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Research paper

Additive effects of depression and obesity on neural correlates of inhibitory control

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ABSTRACT

Background: Depression and obesity are associated with impaired inhibitory control. Behavioral evidence indicates an exacerbating additive effect when both conditions co-occur. However, the underlying neural mechanisms remain unclear. Moreover, systemic inflammation affects neurocognitive performance in both individuals with depression and obesity. Here, we investigate additive effects of depression and obesity on neural correlates of inhibitory control, and examine inflammation as a connecting pathway.

Methods: We assessed inhibitory control processing in 64 individuals with obesity and varying degrees of depressed mood by probing neural activation and connectivity during an fMRI Stroop task. Additionally, we explored associations of altered neural responses with individual differences in systemic inflammation. Data were collected as part of the BARICO (Bariatric surgery Rijnstate and Radboudumc neuroimaging and Cognition in Obesity) study.

Results: Concurrent depression and obesity were linked to increased functional connectivity between the supplementary motor area and precuneus and between the inferior occipital and inferior parietal gyrus. Exploratory analysis revealed that circulating inflammation markers, including plasma leptin, IL-6, IL-8, and CCL-3 correlated with the additive effect of depression and obesity on altered functional connectivity.

Limitations: The observational design limits causal inferences. Future research employing longitudinal or intervention designs is required to validate these findings and elucidate causal pathways.

Conclusion: These findings suggest increased neural crosstalk underlying impaired inhibitory control in individuals with concurrent obesity and depressed mood. Our results support a model of an additive detrimental effect of concurrent depression and obesity on neurocognitive functioning, with a possible role of inflammation.

1. Introduction

Obesity and depression are two highly prevalent health conditions that often co-occur (NCD Risk Factor Collaboration, 2017; World Health Organization, 2023). Extensive longitudinal studies have established a strong bidirectional link between the two conditions, with obesity increasing the risk of developing depression (Frank et al., 2022; Luppino et al., 2010; Martin-Rodriguez et al., 2016) and depression exacerbating the risk of developing obesity (Milaneschi et al., 2019). However, very little is known about how these conditions interact to influence cognitive functioning.

Both obesity and depression have been linked to impairments in

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inhibitory control (Lavagnino et al., 2016; Restivo et al., 2017; Yang et al., 2018). Inhibitory control refers to the cognitive ability to suppress automatic responses or inappropriate behavior and can be assessed, among others, with response conflict tasks (Bari and Robbins, 2013). Inhibitory control is essential for goal-directed behavior and holds great clinical importance. Deficits in inhibitory control are thought to contribute to the development and maintenance of obesity (Nederkoorn et al., 2006; Stice and Burger, 2019; Yokum and Stice, 2023) and are considered an important vulnerability factor for depression (Grahek et al., 2018). Furthermore, inhibitory control has been found to predict treatment response and long-term outcomes in both obesity (Stinson et al., 2018; Xu et al., 2017) and depression (Dhami et al., 2023; Tozzi et al., 2020).

Behavioral evidence suggests that both obesity (Lavagnino et al., 2016; Yang et al., 2018) and depression (Epp et al., 2012; Li et al., 2021) negatively affect inhibitory control. Importantly, behavioral reports indicate that these negative effects are exacerbated when both conditions co-occur, leading to greater impairments in processing speed (Restivo et al., 2017) and deficits in daily life executive functioning (Dingemans et al., 2019), compared to those with obesity alone. Moreover, individuals with depression and obesity show poorer executive functioning, compared to individuals with depression and healthy body weight (Hidese et al., 2018). Thus, the notion of an additive effect of the two conditions has been put forward, suggesting that depression may exacerbate the cognitive deficits associated with obesity and vice versa (Restivo et al., 2017). However, the neurocognitive mechanisms underlying these additive deficits remain unclear, as there is a paucity of neuroimaging studies on inhibitory control in obesity (Lavagnino et al., 2016).

Emerging neuroimaging data suggests that alterations in neural activation may contribute to these behavioral deficits, but findings are inconsistent and may be influenced by small sample sizes. Preliminary studies in individuals with obesity have reported reduced activation in the insula, supplementary motor area (SMA), inferior parietal cortex, and the cuneus during inhibitory control processing using a stop signal task (Hendrick et al., 2012). This aligns with reports linking higher body mass index (BMI) to lower insula activation using a similar task (Filbey and Yezhuvath, 2017). In contrast, a different small-scale study on obesity reports opposing results, with increased activation in the insula, SMA, cingulate gyrus, frontal, and occipital regions using a Stroop task (Balodis et al., 2013). Similarly, research on depression has shown substantial variability in activation patterns, a finding underscored by a comprehensive meta-analysis which demonstrated a lack of convergence across studies using cognitive tasks (Müller et al., 2017). Recent connectome-based research highlights the value of functional connectivity in reconciling these findings, indicating hyperconnectivity within a network that includes the dorso-lateral prefrontal cortex, the cingulate cortex/SMA, and the precuneus (Cash et al., 2023). Taken together, these studies suggest inhibitory control-related deficits in multiple cortical regions in both depression and obesity; however, findings are mixed and it is unclear whether they are specific to either condition or interact.

One factor that may help explain the inconsistent findings is low-grade systemic inflammation. Elevated levels of peripheral inflammation have been implicated in both conditions (Graßmann et al., 2017; Osimo et al., 2020). In obesity, adipocyte expansion leads to increased leptin secretion, activating inflammatory pathways. This results in an upregulated expression of pro-inflammatory cytokines, including interleukin (IL)-1β, IL-6, tumor necrosis factor (TNF)-α (Park et al., 2010), C-C-motif chemokine ligand (CCL)2, CCL3, haptoglobin, and migration inhibitory factor (MIF) (Huber et al., 2008; Morrison and Kleemann, 2015; Vázquez-Moreno et al., 2020), leading to increased C-reactive protein (CRP) production (de Heredia et al., 2012). Similarly, stress-induced systemic inflammation has been proposed as a key factor in the development of depression (Kiecolt-Glaser et al., 2015), with studies linking depressive symptoms to alterations in peripheral inflammation markers, including IL-1β, IL-6, IL-8, CRP, TNFα, serum amyloid A (SAA) (Çakici et al., 2020; Liu et al., 2012; Osimo et al., 2020; van Dooren et al., 2016), CCL2, CCL3, haptoglobin, and MIF (Leighton et al., 2018; Maes et al., 1993; Sforzini et al., 2023). Crucially, mounting evidence suggests that peripheral inflammation is linked to poorer neurocognitive performance in both conditions (Chen et al., 2021; Shi et al., 2022; Tsai et al., 2017), and influences brain activation in key areas for inhibitory control, such as the prefrontal cortex and the striatum (Kraynak et al., 2018). Thus, understanding how inflammation mediates the impairment of inhibitory control could provide valuable insights into the combined effect of depression and obesity on neurocognitive processing.

Here, we examine inhibitory control processing in a relatively large sample of individuals with concurrent obesity and partially depressed mood by probing neural responses during the Stroop task (Stroop, 1935), a well-established measure of inhibitory control (Cieslik et al., 2015). Our first aim was to determine whether individuals with elevated obesity and depressed mood exhibit altered neural activation during inhibitory control processing, focusing on brain regions sensitive to inflammation (Kraynak et al., 2018). Secondly, we investigated depression-obesity dependent functional connectivity during inhibitory control processing, to assess alterations of neural circuits required for task performance. Finally, we explored the relationship between altered neural responses and individual variations in key markers of systemic inflammation.

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 bariatric surgery. 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). Eleven participants had to be excluded. A total of 64 individuals (nine men, 14 %) were included in the analyses. Details are provided in Supplemental Methods.

This sample overlaps with previous studies of the BARICO project (Custers et al., 2023, 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. Depressive symptoms were assessed with the Dutch version of the Beck Depression Inventory (BDI) version IA (Beck and Steer, 1993). To capture interaction effects between depression and obesity, a composite score of depression symptoms and BMI was calculated as the sum of the z-scored values. Blood samples were collected to assess inflammation markers, including CRP, leptin, serum amyloid A (SAA), tumor necrosis factor-α, IL-1β, IL-6, IL-8, CCL2, CCL3, haptoglobin, and MIF levels. Details are provided in Supplemental Methods.

To examine the relationship between depression, obesity and inflammation, we calculated partial Spearman's rank correlations, controlling for age and sex (assigned at birth) using R (RRID: SCR_001905, version 4.3.2). In the analyses of depression, BMI was included as an additional covariate of no interest and conversely, the analysis of BMI was controlled for depression. Inflammatory markers associated with depression, obesity, or the composite score were selected for subsequent brain-inflammation analyses.

2.3. Stroop task

Inhibitory control (i.e., response conflict processing) was assessed 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. 1A), 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).

Mean response time (RT) of correct trials and response accuracy were analyzed as measures of task performance (Fig. 1B,C). 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 0.9 % of all data).

2.4. Analysis of fMRI activation

Functional images were subjected to preprocessing procedures, which included realignment, slice timing correction, spatial normalization, and smoothing. Details are provided in Supplemental Methods. Second-level analysis comprised a one-sample *t*-test on the contrast of interest [incongruent>congruent], including age and sex as covariates of no interest. To explore the potential association with systemic inflammation, we focused our analysis on brain regions susceptible to peripheral inflammation (Kraynak et al., 2018) using an inflammation-sensitive brain mask (Supplemental Methods, Table S1). Statistically significant clusters of activation were obtained using a cluster-defining threshold of pFWE < 0.05 (peak-level) and a spatial extent of $k = 10$ voxels, controlling the family-wise-error (FWE) rate at $\alpha \leq 0.05$ across the search space. Mean beta values from the five clusters with the largest differences in activation between conditions were extracted for subsequent correlation analyses. To probe whether higher depression or obesity scores were linked to alterations in brain activation during response conflict, we included depression, obesity, and the depression-obesity composite scores as regressors in separate second-level GLMs, using a cluster-defining threshold of $p < 0.001$ and controlling the FWE rate at $\alpha \leq 0.05$ across the search space. Results were labelled according to the anatomical structure they overlapped with the highest probability using the Automated Anatomical Labeling atlas 3v1 (Rolls et al., 2020), and assigned to large-scale functional brain networks based on their spatial location (Yeo et al., 2011). Results were visualized as dual-coded images (Allen et al., 2012) using the *nanslice* package (https://github.com/spinicist/nanslice). The unthresholded T-map representing the neural activation for the contrast [incongruent>congruent] is available on NeuroVault (RRID:SCR_003806; https://identifiers.org/neurovault.image:782521).

2.5. Analysis of fMRI connectivity

We examined functional connectivity of response conflict-sensitive regions during inhibitory control, using generalized psychophysiological interaction (gPPI) analyses (McLaren et al., 2012) with the five clusters with the largest differences in activation between conditions [incongruent > congruent] as seed regions (Fig. 3A). Details are provided in Supplemental Methods. A second-level analysis used a one-sample *t*-test on the contrast image to probe connectivity changes during response conflict, including age and sex as covariates of no interest. Additionally, to probe whether higher depression and obesity scores were associated with alterations in functional connectivity during response conflict, we included depression and obesity scores, and the depression-obesity composite scores as regressors in separate second-level GLMs. In the analyses of depression, BMI was included as additional covariate of no interest and conversely, the analyses of BMI was controlled for depression. 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 whole brain. Unthresholded T-maps representing the task-connectivity and the associations between task-connectivity and depression, BMI, and the depression-obesity composite score for the contrast [incongruent > congruent] are available on NeuroVault (RRID:

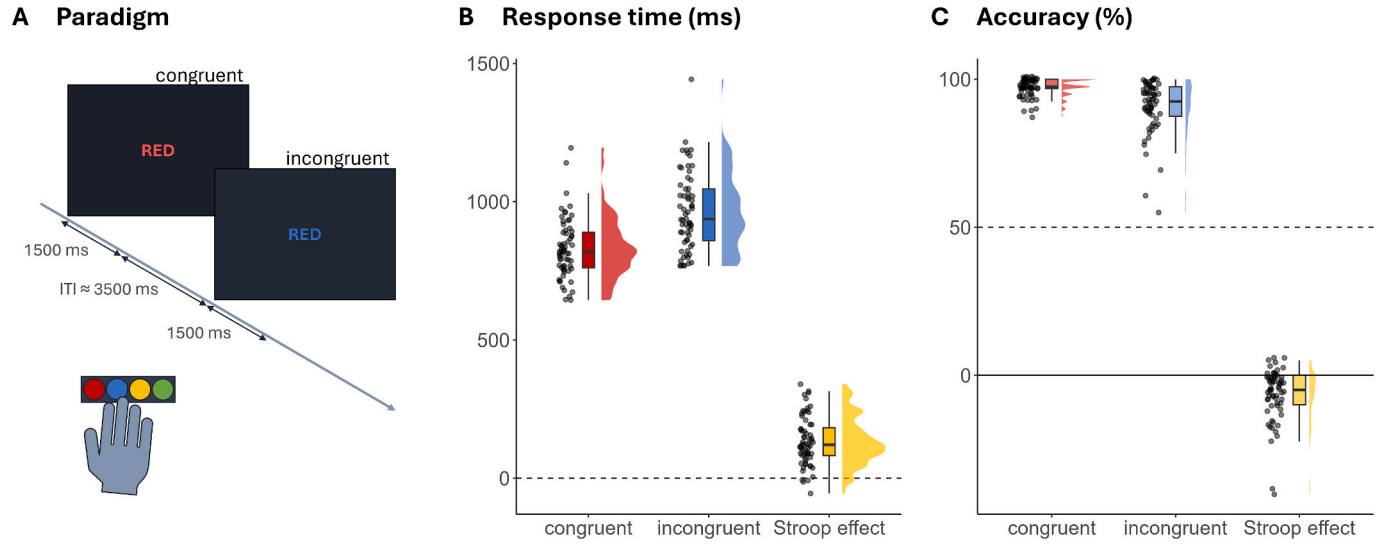

Fig. 1. Color-word Stroop task. A. Paradigm. In the congruent condition, the color of the ink and the color word matched. In the incongruent condition, there was a mismatch between the color of the ink and the color word. The duration of each stimulus lasted 1500 ms and the inter-trial interval (ITI) 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. B. 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. C. Accuracy results. The Stroop effect was calculated as the difference in mean accuracy of trials between the incongruent and the congruent condition. 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.

SCR_003806; https://identifiers.org/neurovault.image:12628).

2.6. Brain-behavior and brain-inflammation analysis

The second aim of the study was to explore associations between neural measures, task performance, and inflammatory markers. Analyses were performed in R (RRID:SCR_001905, version 4.3.2). To account for the skewed distribution of the performance and inflammation measures, relationships between neural measures, performance, and inflammation were computed as partial Spearman's rank correlations, using the residuals after controlling for age and sex. In the analyses of depression-specific alterations, BMI was included as additional covariate of no interest and conversely, the analyses of obesity-specific alterations were controlled for depression. For performance, separate associations for response time and accuracy were tested. The significance level for the brain-behavior analyses was set to $\alpha = 0.05$, Holm adjusted for two comparisons (Holm, 1979). For inflammation, each of the measures associated with depression, obesity, or the depression-obesity composite score was tested. Due to the exploratory nature of this research question, uncorrected *p*-values are reported. To assure the robustness of our results, bias-corrected and accelerated bootstrap confidence intervals were computed with 10′000 permutations, using the *parameters* package (Lüdecke et al., 2020).

3. Results

3.1. Demographic and inflammation results

Descriptive statistics of the participants are presented in Table 1. Twenty-nine participants (46 %) of the sample scored above the cut-off for mild to moderate depression (BDI score > 9), and 45 participants (70 %) had elevated CRP levels (> 3 mg/l), a crude measure for systemic inflammation (Ishii et al., 2012). We first assessed the relationship between the depression-obesity composite score and inflammation. Elevated depressive symptoms were related to lower IL-8 (rho = −0.29, $p = 0.019$; bootstrap 95 %-CI [−0.51, −0.03]) and MIF (rho = −0.31, $p = 0.014$; bootstrap 95 %-CI [−0.51, −0.05]). Greater BMI was associated with higher CRP (rho = 0.33, $p = 0.008$; bootstrap 95 %-CI [0.08, 0.53]), leptin (rho = 0.27, $p = 0.034$; bootstrap 95 %-CI [0.01, 0.48]), and CCL3 (rho = 0.34, $p = 0.005$; bootstrap 95 %-CI [0.08, 0.56]). Higher depression-obesity composite scores were related to higher CRP (rho = 0.28, $p = 0.024$; bootstrap 95 %-CI [0.04, 0.48]), leptin (rho = 0.36, $p = 0.003$; bootstrap 95 %-CI [0.11, 0.56]), IL-6 (rho = 0.27, $p = 0.028$; bootstrap 95 %-CI [0.03, 0.48]), and CCL3 (rho = 0.29, $p = 0.022$; bootstrap 95 %-CI [0.03, 0.48]) (Figs. S1, S2). These six inflammatory markers were selected for subsequent brain-inflammation analyses.

Table 1
Participants' demographic and clinical characteristics.

Characteristic	$N = 64$	
	Mean (SD) / n (%)	[Range]
Age	45.21 (5.99)	[36.16, 55.94]
Sex assigned at birth (female / male)	55 (86 %) / 9 (14 %)	
Educational level (low / middle / high) [1]	8 (13 %) / 32 (50 %) / 24 (38 %)	
BMI (kg/m^2)	40.22 (3.40)	[32.80, 52.90]
Waist circumference (cm) [2]	120.93 (9.87)	[101.00, 145.00]
BDI	9.25 (5.54)	[1.00, 24.00]
Leptin (ng/ml)	65.06 (24.83)	[17.16, 141.02]
CRP (µg/ml)	7.31 (7.69)	[0.49, 49.59]
SAA (µg/ml)	13.46 (16.70)	[0.75, 111.49]
TNF-α (pg/ml)	4.25 (1.76)	[1.06, 9.98]
IL-1β (pg/ml)	0.38 (1.06)	[0.00, 7.59]
IL-6 (pg/ml)	2.67 (2.31)	[0.22, 14.76]
IL-8 (pg/ml)	8.35 (4.24)	[2.87, 28.53]
CCL2 (pg/ml)	148.45 (33.10)	[74.48, 266.96]
CCL3 (pg/ml)	19.20 (8.39)	[2.28, 42.55]
Haptoglobin (µg/ml)	861.70 (360.16)	[219.96, 2167.84]
MIF (ng/ml)	11.59 (8.94)	[1.85, 48.24]
Antidepressant medication	7 (11 %)	
Oral antidiabetic medication	7 (11 %)	
Insulin	3 (4.7 %)	
Antihypertensive medication	14 (22 %)	
Obstructive sleep apnea	16 (16 %)	
Smoking	7 (11 %)	

[1] According to the Verhage score (Verhage, 1965): 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).
[2] $n = 56$.

3.2. Behavioral results

Comparing the Stroop task conditions, we found a robust Stroop effect with a large effect size for response time (mean Δ response time = 131.01 ± 88.03, t(63) = 11.91, $p < 0.0001$, $d = 1.49$) and a moderate effect size for response accuracy (mean Δ accuracy = −6.56 ± 8.87, t(63) = −5.92, $p < 0.0001$, $d = -0.74$), which confirmed the presence of response automaticity in our sample (Fig. 1B,C). Notably, there was no evidence for correlations of individual performance differences (Δ response time and Δ accuracy) with depression, BMI, and depression-obesity composite scores (all $p > 0.45$). This independence from task performance mitigates potential behavioral confounds in interpreting the neuroimaging data, such that differences in neural activation can be attributed to changes in the allocation of resources to meet task demands, rather than nonspecific changes linked to alterations in behavioral performance. In terms of inflammation markers, there was a significant association between individual CCL3 levels and the response time (Δ response time; rho = 0.30, $p = 0.033$; bootstrap 95 %-CI [0.06, 0.50]) and the accuracy Stroop effect (Δ accuracy; rho = −0.27, $p = 0.016$; bootstrap 95 %-CI [−0.46, −0.04]).

3.3. Neuroimaging results

3.3.1. Brain activation during response conflict

We identified inhibitory control processing areas as brain regions that showed 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). Consistent with previous work on response conflict (i.e., cognitive action regulation, (Langner et al., 2018)), this contrast revealed prominent activation in the expected brain regions, the strongest five being located in the left SMA (ventral attention network), the left middle frontal gyrus (MFG inferior and superior, fronto-parietal network), the left inferior occipital gyrus (dorsal attention network), and the right caudate nucleus (Fig. 2B; see Table S2 for a summary of all clusters and coordinates).

To investigate the association of the observed brain activation and participants' performance and inflammation levels, mean beta values of the five strongest clusters were extracted. Subsequent correlation analyses revealed moderate correlations between neural activation of the SMA and the response time Stroop effect (Δ response time; rho = 0.32, $p = 0.02$; bootstrap 95 %-CI [0.07, 0.52]), and between the caudate nucleus and the response time (rho = 0.34, $p = 0.006$; bootstrap 95 %-CI [0.09, 0.55]) and accuracy Stroop effect (Δ accuracy, rho = −0.37, $p = 0.005$; bootstrap 95 %-CI [−0.58, −0.13]), indicating that increased conflict-related activation in these regions was related to poorer performance during the incongruent compared to the congruent condition (Fig. 2C).

In a second step, we examined whether participants' brain activation during response conflict processing was related to depression, BMI, or the composite depression-obesity scores, by including these parameters in separate GLMs. No evidence for an association between activation and

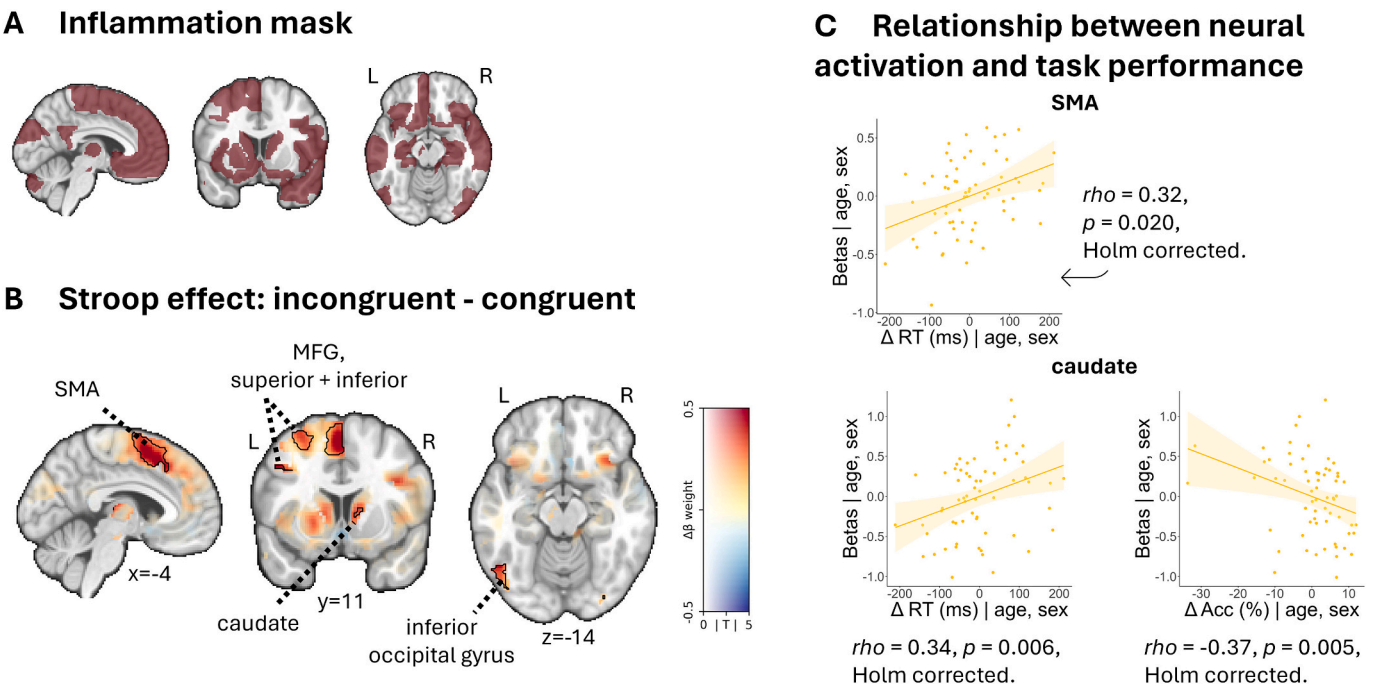

Fig. 2. Neural activation during inhibitory control processing (Stroop effect) and its relationship to task performance. A. The Stroop effect was calculated within a mask of inflammation-sensitive brain regions (Kraynak et al., 2018), see Supplemental Methods for further details (Table S1). B. During inhibitory control processing, participants showed greater activation in several brain regions, including the left supplementary motor area (SMA), two clusters in the left middle-frontal gyrus (MFG, superior + inferior), the right caudate nucleus, and the left inferior-occipital 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 (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 Participants with greater neural activation in the SMA (Δ response time, bootstrap 95 %-CI [0.07, 0.52]) and the caudate nucleus cluster showed poorer task performance (Δ response time and Δ accuracy, bootstrap 95 %-CI [0.09, 0.55] and [−0.58, −0.13]).

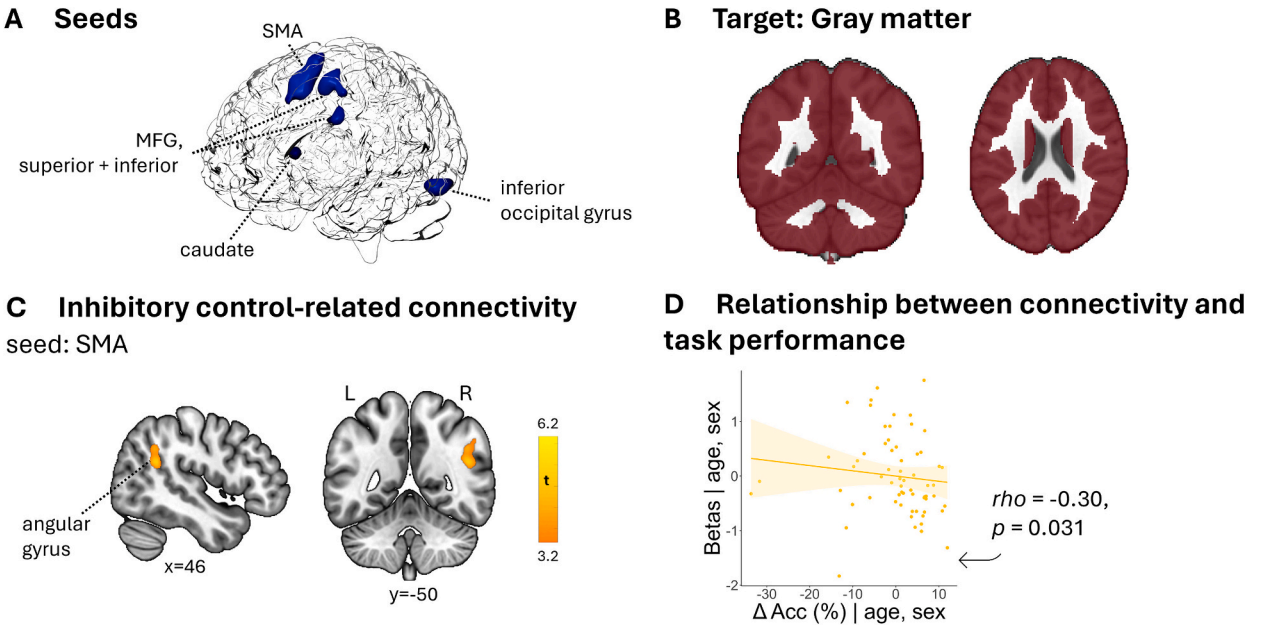

Fig. 3. Functional connectivity during response conflict processing (Stroop effect) and its relationship to task performance. A. The gPPI analyses were seeded in five conflict-processing regions, that showed the strongest neural activation for the contrast of interest (incongruent > congruent; dark blue). B. gPPI connectivity was calculated from the seed regions to every gray-matter voxel in the brain (dark red). C Functional connectivity during response conflict processing revealed increased connectivity between the left supplemental motor area (SMA) and the right angular gyrus (k = 143, pFWE = 0.003; covariates: age, sex). D Participants with greater functional connectivity showed poorer task performance (Δ accuracy), bootstrap 95 %-CI[−0.52, −0.05]. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

depression, obesity, or the depression-obesity composite score was observed.

3.3.2. Task connectivity during response conflict

To investigate conflict-related functional connectivity, we conducted gPPI analyses using the five clusters showing the strongest peak activation in the (incongruent>congruent) GLM contrast as seed regions (Fig. 2B+3A). Of these regions, the seed in the SMA showed increased connectivity with a right angular gyrus cluster (default mode network) during response conflict (k = 143, pFWE = 0.003) (Fig. 3C, Table S3). This connectivity pattern held when controlling for depression, BMI, or the depression-obesity composite. Subsequent correlation analyses with task performance revealed a moderate negative association between the connectivity and the accuracy Stroop effect (rho = −0.30, p = 0.031; bootstrap 95 %-CI[−0.52, −0.05]), indicating that increased conflict-related connectivity between the SMA and the angular gyrus was related to less accurate responses during the incongruent compared to the congruent condition (Fig. 3D).

3.3.3. Depression- and obesity-specific effects

We next examined depression- and obesity-specific connectivity alterations to assess the separate contributions of each condition. Participants with elevated depression scores showed greater functional connectivity between the seed in the left superior MFG and the left precuneus (k = 164, pFWE = 0.001; covariates: BMI, age, sex) (Fig. 4A, Table S3), suggesting they require more fronto-parietal crosstalk during inhibitory control. These results held when antidepressants use was included as additional confound (Table S4). Conversely, individuals with greater obesity showed weaker functional connectivity between the seed in the left superior MFG and the right fusiform gyrus (k = 255, pFWE <0.001; covariates: depression, age, sex), and between the seed in the left inferior MFG and the left superior frontal gyrus, medial (k = 118, pFWE = 0.009; covariates: depression, age, sex), suggesting less crosstalk between the fronto-parietal and the visual network and between the fronto-parietal and the default mode network (Figs. 4B, 5F). Partial correlation analyses showed no evidence for an association between depression- or obesity-specific connectivity alterations and performance (Δ response time and Δ accuracy; all p > 0.13).

With regard to inflammation markers, there was a significant

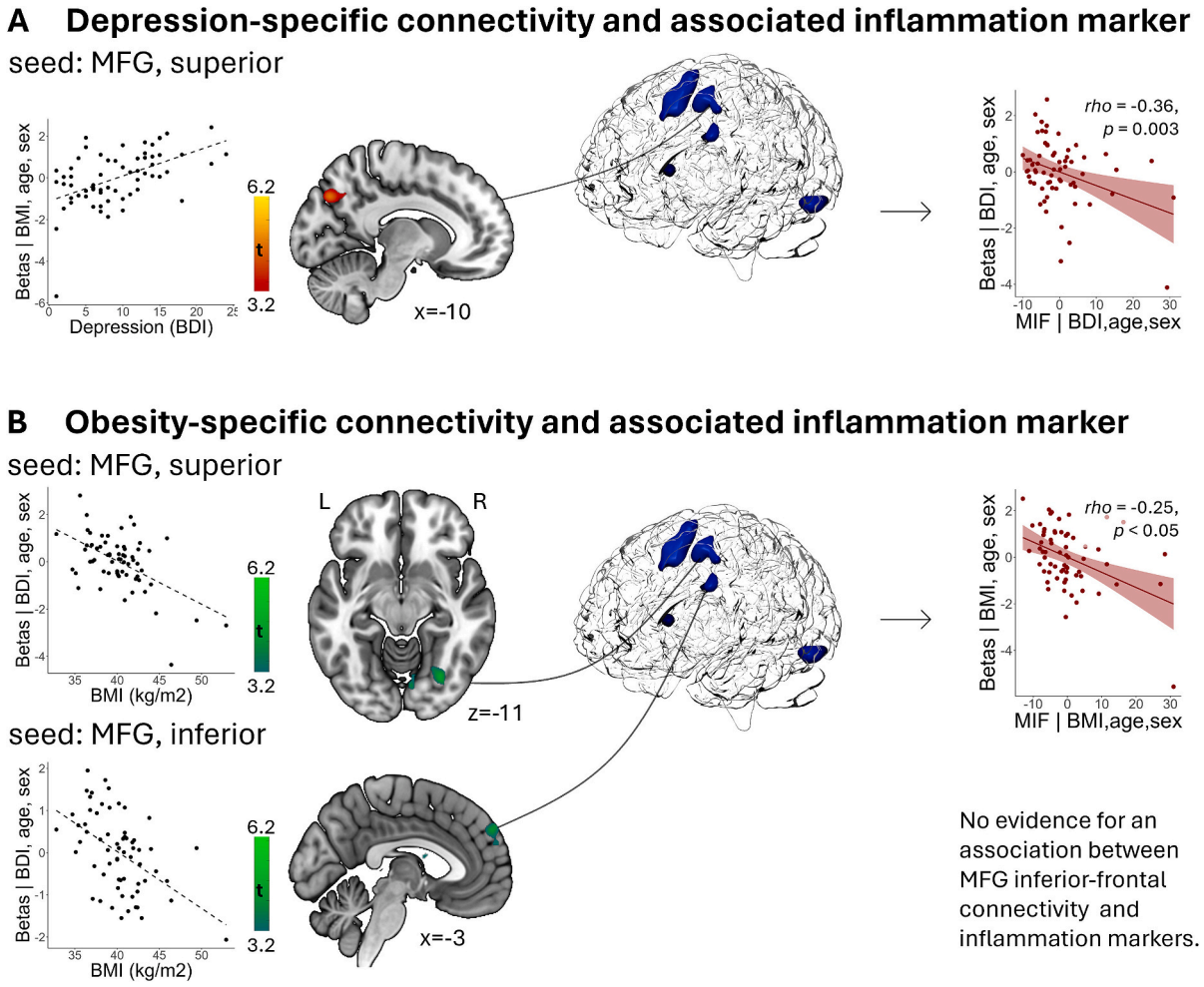

Fig. 4. Depression- and obesity-specific connectivity alterations and their relation with inflammation. The gPPI analyses were seeded in five conflict-processing regions, that showed the strongest neural activation for the contrast of interest (incongruent > congruent; dark blue). A. Participants with elevated depression scores showed greater functional connectivity between the seed in the left superior middle-frontal gyrus (MFG), and the left precuneus. Scatterplots on the left show the covariation of control-related connectivity strength and depression for illustrative purposes. Depression-specific connectivity alterations were negatively associated with individual variations in MIF values. B. Participants with higher BMI showed weaker functional connectivity between the seed in the left superior MFG and the right fusiform gyrus, and between the seed in the left inferior MFG and the left medial superior-frontal gyrus. Scatterplots on the left show the covariation of control-related connectivity strength and obesity. Obesity-specific connectivity alterations between MFG superior-fusiform gyrus were negatively associated with individual variations in MIF values. See Table S3 for a full list and Montreal Neurological Institute (MNI) coordinates of significant clusters. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

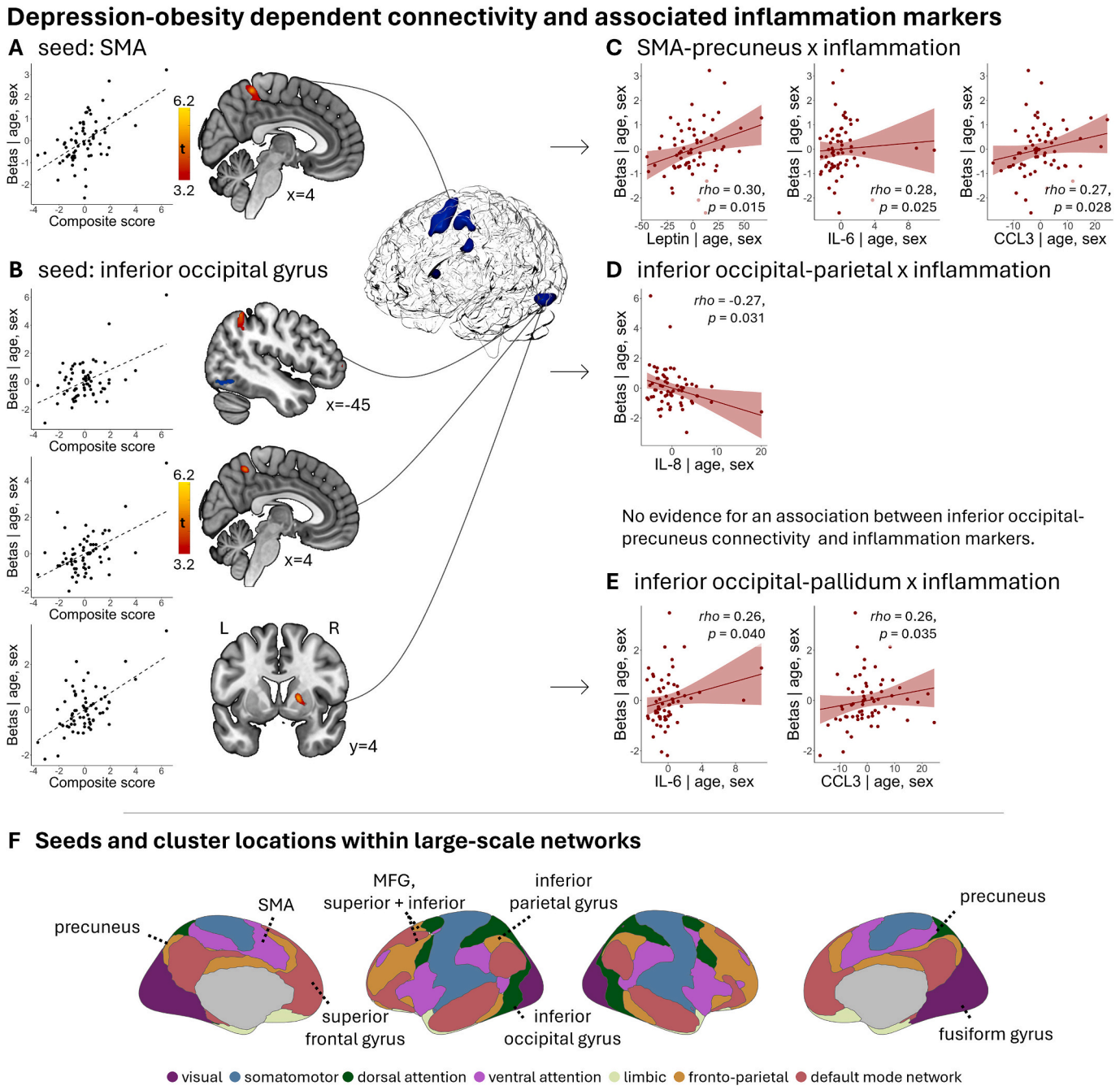

Fig. 5. Depression-obesity dependent connectivity alterations and their relation to inflammation. The gPPI analyses were seeded in five conflict-processing regions, that showed the strongest neural activation for the contrast of interest (incongruent > congruent; dark blue). Participants with higher depression-obesity composite scores showed greater functional connectivity A. between the seed in the left supplemental motor area (SMA) and the right, and B. between the seed in the left inferior occipital and the left inferior parietal gyrus, the right precuneus, and the right pallidum/putamen. Scatterplots on the left show the distributions and covariation of control-related connectivity strength the depression-obesity composite score for illustrative purposes. C-E. Depression-obesity dependent connectivity alterations were significantly correlated with individual levels of inflammation markers. Please note, that the correlations in E. should be considered as weak evidence, due to bootstrap confidence intervals crossing zero. F. Assignment of gPPI seeds and clusters to functional brain networks (Mowinckel, 2021; Yeo et al., 2011). See Table S3 for a full list and Montreal Neurological Institute (MNI) coordinates of significant clusters. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

negative correlation between depression-specific connectivity alterations of the MFG superior-precuneus and individual MIF values (rho = −0.36, $p = 0.003$; bootstrap 95 %-CI [−0.56, −0.12]) (Fig. 4A). Similarly, there was a significant negative correlation between obesity-specific connectivity alterations of the MFG superior-fusiform gyrus connection and individual MIF values (rho = −0.25, $p = 0.049$; bootstrap 95 %-CI [−0.44, −0.01]) (Fig. 4B). There was no evidence for associations between depression- or obesity-specific connectivity alterations and other inflammation markers (CRP, IL-6, IL-8, leptin, CCL3) (all $p > 0.13$).

3.3.4. Additive effects of depression and obesity

We then examined whether individuals with co-occurring elevated depression and obesity levels exhibit control-related connectivity

alterations. Participants with higher depression-obesity composite scores showed greater functional connectivity between the seed in the left SMA and the right precuneus (k = 172, pFWE = 0.001; covariates: age, sex), and between the seed in the left inferior occipital gyrus and the left inferior parietal gyrus (k = 83, pFWE = 0.048; covariates: age, sex), the right precuneus (k = 87, pFWE = 0.040; covariates: age, sex), and the right pallidum/putamen (k = 83, pFWE = 0.048; covariates: age, sex) (Fig. 5A,B, Table S3). The SMA-precuneus and the inferior occipital-inferior parietal gyrus connection held when antidepressant use was included as additional confound (Table S4). The findings suggests that participants with co-occurring elevated depression and obesity levels require more crosstalk within the ventral and dorsal attention network, and between regions of the fronto-parietal and dorsal attention network during inhibitory control (Fig. 5F). Partial correlation analyses showed no evidence for an association between these depression-obesity dependent connectivity alterations and performance (Δ response time and Δ accuracy) (all $p > 0.14$).

In examining the link between depression-obesity dependent connectivity alterations and individual inflammation markers, the SMA-precuneus connection showed significant positive correlations with several inflammation markers, including leptin (rho = 0.30, $p = 0.015$; bootstrap 95 %-CI [0.05, 0.53]), IL-6 (rho = 0.28, $p = 0.025$; bootstrap 95 %-CI [0.04, 0.48]), and CCL3 (rho = 0.27, $p = 0.028$; bootstrap 95 %-CI [0.01, 0.49]). Conversely, a significant negative correlation was identified between the inferior occipital-inferior parietal gyrus connection and IL-8 levels (rho = −0.27, $p = 0.031$; bootstrap 95 %-CI [−0.49, −0.03]). Further correlations of the inferior occipital-pallidum connection with IL-6 (rho = 0.26, $p = 0.040$; 95 %-CI [0.00, 0.48]) and CCL3 (rho = 0.26, $p = 0.035$; 95 %-CI [−0.01, 0.49]) yielded bootstrap confidence intervals including zero, hinting at insufficient evidence for a correlation (Fig. 5).

4. Discussion

Obesity and depression are associated with deficits in inhibitory control (Epp et al., 2012; Lavagnino et al., 2016; Li et al., 2021; Restivo et al., 2017; Yang et al., 2018). Here, we investigated the neural mechanism underlying impaired inhibitory control in individuals with both obesity and depressed mood. Our findings reveal increased functional connectivity within the ventral attention network (SMA-precuneus) and between regions of the fronto-parietal and dorsal attention network (inferior occipital-inferior parietal gyrus), suggesting heightened crosstalk among these networks during inhibitory control. Notably, exploratory evidence suggest that increased low-grade systemic inflammation could underlie these effects, as blood inflammation markers were associated with the neural alterations. Findings provide first evidence of neural features contributing to an additive detrimental effect of depression and obesity on neurocognitive function, beyond condition-specific effects.

4.1. Depression- and obesity-specific effects

To examine the unique contributions of depression and obesity on functional connectivity, we first investigated condition-specific effects. Notably, depression was associated with increased functional connectivity between the superior MFG and the precuneus, both part of the fronto-parietal network. This aligns with previous network-level findings in individuals with major depression, indicating hyperconnectivity of the dorso-lateral prefrontal cortex and the precuneus during cognitive tasks (Cash et al., 2023) and increased intrinsic connectivity between the MFG and precuneus (Cheng et al., 2018).

Furthermore, our findings showed an obesity-specific effect, revealing weaker connectivity between the MFG and the superior frontal medial gyrus, within the fronto-parietal and default mode network in individuals with higher obesity levels. A similar reduction in connectivity was observed between the MFG and the fusiform gyrus, implicating both the fronto-parietal and visual networks in individuals with elevated obesity levels. These findings are in partial concordance with previous research on impulsive decision-making, showing decreased connectivity in a dorso-lateral frontal region within the fronto-parietal network in individuals with obesity (Zhang et al., 2022).

4.2. Additive effects of depression and obesity

To investigate the additive effect of co-occurrent depression and obesity on functional connectivity, we next assed depression-obesity dependent connectivity alterations. Findings from whole-brain functional circuit analyses revealed hyperconnectivity of the SMA and the inferior occipital gyrus in individuals with both elevated obesity and depressed mood, when processing incongruent compared to congruent stimuli. Specifically, we observed increased functional connectivity between the SMA, a region central for inhibitory control and planning (Langner et al., 2018), and the precuneus, which also plays a role in response inhibition (Barber and Carter, 2005; Criaud et al., 2017; Lemire-Rodger et al., 2019). Previously, increased precuneus engagement has been interpreted as heightened visual attention due to increased task demands (Barber and Carter, 2005). While the increased depression-obesity-related connectivity was not associated with task performance, it is worth noting that greater neural activation and connectivity of the SMA – independent of BMI or depressive symptoms – were associated with poorer task performance. Importantly, these results are in line with reports in another cognitive domain, working memory, where concurrent depression and obesity were found to lead to greater engagement of the precuneus, than either condition alone (Restivo et al., 2020).

Furthermore, we observed increased functional connectivity between the inferior occipital gyrus and the inferior parietal gyrus, the pallidum/putamen, and the precuneus. The inferior occipital gyrus is known as the *visual word form area*, a site involved in word reading and attention (Chen et al., 2019; Dehaene and Cohen, 2011). Its increased connectivity with regions involved in somatosensory integration and attention suggests heightened neural demands in individuals with both obesity and depression during inhibitory control, requiring the inhibition of reading.

4.3. Associations with systemic inflammation

Biological pathways suggest a link between elevated levels of circulating inflammation markers and changes in the availability and function of neurotransmitters crucial for inhibitory control (Haroon et al., 2012; Robbins and Arnsten, 2009). Our study explored this link by examining how individual inflammation levels relate to neurocognitive alterations, finding significant associations between functional connectivity alterations and selected inflammation measures.

Regarding depression- and obesity-specific connectivity alterations, the inflammation marker MIF was associated with condition-specific connectivity alterations in distinct brain regions and was negatively correlated with individual depression levels. Known for its pro-inflammatory effects and its involvement in the development of inflammatory diseases (Morrison and Kleemann, 2015), MIF has a complex relationship with both depression and obesity. In depression, circulating MIF has been discussed as both a pro- and antidepressant marker, with increased plasma levels linked to better treatment responses in depressed patients (Bloom and Al-Abed, 2014). In obesity, its pro-inflammatory contributions to disease progression are well-documented (Morrison and Kleemann, 2015). However, MIF may also have protective effects against metabolic stress-related pathologies through regulatory mechanisms that depend on the specific pathophysiological context and cellular microenvironment (Leyton-Jaimes et al., 2018; Morrison and Kleemann, 2015). Given the observed negative association with hyperconnectivity, it appears that the protective effects of MIF are predominant in the present cohort.

Our study further examined the additive effect of depression and obesity and their shared link with inflammation markers. Elevated levels of leptin, IL-6, and CCL-3 were correlated with higher depression-obesity composite scores and demonstrated positive associations with hyperconnectivity related to the co-occurrence of both conditions. Specifically, connectivity between the SMA and the precuneus increased as a function of increasing leptin, IL-6, and CCL-3. This finding aligns with previous research indicating increased SMA activity during a Stroop task under acutely induced inflammation (Harrison et al., 2009) and supports the notion that elevated peripheral inflammation markers can adversely affect neurocognitive performance in individuals with depression and obesity (Chen et al., 2021; Shi et al., 2022; Tsai et al., 2017). Moreover, IL-8 demonstrated an inverse correlation with depression levels and was negatively associated with hyperconnectivity between the inferior occipital and the inferior parietal gyrus. This pattern is consistent with studies reporting decreased IL-8 levels in individuals with first-episode depression (Çakici et al., 2020). Taken together, these distinct patterns of inflammatory levels and neural alterations highlight the nuanced roles that different inflammation markers play in modulating neurocognitive functions in the context of comorbid depression and obesity.

4.4. Clinical implications

Our results reveal a distinct neural pattern of inhibitory control disruption in individuals with concurrent depression and obesity. Considering the critical role of inhibitory control in predicting treatment responses and long-term health outcomes (Dhami et al., 2023; Stinson et al., 2018; Tozzi et al., 2020; Xu et al., 2017), our findings underscore the necessity of integrated treatment strategies for both conditions. By simultaneously addressing depressive symptoms and obesity, integrated treatment approaches may attenuate their exacerbating effects and promote beneficial effects of mutual improvement. This notion is supported by reports of improved weight control in individuals with obesity following depression treatment (Jantaratnotai et al., 2017) and evidence from longitudinal obesity studies, indicating that reductions in systemic inflammation and depressive symptoms can contribute to cognitive improvements post-bariatric surgery (Vreeken et al., 2023).

4.5. Limitations

It is important to note that the observational nature of the present study limits our ability to draw causal conclusions. While our exploratory analyses identified associations between inflammation markers and the neurocognitive effects of depression and obesity, these findings will need to be replicated in future confirmatory research. Future research should ideally employ longitudinal or interventional designs to clarify potential causal relationships.

Our investigation into the neurocognitive effects of depression and obesity and their link to inflammation were guided by meta-analytic findings of inflammation-sensitive brain regions (Kraynak et al., 2018). However, previous reports of inflammation-induced neural alterations in inhibitory control processing employed interventional designs, inducing acute inflammation using typhoid vaccinations (Brydon et al., 2008; Harrison et al., 2009). Acute inflammatory responses reflect a higher state of inflammation than low-grade chronic inflammation and the neural effects of it may not fully overlap. Nonetheless, the presently observed associations between the additive effect of co-occurring obesity and depression and inflammation markers largely point in the same direction as previous reports of acute inflammation, with inflammation being associated with an upregulated neural response.

Lastly, the complexity of depression, characterized by heterogeneous combinations of symptoms and corresponding neurocognitive changes (Drysdale et al., 2017; Williams, 2017), presents additional challenges. Our use of BDI scores, a well-established measure of depression severity (Beck et al., 1988), did not capture the direction of appetite changes, a key marker of depression subtypes associated with immuno-metabolic dysregulation (Simmons et al., 2020). Furthermore, it is important to recognize that the BDI cannot replace a diagnostic interview for accurate diagnosis (Hayden et al., 2012). The scores reported here should be interpreted as dimensional indicators of the symptoms experienced, rather than a definitive clinical diagnoses. Future studies would benefit from incorporating more targeted measures of inflammation-related depression symptoms and using structured diagnostic interviews to capture the full range of heterogeneity within depression and ensure broader generalizability.

4.6. Conclusion

We explored the neural mechanism underlying impaired inhibitory control in individuals experiencing both obesity and depressed mood. Taken together, our results show that heightened functional connectivity within the fronto-parietal, ventral, and dorsal attention network is a central feature contributing to impaired inhibitory control in these individuals. Moreover, our findings suggest that inflammatory processes may contribute to these neurocognitive alterations. Our findings support a model of additive detrimental effects of concurrent depression and obesity on inhibitory control, in which the combined effects exceed condition-specific effects.

CRediT authorship contribution statement

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

Declaration of competing interest

None.

Data availability

All data from this study are available upon request from the corresponding authors. All stimuli, the stimulus presentation scripts, and scripts for the main analyses are available at https://doi.org/10.17605/osf.io/n5y9g.

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report; and in the decision to submit the article for publication.

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).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jad.2024.06.093.

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