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Full-length Article

Surgery-induced reduction in inflammation relates to improved neural inhibitory control in obesity

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ABSTRACT

Obesity is associated with impaired inhibitory control and low-grade systemic inflammation. Systemic inflammation adversely affects neurocognitive performance. Here, we investigate the effects of metabolic bariatric surgery on systemic inflammation and its influence on neural mechanisms underlying inhibitory control. In a sample of 47 individuals with severe obesity, we assessed inhibitory control processing pre- and 2 years post-bariatric surgery by probing neural activation and connectivity during an fMRI Stroop task. We investigated whether surgery-induced changes in plasma markers of systemic inflammation were related to changes in altered neural responses. Data were collected as part of the BARICO (Bariatric surgery Rijnstate and Radboudumc neuroimaging and Cognition in Obesity) study. Longitudinal analyses revealed decreased Stroop-related activation in the caudate nucleus and the left insula following surgery. These activation changes were accompanied by inflammation-related changes in functional coupling with medial superior frontal regions. Specifically, greater post-surgery decreases in leptin (pro-inflammatory) were associated with decreased connectivity between the anterior insula and the medial superior frontal regions, while increases in macrophage migration inhibitory factor (MIF, potentially neuroprotective) were linked to enhanced connectivity between the caudate nucleus and the medial superior frontal gyrus. Importantly, improved functional coupling between the caudate nucleus and the medial superior frontal gyrus was predictive of better task performance. Our findings suggest that surgery-induced reductions in systemic inflammation may improve inhibitory control in individuals with obesity by promoting neural changes in inflammation-sensitive brain regions and their functional interactions.

This protocol was prospectively registered with the Dutch Trial Register Onderzoekmetmensen.nl, with trial number NTR29050.

1. Introduction

Obesity is an increasingly prevalent condition that is associated with both significant deficits in inhibitory control and low-grade systemic inflammation (Chen et al., 2021; World Health Organization, 2024; Yang et al., 2018). To mitigate the serious health consequences of obesity, metabolic bariatric surgery can be used to induce weight loss (Colquitt et al., 2014). However, very little is known about how the surgery-related decrease of systemic inflammation impacts neurocognitive functioning.

Research has linked obesity to impairments in inhibitory control (Lavagnino et al., 2016; Restivo et al., 2017; Yang et al., 2018). Inhibitory control, the cognitive ability to suppress automatic responses or inappropriate behavior, can be assessed with response conflict tasks

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(Bari & Robbins, 2013). This ability is essential for goal-directed behavior, and deficits in inhibitory control are thought to contribute to both the development and maintenance of obesity (Nederkoorn et al., 2006; Stice & Burger, 2019; Yokum & Stice, 2023). Moreover, inhibitory control has been shown to predict treatment response and long-term outcomes in individuals with obesity (Stinson et al., 2018; Xu et al., 2017). At the neural level, fronto-parietal circuits and the insula have been proposed to play a central role in inhibitory control (Hung et al., 2018; Zhang et al., 2017). Emerging neuroimaging data suggests that alterations in neural activation in obesity may contribute to the observed behavioral deficits in inhibitory control, but findings are inconsistent and may be influenced by small sample sizes. Preliminary studies report reduced activation in regions including the supplementary motor area (SMA) and the insula during inhibitory control tasks like the stop signal task (Hendrick et al., 2012), and link higher body mass index (BMI) with lower insula activation (Filbey & Yezhuvath, 2017). Conversely, other studies report increased activation in these regions. For example, a small-scale study using a Stroop task observed increased activation in both the SMA and the insula in individuals with obesity (Balodis et al., 2013), while a Go/No-Go task study reports increased activation in the left insula and bilateral putamen among individuals with obesity compared to controls (Hsu et al., 2017). Taken together, these studies suggest inhibitory control-related deficits in several brain regions in individuals with obesity. However, findings remain inconclusive, and it is still unclear whether weight-loss treatment can improve these neurocognitive deficits.

These brain alterations are thought to be partly the effect of low-grade systemic inflammation associated with obesity (Li et al., 2023). Obesity is linked to low-grade systemic inflammation, evidenced by elevated levels of peripheral inflammation markers (Graßmann et al., 2017). Adipocyte expansion associated with excess body weight leads to increased leptin secretion and activation of inflammatory pathways, resulting in the upregulated expression of pro-inflammatory cytokines, including interleukin (IL)-6 (Park et al., 2010), C-C-motif chemokine ligand (CCL)3, and macrophage migration inhibitory factor (MIF) (Huber et al., 2008; Morrison & Kleemann, 2015; Vázquez-Moreno et al., 2020). This also induces increased C-reactive protein (CRP) production (de Heredia et al., 2012). Such inflammatory processes in obesity have been linked to increased permeability of the blood–brain barrier and subsequent neuroinflammation (Guillemot-Legris & Muccioli, 2017). Importantly, mounting evidence suggests that systemic inflammation is linked to poorer neurocognitive performance (Chen et al., 2021; Shi et al., 2022) and influences brain activation in key areas responsible for inhibitory control, such as the prefrontal cortex and the striatum (Kraynak et al., 2018). Understanding how inflammation mediates the impairment of inhibitory control could provide valuable insights into the neurocognitive effects of obesity.

Effective treatment for obesity aims to achieve long-term weight loss. Metabolic bariatric surgery is a way to induce rapid and sustained weight loss by limiting food intake and nutrient absorption through anatomical modifications of the gastrointestinal tract (Arterburn et al., 2020; Colquitt et al., 2014). A common procedure, Roux-en-Y gastric bypass (RYGB), involves bypassing most of the stomach and proximal small intestine, thereby excluding these regions from nutrient transit and restricting nutrient absorption. Such surgery-induced weight loss has been associated with improvements in cognitive function and significant reductions in systemic inflammation (Handley et al., 2016; Thiara et al., 2017; Vreeken et al., 2023). Moreover, decreases in inflammation following RYGB have been found to predict cognitive improvements 6 months after surgery (Vreeken et al., 2023). However, the neural mechanisms through which surgery-induced decreases in systemic inflammation impact neurocognitive functioning remain unclear.

Here, we employed a longitudinal design to identify long-term changes in both systemic inflammation and brain parameters in individuals with obesity. We examined inhibitory control processing before and 2-years after metabolic bariatric surgery (RYGB), by probing neural responses during the Stroop task (Stroop, 1935), a well-established measure of inhibitory control (Cieslik et al., 2015). First, we investigated whether surgery-induced changes in key markers of systemic inflammation were linked to changes in neural activation during inhibitory control processing, focusing on brain regions sensitive to inflammation (see Kaufmann et al., 2024). Second, we investigated associated changes in functional connectivity during inhibitory control processing, to assess alterations of neural circuits required for task performance. Third, we investigated whether inflammation-related changes in neural responses were linked to changes in behavior. The findings provide insights into the relationship between long-term changes in systemic inflammation and brain parameters, elucidating the mechanisms underlying cognitive improvement following weight loss.

2. Methods and Materials

2.1. Participants

Seventy-five women and men (aged 35–55) with severe obesity, i.e., BMI > 40 kg/m^2 or > 35 kg/m^2 with comorbidities (Fried et al., 2008), were enrolled in the study prior to metabolic bariatric surgery (RYGB). Participants were recruited as part of the larger study protocol of the *BARICO* (Bariatric surgery Rijnstate and Radboudumc neuroimaging and Cognition in Obesity) project (Vreeken et al., 2019). 62 participants completed the pre-surgery assessment and the 2-year follow-up, twelve of which had to be excluded due to insufficient accuracy on the Stroop task (< 50 %). Three additional participants were excluded due to severely elevated inflammation levels (see clinical measures). A total of 47 individuals (seven men, 15 %) were included in the analyses (Fig. 1**A**). Details are provided in Supplemental Methods.

This sample overlaps with previous studies of the BARICO project (Custers et al., 2023, 2024; Kaufmann et al., 2024; Vreeken et al., 2022, 2023). All participants provided written informed consent prior to participation. The study protocol complied with the Declaration of Helsinki and the ICH Harmonised Tripartite Guideline for Good Clinical Practice, was approved by the local ethics review board, the medical review ethics committee (METC Oost-Nederland NL63493.091.17), and was registered in the Dutch Trial Register (protocol number: NTR29050).

2.2. Clinical measures

Current height and weight were used to calculate participants' BMI as a measure of obesity. Further anthropometric measures included waist circumference, as a measure of abdominal adiposity, and percentage of total body weight loss (TBWL%). Depressive symptoms were assessed with the Dutch version of the Beck Depression Inventory (BDI) (Beck & Steer, 1993). Blood samples were collected at each time point to assess inflammation markers, including CRP, leptin, IL-6, IL-8, CCL3, and MIF. These inflammation markers were selected based on previous work of our group, which identified them as being linked to obesity, depression, and associated brain alterations prior to surgery (Kaufmann et al., 2024). To ensure that elevated inflammation levels at baseline were due to chronic rather than acute inflammation, the latter being indicated by severely elevated values, participants with inflammation levels exceeding 3 standard deviations above the mean were excluded. Further details are provided in Supplemental Methods. To examine changes in clinical measures, paired Welch's t-tests were calculated between baseline and follow-up measures. Four of the six inflammation markers showed significant changes at follow-up and were considered for further analyses. Associations between changes in clinical measures were calculated as partial Spearman's rank correlations, controlling for age and sex (assigned at birth), using R (RRID:SCR_001905, version 4.4).

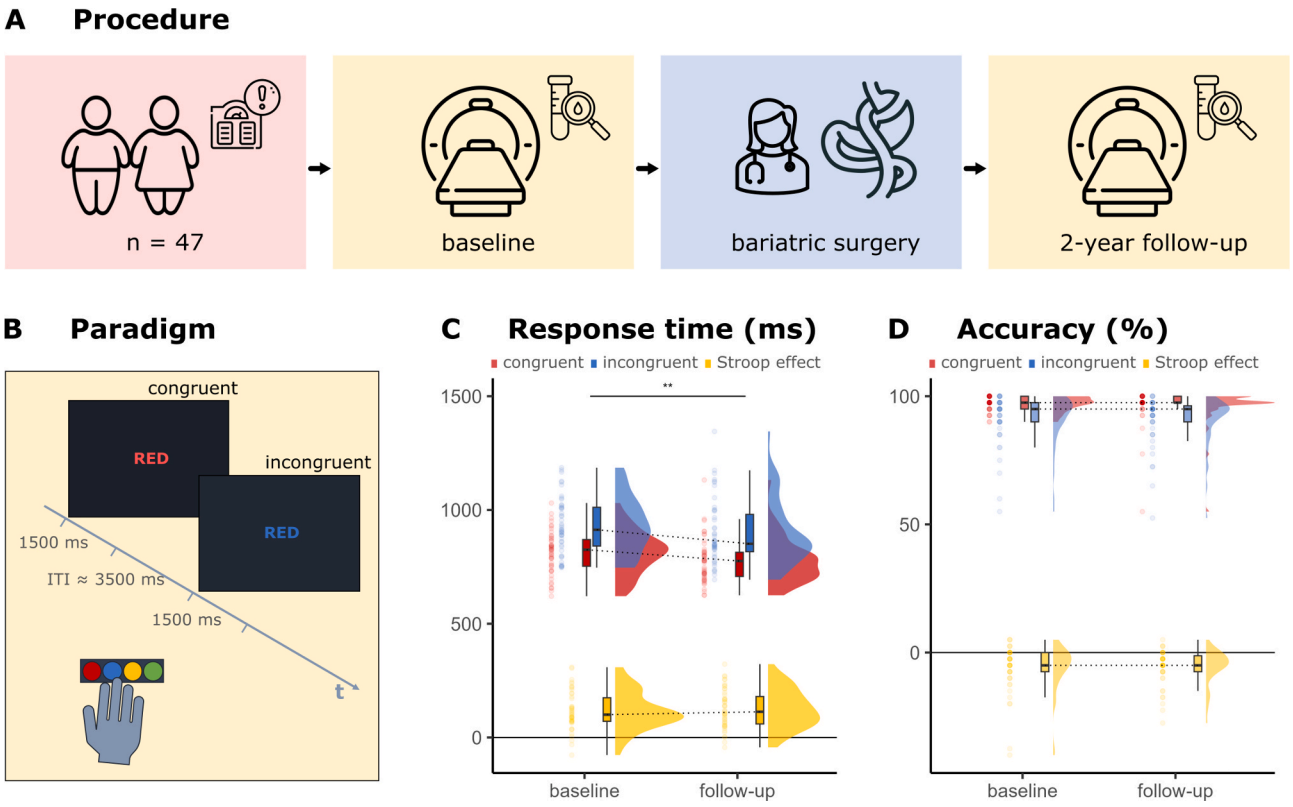

Fig. 1. Overview of study design and surgery-related changes in performance. A Procedure. Patients qualifying for metabolic bariatric surgery were scanned before and 2 years after surgery. Blood samples were collected at each time point to assess inflammation markers. **B Color-word Stroop task paradigm.** In the congruent condition, the color of the ink and the color word matched. In the incongruent condition, there was a mismatch between the color of the ink and the color word. The duration of each stimulus lasted 1500 ms and the inter-trial interval (ITI) ranged from 2000 to 4000 ms. Participants were asked to respond to the ink color – instead of the meaning of the word – as fast and accurately as possible by pressing color-coded keys with the right hand. The order of words was pseudorandomized and counterbalanced across participants. **C Response time results.** The Stroop effect was calculated as the difference in mean response time of correct trials between the incongruent and the congruent condition. Response time across both conditions decreased statistically significantly after surgery, indicating participants were responding faster at follow-up. ** $p < 0.01$. **D Accuracy results.** The Stroop effect was calculated as the difference in mean accuracy of trials between the incongruent and the congruent condition. There was no evidence for a change in accuracy between sessions. Boxplots show the median as horizontal marker, the edges of the box represent the 25th and 75th percentiles, and the whiskers span 1.5 interquartile ranges.

2.3. Stroop task

Inhibitory control (i.e., response conflict processing) was assessed at both time points using a Dutch version of the color-word Stroop paradigm during fMRI. Participants were asked to indicate the color of four color words, presented either in the same color as the word (*congruent condition*, e.g. 'red' in red ink) or in a different color (*incongruent condition*, e.g. 'red' in blue ink, Fig. 1**B**), by pressing a corresponding button and ignoring the meaning of the word. Possible colors were red, blue, yellow, and green. To familiarize themselves with the task and the color-button contingency, participants first performed 10 practice trials with feedback. Subsequently, the task consisted of a total of 80 trials and lasted approximately 10 min. The task was delivered using Presentation (RRID:SCR_002521). All stimuli and the task code are available at the Open Science Framework (https://dx.https://doi.org/10.17605/osf.io/c5dvh).

Mean response time (RT) of correct trials and response accuracy were analyzed as measures of task performance (Fig. 1**C,D**). Response times were trimmed before analysis to eliminate anticipation or late responses, considering response times between 200 ms and 3 standard deviations of the participant-and-condition-specific mean response time as valid trials (excluding < 0.01 % of all data). Paired Welch's t-tests were calculated to compare baseline and follow-up measures.

2.4. Statistical analyses

The statistical analyses had three aims. First, we investigated brain activation changes within distinct inflammation-sensitive regions relevant for inhibitory control processing using ROI-wise linear mixed-models. Second, we investigated inflammation-specific changes of functional connectivity within these inflammation-sensitive regions. Third, we investigated whether inflammation-related changes in neural responses were linked to changes in behavior. Scripts for the main analyses are available at the Open Science Framework (https://doi.org/10.17605/osf.io/zxtks).

2.5. Analysis of fMRI activation

Functional images were subjected to preprocessing procedures, including realignment, slice timing correction, spatial normalization, and smoothing. We generated a single contrast image per participant for the following comparisons: the main task effect [incongruent > congruent] at baseline [$\text{incongruent}_{\text{baseline}} - \text{congruent}_{\text{baseline}}$] and follow-up [$\text{incongruent}_{\text{follow-up}} - \text{congruent}_{\text{follow-up}}$], and the change of activation over time [follow-up > baseline] using the contrast [($\text{incongruent}_{\text{follow-up}} - \text{congruent}_{\text{follow-up}}$) – ($\text{incongruent}_{\text{baseline}} - \text{congruent}_{\text{baseline}}$)]. Details are provided in Supplemental Methods. Second-

level analyses comprised one-sample t-tests for the contrasts [incongruent > congruent] at both baseline and follow-up, and for the [follow-up > baseline] contrast, with age and sex as covariates of no interest. Statistically significant activation clusters were identified using a cluster-defining threshold of $p < 0.001$ and a minimum spatial extent of 10 voxels, controlling the family-wise error (FWE) rate at $\alpha \leq 0.05$ within a mask of inflammation-sensitive brain regions (see section 2.7).

Signal level within the five clusters showing the strongest activation differences at baseline were calculated by extracting the mean beta values from participants' first-level contrast maps for the [incongruent > congruent] comparisons at baseline and follow-up. These values were then used for linear mixed-effects analyses. The mixed models included brain activation as dependent variable, with time, age, and sex as fixed effects, and a random intercept for each participant. The significance level for the mixed-effects analyses was set to $\alpha \leq 0.05$, FDR-corrected for multiple regions of interest (Benjamini & Hochberg, 1995).

Results were labeled according to the Automated Anatomical Labeling atlas 3v1 (Rolls et al., 2020) using AtlasReader (Notter et al., 2019). Results were visualized as dual-coded images (Allen et al., 2012) using the *nanslice* package (https://github.com/spinicist/nanslice). The unthresholded T-maps representing the neural activation for the contrast [incongruent > congruent] at baseline and follow-up are available on NeuroVault (RRID:SCR_003806; https://identifiers.org/neurovault.image:887947).

2.6. Analysis of fMRI connectivity

We examined the functional connectivity of response conflict sensitive regions during inhibitory control using generalized psychophysiological interaction (gPPI) analyses (RRID: SCR_009489; McLaren et al., 2012), with the five clusters showing the largest differences in activation between conditions at baseline serving as seed regions. Details are provided in Supplemental Methods. A second-level analysis used one-sample t-tests on the contrast images to probe connectivity changes during response conflict, including age and sex as covariates of no interest. Statistically significant clusters of task-modulated connectivity were obtained using a cluster-defining threshold of $p < 0.001$, controlling the family-wise-error rate at $\alpha \leq 0.05$ across the target space of inflammation-sensitive brain regions (Kraynak et al., 2018). To probe whether changes in inflammation markers were linked to changes in brain connectivity during response conflict, we included change scores of CRP, leptin, IL-6, and MIF as regressors in separate second-level GLMs. These analyses used a cluster-defining threshold of $p < 0.001$ and controlled the FWE rate at $\alpha \leq 0.0125$ across the target space and the four comparisons. Results were labelled according to the Automated Anatomical Labeling atlas 3v1 (Rolls et al., 2020). Unthresholded T-maps representing the inflammation-specific changes in task connectivity for the contrast [follow-up > baseline] are available on NeuroVault (RRID:SCR_003806; https://identifiers.org/neurovault.collection:17746).

2.7. Inflammation-sensitive mask

To investigate the relationship between changes in systemic inflammation and changes in neural activation, we focused our second-level analysis on brain regions known to be sensitive to inflammation markers. Specifically, we used an empirically derived map of brain regions sensitive to systemic inflammation (Kraynak et al., 2018), accessible via NeuroVault (https://identifiers.org/neurovault.image:57867). A map with a stringent extent-based threshold (voxel-wise $\alpha = 0.001$) was selected and binarized. To define anatomically meaningful analysis units, we then selected all parcels from the Automated Anatomical Labelling atlas 3v1 (Rolls et al., 2020), that contained at least one voxel from the binarized map. This selection process yielded an inflammation-sensitive brain mask, while ensuring meaningful and comprehensive brain parcels. The final binarized map is available on NeuroVault (RRID: SCR_003806; https://identifiers.org/neurovault.image:868591). Further details are provided in Supplemental Methods.

2.8. Inflammation-behavior, inflammation-brain, and brain-behavior analyses

To investigate associations between participants' neural measures, task performance, and inflammation markers, we used linear mixed-effect models. Model assumptions, including normality of residuals, homoscedasticity, and linearity, were thoroughly checked. In cases where these assumptions were violated, Spearman rank correlations were calculated using the residuals of the change scores, controlling for age and sex. This approach provided a robust alternative to examine the relationships between variables, while mitigating the impact of assumption violations.

For the inflammation-behavior analyses, we used linear mixed-effect models with the accuracy or response time Stroop effect as dependent variable. Inflammation markers (one at a time), time, age, and sex were included as fixed effects, with a random intercept for each participant. For the inflammation-brain and brain-behavior analyses, we calculated signal levels within brain activation and connectivity clusters that showed significant change between baseline and follow-up, by extracting the mean beta values from participants' first-level contrast maps for the [incongruent > congruent] comparisons at both time points. We employed linear mixed-effect models with brain activation or connectivity as dependent variable. Inflammation or performance markers (one at a time), time, age, sex, and the interaction between inflammation/performance marker and time were fixed effects, with a random intercept for each participant.

All fixed effects parameters were z-standardized to facilitate interpretation and improve numerical stability. Linear mixed effects modeling was performed in R (RRID:SCR_001905, version 4.4), using the R packages *lme4* (RRID:SCR_015654) and *lmerTest* (RRID: SCR_015656). The significance level for the mixed-effects analyses was set to $\alpha \leq 0.05$, FDR-corrected for multiple regions of interest and inflammation markers (Benjamini & Hochberg, 1995).

3. Results

3.1. Demographic and anthropometric results

Descriptive statistics of the participants are summarized in Table 1. At baseline, 20 participants (43 %) scored above the cut-off for mild to moderate depression (BDI score > 9). At follow-up, this number had decreased to 3 participants (6.7 %). Of the four participants who reported taking antidepressant medication at baseline, one had discontinued its use at follow-up.

3.2. Inflammation results

Before surgery, 32 participants (68 %) had elevated CRP levels (> 3 mg/l), a crude measure for systemic inflammation (Ishii et al., 2012). At the 2-year follow-up, only 3 participants (6.4 %) still showed elevated CRP levels. Both leptin and IL-6 levels also decreased significantly after surgery, while MIF levels showed a significant increase. These four inflammation markers with significant changes at follow-up were considered for subsequent analyses examining relationships with behavior and brain changes. Levels of all inflammatory markers are summarized in Table 2. Decreased leptin levels were associated with decrease in BMI ($rho = 0.47, p < 0.001, q < 0.004$; 95 %-CI [0.20, 0.67]) and TBWL% ($rho = -0.49, p < 0.001, q < 0.002$; 95 %-CI [-0.69, −0.23]), while the other markers showed no such associations.

3.3. Behavioral results

Comparing the Stroop task conditions, we observed a robust Stroop

Table 1
Demographic and clinical characteristics.

Characteristic	baseline, N = 47 Mean (SD), [Range] / n (%)	follow-up, N = 47 Mean (SD), [Range] / n (%)	p-value paired *t*-test
Age	45.4 (6.3, [36.2, 55.2]	–	
Sex assigned at birth (female / male)	40 (85 %) / 7 (15 %)	–	
Education level (low / middle / high) [a]	5 (11 %) / 20 (43 %) / 22 (47 %)	–	
BMI (kg/m[b])	40.3 (2.6), [34.7, 47.8]	26.1 (2.8), [19.0, 31.3]	<0.001
Waist circumference (cm)	121.0 (9.7), [106.0, 145.0] [b]	91.3 (9.8), [70.0, 118.0] [c]	<0.001
Total body weight loss (TBWL%)	–	34.9 (6.8), [22.9, 51.3]	
Depression (BDI)	8.8 (5.0), [1.0, 22.0] [c]	3.6 (4.0), [0.0, 21.0] [d]	<0.001
Medication use			
Antidepressants	4 (8.5 %)	3 (6.4 %) [d]	
Oral antidiabetics	5 (11 %)	2 (4.3 %) [d]	
Antihypertensives	11 (23 %)	3 (6.4 %) [d]	
Insulin therapy	3 (6.4 %)	1 (2.1 %) [d]	

[a] According to the Verhage score (Verhage, 1964): low ≤ 4, middle = 5, high ≥ 6, based on the Dutch educational system, akin to the International Standard Classification of Education (UNESCO Institute for Statistics, 2012).
[b] n = 40.
[c] n = 46.
[d] n = 45.

Table 2
Inflammation levels at baseline and follow-up.

Characteristic	baseline, N = 47 Mean (SD), [Range]	follow-up, N = 47 Mean (SD), [Range]	p-value paired *t*-test
CRP (ug/ml)	6.08 (5.35), [0.49, 26.69]	1.19 (1.46), [0.10, 6.88]	<0.001
Leptin (ng/ml)	64.38 (24.83), [17.16, 136.77]	14.55 (10.54), [1.30, 57.09]	<0.001
IL-6 (pg/ml)	2.15 (1.11), [0.42, 5.36]	0.63 (0.67), [0.02, 3.19]	<0.001
IL-8 (pg/ml)	8.40 (3.58), [2.87, 17.40]	9.78 (4.61), [2.41, 25.06]	0.055
MIF (ng/ml)	11.60 (8.20), [1.85, 39.61]	21.92 (13.42), [4.94, 76.21]	<0.001
CCL3 (pg/ml)	18.44 (7.50), [0.00, 41.96]	19.42 (8.61), [4.23, 62.24]	0.4

effect with a large effect size for response time (*baseline*: Δ response time = 116.86 ± 84.05, t(46) = 9.53, p < 0.001, d = 1.39; *follow-up*: Δ response time = 124.59 ± 85.45, t(46) = 10.00, p < 0.001, d = 1.46) and a moderate to large effect size for response accuracy (*baseline*: Δ accuracy = -5.96 ± 9.22, t(46) = -4.43, p < 0.001, d = -0.65; *follow-up*: Δ accuracy = -5.53 ± 6.84, t(46) = -5.55, p < 0.001, d = -0.81). These results confirmed the presence of response automaticity at both sessions (Fig. 1**C,D**). Comparative analysis between the sessions revealed a statistically significant decrease in response time across conditions, indicating that participants were responding faster at follow-up (mean difference = -34.05 ± 85.78, t(46) = -2.721, $p < 0.01$, $d = -0.40$) (Fig. 1**C**). There was no evidence of change in the Stroop effect for response time or accuracy over time (all $p > 0.50$). However, there was a trend suggesting that individuals with a greater decrease in CRP also showed a greater improvement in the Stroop accuracy effect, indicating improved performance (*rho* = -0.32, 95 %-CI [-0.56, −0.03], $p = 0.014$, $q = 0.056$). Changes in other inflammation markers were not associated with changes in performance (all $p > 0.40$).

3.4. Neuroimaging results

3.4.1. Changes in brain activation during response conflict

We identified inhibitory control processing areas as brain regions with greater activation for the [incongruent > congruent] GLM contrast within a mask of inflammation-sensitive brain regions, controlling for age and sex of participants (Fig. 2**A**). At baseline, this contrast revealed prominent activation in brain regions associated with response conflict processing (Langner et al., 2018), with the five strongest located in the left SMA, the left middle frontal gyrus (MFG), the left anterior insula extending to the putamen and caudate, the right anterior insula, and the right caudate nucleus (Fig. 2**B;** see **Table S2** for a summary of all clusters and coordinates).

Based on these results, we investigated changes in task-related brain activation of the left SMA, the left MFG, the left and right insula, and the right caudate nucleus between baseline and the 2-year follow-up. Linear mixed-effects analyses revealed a significant decrease in activation over time in the caudate nucleus (beta = -0.14, 95 % CI [-0.26, −0.03], $t(88) = -2.44$, $p = 0.017$, $q = 0.04$) and left insula (beta = -0.13, 95 % CI [-0.23, −0.03], $t(88) = -2.48$, $p = 0.015$, $q = 0.04$) (Fig. 2**C**).

Next, we investigated the association between brain activation and inflammation measures (CRP, leptin, IL-6, and MIF). Linear mixed-effect models showed no statistically significant effects (all $p > 0.06$) (**Table S3**). Further linear mixed-effects analyses examining associations between activation and performance measures showed no evidence for an association between brain activation and the Stroop effects (**Table S4**).

3.4.2. Changes in task connectivity during response conflict

To investigate changes in functional connectivity, we conducted gPPI analyses using the five clusters showing the strongest peak activation at baseline in the [incongruent > congruent] GLM contrast as seed regions (Fig. 2**B** + **3B**) within the mask of inflammation-sensitive brain regions (Fig. 2**A**). There was no evidence for general connectivity changes within these regions.

We next examined specific inflammation-related connectivity changes for CRP, leptin, IL-6, and MIF, to assess the influence of surgery-induced changes in individual inflammation levels (Fig. 3**A,** **Table S5**). Participants with greater decrease in leptin showed a greater decrease in connectivity between the left insula and the medial part of the left superior frontal gyrus (SFGmed) ($k = 138$, pFWE < 0.001). Furthermore, a greater increase in MIF was linked to a greater increase in connectivity between the right caudate nucleus and the left SFGmed ($k = 121$, pFWE < 0.004).

Notably, subsequent mixed-model analyses revealed that higher MIF-related connectivity was associated with a smaller (i.e. less negative) accuracy Stroop effect ($b = 0.37$, SE = 0.15, t(86) = 2.42, $p = 0.018$, $q = 0.036$), indicating better performance in the incongruent condition. This effect was driven by baseline, as indicated by a significant interaction effect (b = -0.70, SE = 0.26, t(86) = -2.73, p = 0.008, $q = 0.015$) (**Table S6**).

4. Discussion

Controlling automatic or prepotent responses is an essential skill for navigating situations with competing demands. Individuals with obesity often exhibit deficits in this domain, referred to as impaired inhibitory control (Lavagnino et al., 2016; Restivo et al., 2017; Yang et al., 2018). Low-grade systemic inflammation, which is prevalent in obesity, has been associated with increased deficits in inhibitory control (Chen et al., 2021; Shi et al., 2022). However, little is known about how metabolic bariatric surgery-induced decreases in systemic inflammation affect the neural processing of inhibitory control in individuals with obesity. This study extends previous reports on the association between systemic

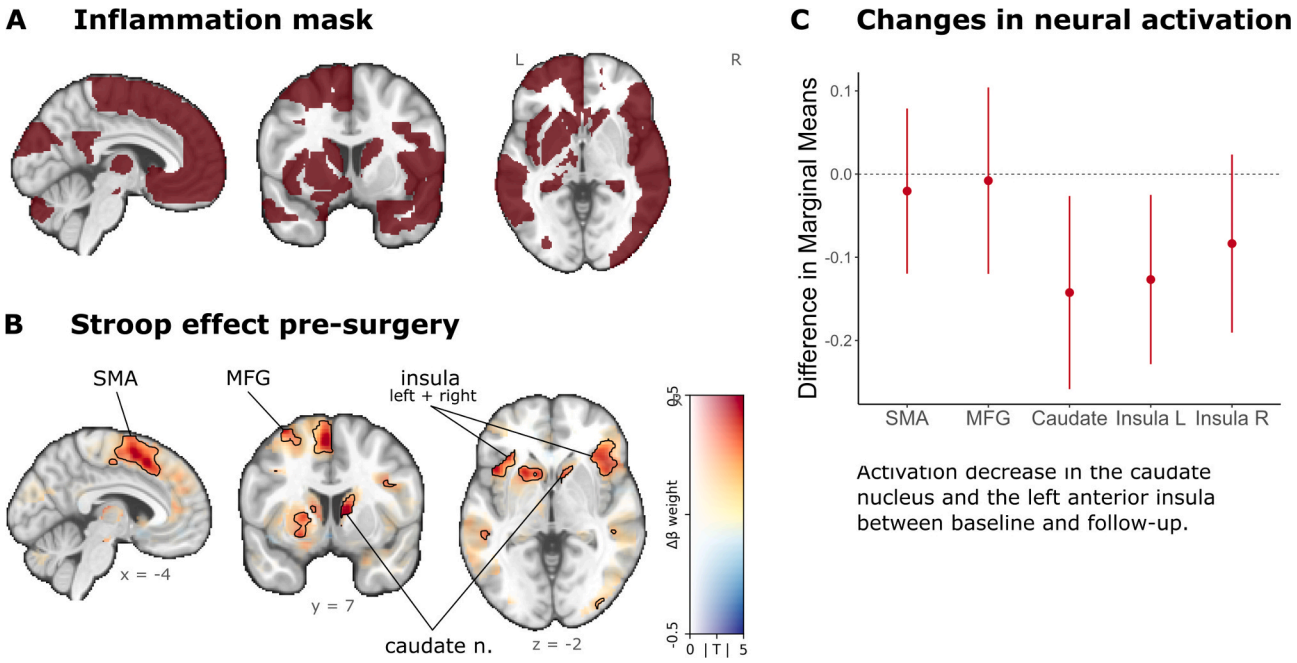

Fig. 2. Neural activation during inhibitory control processing. A The Stroop effect was calculated within a mask of inflammation-sensitive brain regions (Kraynak et al., 2018), see Supplemental Methods for further details. B During inhibitory control processing at baseline, participants showed greater activation in several brain regions, including the left supplementary motor area (SMA), the left middle-frontal gyrus (MFG), the left and right insula, and the right caudate nucleus. Dual-coded contrast: color indicates the estimated regression coefficient (vertical axis of color bar) and transparency corresponds to the absolute t-statistic values (horizontal axis of color bar). Significant clusters (pFWE < 0.05) are contoured black to facilitate the interpretation. See Table S2 for a full list and Montreal Neurological Institute (MNI) coordinates of significant clusters. C Neural activation within the caudate nucleus and the left insula showed a significant decrease across time (follow-up > baseline).

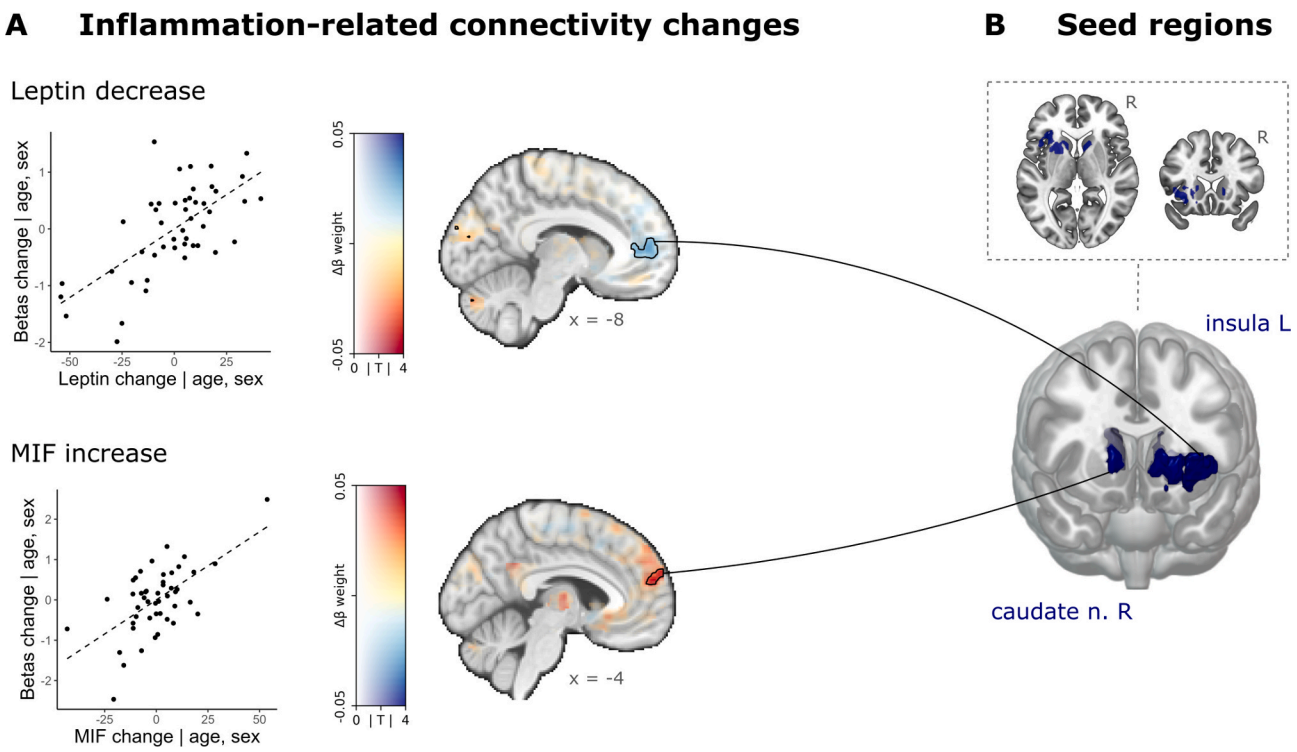

Fig. 3. Change in conflict-related functional connectivity between baseline and the 2-year follow-up. A Inflammation-related connectivity analyses showed decreased leptin values being related to decreased connectivity between the left insula and the left medial superior frontal gyrus. Increased MIF levels were associated with increased connectivity between the caudate nucleus and the medial part of the left superior frontal gyrus. Dual-coded contrast: color indicates the estimated regression coefficient (vertical axis of color bar) and transparency corresponds to the absolute t-statistic values (horizontal axis of color bar). Significant clusters (*p*FWE < 0.05) are contoured black to facilitate the interpretation. **B** Seed regions. See **Table S5** for a full list and Montreal Neurological Institute (MNI) coordinates of significant clusters.

inflammation and cognitive function six months after surgery (Vreeken et al., 2023) by examining surgery-induced changes in inflammation markers two years after surgery and directly linking them to changes in neurocognitive function during an inhibitory control task. Results revealed lasting surgery-induced changes in inflammation markers, alongside decreased brain activation in inflammation-sensitive regions (Kraynak et al., 2018), specifically the caudate nucleus and the left insula. These changes in activation were accompanied by inflammation-related alterations in functional coupling with medial superior frontal regions (SFGmed), brain areas implicated in inhibition, decision-making, and self-control (Euston et al., 2012). Crucially, increased functional coupling between the caudate nucleus and the SFGmed during inhibitory control processing predicted better task performance, with stronger crosstalk observed in individuals demonstrating greater task accuracy. Our findings provide evidence that surgery-induced decreases in systemic inflammation may improve inhibitory control in individuals with obesity by altering functional coupling in fronto-striatal regions.

4.1. *Inflammation-sensitive regions show decreased activation after surgery*

Following surgery, we observed a decrease in brain activation within inflammation-sensitive regions during inhibitory control processing following surgery, along with reduced inflammation measures. Specifically, activation in the right caudate nucleus and left anterior insula was significantly lower at follow-up than at baseline. This decrease in activation may reflect a normalization process, as previous studies have shown that individuals with obesity exhibit heightened activation in regions such as the insula, caudate nucleus, and putamen during response inhibition tasks compared to non-obese controls (Balodis et al., 2013; Hsu et al., 2017). Although the relatively long two-year interval between assessments makes learning effects on these findings less likely, we cannot fully rule out general test–retest effects due to the lack of a control group. Nonetheless, evidence from a case-controlled study in adolescents also shows improved executive function and post-surgical reductions in brain activation during an N-back task in the anterior insula (Pearce et al., 2017). Moreover, *meta*-analyses of behavioral data support improvements in executive function following weight-loss interventions, including metabolic bariatric surgery (Siervo et al., 2011; Thiara et al., 2017), though such performance improvements were not found currently. Taken together, these results suggest that post-surgery weight loss may alleviate hyperactivation in brain regions involved in inhibitory control. The observed decrease in activation post-surgery may indicate more efficient processing of response conflicts, requiring less neural activity for the same level of performance.

4.2. *Inflammation-specific connectivity changes*

Functional circuit analyses revealed inflammation-specific connectivity changes between control-processing regions and the SFGmed. Notably, regions with a significant post-surgery decrease in activation also showed inflammation-specific changes in connectivity. Specifically, a greater decrease in leptin levels was associated with decreased connectivity between the SFGmed and the left insula, while a greater increase in MIF was linked to increased connectivity between the SFGmed and the right caudate nucleus. The SFGmed is implicated in a wide range of processes and is thought to function as a central hub, integrating and coordinating adaptive behavior (Roy et al., 2012). It plays a critical role in decision-making processes, such as response conflict monitoring (Alexander & Brown, 2011; Botvinick et al., 2004), and supports the stable maintenance of task control (Dosenbach et al., 2008 and 2007).

The **leptin-associated decrease** in functional connectivity between the insula and the SFGmed aligns with findings from leptin substitution therapy in lipodystrophy, where leptin was positively associated with intrinsic connectivity in regions including the insula and the medial prefrontal cortex (Schlögl et al., 2016). Leptin exerts a pro-inflammatory effect on the body (Abella et al., 2017) and is closely linked with adipose tissue mass, with levels known to decrease following weight loss (Maffei et al., 1995). Peripheral inflammation markers such as leptin can modulate fronto-striatal circuits both by directly acting on receptors in the striatum and by indirect effects via the ventral tegmental area (Janssen et al., 2019). The anterior insula, known to play a role in attentional control (Nelson et al., 2010), has a close functional and anatomical relationship with medial prefrontal regions (Dosenbach et al., 2007; Nelson et al., 2010). Given the functional role of SFGmed-insula connectivity in stable task control (Dosenbach et al., 2007; Nelson et al., 2010) and the link between improved leptin levels and better post-surgery cognitive function (Alosco et al., 2015; Nozari et al., 2023), the observed leptin-associated decrease in functional coupling between these regions suggests that surgery-induced reductions in leptin may contribute to a shift towards more adaptive neural processing patterns.

The **MIF-associated increase** in functional connectivity between the caudate nucleus and the SFGmed is consistent with prior findings in obesity research, which have linked higher BMI to lower intrinsic connectivity between the right caudate nucleus and the SFGmed/anterior cingulate cortex (Zhao et al., 2021). The SFGmed, which projects unilaterally to the caudate nucleus (Euston et al., 2012), shows increased connectivity with the caudate in conditions characterized by excessive control behaviors, such as obsessive–compulsive disorders (Apergis-Schoute et al., 2018). Given the well-documented impairments in cognitive control in individuals with obesity, the observed MIF-associated increase in connectivity may reflect improvements in neurocognitive functioning. Notably, this increase was associated with higher accuracy during the incongruent condition of the Stroop task. Although MIF is typically recognized for its pro-inflammatory role in obesity progression (Morrison & Kleemann, 2015), it also exerts context-dependent protective effects against metabolic and cellular stress (Leyton-Jaimes et al., 2018; Morrison & Kleemann, 2015). These dual roles are mediated through interactions with both chemokine receptors (CXCR2, CXCR4, CXCR7) and non-chemokine receptors (CD74), the latter being implicated in cell survival and tissue repair mechanisms (Kapurniotu et al., 2019). Importantly, MIF also acts intracellularly within neurons, contributing to cellular homeostasis and reducing neurotoxicity by stabilizing misfolded proteins and modulating neuroprotective stress-response pathways (Kapurniotu et al., 2019). In the developing brain, MIF has further been shown to promote microglial proliferation and neuroprotection following cortical injury (Pawig et al., 2015). The post-surgical increase in MIF levels observed in our cohort aligns with earlier findings in individuals undergoing metabolic bariatric surgery, who showed a stable increase in MIF levels from pre-surgery to two years postoperatively (van Dielen et al., 2004) (but see also Kleemann and Bucala (2010)). Although the precise functional consequences of this increase remain to be fully elucidated, our results suggest that, in this context, elevated MIF may reflect neuroprotective or compensatory mechanisms supporting improved neurocognitive performance. This interpretation is supported by the observed relationship between MIF-associated changes in brain connectivity and performance improvements on the inhibitory control task.

The observed performance improvements in response time in this study align with *meta*-analytic findings showing improved cognitive function, including executive function as measured by the Stroop task, 12 months post-surgery (Tao et al., 2024), as well as reports of sustained executive function improvements three to four years after surgery (Alosco et al., 2014). Together, these findings suggest that weight-loss-related changes in inflammation markers may promote more efficient inhibitory control processing by reshaping functional coupling of inflammation-sensitive brain regions. Obesity-induced systemic inflammation appears to have a substantial but reversible impact on brain function during inhibitory control. Overall, these findings indicate that sustained weight loss may help reverse cognitive impairments

linked to elevated BMI (Bocarsly et al., 2015; Hendrick et al., 2012; Vainik et al., 2013), highlighting the potential cognitive benefits of reducing obesity-related systemic inflammation.

4.3. Limitations

The lack of a non-surgical control group, such as a no-intervention group or one undergoing structured caloric restriction without surgery, limits our ability to draw definitive causal conclusions about the effects of metabolic bariatric surgery on systemic inflammation and neural connectivity. In principle, improvements in task performance and corresponding changes in brain function could occur independently of inflammation-related changes, for example due to practice effects or unrelated neuroplasticity over time. In addition, the sample of this study comprised more women than men, precluding any subgroup analyses. Future studies would benefit from a more balanced sample, allowing the investigation of potential sex differences (Braga Tibaes et al., 2024; Lasselin et al., 2018; ter Horst et al., 2020).

4.4. Conclusion

The use of a longitudinal design enabled us to identify long-term changes in both systemic inflammation and brain parameters. Our findings suggest that surgery-induced decreases of systemic inflammation may improve inhibitory control in individuals with obesity through neural mechanisms involving inflammation-sensitive brain regions and their crosstalk. This underscores the potential cognitive benefits of weight loss interventions in managing obesity and highlights the importance of addressing systemic inflammation in therapeutic strategies.

5. Ethical Standards

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national committees on human experimentation, the METC Oost-Nederland (NL63493.091.17), with the Helsinki Declaration of 1975, as revised in 2008, and the ICH Harmonised Tripartite Guideline for Good Clinical Practice. The study was registered in the Dutch Trial Register (protocol number: NTR29050).

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CRediT authorship contribution statement

Lisa-Katrin Kaufmann: Writing – review & editing, Conceptualization, Visualization, Formal analysis, Writing – original draft. **Emma Custers:** Investigation, Writing – review & editing, Data curation. **Debby Vreeken:** Data curation, Investigation. **Jessica Snabel:** Investigation, Methodology. **Martine C. Morrison:** Methodology, Supervision. **Robert Kleemann:** Conceptualization, Writing – review & editing, Resources, Supervision. **Maximilian Wiesmann:** Writing – review & editing, Supervision. **Eric J. Hazebroek:** Writing – review & editing, Supervision. **Esther Aarts:** Supervision, Funding acquisition, Writing – review & editing, Resources, Conceptualization. **Amanda J. Kiliaan:** Writing – review & editing, Resources, Conceptualization, Supervision, Funding acquisition.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bbi.2025.07.012.

Data availability

Data from this study are available upon request from the last authors. All stimuli, the stimulus presentation scripts, and scripts for the main analyses are available at https://doi.org/10.17605/osf.io/h846n.

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