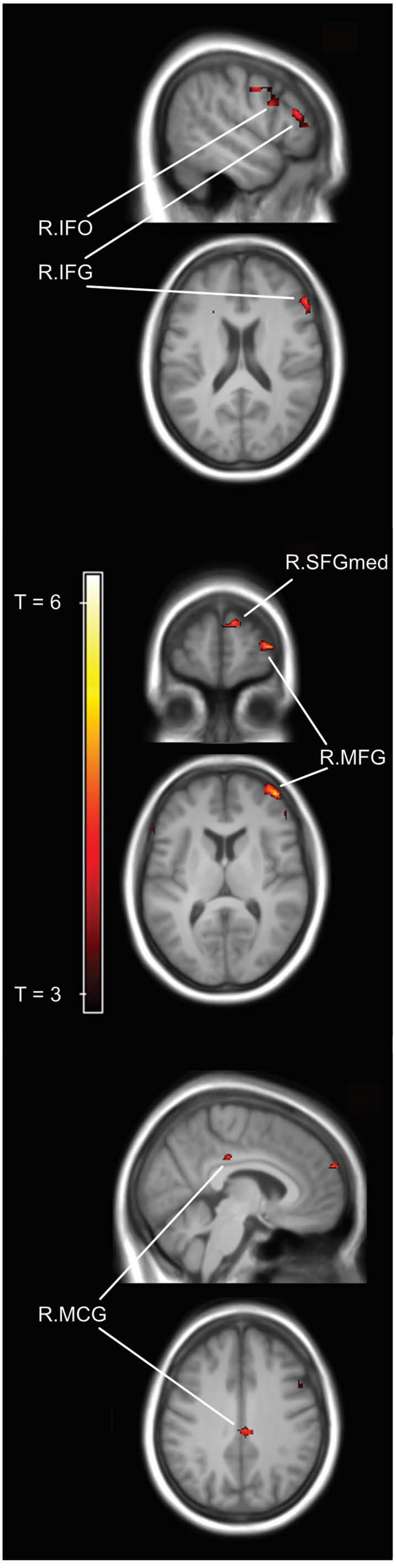
Table 2. Regions in which brain activation during no-go food items was significantly different pre- and post RYGB surgery

			cluster size	Z-score	Peak coordinates		
					x	y	z
DESSERT							
$no\text{-}go_{pre} < no\text{-}go_{post}$	R	Middle Frontal Gyrus / Lateral PFC	30	4.42	45	54	6
	R	Medial Superior Frontal Gyrus / Medial PFC	23	4.02	12	60	27
	R	Inferior Frontal Gyrus (Tri) / Dorsolateral PFC	15	3.87	57	27	18
	R	Middle Cingulum (posterior part)	10	3.59	3	-27	33
	R	Inferior Frontal Operculum	10	3.53	51	9	24
VEGETABLE							
$no\text{-}go_{pre} > no\text{-}go_{post}$	R	Hypothalamus	10	3.65	3	3	-12
	L	Superior Temporal Pole	11	3.63	-36	12	-27
	R	Parahippocampal gyrus	9	3.34	18	-15	-21

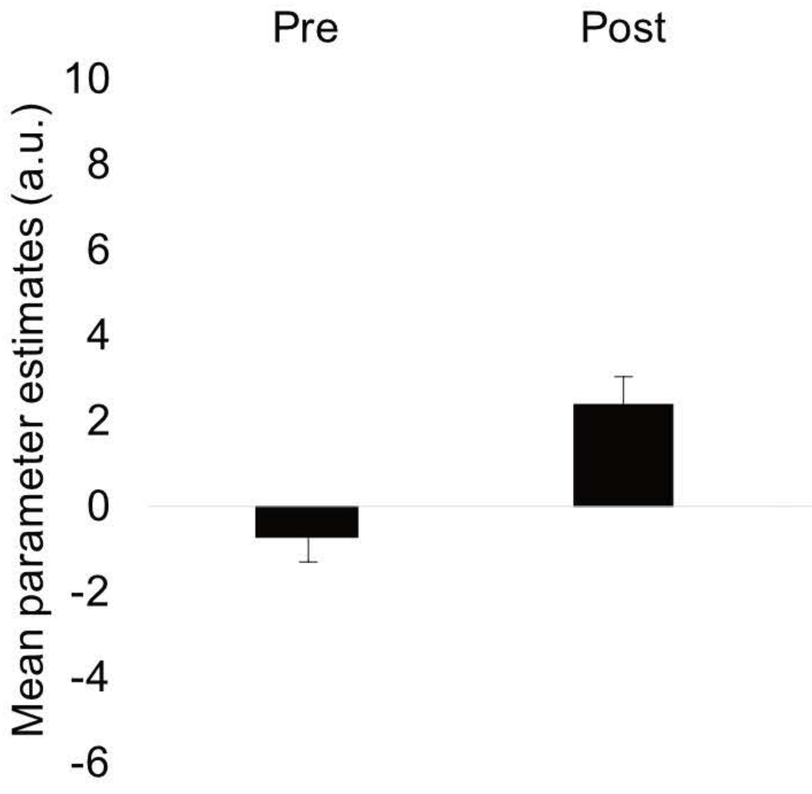
BLOCK 1:
GO = vegetables
NO GO = desserts

BLOCK 2:
GO = desserts
NO GO = vegetables

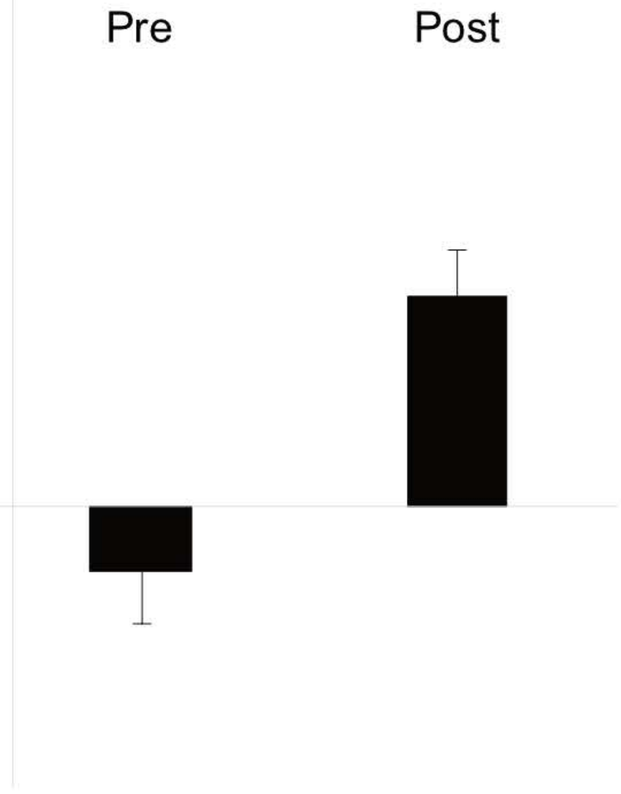




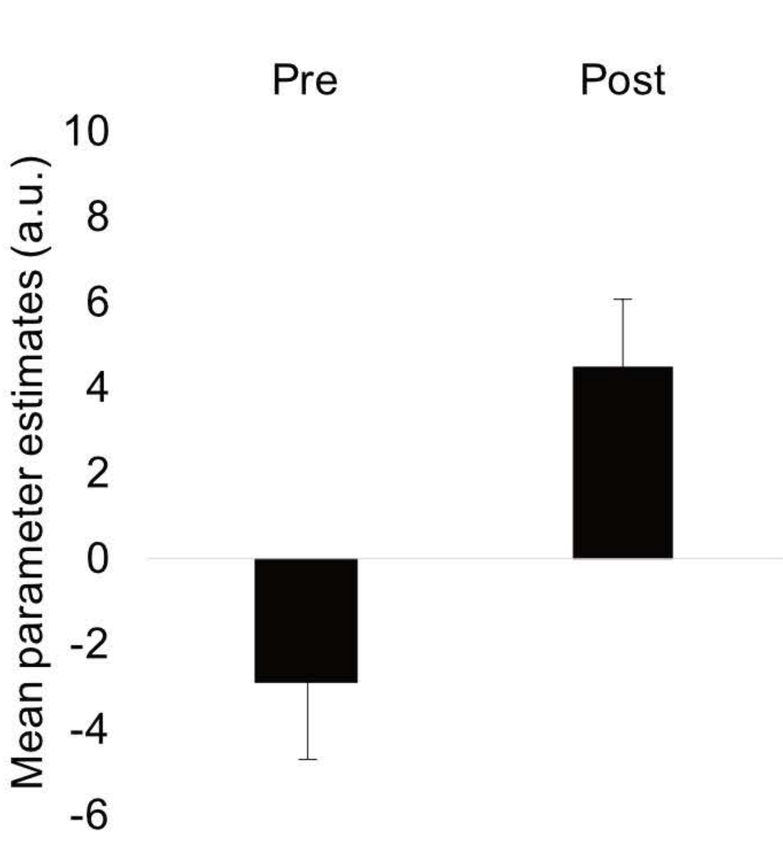
R. Inferior Frontal Operculum (MNI 51 9 24)



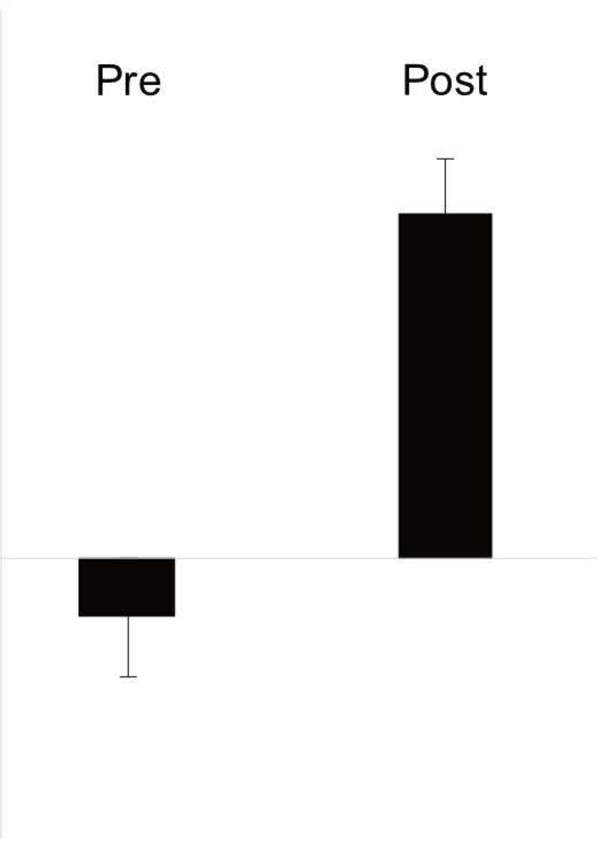
R. Inferior Frontal Gyrus (MNI 57 27 18)



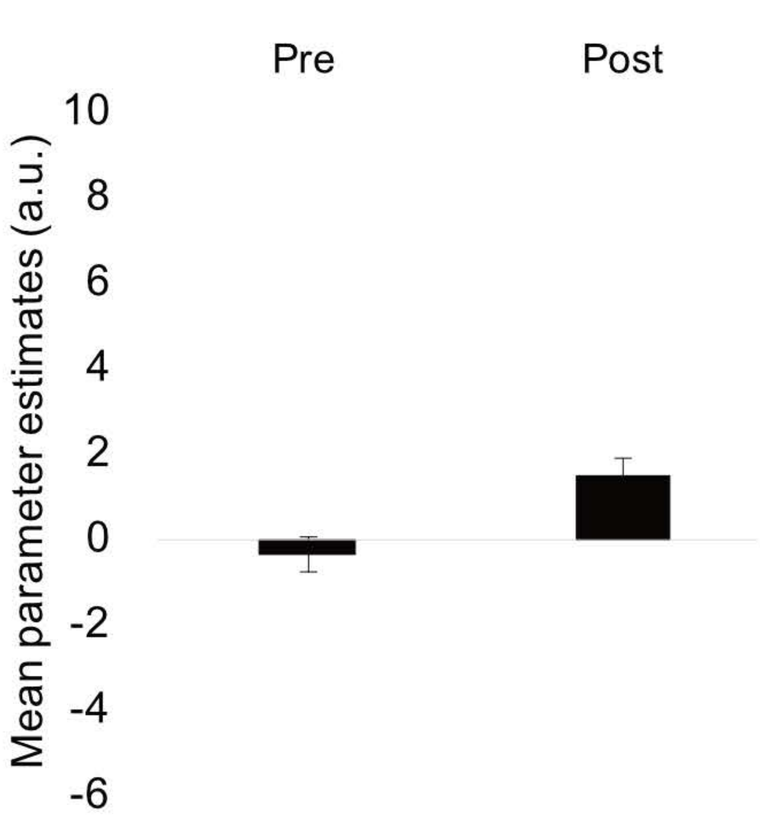
R. Medial Superior Frontal Gyrus (MNI 12 60 27)



R. Middle Frontal Gyrus (MNI 45 54 6)



R. Middle Cingulate Gyrus (MNI 3 -27 33)



R. Hypothalamus
(MNI 3 3 -12)

R. Parahippocampal Gyrus
(MNI 18 -15 -21)

L. Superior Temporal Pole
(MNI -36 12 -27)