Vagus nerve stimulation increases stomach-brain coupling via a vagal afferent pathway

Sophie J. Müller [a], Vanessa Teckentrup [a, f], Ignacio Rebollo [b], Manfred Hallschmid [c, d, e], Nils B. Kroemer [a, g, *]

[a] University of Tübingen, Tübingen Center for Mental Health, Department of Psychiatry and Psychotherapy, 72076, Tübingen, Germany
[b] German Institute of Human Nutrition (DIfE), Department of Decision Neuroscience and Nutrition (DNN), Potsdam-Rehbruecke, 14558, Nuthetal, Germany
[c] University of Tübingen, Tübingen Center for Mental Health, Department of Medical Psychology and Behavioral Neurobiology, 72076, Tübingen, Germany
[d] German Center for Diabetes Research (DZD), 85764, München-Neuherberg, Germany
[e] Institute for Diabetes Research and Metabolic Diseases of the Helmholtz Center Munich at the Eberhard Karls University Tübingen, 72076, Tübingen, Germany
[f] Trinity College Institute of Neuroscience, Trinity College Dublin, Dublin 2, Ireland
[g] University of Bonn, Department of Psychiatry and Psychotherapy, 53127 Bonn, Germany

ARTICLE INFO

ABSTRACT

Background: Maintaining energy homeostasis is vital and supported by vagal signaling between digestive organs and the brain. Previous research has established a gastric network in the brain that is phase synchronized with the rhythm of the stomach, but tools to perturb its function were lacking.
Objective: To evaluate whether stomach-brain coupling can be acutely increased by non-invasively stimulating vagal afferent projections to the brain.
Methods: Using a single-blind randomized crossover design, we investigated the effect of acute right-sided transcutaneous auricular vagus nerve stimulation (taVNS) versus sham stimulation on stomach-brain coupling.
Results: In line with preclinical research, taVNS increased stomach-brain coupling in the nucleus of the solitary tract (NTS) and the midbrain while boosting coupling across the brain. Crucially, in the cortex, taVNS-induced changes in coupling occurred primarily in transmodal regions and were associated with changes in hunger ratings as indicators of the subjective metabolic state.
Conclusions: taVNS increases stomach-brain coupling via an NTS-midbrain pathway that signals gut-induced reward, indicating that communication between the brain and the body is effectively modulated by vago-vagal signaling. Such insights may help us better understand the role of vagal afferents in orchestrating the recruitment of the gastric network which could pave the way for novel neuro-modulatory treatments.

© 2022 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

1. Introduction

Communication between the gut and the brain is central for maintaining energy homeostasis [1]. Interoceptive signals from peripheral organs involved in energy metabolism, such as the stomach, convey the physiological state of the body via vagal afferents to the nucleus of the solitary tract (NTS) in the brainstem [2,3]. Afferent vagal signaling from the stomach originates from chemo- and mechanoreceptors located in the stomach wall and mediates hunger and satiety [4]. Efferent vagal signaling modulates digestion by regulating the movement of the gastrointestinal smooth muscles directly or indirectly via the interstitial cells of Cajal which act as pacemakers [5].

Previous research on the stomach-brain axis has established a "gastric network" in the brain, whose activity is coupled to the 0.05 Hz myoelectrical rhythm intrinsically produced in the stomach that paces digestive contractions [6]. Interoceptive signaling has been hypothesized to entrain perceptual and attentional processes

on the neural level [7]; this has been demonstrated for cardiac [8] and respiratory [9] rhythms. Rhythmic signals originating from the stomach and mediated by the vagus nerve have been linked not only to appetite [10,11], but also motivation [12−14], memory formation [15,16] and affect [17]. Consequently, a widespread cortical network relying on a variety of neuromodulatory systems is coupled to the gastric rhythm [18], suggesting a role for gastric network oscillations in neuromodulation and behavior. Furthermore, dysfunctions of this network might be associated with disorders such as Parkinson's disease [19,20] that is characterized by aberrant vagal signaling from the gut and motivational impairments [21], both of which might be mechanistically linked [22].

However, to better characterize the role of the gastric network, causal manipulations are necessary. Such a technique might be provided by transcutaneous auricular vagus nerve stimulation (taVNS). taVNS has been shown to afferently increase activity in the NTS [23−26] and improve motivation [27], memory [28−30], and mood [31,32]. Crucially, gastric motility was also modulated via an efferent vago-vagal pathway [33−35]. To assess the effect of vagal afferent activation on stomach-brain coupling in healthy individuals, we used taVNS with concurrent electrogastrography (EGG) and fMRI (Fig. 1A). We expected taVNS to increase gastric coupling in regions with known vagal afferent projections, such as

the NTS. We further assessed if these stimulation-induced changes in stomach-brain coupling are correlated with changes in metabolic state as quantified by ratings of hunger. Our results show that stomach-brain coupling can be modulated with taVNS via a pathway that conveys gut-induced reward signals, and that this modulation may alter interoception about metabolic state.

2. Methods

2.1. Participants

For this study, we initially recruited 45 healthy participants. Due to dropout (n = 4) and pre-established indices of quality (see SI), the final sample for this analysis was 31 healthy participants. The final sample size provided high power (1-β = 0.90) to study moderate within-subject differences (d_z ~0.6) induced by taVNS versus sham relative to a baseline without stimulation. To ensure eligibility, all participants completed a telephone screening before participation. The study was approved by the ethics committee of the University of Tübingen (reference number 235/2017BO1) and was conducted in accordance with the Declaration of Helsinki. Participants provided written informed consent at the beginning of the first session and received either monetary compensation (56€)
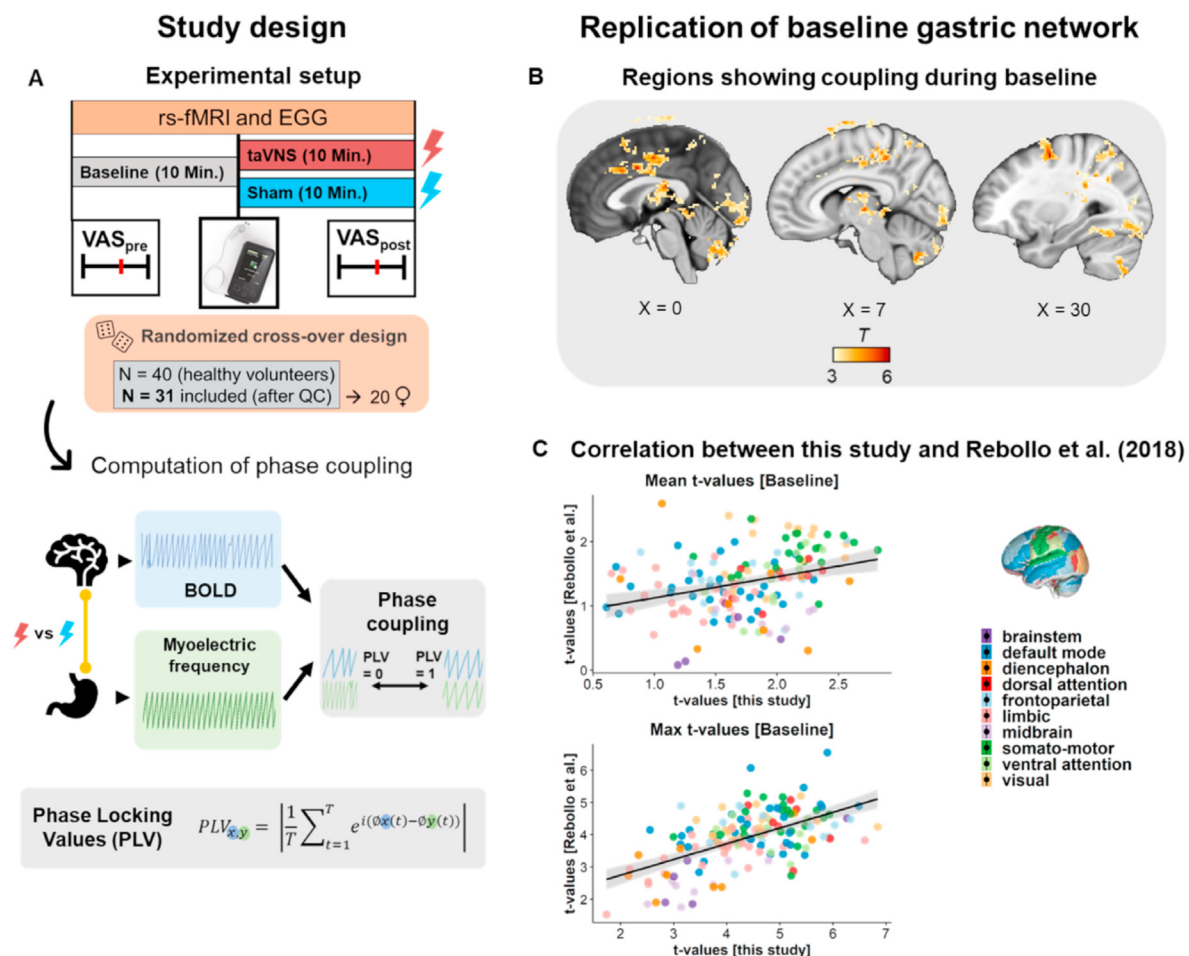
Fig. 1. Study design and corroboration of the gastric network during baseline scans (before stimulation). **A**: We measured resting-state fMRI and electrogastrography (EGG) in 31 healthy participants (20 women) for 10 min during baseline and 10 min during stimulation (taVNS vs. sham, collected on different days). The coupling between the stomach and the brain was expressed by the phase-locking value (PLV), indicating the synchrony between time series. **B**: We replicated the core regions of the canonical gastric network at baseline by observing coupling in the postcentral gyrus, the cingulate gyrus, the precuneus, the occipital cortex, the fusiform gyrus, the inferior frontal gyrus, the inferior and superior parietal lobe, the thalamus, and the inferior cerebellum. **C**: Within anatomically defined brain regions, we observed a moderate to high correlation between PLVs obtained in our sample and the independent sample of Rebollo et al. (2018), average *t*-values: *r* = 0.318, *p* < .001, maximal *t*-values: *r* = 0.57, *p* < .001, *t*-values available in Table S1.

or course credit for participation. Furthermore, they received additional money, office supplies, and snacks depending on their performance in two additional tasks (for details, see Ref. [26]).

2.2. Experimental procedure

Each participant completed two sessions of the same standardized protocol (randomized cross-over design, Fig. 1A). Participants received taVNS in one session, and sham stimulation in the other session with the order being randomized in advance. Participants were asked to enter the experimental session neither hungry nor full (no food or caloric beverages <1h prior to each session). To ensure comparable delays to the last meal, they were asked to eat ~1.5h prior to each session. Next, we measured heart rate, weight, waist and hip circumference, and assessed information about diet, last food, and last drink intake. Afterward, we collected ratings of hunger, fullness, thirst, and mood using the PANAS [36] as visual analog scales (VAS) on a computer.

Thereafter, participants were positioned in the fMRI scanner and all electrodes for EGG and electrocardiography (ECG) were placed according to Rebollo et al. [6]. In line with previous studies [23,27,32], the position of the electrode for taVNS stimulation was located at the right cymba conchae, whereas the electrode was placed at the earlobe of the same ear for sham stimulation (see Figure S3). The skin was cleaned at the position of the electrode using a cotton swab and alcoholic disinfectant. Then, electrode pads were wetted with contact fluid and the electrode was placed at the right ear by the experimenter while surgical tape kept the electrode and cable in position. For both electrode positions, we used the same stimulation protocol except for the stimulation strength. We set the stimulation strength individually using pain VAS. We initialized the stimulation with 1 mA and increased stepwise in 0.1–0.5 mA increments until the strength matched the participants' sensation of "mild pricking" ($M_{taVNS\_strength}$ = 3.56 mA ± 1.07 [1.5–5]). Then, the stimulation was turned off again.

Next, we started the measurements (ECG: 3 channels, EGG: 4 channels) using Brainvision Recorder (BrainProducts, Germany). First, we did an anatomical scan, followed by fieldmaps (~15min). This was followed by 10min of baseline (no stimulation) rs-fMRI measurement. Then, we turned on the stimulation (taVNS or sham) and measured for another ~10min. During rs-fMRI, we showed Inscapes videos without audio to improve compliance while minimizing cognitive load and motion [37]. After the onset of the stimulation, taVNS or sham remained active for the rest of the session.

After rs-fMRI measurements, participants completed tasks (~55min). After exiting the MR scanner, participants completed ratings of hunger, fullness, thirst, and mood again. At the end of each session, we asked participants whether they believed they had received taVNS or sham stimulation in this session (61.3% identified the condition correctly in session 1, $p_{binomial}$ = .075; 70.1% in session 2, $p_{binomial}$ = .005). The second session followed the same procedure and was usually conducted 1-7 days later at the same time of the day.

2.3. taVNS device

To administer the auricular stimulation of the vagus nerve, we used the NEMOS® stimulation device (cerbomed GmbH, Erlangen, Germany). It uses a biphasic stimulation protocol with 30s on (25 Hz), followed by 30s off stimulation. The stimulation intensity was set individually (possible range 0.1–5 mA) for each session until participants reported a mild pricking. We placed the stimulation electrode at the cymba conchae (taVNS) or the earlobe (sham) of the right ear [23,27,32,33]. In the current study, we decided to stimulate the right auricular branch of the vagus nerve because previous research had shown generalizing motivational effects [27] and stronger conditioning effects via mesolimbic dopamine release [38]. We reasoned that stimulating the right ear may provide further insights into crucial mechanisms of gut-brain communication that may support energy homeostasis.

2.4. EGG acquisition

The EGG data were recorded following the procedure published by Rebollo et al. [6] using Brain Vision Recorder (Brain Products, Germany). To prevent the occurrence of phase differences due to unequal distances to the reference electrode, we used four bipolar electrodes for EGG acquisition. The data were recorded with a sampling rate of 5000 Hz with a low-pass filter of 1000 Hz and no high-pass filter. We recorded EGG (and ECG) continuously throughout the whole session and marked the beginning and end of events using Psychtoolbox.

2.5. fMRI data acquisition and preprocessing

fMRI data were acquired on a Siemens 3T PRISMA scanner equipped with a 64-channel RF receiver head coil and preprocessed with fMRIprep (see SI; [26]). The sequence provided high temporal and spatial resolution and a sufficiently high temporal signal-to-noise ratio in the primary ROIs (see Figure S1 and https://neurovault.org/collections/CHANQVEU/).

2.6. Data analysis

2.6.1. Phase coupling

The EGG data was preprocessed using custom scripts implemented in MATLAB adapted from a pipeline published by Rebollo et al. [6] (https://github.com/irebollo/stomach_brain_Scripts; see SI). Briefly, this pipeline identifies the spectral peak of the individual gastric rhythm within the slow frequency normogastric band (0.03–0.07 Hz) for each participant and session.

Next, we extracted BOLD time series from rs-fMRI measurements for each voxel inside the brain mask provided by SPM. We then normalized and z-scored these time series. We denoised the signal using regressors for movement, cerebrospinal fluid, white matter, and respiration using the TAPAS toolbox [39]. Then, we split the time series into the same experimental phases as the EGG data (baseline and stimulation) and bandpass filtered both parts around the corresponding individual EGG peak frequency. Next, we performed a Hilbert transformation to obtain the phase information of the BOLD time series.

To determine the phase coupling between the EGG and BOLD time series, we computed the phase-locking value (PLV) for each voxel [6]. The PLV describes the synchrony between two signals, for example, that they de-/accelerate simultaneously, and can take values from 0 (no synchrony) to 1 (perfect synchrony) (Fig. 1A).

To test whether observed phase coupling exceeds levels occurring by chance, we used a permutation approach. We generated permuted phase sequences by computing chance PLV (CPLV), by circularly shifting the EGG phase signal (signal was cut from the end and prepended) and computing the PLV for each shift (see SI [6]). To replicate the gastric network [6], we first analyzed only the baseline phase.

Next, we analyzed the effect of taVNS on stomach-brain coupling using full-factorial models in SPM12 by computing the interaction effect of Stimulation [taVNS-sham] × Time [stimulation-baseline] and added stimulation order as covariate. Moreover, we analyzed whether taVNS increases the variance in PLV changes using F-tests (taVNS/sham). We performed an

exploratory analysis of the correlation between PLV changes (mean over region) and changes in gastric myoelectric frequency, BMI, and taVNS strength to evaluate potential influential factors that could explain part of the variance. To investigate if metabolic state mediates this effect of taVNS on stomach-brain coupling, we calculated the correlation between changes in coupling due to taVNS (ΔPLV$_{taVNS}$ [stimulation-baseline] - ΔPLV$_{sham}$ [stimulation-baseline]) and changes in metabolic state over the session (post [hunger-satiety] - pre [hunger-satiety]).

To analyze the subjective metabolic state (VAS before and after measurement), we used linear mixed-effects models in lme4 v1.1-21 [40]: *rating ~ stimulation * time+ (1 + stimulation | ID)* (BIC = 1292.5; for the gradient analysis, see SI).

2.6.2. Statistical threshold and software

Our analyses were conducted with MATLAB v2019-2020 and SPM12 (for a full list, see SI). We considered $\alpha < .05$ as significant, except for FWE cluster-corrected t-maps, where we used $p < .001$ ($k \geq 40$) as cluster-forming threshold. The cluster-extent threshold was estimated with AlphaSim [41] based on the smoothness of the maps ($\alpha_{corrected} < .05$, 2000 iterations). For baseline, we thresholded the empirical vs. chance PLV maps using a Monte-Carlo permutation test (cluster-$\alpha = .005$, $\alpha = .025$, 10,000 permutations).

3. Results

We analyzed phase coupling between the fMRI BOLD signal (providing high spatial resolution in deep brain regions) and the myoelectric signal of the stomach using PLV, a measure reflecting the synchrony between time series. First, we successfully replicated the topography of the gastric network as described before [6] during baseline (Fig. 1, Table S1, maps: https://neurovault.org/collections/QNGZBQGF/) indicating that stomach-brain coupling is a robust phenomenon.

3.1. taVNS boosts stomach-brain coupling

To evaluate whether stomach-brain coupling can be enhanced by taVNS, we compared PLV maps during taVNS and sham stimulation (relative to baseline) using a full-factorial model (i.e., Stimulation $\times$ Time interaction). Within our a priori ROIs, taVNS increased stomach-brain coupling in the NTS (Fig. 2A; $p_{svc} = .002$, $t_{max} = 4.33$). On the individual level, 67.8% (21/31; $p_{binom} = .015$) of the participants showed taVNS-induced increases in PLV in the NTS (vs. 45.2% or 14/31 for sham, $p_{binom} = .64$), and 64.5% (20/31) participants showed relative increases in PLV after taVNS compared to sham. Moreover, we observed increases in the dopaminergic midbrain (Fig. 2A; combined mask VTA&SN: $p_{svc} = .037$, peak in VTA: $t_{max} = 3.40$, $p_{svc} = .006$). At a whole-brain level (corrected for multiple comparisons), taVNS increased stomach-brain coupling in transmodal cortical regions, namely in the mid frontal gyrus (Fig. 2B; $t_{max} = 4.97$, $k = 63$) and the precuneus ($t_{max} = 4.25$, $k = 54$). Also, we found an increased inter-individual variance in stomach-brain coupling during taVNS versus sham in several regions ($p < .01$, $F(30,30) > 2.39$), such as the anterior cingulate cortex (Fig. 2B; $F(30,30) = 2.96$, $p = .002$), the left secondary somatosensory cortex ($F(30,30) = 2.94$, $p = .002$), the right insular cortex ($F(30,30) = 2.66$, $p = .005$), and the right supramarginal gyrus ($F(30,30) = 2.52$, $p = .007$), indicating taVNS-induced perturbation.

To assess potential influences of taVNS strength on stomach-brain coupling, we calculated the correlation between taVNS strength and changes in PLV (taVNS-sham). We found strong correlations in both insular cortices (Fig. S2, maps on NeuroVault; right: $t_{max} = 4.52$, $k = 102$; left: $t_{max} = 4.10$, $k = 190$) and the right supramarginal gyrus ($t_{max} = 4.61$, $k = 74$). Crucially, these regions

showed an increased variance during taVNS, indicating that inter-individual differences in stimulation strength (matched according to sensory aspects) might contribute to the observed variance. Still, gastric myoelectric frequency did not change during taVNS in our sample [26], indicating that changes in stomach-brain coupling might precede changes in gastric motility that occur after prolonged stimulation [33].

To evaluate whether taVNS increases coupling in regions that are intrinsically coupled at baseline, we computed the correlation between the effect sizes (d_z) of each region for the baseline and for taVNS-induced changes (taVNS–sham) in PLVs. Both mean ($r = 0.21$, $p = .009$), and maximum effect sizes within each region ($r = 0.44$, $p < .001$) were correlated, demonstrating that taVNS boosted stomach-brain coupling in regions with higher intrinsic coupling at baseline (Fig. 2C, Table S2). However, the largest taVNS effects on PLVs were observed in regions outside the baseline gastric network, notably in the frontoparietal network, the default-mode network (DMN), the midbrain, and the brainstem (Fig. 2D, networks according to Ref. [42]).

Analogous to Rebollo, Wolpert, Tallon-Baudry [18], we also analyzed the hierarchical distribution of the taVNS effect on the gastric network along the first two cortical rs-gradients [43]. These gradients characterize rs-networks in terms of a cortical functional hierarchy, where the first gradient extends from unimodal to transmodal (with two peaks at the extremes) and the second gradient from visual to somatomotor-auditory regions (Fig. 3A). In line with Rebollo et al. (2021), the baseline gastric network was primarily associated with unimodal cortical regions (Fig. 3B; $p < .001$ deviation from the standard rs-gradient, Kolmogorov-Smirnov test). Intriguingly, taVNS shifted this distribution towards transmodal cortical regions, such as the DMN and the frontoparietal network (Fig. 3C; $p < .001$).

3.2. taVNS strengthens the link between changes in stomach-brain coupling and changes in hunger

After demonstrating that taVNS boosts stomach-brain coupling, we analyzed whether changes in subjective ratings of metabolic state (assessed before and after the measurement) were associated with individual differences in taVNS-induced changes. These state ratings showed an increase in hunger during the session ($p < .001$) with inter-individual variability but did not differ depending on the stimulation condition (Fig. 4A; $p_{lme} = .482$). However, we found that taVNS increased the correlation of changes in stomach-brain coupling with changes in hunger ratings in regions across the cortex (Fig. 4B–E), such as the frontal poles (right: $t_{max} = 6.49$, $k = 40$; left: $t_{max} = 5.16$, $k = 137$), the cerebellum ($t_{max} = 5.14$, $k = 200$), the fusiform gyrus ($t_{max} = 4.63$, $k = 92$), the precuneus (left: $t_{max} = 4.54$, $k = 100$; right: $t_{max} = 4.49$, $k = 67$), the inferior parietal lobe ($t_{max} = 4.25$, $k = 60$), and the declive ($t_{max} = 4.41$, $k = 55$, Table S3). In line with the main effect of taVNS, the correlation of taVNS-induced changes in PLV with hunger ratings showed a shift towards transmodal cortical regions (Fig. 3D; $p < .001$ compared to the cortical gradients by Ref. [43]). Collectively, these findings support the idea that taVNS-induced changes in stomach-brain coupling can be sensed, indicating that emulated input via vagal afferents may act as interoceptive signal.

4. Discussion

The recently discovered gastric brain network is thought to play a vital role in energy homeostasis [6,18,44], but the lack of causal manipulations has so far hampered progress in delineating its function in humans. Here, we used non-invasive taVNS to emulate the activation of vagal afferents that are known to regulate the
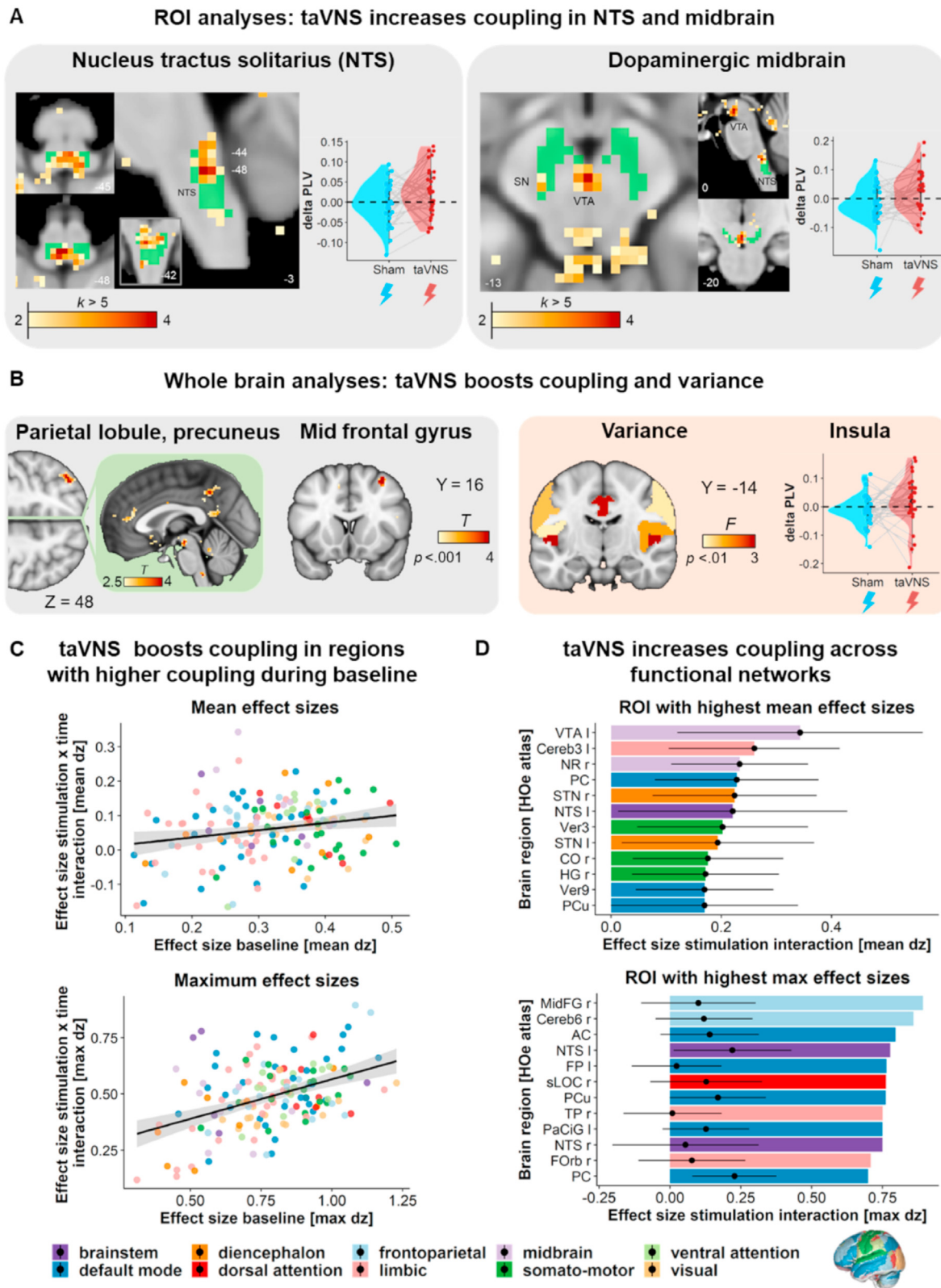
Fig. 2. Transcutaneous vagus nerve stimulation (taVNS) increases stomach-brain coupling. **A**: taVNS boosts coupling in key target regions of vagal afferents: the NTS ($t_{max} = 4.33$, $p_{svc} = .002$) and the dopaminergic midbrain (peak in the VTA/SN: $p_{svc} = .037$, $t_{max} = 3.40$). **B**: taVNS (vs. sham) increases coupling in the precuneus/superior parietal lobe ($t_{max} = 4.25$, $p_{FWE} = .041$) and the mid frontal gyrus ($t_{max} = 4.97$, $p_{FWE} = .019$), and increases variance in PLV changes in several regions such as in both insular cortices and the anterior cingulate (AC) cortex. See also Figure S1. **C**: taVNS boosts coupling in regions that are intrinsically coupled with the stomach at baseline as indicated by Pearson correlations between baseline and stimulation interaction effects: (mean d_z over each region: $r = 0.21$, $p = .009$; maximum d_z within each region: $r = 0.44$, $p < .001$). **D**: Selected regions with the highest voxel-wise effect sizes (dots and error bars show M ± SD). VTA: ventral tegmental area, Cereb: cerebellum, NR: nucleus. ruber, PC: posterior cingulate, STN: subthalamic ncl., NTS: nucleus tractus solitarius, Ver: vermis, CO: central opercular cortex, HG: Heschl's gyrus, PCu: precuneus, MidFG: mid frontal gyrus, sLOC: superior lateral occipital cortex, TP: temporal pole, FOrb: frontal orbital cortex.
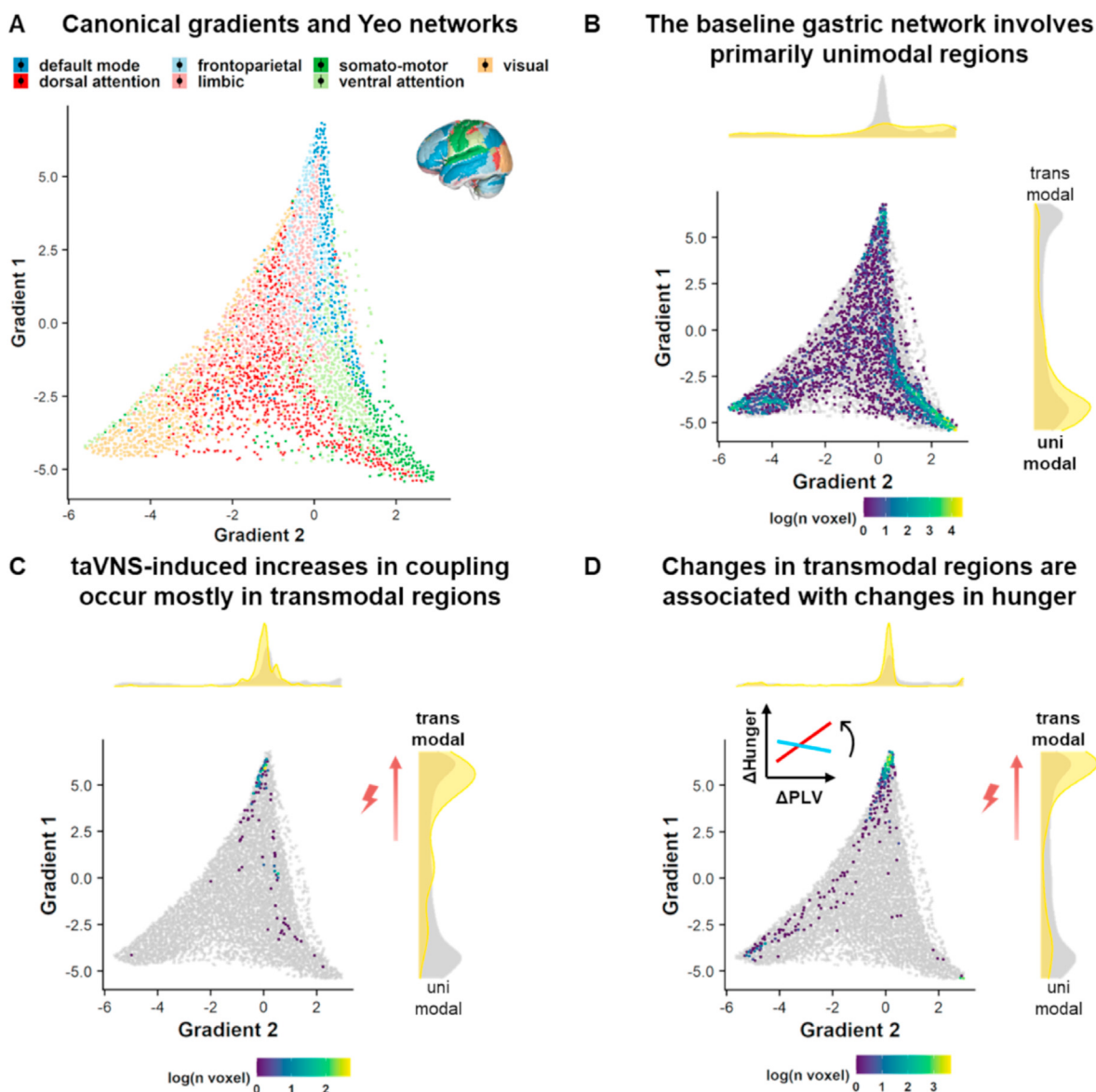
Fig. 3. Non-invasive vagus nerve stimulation (taVNS) primarily boosts coupling in transmodal cortical regions. **A**: Distribution of the cortical gradients described by Margulies, Ghosh, Goulas, Falkiewicz, Huntenburg, Langs, Bezgin, Eickhoff, Castellanos, Petrides, Jefferies, Smallwood [43]. Each dot depicts a bin of voxels (100 bins per gradient) and was color-coded according to the predominant Yeo network in each bin. Gradient 1 extends from uni-to transmodal regions while gradient 2 extends from visual to somato-motor-auditory regions. **B**: Comparison of the distribution of voxels that show significant taVNS-induced changes in coupling (highlighted) with the standard cortical gradients described by Margulies, Ghosh, Goulas, Falkiewicz, Huntenburg, Langs, Bezgin, Eickhoff, Castellanos, Petrides, Jefferies, Smallwood [43] depicted in grey. The colors indicate the numbers of voxels per bin. In line with Rebollo et al. (2021), the voxels of the baseline gastric network belonged primarily to unimodal regions, such as visual and somato-motor areas. **C**: In contrast, taVNS increased stomach-brain coupling primarily in transmodal regions, such as the default mode network and the frontoparietal network, which is in line with an increase in parasympathetic modulation. **D**: Distribution of voxels that show a significant correlation between taVNS-induced changes and sensed changes in hunger (highlighted) compared to the standard cortical gradients described by Margulies, Ghosh, Goulas, Falkiewicz, Huntenburg, Langs, Bezgin, Eickhoff, Castellanos, Petrides, Jefferies, Smallwood [43] depicted in grey. Intriguingly, taVNS-induced changes in stomach-brain coupling were correlated with subjectively sensed changes in hunger mostly in transmodal cortical regions as well, suggesting that changes in stomach-brain coupling in transmodal cortical regions may play a role in sensing interoceptive signals related to hunger (i.e., metabolic state). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

intrinsic rhythm of the stomach via a vago-vagal pathway [45]. For the first time in humans, we show that taVNS applied at the right ear boosts stomach-brain coupling in the NTS and the dopaminergic midbrain, a pattern that strongly resembles the pathway for gut-induced reward via the right nodose ganglion previously described in rodents [38]. Furthermore, we demonstrate increased coupling in transmodal cortical regions, as well as in regions that display high intrinsic coupling under baseline conditions. Crucially,

we also show that taVNS increases the correlation between changes in stomach-brain coupling and in subjectively sensed hunger, again primarily in transmodal cortical regions. Consequently, we conclude that taVNS modulates stomach-brain coupling via an NTS-midbrain pathway, while changes in cortical coupling might reflect stronger integration of interoceptive signals encoding the current metabolic state of the body. Collectively, these results point to a vital role of the gastric network in supporting the maintenance
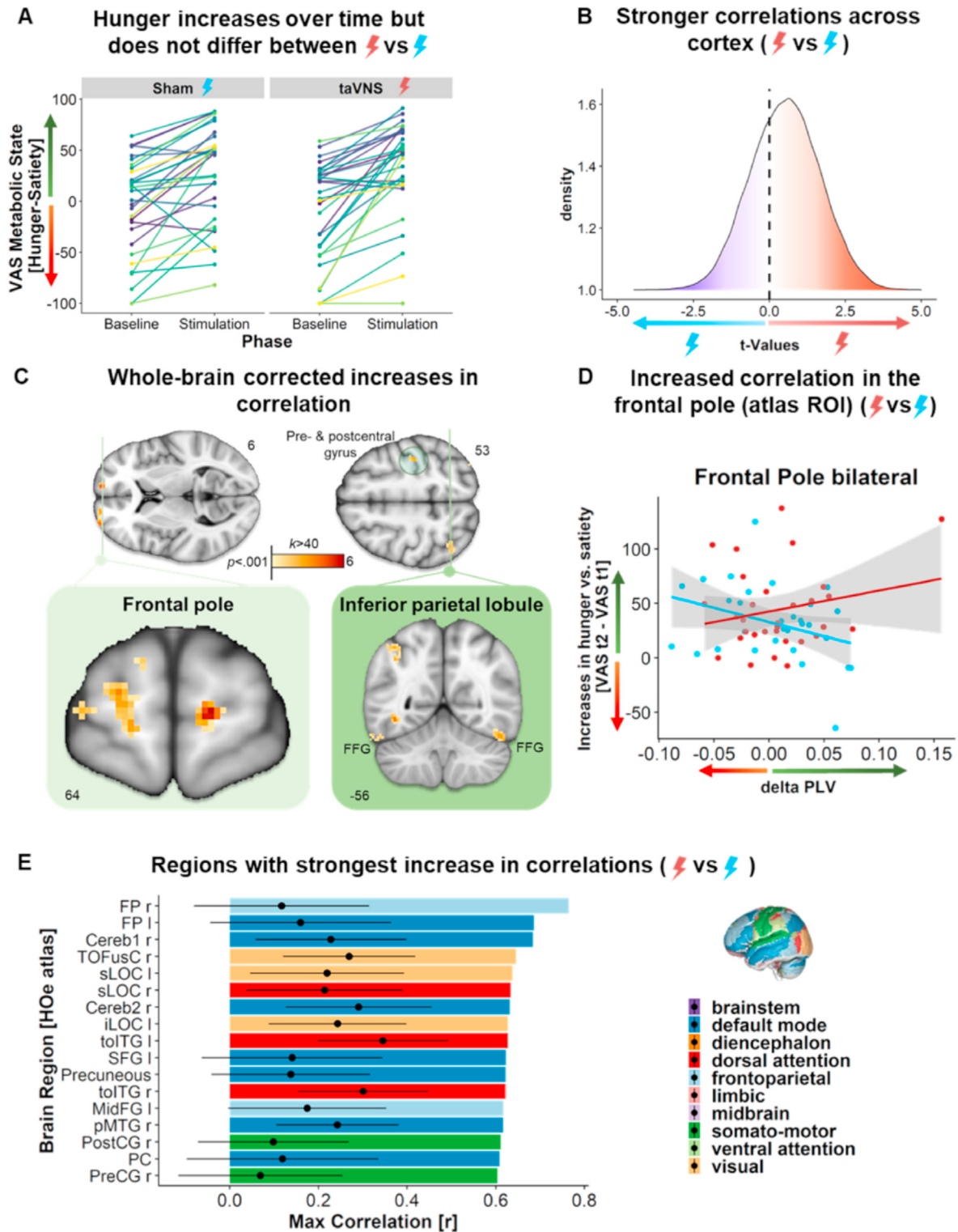
Fig. 4. taVNS increases the correspondence of changes in stomach-brain coupling with subjective changes in metabolic state. **A**: Participants became hungrier during the scan ($p < .001$), but there was no interaction with stimulation ($p = .482$). **B**: taVNS increased the correlation between increases in hunger and changes in stomach-brain coupling across the cortex (density plot of the change in correlation (taVNS vs sham) of all cortical voxels, positive values indicate higher correlation). **C**: Clusters of voxels showing significant increases in correlation with subjective changes in metabolic state after whole-brain correction for multiple comparisons: frontal poles ($t_{max} = 6.49$), fusiform gyrus ($t_{max} = 4.63$), precuneus ($t_{max} = 4.54$), and inferior parietal lobe ($t_{max} = 4.25$; Table S3, maps on NeuroVault). **D**: taVNS increases the correlation between PLV changes and metabolic state ratings in the frontal poles (regions from Harvard-Oxford brain atlas). **E**: During taVNS, several regions showed an increased correlation between changes in coupling and metabolic state and the strongest effects were found in the DMN, the visual network, the frontoparietal network, and the dorsal attention network. Correlation was calculated voxelwise across each ROI, bars show the maximum r, dots and error bars indicate mean ± standard deviation. [FP: frontal pole, Cereb: cerebellum, TOFusC: temporal occipital fusiform gyrus, sLOC: superior lateral occipital cortex, iLOC: inferior lateral occipital cortex, toITG: temporooccipital inferior temporal gyrus, MidFG: mid frontal gyrus, pMTG: posterior middle temporal gyrus, PostCG: postcentral gyrus, PC: posterior cingulate, PreCG: precentral gyrus].

of energy homeostasis opening new avenues for neuromodulatory treatments.

4.1. Anatomical pathways for the taVNS effect on the gastric network

Since the NTS is the main entry point of vagal afferents to the brain and is robustly activated by taVNS [23,24,26,46], we expected taVNS to increase stomach-brain coupling, which was confirmed. The NTS is a crucial part of the gastric-vagal reflex: vagal afferents delivering interoceptive information from the stomach reach the NTS, get integrated and projected to the dorsal vagal motor nucleus, which then sends efferent commands back to the stomach [45,47–49]. Previous findings also suggest the involvement of this pathway in the efferent modulation of gastric frequency following vagal stimulation in humans [33–35]. Although the anatomical pathways mediating the integration of gastric signals in the brain are not fully resolved [50], it is known that the NTS projects to the parabrachial nuclei and the thalamus which acts as a relay station to cortical regions of the gastric network [18,51]. In addition, the NTS also projects to the dopaminergic midbrain which is involved in reward, nutrient sensing, and food-seeking behavior [38,52]. In line with previous work, we found that taVNS boosts stomach-brain coupling in the VTA/SN, which adds to the growing literature suggesting a role for dopamine in the control of digestion [53]. Modulations of the VTA may also occur indirectly via the parabrachial nuclei [54,55]. From a clinical perspective, increased stomach-brain coupling in the VTA/SN provides potential applications to prevalent gastrointestinal symptoms in several disorders, such as mood and anxiety disorders [56–58] or Parkinson's disease (PD) [59–62], in which the dopaminergic midbrain is severely affected [63]. Illustratively, taVNS improved gastrointestinal symptoms in PD, highlighting the potential of clinical applications [64]. To summarize, our results suggest that a vagal-midbrain pathway may facilitate the integration of metabolic signaling into larger brain networks potentially shaping goal-directed behavior to ensure that metabolic demands are met.

4.2. The role of the gastric network in maintaining metabolic balance

Since feeding and digestion are vital functions of the digestive system, the gastric network likely supports the long-term maintenance of energy homeostasis [18,44,50]. Our finding that taVNS increases the correlation between changes in stomach-brain coupling and subjectively sensed changes in metabolic state provides intriguing support for the alleged link between the gastric network and interoception. This is in line with work showing that activity in the gastric network is related to future weight loss [65]. We found that transmodal regions showed the highest increase in correlation with sensed hunger during taVNS. This possibly reflects the hierarchically overarching integration of metabolic feedback, which is buffered in unimodal cortical areas, into larger transmodal brain networks after vagal afferent activation. The strong involvement of visual regions might reflect increased visual attention [18,66,67] and corresponding changes in pupil dilation and alpha oscillations may indicate increased (visual) arousal [68–70]. Relatedly, the highest increase in correlation was found in the frontal poles, which are part of the salience network and DMN, and are involved in goal-directed behavior and metacognition [71–76] as well as in reward-related decision making [77,78]. This supports the idea of a relationship between hunger-dependent alterations in stomach-brain coupling and food-seeking behavior. We conclude that vagal afferent stimulation facilitates the integration of metabolic information from unimodal representations into a transmodally-extended gastric network, which may help coordinate behavioral adaptation to ensure long-term energy homeostasis.

4.3. Gastric signaling as a common reference point for intero- and exteroception

The constant rhythmical input from the stomach may act as a common reference point for the alignment and coordination of both interoceptive and exteroceptive brain networks [18]. Our finding of increased coupling in transmodal cortical regions during taVNS (vs. unimodal cortical regions during baseline) provides the first causal support for this theory. As we emulated interoceptive signals by afferently stimulating the vagus nerve, the stronger involvement of higher-order transmodal regions, which integrate activity across sensory-motor/unimodal regions [79], might mirror the coordinated hierarchical integration of altered visceral inputs across brain networks. Our results therefore suggest that the baseline gastric network reflects ongoing integration of low-level interoceptive information. Once vagal afferents are activated, the gastric network expands to reflect heightened integration across modalities, leading to changes in the awareness of the metabolic state of the body which may facilitate adaptations of goal-directed behavior, such as food-seeking. Crucially, the higher-order integration of the transmodal cortex during taVNS is in line with a boost in parasympathetic activity, whereas the baseline gastric network is affected by sympathetic regulation [18,51,80,81].

Strikingly, several cortical regions also show increased variance in stomach-brain coupling during taVNS (vs. sham), such as the insula and the ACC. The insula displays a viscerotopic organization [82] and has not only been linked to interoception, but also saliency [83]. It shows rich connections to unimodal areas and processes multisensory information, including both interoceptive and exteroceptive signaling [84]. Furthermore, the insula is involved in the parasympathetic regulation of the stomach [80]. While BMI or changes in gastric frequency did not explain an increased variance during taVNS, we found strong associations between PLV changes and taVNS strength in the bilateral insula and the right supramarginal gyrus. These findings pose the intriguing question whether stomach-brain coupling could be parametrically modulated by adjusting the stimulation strength, which requires extended designs in the future. Relatedly, examining spatiotemporal dynamics of digestive signals during taVNS beyond gastric myoelectric frequency (a gross spatial mean) could provide more mechanistic insights into the intricate progression of signals along the stomach curvature [85]. We conclude that taVNS boosts the integration of interoceptive signaling in transmodal cortical regions, potentially modulating arousal in a parasympathetic network.

4.4. Limitations

Despite the novel insights provided by our unique investigation combining taVNS with concurrent fMRI and EGG recordings, there are limitations that will need to be addressed in future work. First, it is not known whether the duration of taVNS alters effects on stomach-brain coupling. Our design used a duration of 10min for each experimental phase, analogous to baseline measurements of previous work [6]. However, longer taVNS periods might elicit different changes in stomach-brain coupling as they may evoke effects on gastric frequency and motility which have been demonstrated after longer stimulation periods [33,35,86]. Second, it is not known whether left-vs. right-sided stimulation leads to comparable effects on the gastric network, as lateralization differences between visceral fibers of the vagus nerve might play a role

[87]. Notably, the identified NTS-midbrain pathway resembles gut-induced reward after invasive stimulation of the right nodose ganglion in rodents [38]. Intriguingly, combining left- and right-sided stimulation [88] may also boost effects and future work may explore how taVNS-induced effects can be optimized. Third, we invited participants in an intermediate metabolic state (neither hungry, nor full). Future studies should include objective measures (e.g., glucose levels) and systematically investigate different states using more extensive interoceptive measures (such as interoceptive awareness and accuracy [89]). Fourth, potential interactions of the gastric network with exteroceptive input (e.g., visual or olfactory food cues) should be examined to gain insights into the alleged link between the gastric network and food-seeking behavior. Fifth, we provide the first evidence that taVNS increases stomach-brain coupling, but larger studies are necessary to investigate potential inter-individual differences with sufficient power.

4.5. Summary and conclusion

Procuring sufficient energy for survival is crucial and the recently discovered gastric network may play a vital role in ensuring long-term energy homeostasis. In support of this idea and in accordance with the previously established pathway for gut-induced reward [38], we showed that non-invasive stimulation of vagal afferents at the right ear via taVNS increases stomach-brain coupling in the NTS and the dopaminergic midbrain. Furthermore, we demonstrated increased stomach-brain coupling in transmodal cortical regions, including an increased correlation with changes in ratings of hunger. We conclude that taVNS is an effective method to modulate stomach-brain coupling, providing an important technique to causally study the function of the gastric network. Consequently, taVNS may open an avenue to future treatments of gastrointestinal, or more broadly, somatic symptoms of a broad array of disorders. In addition, work on vagal afferent signaling using the experimental control provided by taVNS could help us better understand inter-individual differences in non-homeostatic eating, such as emotional or disinhibited eating.

5. Data and code availability

The analyses are based on code published by Rebollo, Devauchelle, Beranger, Tallon-Baudry [6] that is available on: https://github.com/irebollo/stomach_brain_Scripts. All unthresholded group-level maps of the results are uploaded on NeuroVault: https://neurovault.org/collections/QNGZBQGF/.

Financial disclosure

The authors declare no competing financial interests.

CRediT authorship contribution statement

Sophie J. Müller: Software, Investigation, Data curation, Formal analysis, Visualization, Writing – original draft. **Vanessa Teckentrup:** Software, Methodology, Validation, Investigation, Formal analysis, Writing – review & editing, Project administration. **Ignacio Rebollo:** Software, Methodology, Formal analysis, Writing – review & editing. **Manfred Hallschmid:** Resources, Supervision, Writing – review & editing. **Nils B. Kroemer:** Conceptualization, Methodology, Formal analysis, Visualization, Writing – review & editing, Project administration, Supervision, Funding acquisition.

Declaration of competing interest

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

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.foodhyd.2022.107917.

References

[1] Waterson MJ, Horvath TL. Neuronal regulation of energy homeostasis: beyond the Hypothalamus and feeding. Cell Metab 2015;22(6):962–70.
[2] Holtmann G, Talley NJ. The stomach-brain axis. Best Pract Res Clin Gastroenterol 2014;28(6):967–79.
[3] Powley TL, Spaulding RA, Haglof SA. Vagal afferent innervation of the proximal gastrointestinal tract mucosa: chemoreceptor and mechanoreceptor architecture. J Comp Neurol 2011;519(4):644–60.
[4] Folgueira C, Seoane LM, Casanueva FF. The brain-stomach connection. Front Horm Res 2014;42:83–92.
[5] Lundgren O. Vagal control of the motor functions of the lower esophageal sphincter and the stomach. J Auton Nerv Syst 1983;9(1):185–97.
[6] Rebollo I, Devauchelle AD, Beranger B, Tallon-Baudry C. Stomach-brain synchrony reveals a novel, delayed-connectivity resting-state network in humans. Elife 2018;7.
[7] Rassi E, Dorffner G, Gruber W, Schabus M, Klimesch W. Coupling and decoupling between brain and body oscillations. Neurosci Lett 2019;711: 134401.
[8] Allen M, Levy A, Parr T, Friston KJ. In the body's eye: the computational anatomy of interoceptive inference. bioRxiv 2019:603928.
[9] Varga S, Heck DH. Rhythms of the body, rhythms of the brain: respiration, neural oscillations, and embodied cognition. Consciousness and Cognition 2017;56:77–90.
[10] Mattes RD, Hunter SR, Higgins KA. Sensory, gastric, and enteroendocrine effects of carbohydrates, fat, and protein on appetite. Current Opinion in Endocrine and Metabolic Research 2019;4:14–20.
[11] Hussain MM, Pan X. Clock genes, intestinal transport and plasma lipid homeostasis. Trends in Endocrinology & Metabolism 2009;20(4):177–85.
[12] Alhadeff AL, Grill HJ. Hindbrain nucleus tractus solitarius glucagon-like peptide-1 receptor signaling reduces appetitive and motivational aspects of feeding. American Journal of Physiology-Regulatory, Integrative and Comparative Physiology 2014;307(4):R465–70.
[13] Kanoski SE, Alhadeff AL, Fortin SM, Gilbert JR, Grill HJ. Leptin signaling in the medial nucleus tractus solitarius reduces food seeking and willingness to work for food. Neuropsychopharmacology 2013;39(3):605–13.
[14] Nord CL, Dalmaijer ES, Armstrong T, Baker K, Dalgleish T. A causal role for gastric rhythm in human disgust avoidance. Curr Biol 2021;31(3):629–634 e3.
[15] Mandal A, Prabhavalkar KS, Bhatt LK. Gastrointestinal hormones in regulation of memory. Peptides 2018;102:16–25.
[16] Suarez AN, Hsu TM, Liu CM, Noble EE, Cortella AM, Nakamoto EM, et al. Gut vagal sensory signaling regulates hippocampus function through multi-order pathways. Nature Communications 2018;9(1).
[17] Mayer EA. Gut feelings: the emerging biology of gut–brain communication. Nature Reviews Neuroscience 2011;12(8):453–66.
[18] Rebollo I, Wolpert N, Tallon-Baudry C. Brain–stomach coupling: anatomy, functions, and future avenues of research. Current Opinion in Biomedical Engineering 2021;18.
[19] Svensson E, Horváth-Puhó E, Thomsen RW, Djurhuus JC, Pedersen L, Borghammer P, et al. Vagotomy and subsequent risk of Parkinson's disease. Annals of Neurology 2015;78(4):522–9.

[20] Heimrich KG, Jacob VYP, Schaller D, Stallmach A, Witte OW, Prell T. Gastric dysmotility in Parkinson's disease is not caused by alterations of the gastric pacemaker cells. npj Parkinson's Disease 2019;5(1).

[21] Mazzoni P, Hristova A, Krakauer JW. Why don't we move faster? Parkinson's disease, movement vigor, and implicit motivation. Journal of Neuroscience 2007;27(27):7105–16.

[22] Breen DP, Halliday GM, Lang AE. Gut-brain axis and the spread of alpha-synuclein pathology: vagal highway or dead end? Mov Disord 2019;34(3):307–16.

[23] Frangos E, Ellrich J, Komisaruk BR. Non-invasive access to the vagus nerve central projections via electrical stimulation of the external ear: fMRI evidence in humans. Brain Stimul 2015;8(3):624–36.

[24] Yakunina N, Kim SS, Nam E-C. Optimization of transcutaneous vagus nerve stimulation using functional MRI. Neuromodulation: Technology at the Neural Interface 2017;20(3):290–300.

[25] Sclocco R, Garcia RG, Kettner NW, Isenburg K, Fisher HP, Hubbard CS, et al. The influence of respiration on brainstem and cardiovagal response to auricular vagus nerve stimulation: a multimodal ultrahigh-field (7T) fMRI study. Brain Stimulation 2019;12(4):911–21.

[26] Teckentrup V, Krylova M, Jamalabadi H, Neubert S, Neuser MP, Hartig R, et al. Brain signaling dynamics after vagus nerve stimulation. NeuroImage 2021;245:118679.

[27] Neuser MP, Teckentrup V, Kühnel A, Hallschmid M, Walter M, Kroemer NB. Vagus nerve stimulation boosts the drive to work for rewards. Nat Commun 2020;11(1):3555.

[28] Giraudier M, Ventura-Bort C, Weymar M. Transcutaneous vagus nerve stimulation (tVNS) improves high-confidence recognition memory but not emotional word processing. Frontiers in Psychology 2020;11.

[29] Vazquez-Oliver A, Brambilla-Pisoni C, Domingo-Gainza M, Maldonado R, Ivorra A, Ozaita A. Auricular transcutaneous vagus nerve stimulation improves memory persistence in naive mice and in an intellectual disability mouse model. Brain Stimul 2020;13(2):494–8.

[30] Jacobs HI, Riphagen JM, Razat CM, Wiese S, Sack AT. Transcutaneous vagus nerve stimulation boosts associative memory in older individuals. Neurobiol Aging 2015;36(5):1860–7.

[31] Kraus T, Hösl K, Kiess O, Schanze A, Kornhuber J, Forster C. BOLD fMRI deactivation of limbic and temporal brain structures and mood enhancing effect by transcutaneous vagus nerve stimulation. Journal of Neural Transmission 2007;114(11):1485–93.

[32] Ferstl M, Teckentrup V, Lin WM, Krautlein F, Kuhnel A, Klaus J, et al. Non-invasive vagus nerve stimulation boosts mood recovery after effort exertion. Psychol Med 2021:1–11.

[33] Teckentrup V, Neubert S, Santiago JCP, Hallschmid M, Walter M, Kroemer NB. Non-invasive stimulation of vagal afferents reduces gastric frequency. Brain Stimul 2020;13(2):470–3.

[34] Hong GS, Pintea B, Lingohr P, Coch C, Randau T, Schaefer N, et al. Effect of transcutaneous vagus nerve stimulation on muscle activity in the gastrointestinal tract (transVaGa): a prospective clinical trial. Int J Colorectal Dis 2019;34(3):417–22.

[35] Steidel K, Krause K, Menzler K, Strzelczyk A, Immisch I, Fuest S, et al. Transcutaneous auricular vagus nerve stimulation influences gastric motility: a randomized, double-blind trial in healthy individuals. Brain Stimul 2021;14(5):1126–32.

[36] Watson D, Clark LA, Tellegen A. Development and validation of brief measures of positive and negative affect: the PANAS scales. J Pers Soc Psychol 1988;54(6):1063–70.

[37] Vanderwal T, Kelly C, Eilbott J, Mayes LC, Castellanos FX. Inscapes: a movie paradigm to improve compliance in functional magnetic resonance imaging. Neuroimage 2015;122:222–32.

[38] Han W, Tellez LA, Perkins MH, Perez IO, Qu T, Ferreira J, et al. A neural circuit for gut-induced reward. Cell 2018;175(3):887–8.

[39] Frässle S, Aponte EA, Bollmann S, Brodersen KH, Do CT, Harrison OK, et al. TAPAS: an open-source software package for translational neuromodeling and computational psychiatry. Frontiers in Psychiatry 2021;12(857).

[40] Bates D, Mächler M, Bolker B, Walker S. Fitting linear mixed-effects models using lme4. Journal of Statistical Software 2015;1(1). 2015.

[41] Song X-W, Dong Z-Y, Long X-Y, Li S-F, Zuo X-N, Zhu C-Z, et al. REST: a toolkit for resting-state functional magnetic resonance imaging data processing. PloS one 2011;6(9):e25031.

[42] Yeo BT, Krienen FM, Sepulcre J, Sabuncu MR, Lashkari D, Hollinshead M, et al. The organization of the human cerebral cortex estimated by intrinsic functional connectivity. J Neurophysiol 2011;106(3):1125–65.

[43] Margulies DS, Ghosh SS, Goulas A, Falkiewicz M, Huntenburg JM, Langs G, et al. Situating the default-mode network along a principal gradient of macroscale cortical organization. Proc Natl Acad Sci U S A 2016;113(44):12574–9.

[44] Choe AS, Tang B, Smith KR, Honari H, Lindquist MA, Caffo BS, et al. Phase-locking of resting-state brain networks with the gastric basal electrical rhythm. PLoS One 2021;16(1):e0244756.

[45] Shapiro RE, Miselis RR. The central organization of the vagus nerve innervating the stomach of the rat. J Comp Neurol 1985;238(4):473–88.

[46] He W, Jing XH, Zhu B, Zhu XL, Li L, Bai WZ, et al. The auriculo-vagal afferent pathway and its role in seizure suppression in rats. BMC Neurosci 2013;14:85.

[47] Waise TMZ, Dranse HJ, Lam TKT. The metabolic role of vagal afferent innervation. Nat Rev Gastroenterol Hepatol 2018;15(10):625–36.

[48] Berthoud HR, Neuhuber WL. Functional and chemical anatomy of the afferent vagal system. Auton Neurosci 2000;85(1–3):1–17.

[49] Neuhuber WL, Berthoud H-R. Functional anatomy of the vagus system – emphasis on the somato-visceral interface. Autonomic Neuroscience 2021:102887.

[50] Azzalini D, Rebollo I, Tallon-Baudry C. Visceral signals shape brain dynamics and cognition. Trends Cogn Sci 2019;23(6):488–509.

[51] Rebollo I, Tallon-Baudry C. The sensory and motor components of the cortical hierarchy are coupled to the rhythm of the stomach during rest. bioRxiv 2021: 2021. 05.26.445829.

[52] Fernandes AB, Alves da Silva J, Almeida J, Cui G, Gerfen CR, Costa RM, et al. Postingestive modulation of food seeking depends on vagus-mediated dopamine neuron activity. Neuron 2020;106(5):778–88. e6.

[53] Anselmi L, Toti L, Bove C, Hampton J, Travagli RA. A nigro-vagal pathway controls gastric motility and is affected in a rat model of parkinsonism. Gastroenterology 2017;153(6):1581–93.

[54] Boughter Jr JD, Lu L, Saites LN, Tokita K. Sweet and bitter taste stimuli activate VTA projection neurons in the parabrachial nucleus. Brain Res 2019;1714:99–110.

[55] Dunckley P, Wise RG, Fairhurst M, Hobden P, Aziz Q, Chang L, et al. A comparison of visceral and somatic pain processing in the human brainstem using functional magnetic resonance imaging. J Neurosci 2005;25(32):7333–41.

[56] Mussell M, Kroenke K, Spitzer RL, Williams JB, Herzog W, Lowe B. Gastrointestinal symptoms in primary care: prevalence and association with depression and anxiety. J Psychosom Res 2008;64(6):605–12.

[57] Huang MH, Wang YP, Wu PS, Chan YE, Cheng CM, Yang CH, et al. Association between gastrointestinal symptoms and depression among older adults in Taiwan: a cross-sectional study. J Chin Med Assoc 2021;84(3):331–5.

[58] Soderquist F, Syk M, Just D, Kurbalija Novicic Z, Rasmusson AJ, Hellstrom PM, et al. A cross-sectional study of gastrointestinal symptoms, depressive symptoms and trait anxiety in young adults. BMC Psychiatry 2020;20(1):535.

[59] Marrinan S, Emmanuel AV, Burn DJ. Delayed gastric emptying in Parkinson's disease. Mov Disord 2014;29(1):23–32.

[60] Santos-Garcia D, de Deus T, Tejera-Perez C, Exposito-Ruiz I, Suarez-Castro E, Carpintero P, et al. [Gastroparesis and other gastrointestinal symptoms in Parkinson's disease]. Rev Neurol 2015;61(6):261–70.

[61] Mrabet S, Ben Ali N, Achouri A, Dabbeche R, Najjar T, Haouet S, et al. Gastrointestinal dysfunction and neuropathologic correlations in Parkinson disease. J Clin Gastroenterol 2016;50(9):e85–90.

[62] Lubomski M, Davis RL, Sue CM. Gastrointestinal dysfunction in Parkinson's disease. J Neurol 2020;267(5):1377–88.

[63] Aurora SK, Shrewsbury SB, Ray S, Hindiyeh N, Nguyen L. A link between gastrointestinal disorders and migraine: insights into the gut-brain connection. Headache 2021;61(4):576–89.

[64] Kaut O, Janocha L, Weismuller TJ, Wullner U. Transcutaneous vagal nerve stimulation improves gastroenteric complaints in Parkinson's disease patients. NeuroRehabilitation 2019;45(4):449–51.

[65] Levakov G, Kaplan A, Yaskolka Meir A, Rinott E, Tsaban G, Zelicha H, et al. Neural correlates of future weight loss reveal a possible role for brain-gastric interactions. Neuroimage 2021;224:117403.

[66] Gidlöf K, Ares G, Aschemann-Witzel J, Otterbring T. Give us today our daily bread: the effect of hunger on consumers' visual attention towards bread and the role of time orientation. Food Quality and Preference 2021;88:104079.

[67] Stockburger J, Schmalzle R, Flaisch T, Bublatzky F, Schupp HT. The impact of hunger on food cue processing: an event-related brain potential study. Neuroimage 2009;47(4):1819–29.

[68] Mridha Z, de Gee JW, Shi Y, Alkashgari R, Williams J, Suminski A, et al. Graded recruitment of pupil-linked neuromodulation by parametric stimulation of the vagus nerve. Nat Commun 2021;12(1):1539.

[69] Sharon O, Fahoum F, Nir Y. Transcutaneous vagus nerve stimulation in humans induces pupil dilation and attenuates alpha oscillations. J Neurosci 2021;41(2):320–30.

[70] Collins L, Boddington L, Steffan PJ, McCormick D. Vagus nerve stimulation induces widespread cortical and behavioral activation. Curr Biol 2021;31(10):2088–20898 e3.

[71] Riedl V, Utz L, Castrillon G, Grimmer T, Rauschecker JP, Ploner M, et al. Metabolic connectivity mapping reveals effective connectivity in the resting human brain. Proc Natl Acad Sci U S A 2016;113(2):428–33.

[72] Henri-Bhargava A, Stuss DT, Freedman M. Clinical assessment of prefrontal lobe functions. Continuum (Minneap Minn) 2018;24(3):704–26. BEHAVIORAL NEUROLOGY AND PSYCHIATRY.

[73] Orr JM, Smolker HR, Banich MT. Organization of the human frontal Pole revealed by large-scale DTI-based connectivity: implications for control of behavior. PLoS One 2015;10(5):e0124797.

[74] Liu H, Qin W, Li W, Fan L, Wang J, Jiang T, et al. Connectivity-based parcellation of the human frontal pole with diffusion tensor imaging. J Neurosci 2013;33(16):6782–90.

[75] Moayedi M, Salomons TV, Dunlop KA, Downar J, Davis KD. Connectivity-based parcellation of the human frontal polar cortex. Brain Struct Funct 2015;220(5):2603–16.

[76] Mansouri FA, Buckley MJ, Mahboubi M, Tanaka K. Behavioral consequences of selective damage to frontal pole and posterior cingulate cortices. Proc Natl Acad Sci U S A 2015;112(29):E3940–9.

[77] Rushworth MF, Kolling N, Sallet J, Mars RB. Valuation and decision-making in frontal cortex: one or many serial or parallel systems? Curr Opin Neurobiol 2012;22(6):946–55.

[78] Rushworth MF, Noonan MP, Boorman ED, Walton ME, Behrens TE. Frontal cortex and reward-guided learning and decision-making. Neuron 2011;70(6): 1054–69.

[79] Mesulam MM. From sensation to cognition. Brain 1998;121(Pt 6):1013–52.

[80] Levinthal DJ, Strick PL. Multiple areas of the cerebral cortex influence the stomach. Proc Natl Acad Sci U S A 2020;117(23):13078–83.

[81] Fedorova TD, Knudsen K, Hartmann B, Holst JJ, Viborg Mortensen F, Krogh K, et al. In vivo positron emission tomography imaging of decreased para-sympathetic innervation in the gut of vagotomized patients. Neuro-gastroenterol Motil 2020;32(3):e13759.

[82] Cechetto DF, Saper CB. Evidence for a viscerotopic sensory representation in the cortex and thalamus in the rat. J Comp Neurol 1987;262(1):27–45.

[83] Menon V, Uddin LQ. Saliency, switching, attention and control: a network model of insula function. Brain Struct Funct 2010;214(5–6):655–67.

[84] Evrard HC. The organization of the primate insular cortex. Front Neuroanat 2019;13:43.

[85] Sclocco R, Fisher H, Staley R, Han K, Mendez A, Bolender A, et al. Cine gastric MRI reveals altered Gut-Brain Axis in Functional Dyspepsia: gastric motility is linked with brainstem-cortical fMRI connectivity. Neurogastroenterol Motil 2022:e14396.

[86] Zhang Y, Lu T, Dong Y, Chen Y, Chen JDZ. Auricular vagal nerve stimulation enhances gastrointestinal motility and improves interstitial cells of Cajal in rats treated with loperamide. Neurogastroenterol Motil 2021:e14163.

[87] Wang Y, Li SY, Wang D, Wu MZ, He JK, Zhang JL, et al. Transcutaneous auricular vagus nerve stimulation: from concept to application. Neurosci Bull 2021;37(6):853–62.

[88] Altınkaya Z, Öztürk L, Büyükgüdük İ, Yanık H, Yılmaz DD, Yar B, et al. Non-invasive vagus nerve stimulation in a hungry state decreases heart rate variability and wanting of a palatable drink. bioRxiv 2022. https://doi.org/10.1101/2022.05.18.492424.

[89] Legrand N, Nikolova N, Correa C, Brændholt M, Stuckert A, Kildahl N, et al. The heart rate discrimination task: a psychophysical method to estimate the accuracy and precision of interoceptive beliefs. Biol Psychol 2022;168:108239. https://doi.org/10.1016/j.biopsycho.2021.108239.