

# Non-invasive vagus nerve stimulation normalizes food liking and improves liking ratings in depression<sup>☆</sup>

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## ABSTRACT

Vagus nerve stimulation has shown potential to treat major depressive disorder (MDD) and the vagus nerve plays a prominent role in the regulation of food reward and energy metabolism. However, previous studies using vagus nerve stimulation yielded conflicting results regarding changes in food reward in healthy participants and participants with MDD. We investigated the acute effects of right transcutaneous auricular vagus nerve stimulation (taVNS) on ratings of liking and wanting of food and non-food items in 62 participants, including 31 patients with MDD. To test for taVNS-induced changes and evaluate group differences and associations with symptoms, we performed linear mixed-effects analysis with group-wise post hoc comparisons. taVNS increased liking of food cues in patients with MDD ( $p = 0.020$ ), but not in healthy participants ( $p = 0.92$ ). Specifically, taVNS induced larger improvements in food liking ratings with increasing scores of anhedonia ( $p = 0.029$ ). Notably, across all participants, taVNS effects were negatively correlated ( $p_{boot} = 0.002$ ) with the individual hedonic response (i.e., average food liking) suggesting a normalization effect such that lower food liking gets boosted and higher liking attenuated following taVNS. Our results show that taVNS acutely ameliorates hedonic responses to food in MDD suggesting that it could provide a powerful adjuvant to rapidly improve food hedonics. Further investigation is needed to examine taVNS effects on anhedonia beyond food rewards.

## 1. Introduction

Major depressive disorder (MDD) is a highly prevalent, disabling, and recurrent disorder (Whiteford et al., 2013). One in five adults is affected over the course of their life and the social and economic burden is substantial (Hasin et al., 2018). Despite the high prevalence, neurobiological pathomechanisms are still poorly understood. Since MDD is a heterogeneous syndrome rather than a unitary disorder (Pizzagalli, 2014; Vrieze et al., 2014), there is an increasing focus on specific symptoms to unravel the neurobiological mechanisms of MDD and improve treatment specificity (Keedwell et al., 2005; Keller et al., 2013; Young et al., 2016). One of the core symptoms of MDD is anhedonia, the experienced loss of pleasure, motivation, and interest to pursue rewards

including food. It affects up to 70 % of MDD patients (Shankman et al., 2014) and is seen as a predictor of suicide and poorer response to pharmacological treatments (Craske et al., 2016). Crucially, deficits in experiencing pleasure can arise from impaired reward processing (Rizvi et al., 2016). Reward processing entails different aspects such as interest/desire (“wanting” a reward), hedonic response (“liking” a reward) and feedback integration/learning, which can independently be affected in anhedonia (Husain and Roiser, 2018; Rizvi et al., 2016; Treadway et al., 2011). Here, we focused on an anticipatory phase, conceptualized by either wanting (i.e., incentive salience to obtain a reward) or liking (i.e., expected hedonic impact) (Rømer Thomsen et al., 2015). Notably, although liking is often conceptualized as a consummatory facet, it is also a meaningful construct capturing the long-run expected value of an

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outcome independent of its momentary salience (Dayan, 2022). Food is a primary reward and decreased pleasure in anticipating or consuming palatable food is typically an indication of anhedonia (Coccarello, 2019). Furthermore, changes in appetite and weight are diagnostic markers of MDD according to DSM-5 (Simmons et al., 2020) and differences in the functional connectivity of the reward circuit are robustly associated with appetite-related changes (Kroemer et al., 2022). Consequently, studying changes in food reward processing could help unravel appetite-related neurobiological mechanisms in MDD and neuromodulation techniques targeting these circuits might pave new avenues to normalize reward function, particularly in patients suffering from anhedonia.

Invasive vagus nerve stimulation (iVNS) is an approved and effective therapeutic tool for treatment-resistant MDD (Bottomley et al., 2020). Due to its bidirectional communication with the gastrointestinal tract, the vagus nerve forms an essential part of the gut–brain axis (Breit et al., 2018) and plays a pivotal role in the regulation of food intake and metabolic processes according to homeostatic needs (Berthoud, 2008; de Araujo et al., 2012; de Lartigue and Diepenbroek, 2016; Waise et al., 2018; Yuan and Silberstein, 2016). It contributes to energy homeostasis by conveying satiety (Chaudhri et al., 2008; de Lartigue and Diepenbroek, 2016; Peters et al., 2006; Waise et al., 2018) and motivational signals (Han et al., 2018; Neuser et al., 2020). Mimicking vagal satiety signaling by applying iVNS has been shown to alter food intake and induce weight loss in animal studies (Dai et al., 2020; Sobocki et al., 2005; Val-Laillet et al., 2010), although results from human studies remain inconsistent to date (Pelot and Grill, 2018). Notably, vagal afferent signals have been shown to modulate monoaminergic neurotransmission, which is associated with motivation and reward processing (de Araujo et al., 2012; Fernandes et al., 2020). In line with hypothesized changes in monoamine release, we have shown that non-invasive transcutaneous auricular VNS (taVNS) altered reward learning and boosted the vigor to work for rewards (Kühnel et al., 2020; Neuser et al., 2020). These observations are flanked by neuroimaging studies in humans demonstrating that VNS leads to increased BOLD responses in regions beyond the nucleus of the solitary tract (NTS), such as the striatum, amygdala, and insula (Frangos et al., 2015; Teckentrup et al., 2020), which play an important role in motivational and hedonic processes (Berridge and Robinson, 2016; Warlow and Berridge, 2021). However, three recent studies showed no evidence of taVNS-induced effects on anticipatory liking and wanting ratings of food, or the amount of ingested food in healthy participants (Alicart et al., 2020; F. K. Müller et al., 2022; Obst et al., 2020). In contrast, in a small pilot study, Öztürk et al. (2020) found taVNS-induced increases in food liking after the consumption of low-fat food. Furthermore, in a sample of participants with MDD, Bodenlos et al. (2007) reported a significant iVNS-induced increase of individual differences in cravings of sweet food. In conclusion, VNS may affect food-reward responses with preliminary evidence indicating that stimulation effects could differ between healthy control participants (HCP) and people suffering from MDD and anhedonia.

To close this gap, the aim of the study was to compare the effects of non-invasive taVNS on ratings of food reward in participants with MDD versus HCPs. Specifically, we hypothesized that effects of taVNS would be elicited in participants with MDD, as previous studies showed changes in food craving in MDD (Bodenlos et al., 2007), but no consistent effect in healthy participants (Alicart et al., 2020; F. K. Müller et al., 2022; Obst et al., 2020). To this end, we used a food cue reactivity task (FCR; F. K. Müller et al., 2022) while administering right taVNS (or sham stimulation (Ellrich, 2011; Peuker and Filler, 2002)), that has been shown to have stronger motivational effects in rodents (Han et al., 2018) and humans (Neuser et al., 2020). Using a randomized cross-over design, we investigated if taVNS alters subjective liking and wanting of food cues and whether taVNS-induced effects differ in participants with MDD. Subjective cue-induced ratings are well established as a measure of food reward (Charbonnier et al., 2016; F. K. Müller et al.,

2022; Schulz et al., 2024) and they predict eating behavior (Boswell and Kober, 2016). To account for interindividual heterogeneity of MDD symptoms, we examined whether taVNS-induced changes are associated with anhedonia (measured with the SHAPS questionnaire) and reduced reward approach (measured with the behavioral activation system, BAS, questionnaire). We found that taVNS increased food liking in participants with MDD and gains were correlated with anhedonia, exerting a normalizing effect on food liking in all participants.

## 2. Methods

### 2.1. Participants

For the current study, we enrolled 34 HCP and 31 participants with MDD matched on the group level for age, sex, and BMI (Table 1). Participants were between 19 and 61 years old ( $M = 34.3$ ), right-handed, German speaking, physically healthy and did have other comorbid mental disorders apart from anxiety and trauma-related disorders in the MDD and specific phobias ( $N = 5$ ) in the HCP group. HCP were only included if they never fulfilled the criteria for a major depressive episode. For the reported analyses, we excluded one HCP who reported taking a SSNRI for their anxiety disorder and another two HCPs who did not complete the second session (total  $N = 62$ , MDD = 31). MDD diagnosis was based on telephone screenings, where we interviewed candidates according to the German Structured Clinical Interview for DSM IV (SCID-I) (Fydrich et al., 1997). Additionally, current depression severity was assessed using the German version of the Beck Depression Inventory II (BDI-II) (Beck et al., 1996; Kühner et al., 2007). Of the 31 participants with MDD, 19 were taking antidepressant medication at the time of the telephone screening (Figs. S1–2) and medication was stable for at least two months. Out of those 19 participants, 7 were taking SSRIs (escitalopram, sertraline, fluoxetine), 3 were taking SSNRIs (venlafaxine, duloxetine), 3 were taking TCA (amitriptyline, doxepin, tianeptine), and 1 participant was taking the tetracyclic mirtazapine. Bupropion (SNDR) in combination with fluoxetine was taken by ten patient each. In two additional participants, the primary antidepressant (venlafaxine, amitriptyline) was augmented by quetiapine, an atypical antipsychotic drug, and in another participant, the antidepressant could not be determined (see SI). In each session, participants received snacks and money they had won during the behavioral session. After completion of the second session, participants received a fixed compensation of 32€ or an equivalent partial course credit. The study was approved by the local ethics committee (the Institutional Review Board of the Faculty of Medicine, University of Tübingen) and was conducted in accordance

**Table 1**  
Demographics and questionnaire scores.

Variable	N	Overall, N = 62 <sup>a</sup>	HCP, N = 31 <sup>a</sup>	MDD, N = 31 <sup>a</sup>	p-value
Sex	62				–
Male		20 (32 %)	11 (35 %)	9 (29 %)	–
Female		42 (68 %)	20 (65 %)	22 (71 %)	–
Age	62	34.3 (13.2) [23]	36.9 (14.1) [28]	31.6 (12.1) [11.5]	0.146
Body mass index (BMI)	62	24.3 (3.4) [5]	24 (3.4) [5]	24.5 (3.5) [4.6]	0.595
Waist-to-hip ratio (WtHR)	62	0.8 (0.1) [0.1]	0.8 (0.1) [0.1]	0.8 (0.1) [0.1]	0.991
Beck Depression Inventory (BDI-II)	62	12.6 (10.6) [16]	4.4 (4.5) [6]	20.8 (8.3) [12]	<0.001
Snaith Hamilton Pleasure Scale (SHAPS)	62	2.5 (2.9) [5]	1 (2.5) [1]	3.9 (2.5) [3.5]	<0.001
Behavioral Activation System (BAS)	62	37.7 (5.8) [7.8]	39.7 (4.5) [6]	35.7 (6.3) [9.5]	0.004

Note. P-values are results of a Student's two-sample t-test.

<sup>a</sup> n (%); Mean (SD) [IQR].

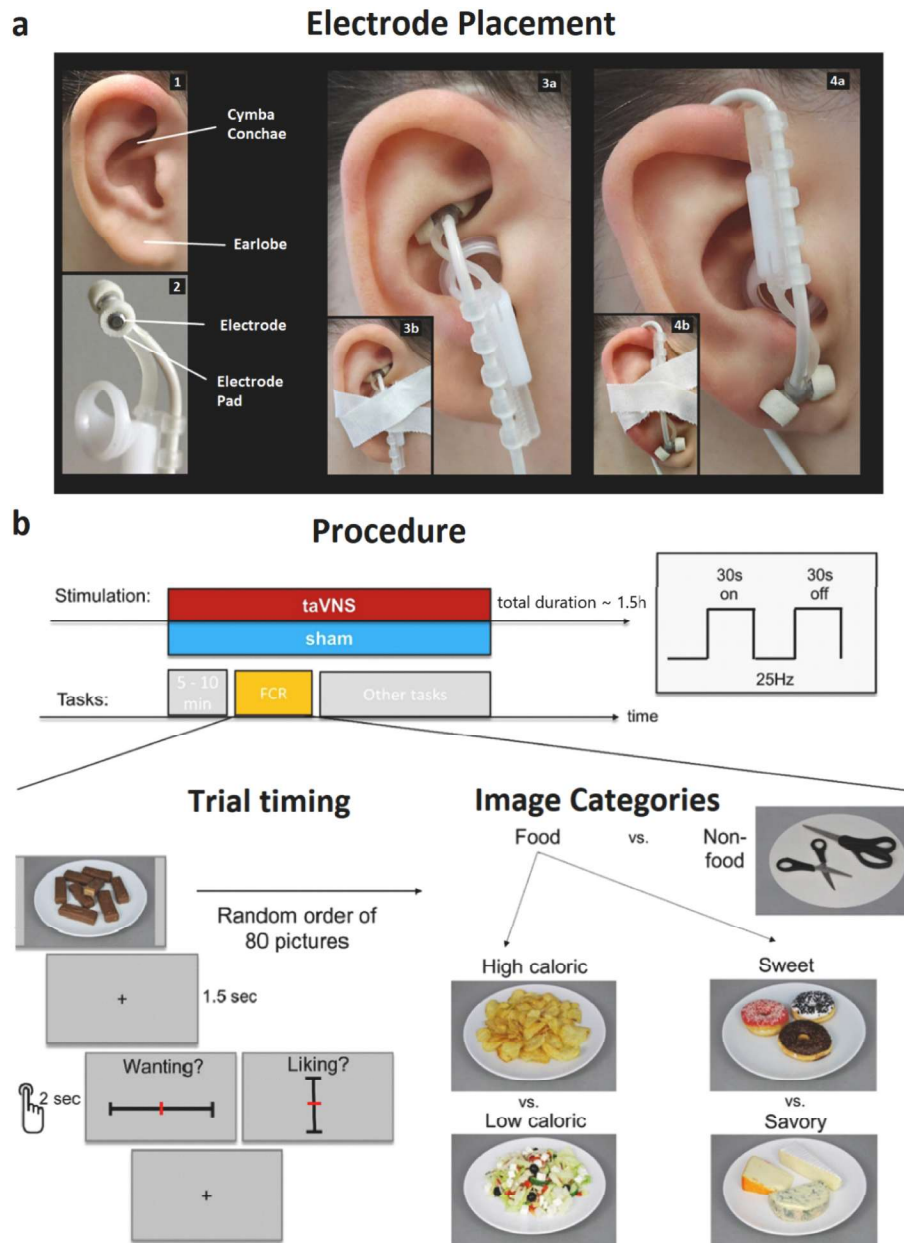
with the ethical code of the World Medical Association (Declaration of Helsinki).

## 2.2. Experimental procedure

The study followed a single-blinded, randomized crossover design. Similar to a previous study (F.K. Müller et al., 2022), each participant completed two sessions receiving either sham or taVNS with a delay of 2–15 d between sessions (*median* = 4 d, *IQR* = 3.8). Participants were informed that the study involves both taVNS and sham stimulation. During recruitment, IDs were consecutively assigned to each participant and stimulation order (taVNS or sham first) was randomized (i.e., fixed) to IDs before the first participant was included. Both sessions started at

approximately the same time and participants were asked to fast (including caffeinated drinks) for 3–5 h ( $M = 3.9$ ,  $SD = 1.9$ ; corresponding to a state of neither hungry nor full, Fig. S3) and refrain from consuming alcohol 48 h before each session. After each session, participants further guessed the stimulation condition (sham or taVNS). Correct responses occurred at chance level (*recorded guesses*: 124, *correct guesses*: 67, *accuracy*: 54.0 %,  $p_{\text{binom}} > 0.1$ ), indicating that blinding was successful.

Each session started with measurements of weight, height, hip and waist circumference as well as pulse rate. Next, participants completed the BDI-II and the first of the three mood and metabolic state (hunger and fullness) assessments collected throughout the session (Ferstl et al., 2021). Next, the taVNS electrode was applied and stimulation strength



**Fig. 1.** Schematic summary of electrode placement and experimental procedure (adapted from (F. K. Müller et al., 2022)). A: The electrode is placed at the cymba conchae of the inner ear during taVNS (3a) and at the earlobe during sham (4a). In both cases, the electrode is secured by tape. B: The biphasic on- and off-duty stimulation starts 5–10 min before the food-cue reactivity (FCR) task which is then followed by additional tasks. The FCR task required participants to submit their rating of liking and wanting of different food (including high-caloric food ( $N = 36$ ) and low-caloric food ( $N = 24$ )). As well as savory food ( $N = 27$ ) and sweet food ( $N = 33$ ) and non-food items. Example food items: potato chips high-calorie and salty, donuts high-calorie and sweet, salad low-calorie salty, and cheese high-calorie and salty.

was calibrated. The first experimental task was the food cue reactivity (FCR) task, which started 5–10 min after stimulation onset and lasted approximately 30 min. The FCR task was then followed by an effort allocation task (Ferstl et al., 2024; Neuser et al., 2020) and a reward learning task (Kühnel et al., 2020). The task order was identical across participants and the stimulation was administered throughout the session (total duration of stimulation in a session:  $M = 1.46$  h;  $SD = 0.13$ ). After the completion of the tasks, the BDI-II questionnaire was administered for a second time alongside other questionnaires (not reported here). Each of the two sessions took about 2.5 h.

### 2.3. Right transcutaneous vagus nerve stimulation

Transcutaneous vagus nerve stimulation of the auricular branch followed the same protocol as described in our previous work (F. K. Müller et al., 2022; Neuser et al., 2020). We used the NEMOS device (Cerbomed GmbH, Erlangen) which delivers biphasic 25 Hz stimulation, alternating between 30 s stimulation and 30 s pause. Depending on the stimulation condition, electrodes were placed either at the cymba conchae of the right external ear for taVNS or at the right earlobe (not innervated by the vagus nerve) for sham stimulation (Farmer et al., 2020; Frangos et al., 2015; Peuker and Filler, 2002) (Fig. 1). To account for individual differences in the subjective experience of the stimulation, strength was individually adjusted using pain VAS. Strength was increased until participants reported a ‘tingling’ sensation below the pain threshold on the VAS (Frangos et al., 2015) (stimulation:  $M = 1.25$  mA,  $SD = 0.50$ . sham:  $M = 1.43$  mA,  $SD = 0.53$ ). No stimulation side effects were observed.

### 2.4. Food-cue reactivity task

Food wanting and liking ratings were measured using a FCR task (Fig. 1) that we have previously used to study taVNS effects in healthy participants (F. K. Müller et al., 2022). Briefly, participants rated pictures of food and non-food control items (e.g., stationery) on separate liking and wanting VAS. The vertically labeled liking scale ranged from –100 (strongest disliking imaginable) to 100 (strongest liking imaginable) (Lim et al., 2009), while the wanting scale was oriented horizontally and ranged from 0 (not wanted at all) to 100 (strongly wanted). In total, 60 food and 20 non-food images were selected from a set of 80 food and 40 non-food items (Charbonnier et al., 2016) and presented twice per session. Every participant was presented with an identical image sample, but the presentation order was randomized across subjects and sessions. Food images were further classified by caloric density (high-caloric vs. low-caloric food) and taste quality (sweet vs. savory) according to Charbonnier et al. (2016). The images were shown for 1.5 s each and ratings on the VAS could be submitted within a 2 s interval by moving the left joystick of an Xbox 360 controller and confirming the choice with a button press (Fig. 1).

### 2.5. Questionnaires

Participants completed additional questionnaires at home to assess symptoms of reward processing. We used the German version of the Snait Hamilton Pleasure Scale (SHAPS; Franz et al., 2008; Snaith et al., 1995) as a dimensional measure of anhedonia and the BAS subscale from the German version of the Behavioral Inhibition System/Behavioral Activation System questionnaire (BIS/BAS; Carver and White, 1994; Strobel et al., 2001) as a continuous measure of the disposition to actively pursue rewards.

### 2.6. Data analysis

To investigate taVNS effects and whether they differed in participants with MDD compared to HCP, we estimated mixed-effects models for liking and wanting separately (lmerTest-package in R (Kuznetsova

et al., 2017)). The main model (eq. (1)) included the predictors *Image Type* (non-food vs. food, centered), *Stimulation* (sham vs. taVNS, dummy coded) as well as their interaction as within-subject factors and *Group* (HCP vs. MDD, centered) as a participant-level factor allowing for cross-level interactions. To additionally explore the association between depression severity and stimulation effects, we substituted *Group* with continuous BDI scores (eq. (1)). The sample size is sufficient to investigate this three-way interaction since the cross-level interaction only includes one between-participant factor (MDD vs. HCP) while taVNS effects and food specificity were estimated within participants as well. We controlled for sex, age, and BMI by including them as additional participant-level factors (centered). To account for order effects (stimulation first vs. second), we entered *Order* (centered) and the *Stimulation* × *Order* interaction (see eq. (1)).

$$(1) \text{ Rating} \sim \text{cImage\_Type} * \text{cGroup/cBDI} * \text{Stimulation} + \text{Stimulation} * \text{cOrder} + \text{cAge} + \text{cBMI} + \text{cSex} + (1 + \text{cImage\_Type} * \text{Stimulation} | \text{ID})$$

The model included a random intercept and the random slopes for all within-subject factors as recommended (Heisig and Schaeffer, 2019). To characterize potential differences in stimulation effects between HCP and MDD, we performed group-specific post hoc comparisons (emmeans; Lenth, 2021) between taVNS and sham. For all following post hoc comparisons and analyses focusing on inter-individual differences in reward responsivity (e.g., anhedonia), we included only food images since the non-food items (i.e., stationary objects) should not elicit significant hedonic or motivational responses that taVNS would modulate. Likewise, sensitivity analyses regarding metabolic characteristics (trait and state) and macronutrient content of the food items were only conducted for food images.

### 2.7. Associations of taVNS-induced changes with trait-like reward processing

The effects of taVNS in participants with MDD may be related to differences in reward processing. To test this, we adapted our main model (see eq. (1)) by selecting only food images and including SHAPS and BAS scores (centered) as well as their interactions instead of the *Group* factor (HCP vs. MDD). Second, we investigated whether taVNS effects depend on individual rating intercepts (i.e., average ratings of each participant) using the same adapted model. To this end, we calculated the Pearson's correlation between taVNS effects and individual rating intercepts (i.e., averages) and conducted a permutation test with 10,000 repetitions for significance testing. Individual taVNS effects were derived from an adapted model (stimulation effect centered) as the individual slopes of the stimulation effect. Here, we used intercepts instead of sham ratings as a more appropriate estimate of individual baseline ratings since the association between sham ratings and stimulation effects might be inflated by regression to the mean and would likely lead to an overestimation of the association (Yu and Chen, 2015).

### 2.8. Sensitivity analyses

To rule out interfering effects of antidepressants, we estimated an additional model including only participants with MDD, where we included a medication variable (AD use vs. no AD use; eq. (1)). In addition, we tested whether the results changed when i) excluding covariates, ii) including time between sessions as additional covariate (in interaction with stimulation), iii) including the wanting ratings of each trial to determine whether effects are specific for liking beyond wanting. Moreover, we explored whether our results are explained by differences in state and trait metabolism or are driven by specific macronutrients.

2.8.1. taVNS and metabolic state

Food rating and taVNS effects might depend on interindividual differences in metabolic state or trait-like characteristics. For example, body fat mass, hours since the last meal, and perceived hunger might affect food liking (Charbonnier et al., 2018; Goldstone et al., 2009). Thus, to explore effects of differences in metabolism and indirect indicators of leptin (Monti et al., 2006; Ruhl and Everhart, 2001), we tested models including the interaction between stimulation and either waist circumference, BMI, or current self-reported metabolic state (Hunger – Satiety/100) using VAS ratings (see SI).

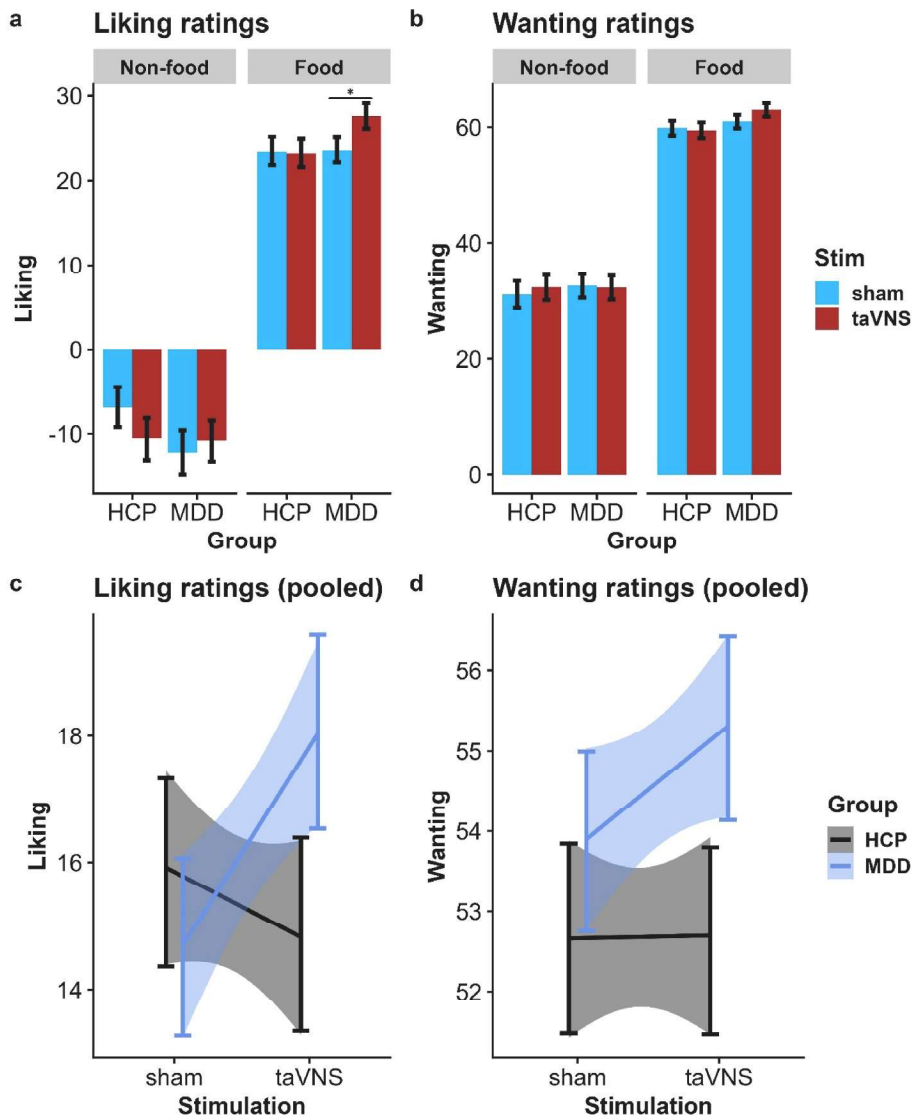
2.8.2. Macronutrient specific taVNS effects

Since stimulation effects or group differences between patients with MDD and HCP could be specific for certain types of food (Bodenlos et al., 2007; Öztürk et al., 2020), we performed a sensitivity analysis only including food images and partitioning them according to their caloric density (high-calorie vs. low-calorie food) and taste quality (sweet vs. savory). Food ratings and taVNS effects might also depend on specific macronutrients (Thurn et al., 2025), as suggested by a recent study that proposes differential vagal pathways engaging in sugar and fat sensing

(McDougle et al., 2022). To explore specific taVNS-induced changes, we included either the categories of the food items or sugar and fat content (g/100g) of the depicted food items in the mixed-effects models together with their interaction with stimulation (see SI).

2.9. Statistical threshold and software

All statistical tests were two-tailed with an alpha  $\leq 0.05$  as the significance threshold for the main model (model 1). Sensitivity analyses exploring potential interactions with multiple related predictors (e.g., food categories or macronutrients) would have been corrected for multiple testing using the false discovery rate if significant at an uncorrected level. For data analysis, we used the packages ‘lmerTest’ (Kuznetsova et al., 2017), ‘emmeans’ (Lenth, 2021). For data visualization, we used ‘ggplot2’ (Wickham, 2016) all within R Studio using and Rv4.1.1 (R Core Team, 2021).



**Fig. 2.** taVNS boosts food liking in participants with major depressive disorder (MDD) A: Food images were liked more compared to non-food images. B: Food images were wanted more compared to non-food images. C: taVNS increased food liking in the MDD ( $t(59) = 2.39, p = 0.020, dz = 0.13$ ), but not in the HCP group ( $t(59) = -0.18, p = 0.915, dz = -0.00$ ) (Group  $\times$  Stimulation (pooled).  $b = 4.34, t(59) = 2.26, p = 0.027$ ). D: taVNS-induced changes in wanting were non-significant (Group  $\times$  Stimulation (pooled).  $b = 1.44, t(59) = 0.73, p = 0.466$ ). Depicted are means and 95 % confidence intervals.

### 3. Results

#### 3.1. taVNS increases food liking in participants with MDD

To assess taVNS effects on liking and wanting ratings, we calculated mixed-effects models. As expected, both liking and wanting ratings were higher for food compared to non-food pictures during sham (liking:  $b = 33.07$ ,  $t(60) = 10.31$ ,  $p < 0.001$ ; wanting:  $b = 28.52$ ,  $t(60) = 10.16$ ,  $p < 0.001$ ; Fig. 2). In contrast, liking and wanting did not differ between HCP and participants with MDD during sham (liking:  $b = -1.51$ ,  $t(57) = -0.49$ ,  $p = 0.625$ ; wanting:  $b = 1.67$ ,  $t(58) = 0.63$ ,  $p = 0.532$ ; negative values indicate lower values in patients with MDD) although participants with MDD showed less preference for low sugar compared to high sugar food than HCP (Group  $\times$  Sugar Content.  $b = -0.26$ ,  $t(61) = 2.04$ ,  $p = 0.046$ ; see SI).

taVNS did not affect either liking or wanting ratings (liking:  $b = 1.12$ ,  $t(59) = 1.01$ ,  $p = 0.248$ ; wanting:  $b = 0.73$ ,  $t(59) = 0.63$ ,  $p = 0.462$ ) across all participants. However, taVNS increased liking ratings more strongly in patients with MDD compared to HCP (Group  $\times$  Stimulation.  $b = 4.34$ ,  $t(59) = 2.26$ ,  $p = 0.027$ ) while wanting ratings were not significantly affected (Group  $\times$  Stimulation.  $b = 1.44$ ,  $t(59) = 0.73$ ,  $p = 0.466$ ; Fig. 2). Notably, stimulation effects for liking increased with the severity of depressive symptoms across groups (liking: BDI  $\times$  Stimulation,  $b = 0.20$ ,  $t(59) = 2.24$ ,  $p = 0.029$ ; wanting: BDI  $\times$  Stimulation,  $b = 0.07$ ,  $t(59) = 0.75$ ,  $p = 0.456$ ). Post hoc comparisons between liking ratings during taVNS and sham showed that the interaction was driven by taVNS significantly increasing food liking in MDD ( $t(59) = 2.39$ ,  $p = 0.020$ ,  $dz = 0.13$ ), but not in HCP ( $t(59) = -0.18$ ,  $p = 0.915$ ,  $dz = -0.00$ ).

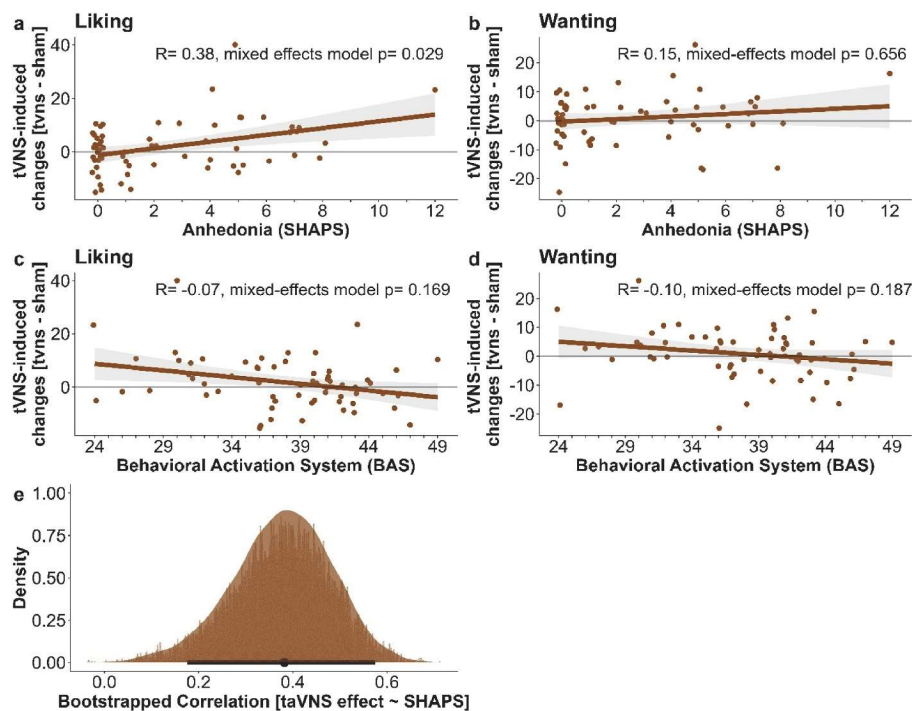
Stimulation effects were not affected by i) reducing the included covariates (Tables S1–3), ii) additionally correcting for wanting of the items (Tables S4–6), iii) time between sessions (Tables S7–8), iv)

antidepressant medication, or v) metabolic indicators such as waist circumference (indicative of abdominal fat), BMI, or self-reported metabolic state (Figs. S1–S6). Notably, our finding that taVNS effects on liking ratings are greater in the MDD group (Stimulation  $\times$  Group) and that taVNS increases food liking in participants with MDD was robust across all models (see SI p. 6).

Additionally, we explored specific effects for high-calorie vs. low-calorie as well as sweet vs. savory foods. However, differences between HCP and MDD groups and stimulation effects were not specific for food subgroups when correcting for multiple comparisons across these exploratory analyses (for details, see SI).

#### 3.2. taVNS increases food liking in participants with greater anhedonia and normalizes food liking across groups

Next, we examined associations of anhedonia (i.e., SHAPS) and impulsivity (BAS) with taVNS-induced changes in food liking and wanting. We entered SHAPS and BAS scores as participant-level predictors and included their cross-level interaction with stimulation (see SI). During sham, SHAPS scores were not associated with food liking or wanting (liking:  $b = -0.42$ ,  $t(55) = -0.57$ ,  $p = 0.572$ ; wanting:  $b = 0.40$ ,  $t(57) = 0.69$ ,  $p = 0.495$ ). However, when exploring liking of specific food categories, we found that liking but not wanting ratings of food low in sugar and fat was decreased in participants with higher SHAPS scores (liking:  $b = -3.00$ ,  $t(54) = -2.44$ ,  $p = 0.018$ ; wanting:  $b = -1.55$ ,  $t(55) = -1.53$ ,  $p = 0.133$ , see SI), indicating an attenuated hedonic response to food low in macronutrients in anhedonia. Moreover, higher SHAPS scores were associated with stronger taVNS-induced increases in food liking in general (SHAPS  $\times$  Stimulation.  $b = 0.99$ ,  $t(58) = 2.24$ ,  $p = 0.029$ ,  $r = 0.38$ ), but not wanting (SHAPS  $\times$  Stimulation.  $b = 0.19$ ,  $t(58) = 0.42$ ,  $p = 0.675$ ,  $r = 0.15$ ; Fig. 3a–b) and this was still significant when controlling for depressive symptoms excluding anhedonia (Table S9)



**Fig. 3.** taVNS effects on liking ratings depend on anhedonia (SHAPS), but not behavioral activation (BAS). The plots show the difference between individual mean ratings of food images during taVNS vs. sham as a function of questionnaire scores. Positive values represent an increase of ratings following taVNS. A: taVNS-induced changes in liking increase with higher levels of anhedonia ( $b = 0.99$ ,  $t(58) = 2.24$ ,  $p = 0.029$ ,  $r = 0.38$ ). B: taVNS-induced changes in wanting did not depend on anhedonia levels ( $b = 0.19$ ,  $t(58) = 0.42$ ,  $p = 0.675$ ,  $r = 0.15$ ). C: taVNS effects on liking ratings did not depend on BAS scores ( $b = -0.26$ ,  $t(58) = -1.16$ ,  $p = 0.250$ ,  $r = -0.07$ ). D: taVNS effects on wanting ratings were also not associated with BAS scores ( $b = -0.25$ ,  $t(58) = -1.15$ ,  $p = 0.257$ ,  $r = -0.10$ ). E: Bootstrapped distribution of the correlation between taVNS effects and SHAPS scores ( $r = 0.38$ , indicated by dashed line,  $p_{boot} = 0.002$ ) with 95% confidence interval, generated with 10,000 repetitions.

and when controlling for wanting rating of the food items (Table S6). Congruently, taVNS-induced changes in mean liking ratings and individual SHAPS scores are positively correlated (Fig. 3f; correlation [95 % bootstrap CI]:  $r = 0.39$  [0.19, 0.58],  $p_{boot} = 0.002$ ). As expected, during sham, higher BAS scores were associated with higher food wanting ( $b = 0.65$ ,  $t(56) = 2.18$ ,  $p = 0.034$ ), but not significantly with liking ratings ( $b = 0.69$ ,  $t(57) = 1.87$ ,  $p = 0.067$ ). However, in contrast to anhedonia, taVNS-induced changes in food liking (BAS  $\times$  Stimulation.  $b = -0.26$ ,  $t(58) = -1.16$ ,  $p = 0.250$ ,  $r = -0.07$ ) and wanting (BAS  $\times$  Stimulation.  $b = -0.25$ ,  $t(58) = -1.15$ ,  $p = 0.257$ ,  $r = -0.10$ ; Fig. 3c–d) were not significantly associated with BAS scores.

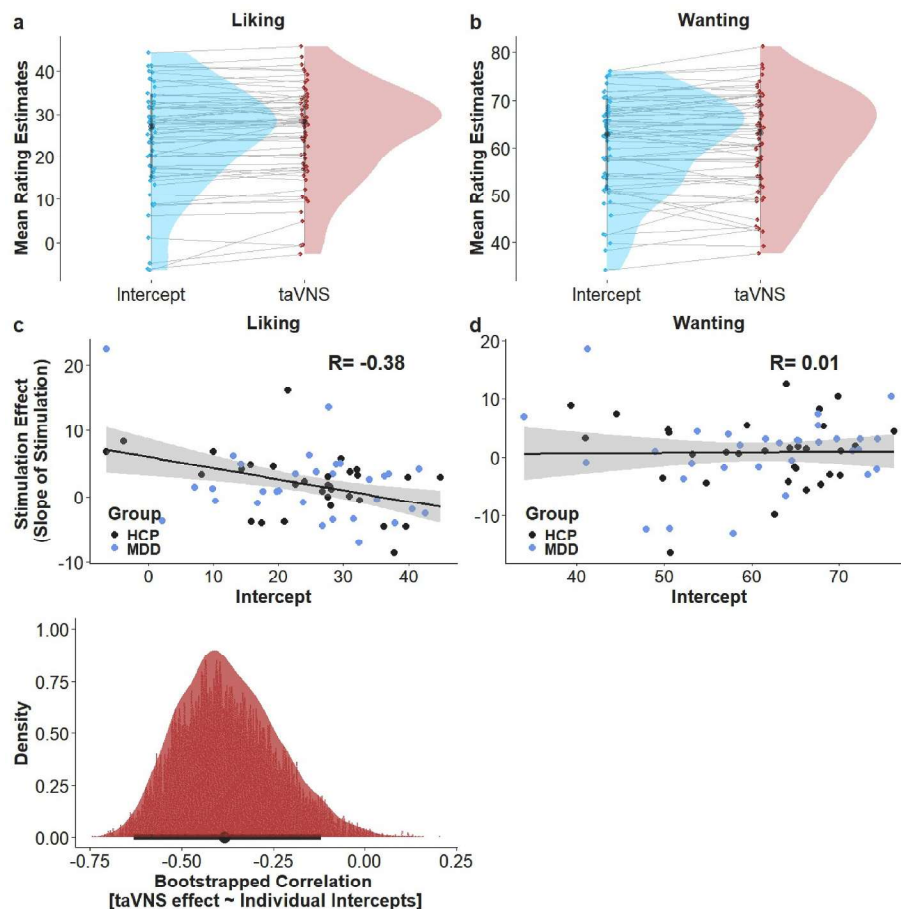
Since taVNS effects were strongest for participants with high levels of anhedonia, individual stimulation effects might depend on the individual's average food reward ratings. In support of a broader role in normalizing food reward ratings, we observed a negative correlation between the average liking rating (i.e., intercept when all predictors are centered) and individual taVNS effects (i.e., slopes for the taVNS effect,  $r = -0.38$ ,  $p_{perm} = 0.002$ ). Thus, taVNS may boost lower and attenuate higher liking ratings (Fig. 4a–c).

#### 4. Discussion

Aberrant food hedonics are an element of anhedonia, a common and difficult to treat symptom of depression (Coccurello, 2019; Craske et al., 2016). Here, we investigated the effects of acute taVNS on liking and wanting ratings of various food and non-food images in participants with and without MDD. In line with previous reports of anti-depressive

effects of VNS, we found that acute taVNS increased liking of food cues in participants suffering from MDD, but not in HCP. Crucially, higher anhedonia was associated with stronger taVNS-induced increases in food liking. Intriguingly, normalization of ratings was also evident across all participants since taVNS boosted low and attenuated high food liking. Taken together, our results indicate that taVNS acutely improves hedonic responses to food in MDD.

Our result that taVNS increases food liking specifically in patients with MDD and, in general in participants with low average food liking and higher scores of anhedonia, helps reconcile conflicting earlier findings in human research. On the one hand, altered ratings of sweet food in patients with MDD have been reported after invasive VNS (Bodenlos et al., 2007), indicating that VNS may both increase and decrease food liking, conceivably depending on individual characteristics. On the other hand, we and others have reported no robust taVNS effects on average food ratings or food intake in healthy participants (Alicart et al., 2020; F. K. Müller et al., 2022; Obst et al., 2020). One potential explanation for these results may be the reported normalizing effect of taVNS on liking ratings, indicating that taVNS can either increase or decrease liking, depending on the average strength of hedonic responses, which varies considerably between people and even within MDD (Rizvi et al., 2016; Swiecicki et al., 2009; Treadway et al., 2011). Crucially, taVNS-induced increases in liking were stronger with increasing levels of anhedonia, a core diagnostic symptom of MDD, that is less responsive to pharmacological treatment (Uher et al., 2012) and is a negative prognostic factor for treatment outcome (Spijker et al., 2001). Moreover, taVNS-induced changes were primarily observed in liking,



**Fig. 4.** taVNS normalizes liking ratings. A: Mean individual liking ratings at the intercept and following taVNS. B: Mean individual wanting ratings at the intercept and following taVNS. C: Lower liking ratings at the intercept are associated with more positive and higher liking ratings with more negative stimulation effects. D: Wanting ratings at the intercept are not associated with stimulation effects. E: Bootstrapped distribution of the correlation between taVNS effects and individual liking ratings intercepts ( $r = 0.38$ , indicated by the dot,  $p_{perm} = 0.002$ ) with 95 % confidence interval, generated with 10,000 repetitions.

and not wanting ratings. This is in line with the idea of liking as an early, editable draft that shapes evaluation (Dayan, 2022) and liking is also conditioned by post-ingestive signals that are conveyed via the vagus nerve (de Araujo et al., 2013; Veldhuizen et al., 2017). Taken together, our results point to a potential acute effect of taVNS on impairments in food hedonics (i.e., a common element of anhedonia) which may contribute to antidepressive effects (Wu et al., 2018).

The normalizing effect of taVNS on food liking raises the question of which neurobiological mechanism may support the differential effects of vagal afferent stimulation. While invasive VNS has mostly been associated with reduced food intake and weight reductions in animals and humans (Bugajski et al., 2007; Yao et al., 2018), recent preclinical work has shown that vagally induced activation of the NTS can either stimulate or suppress feeding depending on the neural population that is activated within the NTS (Chen et al., 2020). Thus, it is conceivable that the net effect of taVNS depends on the tuning of separable neural populations within the NTS, which might be affected by state-like (e.g., metabolic state; Teckentrup and Kroemer, 2024) or trait-like differences (overall hedonic response to food; Smith et al., 2017). Additionally, we have recently shown that taVNS alters myoelectric activity (Teckentrup et al., 2020) in the stomach and increases stomach-brain coupling (S.J. Müller et al., 2022), suggesting that enhanced stomach-brain communication could support the normalization of aberrant hedonic responses to food via interoceptive signaling. Notably, MDD is characterized by heterogeneous symptom profiles, including diverging changes in appetite and body weight during depressive episodes (Milaneschi et al., 2019; Simmons et al., 2016, 2020). Motivational deficiencies (including anhedonia) are more frequent in patients who suffer from loss of appetite and weight (Fletcher et al., 2015; Post and Warden, 2018). Therefore, the normalization effect of taVNS might help recover vegetative symptoms in both melancholic (i.e., characterized by loss of appetite and weight) and atypical depression (i.e., characterized by an increase of appetite and weight). To summarize, acute effects of taVNS point to the potential in normalizing aberrant food hedonics, but more research in patients over extended periods of taVNS is needed to better understand how acute effects could be translated to future treatments with long-term effects on anhedonia.

Despite the notable strengths of our comparatively large taVNS cross-over study in patients with MDD and HCP, there are limitations that have to be addressed in future work. First, due to the positioning of the sham electrode at the earlobe, the study was only single-blinded. Second, contrary to our expectations, food liking and wanting did not significantly differ between groups in the sham condition. The lack of clear group differences in food hedonics is not implausible, however, as impaired food hedonics only constitute one of several manifestations of anhedonia and the extent and direction of altered appetite tend to differ greatly in depression (Milaneschi et al., 2019; Simmons et al., 2016, 2020). Moreover, the sample included predominantly patients with mild to moderate symptoms (Ferstl et al., 2024) and differences might be more pronounced in more affected individuals. Third, we only investigated taVNS effects on hedonic responses to food rewards and not on other rewards with comparable hedonic value, therefore, the impact of taVNS on other reward categories can only be hypothesized. However, since vagal signaling induces changes in monoaminergic transmission (de Araujo et al., 2012; Han et al., 2018; Raedt et al., 2011; Roosevelt et al., 2006), motivation (Ferstl et al., 2024; Kühnel et al., 2020; Neuser et al., 2020), and regions associated with the hedonic value of stimuli (Berridge and Robinson, 2016; Frangos et al., 2015), taVNS might also affect hedonic responses beyond food which remains to be tested in future research. Fourth, the reported results are only based on self-reported wanting and liking and not behavioral or physiological readouts (Finlayson et al., 2008; Hascher et al., 2021; O'Doherty et al., 2006). Therefore, in addition to the reported effects of taVNS on effort invigoration for food and monetary rewards (Ferstl et al., 2024), future work should investigate the effects of taVNS on neural or physiological responses (e.g., pupil size) to (food) rewards, specifically in patients

with MDD. Fifth, while we explored the effect of metabolic state characteristics on acute taVNS effects on food ratings, we did not measure glucose levels directly. Likewise, we did not assess trait-markers of the metabolism such as leptin or fasting glucose and insulin. Future studies should include direct assessments of the metabolism to maximize treatment effects. Lastly, as we investigated the acute effects of taVNS during stimulation on food reward further research is needed to investigate the longer lasting impact of taVNS on reward liking and anhedonia, preferably using longer periods of continuous stimulation and more comprehensive outcome measures capturing the full range of anhedonia symptoms like the SHAPS questionnaire. A longer stimulation period could also address the impact of taVNS on circulating hormones like insulin or glucose (Vosseler et al., 2020).

## 5. Conclusions

To summarize, we observed an increase in food liking specifically in participants with MDD and with greater anhedonia. Likewise, we saw support for a normalizing effect of taVNS on food liking across the sample since higher liking ratings were attenuated and lower ratings were boosted during taVNS. We conclude that taVNS may help to improve aberrant food reward responses while exerting little effect on moderate liking ratings. This may reconcile conflicting previous findings in mostly healthy populations. Therefore, taVNS may be a promising therapeutic tool to acutely improve alterations in food reward processing. Our finding that greater anhedonia is associated with stronger taVNS-induced improvements might help allocate taVNS as an adjuvant treatment according to a patient's individual profile in the future, which is in line with calls for a more personalized approach in psychiatry (Carter et al., 2012; Green et al., 2017; Malhi and Mann, 2018).

## CRedit authorship contribution statement

**Vincent Koeppe:** Writing – original draft, Formal analysis. **Johannes Klaus:** Writing – original draft, Project administration, Investigation. **Magdalena Ferstl:** Writing – review & editing, Project administration, Investigation, Data curation. **Franziska K. Müller:** Writing – review & editing, Investigation. **Anne Kühnel:** Writing – review & editing, Methodology, Formal analysis. **Nils B. Kroemer:** Writing – original draft, Supervision, Funding acquisition, Formal analysis, Conceptualization.

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## Ethics approval and consent to participate

The study was reviewed and approved by the ethics committee of the medical faculty at the university of Tübingen. All participants provided written and informed consent before participating in the study.

## Declaration of competing interest

The authors declare that they have no known competing financial

interests or personal relationships that could have appeared to influence the work reported in this paper.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jpsychores.2025.10.012>.

## Data availability

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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