


Altered food liking in depression is driven by macronutrient composition

Lilly Thurn¹ , Corinna Schulz^{1,2} , Diba Borgmann⁴ , Johannes Klaus² ,
Sabine Ellinger⁵ , Martin Walter^{2,6,7,8}  and Nils B. Kroemer^{1,2,3} 

Original Article

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Corresponding author:

Nils B. Kroemer;

Email: nkroemer@uni-bonn.de

¹Section of Medical Psychology, Department of Psychiatry & Psychotherapy, Faculty of Medicine, University of Bonn, Bonn, Germany; ²Department of Psychiatry & Psychotherapy, Tübingen Center for Mental Health, University of Tübingen, Tübingen, Germany; ³German Center for Mental Health (DZPG), partner site Tübingen; ⁴Novo Nordisk Foundation Center for Basic Metabolic Research, Faculty of Health and Medical Sciences, University of Copenhagen, Denmark; ⁵Institute of Nutritional and Food Sciences, Human Nutrition, University of Bonn, Bonn, Germany; ⁶Department of Psychiatry & Psychotherapy, University Hospital Jena, Jena, Germany; ⁷Department of Behavioral Neurology, Leibniz Institute for Neurobiology, Magdeburg, Germany and ⁸German Center for Mental Health (DZPG), partner site Jena-Magdeburg-Halle

Abstract

Major depressive disorder (MDD) is characterized by changes in appetite and body weight as well as blunted reward sensitivity ('anhedonia'). However, it is not well understood which mechanisms are driving changes in reward sensitivity, specifically regarding food. Here, we used a sample of 117 participants (54 patients with MDD and 63 healthy control participants [HCPs]) who completed a food cue reactivity task with ratings of wanting and liking for 60 food and 20 non-food items. To evaluate which components of the food may contribute to altered ratings in depression, we tested for associations with macronutrients of the depicted items. In line with previous studies, we found reduced ratings of food wanting ($p = .003$) but not liking ($p = .23$) in patients with MDD compared to matched HCPs. Adding macronutrient composition to the models of wanting and liking substantially improved their fit ($ps < .001$). Compared to carbohydrate-rich foods, patients with MDD reported lower liking and wanting ratings for high-fat and high-protein foods. Moreover, patients with MDD showed weaker correlations in their preferences for carbohydrate- versus fat- or protein-rich foods ($ps < .001$), pointing to potential disturbances in metabolic signaling. To conclude, our results suggest that depression-related alterations in food reward ratings are more specific to the macronutrient composition of the food than previously anticipated, hinting at disturbances in gut–brain signaling. These findings raise the intriguing question of whether interventions targeting the gut could help normalize aberrant reward signals for foods rich in fat or protein.

Introduction

Major depressive disorder (MDD) affects about 280 million people worldwide (Institute of Health Metrics and Evaluation, 2023). It is characterized by diverse symptoms (Fried, Flake, & Robinaugh, 2022; Fried & Nesse, 2015b), such as depressed mood and loss of interest or pleasure ('anhedonia') as cardinal symptoms. MDD also includes opposing somatic symptoms, such as increased versus decreased appetite and body weight, during a depressive episode (Milaneschi, Simmons, van Rossum, & Penninx, 2019; Polivy & Herman, 1976). Although appetite-related symptoms are often not directly treated and may even worsen with antidepressant medication (Himmerich, Minkwitz, & Kirkby, 2015; Kazes et al., 1994), they are comparatively stable across episodes (Stunkard, Fernstrom, Price, Frank, & Kupfer, 1990) and possibly reflect mechanistically distinct subtypes of depression (Cuijpers et al., 2017; Milaneschi et al., 2017; Milaneschi, Lamers, Bot, Drent, & Penninx, 2017; Penninx, Milaneschi, Lamers, & Vogelzangs, 2013; Simmons et al., 2020). Consequently, such opposing changes in appetite and body weight have been associated with differential brain responses to food cues (Simmons et al., 2016) and distinct functional connectivity profiles of the reward circuit (Kroemer et al., 2022). These emerging results suggest that an improved phenotyping of appetite-related symptoms in depression promises a more refined diagnosis of reward dysfunction (Fried & Nesse, 2015a; Fried, Nesse, Zivin, Guille, & Sen, 2014; Schulz et al., 2024). In the long run, such insights may improve the allocation of suitable treatments because effective therapies for somatic symptoms of MDD should conceivably consider the direction of changes in appetite and body weight.

To better characterize appetite-related processes and symptoms, many studies use food cue reactivity (FCR) paradigms (Smeets, Charbonnier, van Meer, van der Laan, & Spetter, 2012; van der Laan, de Ridder, Viergever, & Smeets, 2011). During these FCR tasks, participants view various food images while concurrent brain (Charbonnier et al., 2018; Frank et al., 2010; Guthoff et al., 2010;

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Hare, Camerer, & Rangel, 2009; Kroemer *et al.*, 2013a; Kroemer *et al.*, 2013b) or physiological responses (Rebollo, Schmidt, Longren, & Park, 2021) are collected, or ratings scales are embedded to capture cue-elicited responses guiding eating behavior (e.g., taste, healthiness, wanting, or liking; Charbonnier, van Meer, van der Laan, Viergever, & Smeets, 2015; Müller, Teckentrup, Kühnel, Ferstl, & Kroemer, 2022). Food items from the standardized food battery are typical European foods and have been selected based on recognizability (Charbonnier *et al.*, 2015). Food images are typically contrasted against non-food images (Koepp *et al.*, 2021; Müller *et al.*, 2022), or grouped into categories, for example, based on high versus low energy density (Dimitropoulos, Tkach, Ho, & Kennedy, 2012; Mehta *et al.*, 2012). Recent studies have demonstrated that FCR tasks help reveal nuanced information about the encoding of food reward by considering the macronutrient composition of the depicted food (Motoki, Saito, Suzuki, & Sugiura, 2021; Small & DiFeliceantonio, 2019). For example, DiFeliceantonio *et al.* (2018) have shown supra-additive effects of fat and carbohydrate content on food reward using brain responses and willingness to pay as outcomes. These findings extrapolate previous work on the correspondence between willingness to pay and the true energy density of food but not the perceived energy content (Tang, Fellows, & Dagher, 2014). Such nutritional information is estimated surprisingly quickly as the accuracy of ratings does not improve if participants have more time than 100 ms to evaluate the food (Motoki *et al.*, 2021). Therefore, conventional FCR tasks may provide useful insights about altered food reward processing of macronutrients in depression, even though a comprehensive assessment is lacking to date.

Associating the macronutrient composition of food with markers of reward dysfunction in depression is also promising in light of plausible neurobiological links with disturbed energy metabolism (Borgmann & Fenselau, 2024; Kenny, 2011; Milaneschi *et al.*, 2019). Relating subjective reinforcing values of food to nutritive values of its fat and carbohydrates content relies on parallel neural afferent signaling pathways (de Araujo, Schatzker, & Small, 2020; McDougale *et al.*, 2024; Small & DiFeliceantonio, 2019). Whereas fat-induced reward signals are mainly transmitted via vagal afferents (de Araujo, 2016; de Araujo *et al.*, 2020; Goldstein *et al.*, 2021; Tellez *et al.*, 2013), carbohydrate-induced reward signals are primarily conveyed via portal vein sensors and spinal afferents (Bacharach, Tordoff, & Alhadeff, 2023; Goldstein *et al.*, 2021) although vagal afferents contribute as well (Fernandes *et al.*, 2020). For protein-induced effects, there is mostly indirect evidence pointing to vagal afferent signals (de Lartigue & Diepenbroek, 2016), although subdiaphragmatic vagotomies in rats show that it is not an obligatory pathway for the transfer of energy-related information to the brain (L'Heureux-Bouron *et al.*, 2003). Moreover, distinct gut-innervating sensory neurons differentially control feeding and glucoregulatory neurocircuits, potentially pointing to specific targets for improved metabolic control (Bai *et al.*, 2019; Borgmann *et al.*, 2021; Li *et al.*, 2022; Tan *et al.*, 2020).

Enhanced craving for carbohydrates has often been observed in patients with MDD with an alleged link to increased tryptophan metabolism and brain serotonin levels (Fernstrom, Krowinski, & Kupfer, 1987; Fernstrom & Wurtman, 1971; Markus, 2007; Wurtman & Wurtman, 1995). Accordingly, self-reported differences in macronutrient consumption are associated with a risk for depression in large cross-sectional studies (Cheng, Fu, Lian, Zhan, & Zhang, 2024), and Mendelian randomization studies even suggest a protective effect of carbohydrate intake (Yao *et al.*, 2022). Because depression is often comorbid with obesity (Milaneschi *et al.*, 2019) and type 2 diabetes (Anderson, Freedland, Clouse, & Lustman, 2001;

Geraets *et al.*, 2020; Lustman *et al.*, 2000), altered energy metabolism could contribute to reward deficits and somatic symptoms (Pistis *et al.*, 2021), and an improved knowledge of the pathways contributing to specific depressive symptoms may help identify suitable therapies. Illustratively, recent studies have demonstrated that patients with MDD show altered lipid metabolism (Tkachev *et al.*, 2023), and targeting vagal afferent projections with vagus nerve stimulation could potentially alleviate key symptoms of depression (Edwin Thanarajah & Reif, 2022; Ferstl, Kühnel, Klaus, Lin, & Kroemer, 2024; Teckentrup & Kroemer, 2024), including food reward deficits (Bodenlos *et al.*, 2007; Han *et al.*, 2018; Koepp *et al.*, 2021; McDougale *et al.*, 2024). In sum, evaluating whether altered appetite in depression is specifically correlated with the macronutrient composition of food may reveal physiological relevant insights.

To address the pressing question of whether altered food reward in depression is associated with the macronutrient composition of the depicted food, we investigated patients with MDD and healthy control participants (HCPs) using a conventional FCR task with 60 familiar food and 20 non-food images (Koepp *et al.*, 2021; Müller *et al.*, 2022). In addition, we characterized changes in appetite and body weight in patients with MDD using the SIGH-ADS interview (Williams & Terman, 2003) that covers atypical symptoms of depression. Crucially, we also collected fasting levels of glucose, insulin, and triglycerides to estimate individual differences in insulin sensitivity as measures of metabolic disturbances. To evaluate associations with the macronutrient composition of food, we used linear mixed-effects models predicting wanting and liking ratings using the true nutritional value of the rated food images (Charbonnier *et al.*, 2015). By demonstrating specific associations of reward deficits in depression with foods rich in fat, but not carbohydrates, our study hints at the potential of incorporating macronutrient information into the research of somatic symptoms.

Methods

Participants

As part of an ongoing cross-sectional study, we analyzed a sample of 117 participants (54 diagnosed with MDD and 63 HCPs). The reported results are part of a larger preregistered study about the effects of the gut-brain axis on depression (<https://clinicaltrials.gov/study/NCT05318924>, Fahed *et al.* (2024), Schulz *et al.* (2024)). On average, participants had a mean age of 30 ± 8 years, and a mean body mass index (BMI) of 23.6 ± 3.2 kg/m² (see Table 1). Compared to the group of patients with MDD, we oversampled older HCPs for an additional part of the study involving PET/fMRI (in which only a subset ($N = 26$) of healthy participants were invited). To avoid confounding effects of age, we accounted for age in all mixed-effects analyses (with additional confounds).

All participants were screened for eligibility prior to investigation by phone. Individuals were excluded when over the age of 50 or younger than 20 or if their BMI exceeded 30.0 kg/m² or was below 18.5 kg/m². Furthermore, they were excluded if they had the comorbid disorder schizophrenia, bipolar disorder, severe substance abuse, or a severe neurological condition. HCPs were excluded if a mood or anxiety disorder was present. Due to high comorbidities with anxiety disorders (Kaufman & Charney, 2000), this criterion was not applied to patients with MDD. Individuals were also excluded if they suffered from one of the following conditions within 12 months before screening: eating disorder, obsessive-compulsive disorder, unprocessed trauma and stressor-related disorder, and somatic symptom disorder.

Table 1. Sample characteristics

Characteristics	Overall $N = 117^a$	HCP $N = 63^a$	MDD $N = 54^a$	p -value ^b
Age, years	30.1 ± 7.7	31.9 ± 7.6	28.1 ± 7.3	.007
Females	71 (61%)	38 (60%)	33 (61%)	>.9
Weight, kg	71.6 ± 13.2	72.3 ± 12.4	70.8 ± 14.1	.5
Height, m	1.74 ± 0.09	1.74 ± 0.08	1.73 ± 0.11	.5
Hip circumference, cm	96.3 ± 11.4	96.4 ± 12.4	96.1 ± 10.2	.9
Missing	1	0	1	
Waist circumference, cm	81.4 ± 11.4	80.2 ± 11.1	82.8 ± 11.8	.2
Missing	1	0	1	
Waist-to-Hip Ratio	0.85 ± 0.11	0.83 ± 0.08	0.87 ± 0.14	.11
Missing	1	0	1	
BMI, kg/m ²	23.6 ± 3.2	23.7 ± 3.0	23.5 ± 3.5	.7

^aMean ± SD; n (%).

^bTwo Sample t -test or Pearson's Chi-squared test.

Moreover, they were screened for medication or illnesses influencing body weight and current pregnancy or nursing were additional exclusion criteria for women. Assignment to the MDD group required having MDD at the time of screening (i.e., within 3 months of enrollment) according to DSM-5 criteria. To generalize results to typical patients with MDD, there was no restriction concerning the type of therapy or medication except for changes of medication type or dosage within the preceding 2 months (Supplementary Materials S11). Furthermore, participants were asked to be healthy at the time of testing, and no participants reported the use of antibiotics.

Recruitment took place at the Department of Psychiatry and Psychotherapy, University of Tübingen, Germany and on social media using online advertisements and flyers. Participants were asked to provide written consent prior to the first session. Compensation was given in the form of monetary and food-related rewards (snacks) resulting from the performance in decision-making games. Furthermore, participants received €50 or 5 credit points (if they were students and selected them) for full study completion. The study was approved by the institutional review board that is the local ethics committee of the University of Tübingen, Faculty of Medicine, in accordance with the Declaration of Helsinki (as revised in 2008).

Experimental procedure

The study was conducted at the Department of Psychiatry and Psychotherapy in Tübingen, Germany and consisted of two parts, completed either on one or two separate days. Participants gave written informed consent before beginning the study. Participation included an online assessment with questionnaires, for example, to assess symptoms of depression [Becks Depression Inventory, BDI-II (Hautzinger et al., 2009)] and anhedonia [Snaith-Hamilton Pleasure Scale in German, SHAPS-D (Franz et al., 1998)]. During the first session, we conducted the Structured Clinical Interview for DSM-5 (SCID) (First, 2014). In addition, we used the Structured Interview Guide for the Hamilton Rating Depression Scale with Atypical Depression Supplement (SIGH-ADS) (Williams & Terman, 2003) within the MDD group to calculate delta appetite scores (>0 increase; <0 decrease) that reflect opposing appetite-related symptoms (Kroemer et al., 2022; Schulz et al., 2024). As this part

took approximately 30 min for HCP and up to 2 h for patients with MDD, HCPs were offered to complete both parts within 1 day, whereas patients with MDD were invited to come for the second part on another day. The second part consisted of blood draws and a battery of reward-related tasks. On this day, participants were investigated after an overnight fast (~12 h) in which they were only allowed to consume unsweetened beverages (e.g., water, tea). First, participants had to answer questions in their current subjective metabolic and affective state using visual analogue scales (VAS; Fahed et al. (2024)). Second, fasting blood samples to determine insulin, glucose, ghrelin, and triglyceride levels were analyzed as we reported previously (Fahed et al., 2024; Schulz et al., 2023, Supplementary Materials S12). The experimenters also determined the participants' height, weight, waist and hip circumference, and documented menstrual cycle (if applicable), and time of the last meal and drink. After receiving task-specific instructions, they were asked to complete a battery of reward-related tasks (Schulz et al., 2024), including an FCR task (Müller et al., 2022). The duration of the whole session was about 3.5 h and the FCR task was the first task, taking up about 20 min. Participants were provided water ad libitum. At the end of the session, they received their acquired food rewards and financial compensation.

Food cue reactivity task

To assess anticipatory aspects of food reward, we used an FCR task (Müller et al., 2022). The task consisted of standardized images by Charbonnier et al. (2016) optimized for visual characteristics (homogenous plate with gray background). From this set of images, 60 food images and 20 non-food images depicting office supplies, serving as a control condition, were drawn (Supplementary Materials S13). The task consisted of cue and rating phases. Participants were shown one image before they were asked to evaluate it either based on (a) how much they like the item based on past experiences (liking) or (b) how much they want to receive the depicted item (wanting). Both answers were given on VAS; however, different orientations emphasized the difference in concepts. Liking was rated on a vertical scale (Lim, Wood, & Green, 2009) ranging from -100 (strongest disliking imaginable) to +100 (strongest liking imaginable), whereas wanting was rated on a horizontal scale ranging from

0 (not wanted at all) to 100 (strongly wanted). Each trial started with a black fixation cross on a white screen for 1 s, followed by a (non-) food image for 2 s. Afterward, another fixation cross was shown prior to the rating scale, which was presented for up to 2.8 s to induce fast decision making in participants. The participants could choose their answer using an Xbox controller joystick (Microsoft Corporation, Redmond, WA) and confirm by pressing A, after which a new trial started. To assess liking and wanting separately, all participants viewed the images twice. The order of stimulus presentation and rating was pseudo-randomized. The tasks were completed on a laptop (Lenovo L580) and executed using Psychtoolbox v3.0.18 (Kleiner et al., 2007) in MATLAB (2021b).

Data analysis

Liking and wanting ratings

To evaluate the associations of liking and wanting ratings with macronutrients, we conducted linear mixed-effects models. We divided liking ratings (original range – 100 to 100) by 2 to match the range of wanting ratings (from 0 to 100). These models used either liking or wanting as outcome and included the centered predictors group (HCP versus MDD), BMI, age, and sex (female versus male). Because we used model comparisons in the next step, these base models (M0) were fitted with full maximum likelihood estimation with random intercepts and slopes. Then, we tested three extended models including macronutrient content of the depicted food (z-standardized to ensure convergence) as predictors. Because carbohydrate craving has often been associated with depression, the first extended model (i.e., carbohydrate model, eM1) contained the term carbohydrate content. The second extended model contained the term carbohydrate content and fat content as well as their interaction (i.e., Carbohydrate \times Fat model, eM2a). The third extended model contained the term carbohydrate content and protein content as well as their interaction (i.e., Carbohydrate \times Protein model, eM2b). The latter two extended models were used as alternative models and compared to the base model as well as the carbohydrate model to ensure nested model comparisons. A potentially larger model including all macronutrients was not feasible with all random slopes for the interactions and would likely require more items for robust estimation of the interaction terms. We also evaluated the incremental effect of anhedonia symptoms by adding group-centered SHAPS scores as a predictor. To compare slopes within the linear-mixed effects models, we used the R function `contest` with a *t*-contrast vector comparing the interaction terms of group with carbohydrate, fat, and protein content. To calculate unbiased slope estimates, we ran separate models with restricted maximum likelihood estimation and only including the macronutrient content (z-standardized) as well as the interactions of Carbohydrates \times Fat, or Carbohydrates \times Protein, respectively. These models provide unbiased estimates because they did not include group or demographic variables as predictors while random intercepts and slopes capture individual differences from the group average (extracted with the `coef` function).

Fasting blood levels

As proxies of insulin sensitivity or resistance, we calculated the homeostasis model assessment of insulin resistance (HOMA-IR) using fasting glucose and insulin levels (Matthews et al., 1985; $(\text{insulin [pmol/l]} / 6,945) \times \text{glucose [mg/dl]} / 405$), as well as the triglyceride–glucose index using fasting triglycerides and glucose levels (Unger et al., 2014; $\text{Ln}(\text{triglycerides [mg/dl]} \times \text{glucose [mg/dl]}) / 2$). The samples were analyzed by the Central Laboratory

of the Institute of Clinical Chemistry and Pathobiochemistry of the University Hospital Tübingen. The concentrations of both acylated and unacylated ghrelin were determined in plasma using ELISA kits (#A05306 and #A05319; both from Bertin Bioreagent, Bertin Technologies, Montigny-le-Bretonneux, France; distributed by BioCat, Germany) at the Institute of Nutritional and Food Sciences, Human Nutrition, University of Bonn. To improve the distribution of the obtained blood levels, we used natural log transformation and inspected them using Q-Q plots, indicating that they were well approximated by normal distributions (Schulz et al., 2024).

Statistical threshold and software

All statistical analyses and visualizations were performed using R version 4.3.2 (R Core Team, 2023). The linear mixed-effects models were computed using Satterthwaite's method with the R package `lmerTest` (Kuznetsova, Brockhoff, & Christensen, 2017). The significance threshold was set to $p < .05$.

Results

Patients with MDD report lower food wanting

First, both groups came in roughly at the same time of the day after an overnight fast and reported similar ratings of metabolic state (hunger – satiety) at the time of the blood draw, roughly 20 min before the FCR (Supplementary Figure S14).

To evaluate group differences in food reward ratings, we first used two basal mixed-effects models as references for model comparisons. We predicted either liking or wanting using group and nuisance variables (i.e., BMI, age, and sex) as predictors (grand mean centered). Patients with MDD showed no differences in food liking ($b = -1.68, p = .23; M_{\text{HCP}} = 26.4$ versus $M_{\text{MDD}} = 23.1$ in untransformed units), but reported lower food wanting ($b = -6.22, p = .003; M_{\text{HCP}} = 64.4$ versus $M_{\text{MDD}} = 58.9$) compared to HCPs (for descriptive values of each food item, see Supplementary Materials S15). Adding group-centered SHAPS scores as a predictor revealed that associations with food liking ($b = -0.28, p = .010$) and food wanting ($b = -0.68, p < .001$) were much more pronounced for participants that reported more symptoms of anhedonia.

Adding the macronutrient content of food items substantially improves the model fit of liking ratings

Next, we examined whether adding the carbohydrate content (including an interaction with group with a random slope to capture inter-individual variability) of the depicted food improved the fit of the base models. For food liking, modeling the food's carbohydrate content improved fit considerably, $\chi^2(4) = 300.57, p < .001, \Delta\text{BIC} = 266$. Increasing the carbohydrate content by 1 SD unit (~ 26.5 g/100 g) led to a reduction in liking of $b = -2.28 (p < .001)$. This association was non-significantly attenuated in patients with MDD ($b = 0.91, p = .23$).

We then added the food's content of fat (including interactions with group and carbohydrate content with random slopes for all terms) and observed a considerable improvement compared to modeling only the carbohydrate content, $\chi^2(11) = 377.51, p < .001, \Delta\text{BIC} = 280$. Increasing the fat content by 1 SD unit (~ 13.4 g/100 g) led to a non-significant slight reduction in liking of $b = -0.36 (p = .38)$. This association with fat was non-significantly amplified in patients with MDD ($b = -1.51, p = .071$) and after accounting for the fat content, patients with MDD reported higher liking for foods with a high content of carbohydrates ($b = 1.75,$

$p = .007$). A contrast comparing the slopes for carbohydrates and fat revealed a strong relative preference for carbohydrates in patients with MDD (versus HCPs) compared to fat, $t(117) = 3.44, p < .001$. Fat also enhanced the liking of foods that were rich in carbohydrates, which was reflected in a strong interaction ($b = 2.25, p < .001$). Crucially, we also observed a significant interaction of group with

the term Carbohydrates \times Fat, reflecting that patients with MDD reported higher liking ($b = 1.64, p = .015$; Figure 1a).

Alternatively, we evaluated the interaction of carbohydrates with the protein content of foods. The addition of protein instead of fat led to a smaller improvement in model fit compared to modeling the content of carbohydrates and fat, $\chi^2(11) = 271.62,$

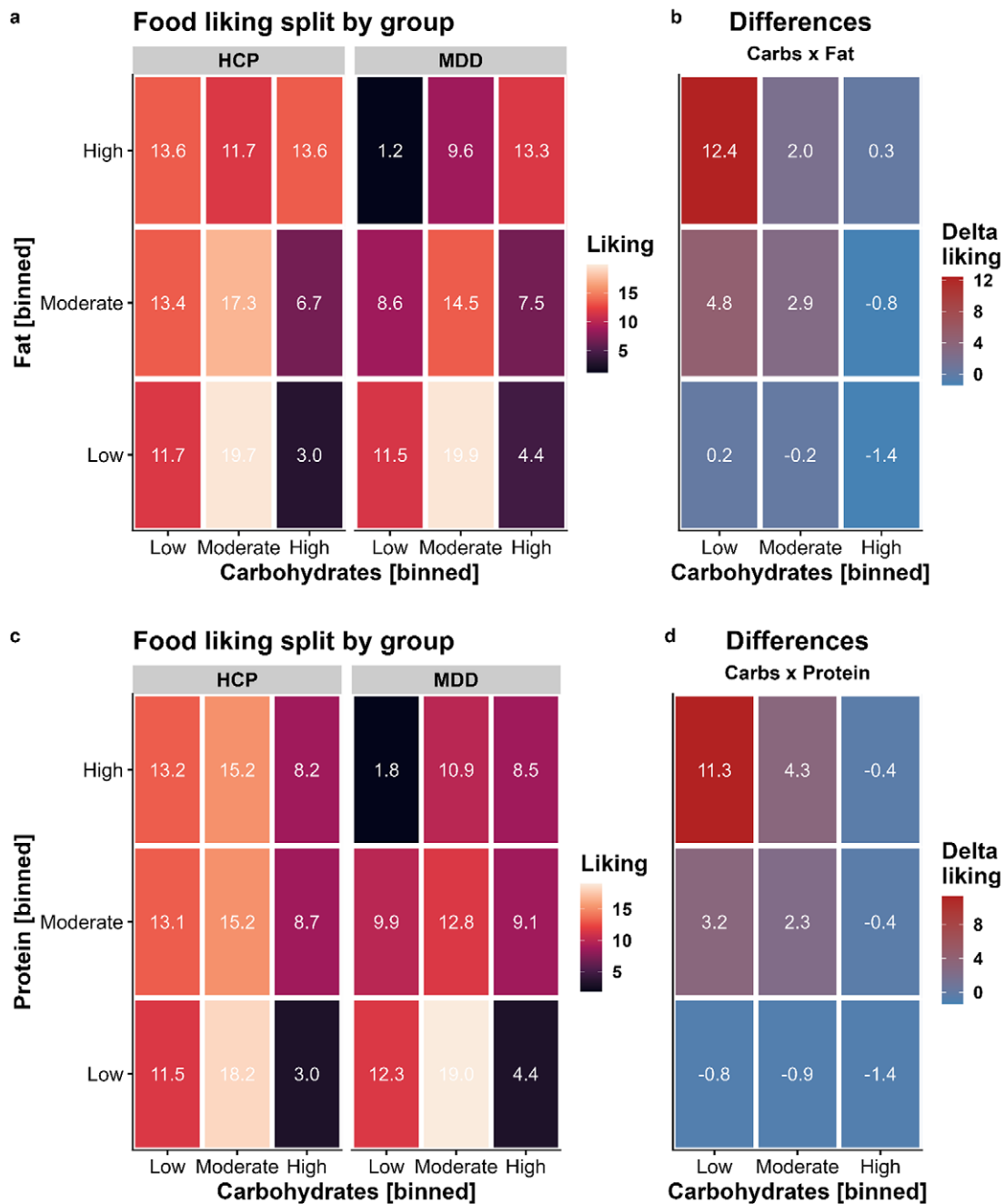


Figure 1. Patients with major depressive disorder (MDD) report lower liking for foods with high content of fat and protein unless they contain carbohydrates as well. To visualize the interaction of different macronutrients and MDD, we binned macronutrient contents for display (A-D). Low corresponds to the lower quartile, moderate to the second and third quartile, and high to the upper quartile. All reported statistics refer to the interaction term derived from liner mixed-effects models using the continuous macronutrient content (corresponding individual estimates are shown in Figure 4). A: Liking ratings split by group and the macronutrients carbohydrates and fat. For display, we binned macronutrient contents so that low corresponds to the lower quartile, moderate to the second and third quartile, and high to the upper quartile. B: Differences between healthy control participants (HCP) and patients with MDD for foods according to their carbohydrate and fat content. Patients with MDD report lower liking for high-fat foods (interaction contrast: $p < .001$). C: Liking ratings split by group and the macronutrients carbohydrates and protein. D: Similar to fat, patients with MDD report lower liking for high-protein foods (interaction contrast: $p = .003$).

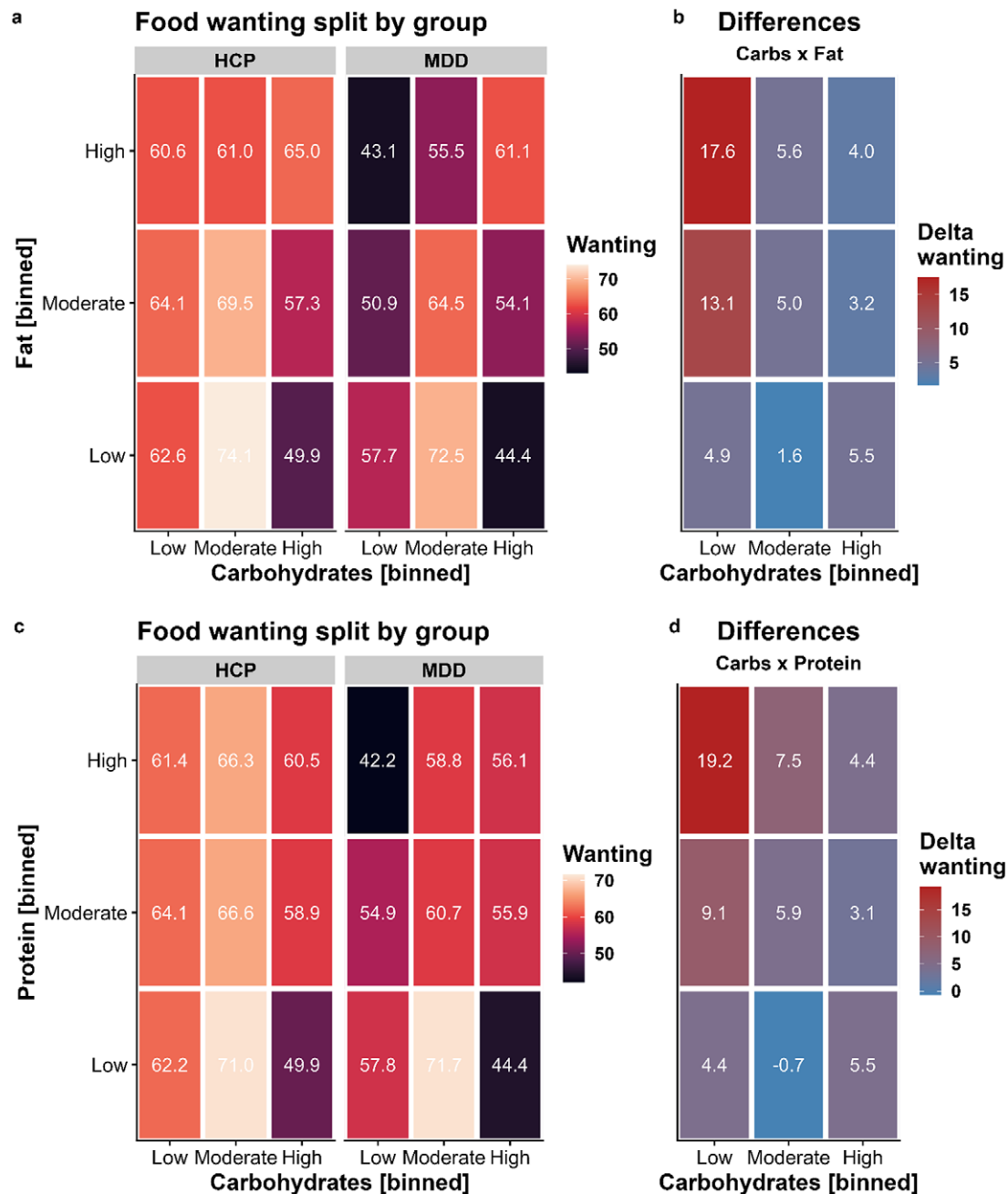


Figure 2. Patients with major depressive disorder (MDD) report lower wanting for foods with high content of fat and protein unless they contain carbohydrates as well. A: Wanting ratings split by group and the macronutrients carbohydrates and fat. For display, we binned content so that low corresponds to the lower quartile, moderate to the second and third quartile, and high to the upper quartile. B: Differences between healthy control participants (HCP) and patients with MDD for foods according to their carbohydrate and fat content. Patients with MDD report lower wanting for high-fat foods (interaction contrast: $p = .019$). C: Wanting ratings split by group and the macronutrients carbohydrates and protein. D: Similar to fat, patients with MDD report lower wanting for high-protein foods (interaction contrast: $p = .028$).

$p < .001$, $\Delta\text{BIC} = 174$ (with the carbohydrate model as reference). Increasing the protein content by 1 SD unit (~ 6.0 g/100 g) led to a reduction in liking of $b = -0.91$ ($p = .027$). This association with protein was amplified in patients with MDD ($b = -1.86$, $p = .024$). A contrast comparing the slopes for carbohydrates and protein revealed a strong relative preference for carbohydrates in patients with MDD compared to protein and HCPs, $t(117) = 3.06$, $p = .003$. Similar to fat, protein also enhanced the liking of foods rich in carbohydrates, leading to a significant interaction term ($b = 0.84$,

$p = .002$). However, patients with MDD did not show an enhanced interaction effect in contrast to fat ($b = 0.55$, $p = .31$; Figure 1b).

Wanting ratings similarly reflect the macronutrient content of food

For food wanting, modeling the food's carbohydrate content improved fit comparable to food liking, $\chi^2(4) = 268.91$, $p < .001$, $\Delta\text{BIC} = 233$. Increasing the carbohydrate content by 1 SD unit

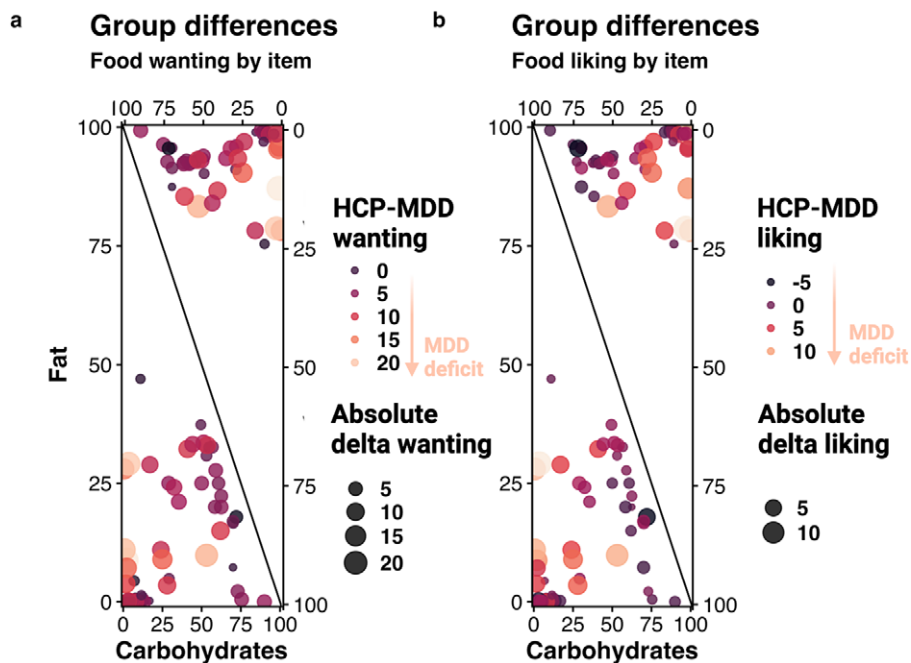


Figure 3. Differences in ratings between patients with major depressive disorder (MDD) and healthy control participants at the item level. First, each dot corresponds to a food item. Second, the size of the dot shows the absolute differences in wanting ratings between the groups, with larger dots indicating larger group differences. In addition, the color of the dot codes the direction of those differences (HCP-MDD, i.e., lighter colors show deficits in patients with MDD). For additional information on the selected items, see [Supplementary Table S13](#). Items are arranged on a scale from 0–100 (carbohydrates versus fat) indicating distribution of carbohydrates and fat per 100 g. A: Group differences in wanting ratings. MDDs show deficits in wanting for items low in carbohydrates and high in fat or protein. B: Group differences in liking ratings. MDDs show deficits in liking for items low in carbohydrates and high in fat or protein.

(~ 26.5 g/100 g) led to a reduction in wanting of $b = -2.72$ ($p < .001$). This association was non-significantly attenuated in patients with MDD ($b = 0.75$, $p = .52$).

Analogous to liking, adding the food's fat content led to a considerable improvement compared to modeling only the carbohydrate content for wanting, $\chi^2(11) = 422.20$, $p < .001$, $\Delta\text{BIC} = 325$. Increasing the fat content by 1 SD unit (~ 13.4 g/100 g) led to a non-significant reduction in wanting of $b = -1.17$ ($p = .058$). This association with fat was non-significantly amplified in patients with MDD ($b = -1.54$, $p = .21$). A contrast comparing the slopes for carbohydrates and fat revealed a moderate relative preference for carbohydrates compared to fat in patients with MDD versus HCPs, $t(117) = 2.38$, $p = .019$. Fat also enhanced the wanting of foods rich in carbohydrates, which was reflected in a strong interaction ($b = 3.75$, $p < .001$). We also observed a non-significant interaction of group with the term Carbohydrates \times Fat, reflecting that patients with MDD reported marginally higher wanting ($b = 1.96$, $p = .052$; [Figure 2a](#)) that was numerically comparable to liking.

The addition of protein instead of fat to the carbohydrate model led to a smaller improvement in model fit compared to modeling the carbohydrate and fat content for food wanting, $\chi^2(11) = 292.73$, $p < .001$, $\Delta\text{BIC} = 196$ (with the carbohydrate model as reference). Increasing the protein content by 1 SD unit (~ 6.0 g/100 g) led to a reduction in wanting of $b = -1.39$ ($p = .022$) and this reduction was more pronounced in patients with MDD ($b = -2.48$, $p = .042$). A contrast comparing the slopes for carbohydrates and protein revealed a moderate relative preference for carbohydrates compared to fat in patients with MDD versus HCPs, $t(117) = 2.22$, $p = .028$. Analogous to liking, protein enhanced the wanting of carbohydrate-rich food, leading to a significant interaction term ($b = 2.03$, $p < .001$), and patients with MDD showed no differences compared to HCPs ($b = 0.33$, $p = .68$; [Figure 2b](#); for item-level results, see [Figure 3](#)).

Carbohydrate cravings have previously been associated with depression. Hence, we started model comparison by adding carbohydrate content and then the interaction with either fat or protein content. A larger model including all macronutrients with random slopes for the interactions was not feasible and would likely require more items for robust estimation of the interaction terms. An exploratory post hoc analysis showed that patients with MDD gave lower ratings for wanting ($b = -4.50$, $p = 0.004$) and liking ($b = -2.89$, $p = 0.005$) for foods rich in protein. Nevertheless, patients with MDD gave higher ratings for wanting ($b = 1.75$, $p = .019$) but not liking ($b = 0.70$, $p = .15$) if foods were rich in both protein and fat ([Supplementary Materials S16](#)).

Patients with MDD show a reduced correlation between macronutrient slopes

To examine whether group differences in food ratings are driven by a disturbed correspondence between macronutrients, we ran additional analyses using unbiased individual estimates of effects (i.e., random slopes reflecting the increase of ratings by one unit of the macronutrient content) derived from modified linear mixed-effects models (see Methods). Notably, patients with MDD showed an attenuated association of individual carbohydrate estimates with fat estimates, $t(113) = -3.78$, $p < .001$, and an attenuated association with protein estimates (each predicted as outcomes by carbohydrate slope estimates), $t(113) = -3.70$, $p < .001$ ([Figure 4](#)). This difference in the correspondence between the macronutrient slopes suggests that patients with MDD have specific impairments in the metabolic sensing of fat and protein content, while preferences for carbohydrate-rich foods are largely unaffected or even enhanced.

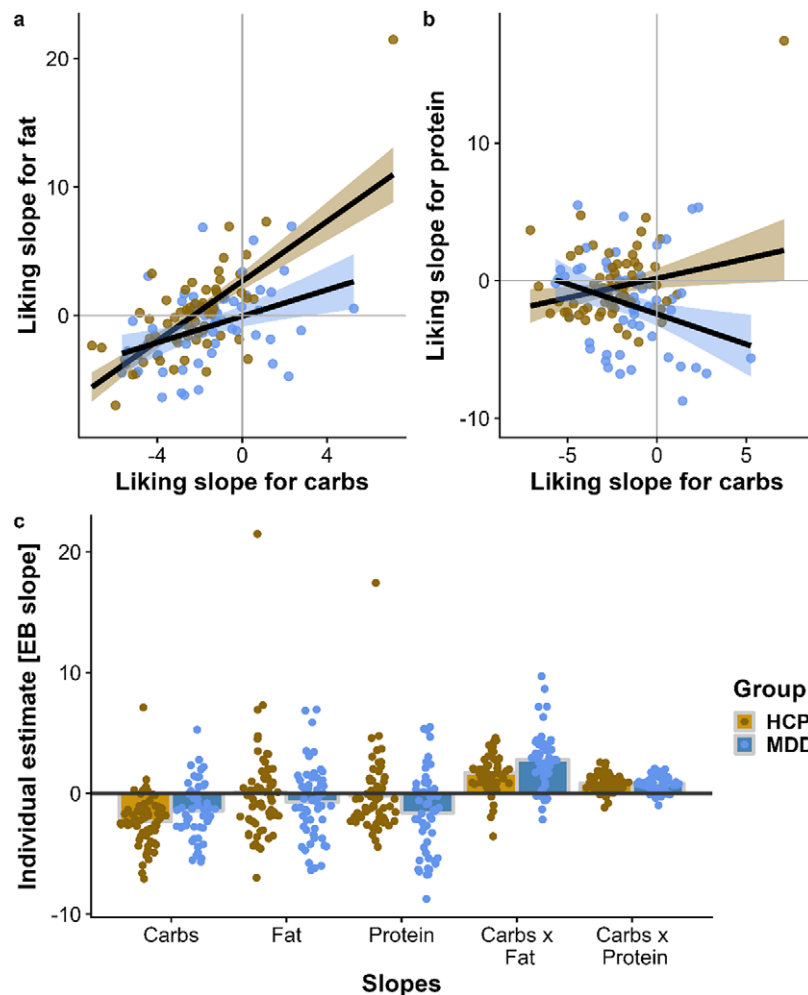


Figure 4. Patients with major depressive disorder (MDD) show attenuated associations between liking slopes for carbohydrates and fat as well as protein. A: Patients with MDD show a weaker correlation between individual estimates of increases in liking per one unit of carbohydrate content (i.e., liking slopes) and increases in liking for fat, $t(113) = -3.78, p < .001$. B: Patients with MDD show a negative correlation between liking slopes for carbohydrates and protein $t(113) = -3.70, p < .001$. C: Individual estimates per macronutrient split by group. The unbiased empirical Bayes (EB) estimates were derived from linear mixed-effects models that did not include group as a regressor. Patients with MDD show higher estimates in likings slopes for carbohydrates and Carbohydrates \times Fat.

Sensitivity and exploratory analyses

After establishing the associations of liking and wanting ratings with the macronutrient content of food, we conducted additional sensitivity analyses to explore associations of food liking ratings with severity, demographic, and metabolic variables (Figure 5). Participants with higher self-reported severity of depressive symptoms, as indexed by the BDI-II, reported lower overall liking ($r = .197, p = .034$) as well as higher liking for food rich in carbohydrates ($r = .250, p = .007$) and Carbohydrates \times Fat ($r = .302, p < .001$). Similarly, participants with more severe anhedonia, as indexed by the SHAPS, reported lower overall liking ($r = .277, p = .003$) and higher liking for food rich in Carbohydrates \times Fat ($r = .204, p = .027$). In contrast, changes in appetite and body weight, as indexed by the delta appetite score, did not correlate with any of the liking estimates. Additional follow-up analyses using the STAI-T to assess trait-like anxiety symptoms suggested robust associations between greater anxiety and liking of food rich in carbohydrates ($r = .321, p < .001$) and Carbohydrates \times Fat ($r = .352, p < .001$). Splitting patients with MDD into low and high anxiety group (Supplementary Materials S17) reveals overall similar

patterns to HCPs versus MDD, further highlighting the unexpected role of anxiety in macronutrient preferences.

Whereas age, sex, and BMI were not significantly associated with overall liking, they showed correlations with macronutrient liking estimates. A higher BMI was associated with higher liking for food rich in Carbohydrates \times Protein ($r = .218, p = .018$). A higher age was associated with lower liking ratings for food rich in carbohydrates ($r = -.370, p < .001$) and Carbohydrates \times Fat ($r = -.297, p = .001$), but higher liking ratings for Carbohydrates \times Protein ($r = .234, p = .011$). Men reported higher liking ratings for food rich in fat ($r = .242, p = .009$) or protein ($r = .252, p = .006$) compared to women.

There were no differences in ghrelin, glucose, or triglycerides levels between participants with and without depression (Supplementary Materials S18). However, insulin levels as well as insulin resistance as measured with the HOMA-IR were higher in participants with depression ($t = -2.4, p = .020$). Metabolic indices (transformed for parametric analyses) primarily showed associations with overall liking ratings. Both higher fasting levels of acyl ($r = .257, p = .011$) and desacyl ghrelin ($r = .251, p = .013$) were associated with higher

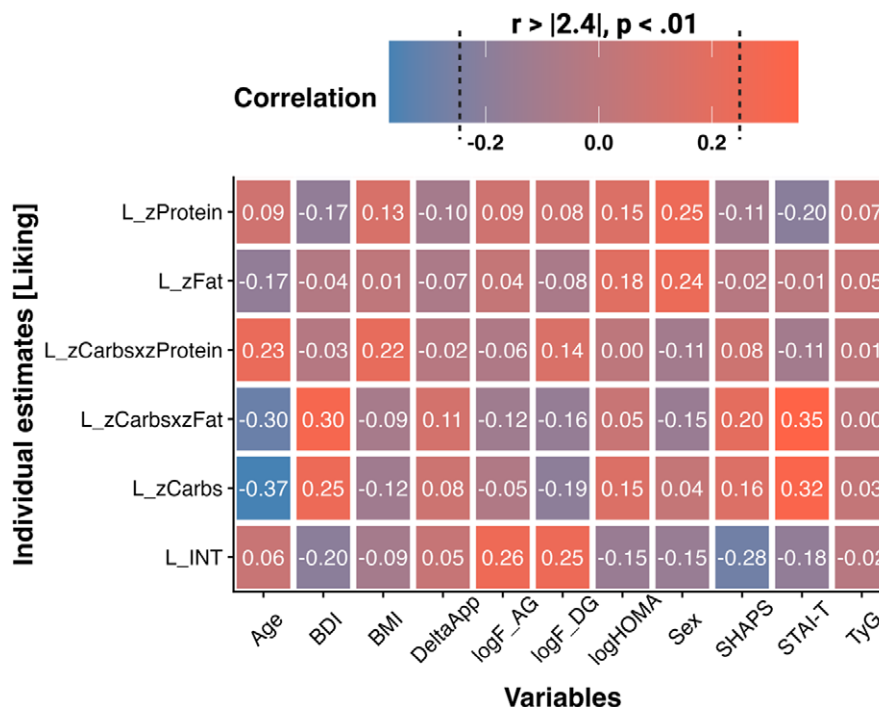


Figure 5. Results of the sensitivity analyses show associations with overall liking (L) and liking slopes reflecting associations of individual ratings with the macronutrient composition of the rated food items. Correlations $\pm .24$ are significant at $p < .01$ ($N = 117$; for ghrelin $N = 97$, thus correlations $\pm .26$ are significant. INT = intercept, BDI = Beck Depression Inventory, BMI = body mass index, F = fasting, AG = acyl ghrelin, DG = desacyl ghrelin, HOMA = Homeostasis Model Assessment, SHAPS = Snaith-Hamilton Pleasure Scale, STAI-T = State-Trait Anxiety Inventory – Trait, TyG = Triglyceride-Glucose Index.

overall liking ratings, with similar correlation coefficients in both groups (see [Supplementary Materials S19](#)). Insulin sensitivity, as indexed by HOMA-IR and the triglyceride-glucose index, showed no significant associations with liking estimates. Associations with wanting slopes were qualitatively similar, and the use of antidepressant medication (antidepressant versus no antidepressant; [Supplementary Materials S11](#)) did not affect the reported associations.

Discussion

Reward dysfunction (anhedonia) is a cardinal symptom of MDD, and somatic symptoms (e.g., altered appetite) are common in severe depression. Although carbohydrate craving has long been recognized as a symptom of depression (Wurtman & Wurtman, 1995), a fully quantitative and experimental investigation of differences in perceived reward using the macronutrient composition of an extensive set of food items was missing to date. Using model comparisons, we demonstrate that the macronutrient composition of food explains substantial variance in individual ratings, providing an opportunity to dissect associations with individual estimates for mechanistic insights, bypassing recall-related biases of self-reported food intake (Ravelli & Schoeller, 2020). Consequently, we show that patients with MDD prefer carbohydrate-rich foods and experience reduced reward from foods rich in fat or protein alone. These reward deficits can be compensated by high carbohydrate content though. Crucially, the reward-enhancing effect of carbohydrate-rich foods was associated with the severity of depressive symptoms and anhedonia. Perhaps surprisingly, we observed no robust associations with the direction of changes in appetite that differentiate subtypes of depression. Instead, we found strong associations with trait-like symptoms of anxiety. These results suggest that preferences for

carbohydrate-rich foods may play a bigger role in the regulation of anxiety- or mood-related symptoms (Christensen & Pettijohn, 2001), compared to somatic symptoms (i.e., delta appetite scores). This interpretation is supported by weak and non-significant associations of metabolic indices with individual estimates reflecting the effect of macronutrients on food reward ratings. To conclude, our results highlight the potential of considering the macronutrient composition of food to better understand candidate drivers of reward-related symptoms in MDD.

In accordance with clinical observations and earlier studies on depression (Paans et al., 2018; Paans et al., 2019; Rose, Koperski, & Golomb, 2010), we observed a shift in liking and wanting ratings of patients with MDD toward foods rich in carbohydrates, compared to fat- or protein-rich foods alone. The significant interaction terms of carbohydrates with fat and protein further suggest that high carbohydrate content can compensate for the reduced perceived reward of foods rich in fat or protein. Notably, the estimated individual preferences for carbohydrates derived from the linear mixed-effects models (random slopes) were associated with symptom severity as indexed by the BDI-II, SHAPS, and STAI-T. Although our cross-sectional study design cannot address causality, preclinical experimental work has shown bidirectional links between dietary intake of carbohydrates and depressive symptoms. For example, a diet rich in refined carbohydrates facilitated anxiety and depressive-like behaviors after stress in mice (Santos et al., 2018), while a high-fat diet desensitizes the output of hypothalamic AgRP neurons, leading to dysregulation of behavior indicative of anxiety and depression (Xia et al., 2021). Moreover, the administration of citalopram, one of the commonly prescribed SSRIs, reduced the preference for fat in male, but not female rats (De la Fuente-Reynoso, Barrios, & Juarez, 2022). In humans, dietary interventions seeking to reduce carbohydrate consumption have

failed to induce robust antidepressive effects so far and, if anything, seem to increase anxiety, although the quality of the evidence is still low (Varaee, Darand, Hassanizadeh, & Hosseinzadeh, 2023). In contrast, recent Mendelian randomization studies even suggest a protective effect of carbohydrate consumption on the risk for depression (Yao *et al.*, 2022). Therefore, longitudinal assessments of food liking and wanting in combination with interventions could be a highly promising approach to improve our understanding of the association between food preferences and depression.

At the mechanistic level, our results are mixed and highlight the necessity for follow-up work. On the one hand, reduced food reward ratings of patients with MDD for fat- and protein-rich foods support the idea that vagal afferent feedback signals might be dysregulated in depression (de Araujo, 2016; de Araujo *et al.*, 2020; de Lartigue & Diepenbroek, 2016; Goldstein *et al.*, 2021; Tellez *et al.*, 2013). This interpretation is supported by the altered correlation between carbohydrate slopes and fat as well as protein slopes in patients with MDD derived from individual ratings of participants. On the other hand, metabolic indices reflecting insulin sensitivity were not associated with the estimated macronutrient slopes, and fasting levels of ghrelin were only associated with overall liking and wanting ratings. Although insulin sensitivity was robustly correlated with self-reported symptoms of anhedonia in our sample (Schulz *et al.*, 2024), it showed no significant associations with food reward ratings. One explanation might be that insulin sensitivity has a stronger effect on the contrast between food and non-food rewards (Kroemer *et al.*, 2013b; Tiedemann *et al.*, 2017), which we did not evaluate here due to the focus on macronutrients. To resolve such open questions, interventional studies using intranasal insulin (Schneider *et al.*, 2022) or ghrelin administration (Malik, McGlone, Bedrossian, & Dagher, 2008) in patients with MDD would be necessary. Our findings that carbohydrate-rich food preferences are preserved in individuals with MDD align with evidence that opioid receptor activity disproportionately alters fat intake compared to carbohydrate intake (Katsuura *et al.*, 2011; Schusdziarra *et al.*, 1983; Taha *et al.*, 2009; Yeomans & Gray, 2002). Given that opioid signaling is often dysregulated in MDD (Jelen *et al.*, 2022), this might explain larger differences in the ratings of foods rich in fat. However, studies measuring or manipulating the opioid system are needed to disentangle the potentially macronutrient-specific reward mechanisms in depression across different metabolic states (*i.e.*, fasted versus sated).

Despite its notable strengths, such as the use of a representative set of well-known European foods that were independently rated in terms of liking and wanting leading to more than 7000 ratings per outcome, the study has several limitations that will need to be addressed in future work. First, due to the cross-sectional study design, it is not possible to answer whether food preferences for carbohydrate-rich foods in depression are functional (*i.e.*, reducing symptoms) or dysfunctional (aggravating symptoms). An interventional design with longitudinal follow-up may help resolve this clinically highly relevant question. Second, we did not collect additional ratings to capture the assumed macronutrient composition of the depicted food items. It is conceivable that subjective evaluations beyond liking and wanting, such as estimated contents of fat or carbohydrates, would shed light on conscious versus subconscious processes related to food preferences (Tang *et al.*, 2014). Relatedly, we collected no data on the typical frequency of consumption of the sampled foods, which might help elucidate potential links with eating behavior and might explain discrepancies to studies that rely on self-reported food intake. Third, we did not measure other circulating peptides, such as leptin, which has been linked to depression (Cao *et al.*, 2018) or LEAP-2, an

antagonist of ghrelin which can influence the activity of ghrelin (Ge *et al.*, 2018; Mani *et al.*, 2019). Finally, our analysis did not further stratify macronutrient categories and future research could provide more nuanced answers by extending the set of pictures to resolve differences within broad macronutrient categories (*e.g.*, sugars versus starch content, saturated versus unsaturated fat).

Depression is characterized by impaired reward sensitivity and opposing changes in appetite and body weight during depressive episodes. In line with previously reported carbohydrate cravings as a symptom of depression, we observed that patients with MDD show a marked preference for foods rich in carbohydrates, compared to foods rich in fat or protein. Moreover, the presence of carbohydrates in foods even compensated for the lower perceived reward in foods rich in fat in patients with MDD as indicated by the modeled interaction terms. Individual preferences for carbohydrates were further associated with depression severity, anhedonia, and trait-like anxiety symptoms, but unexpectedly not with the direction of changes in appetite during the current episode. Taken together, our study highlights that incorporating the macronutrient content of rated food items considerably improves our understanding of food reward deficits in depression and may pave the way for future interventional research. We anticipate that collecting liking and wanting ratings of food items could improve the longitudinal assessment of appetite-related symptoms compared to conventional food frequency questionnaires alone because it does not rely on potentially selective recall.

Supplementary material. The supplementary material for this article can be found at <http://doi.org/10.1017/S0033291724003581>.

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CRedit Author contributions. Lilly Thurn: Formal Analysis, Visualization, Writing- Original draft preparation, Reviewing and Editing. Corinna Schulz: Visualization, Project administration, Investigation, Writing- Reviewing and Editing. Diba Borgmann: Writing- Reviewing and Editing. Johannes Klaus: Project administration, Investigation, Writing- Reviewing and Editing. Sabine Ellinger: Investigation, Writing- Reviewing and Editing. Martin Walter: Conceptualization, Methodology, Funding acquisition. Nils B. Kroemer: Conceptualization, Methodology, Funding acquisition, Supervision, Formal Analysis, Visualization, Writing- Original draft preparation, Reviewing and Editing.

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