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The impact of acute transcutaneous auricular vagus nerve stimulation on food cue reactivity in healthy humans

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Für meine Familie.

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Abbreviation	Meaning
ABVN	Auricular branch of the vagus nerve
BMI	Body mass index
CCK	Cholecystochinin
CE	Conformité Européenne
cVNS	Cervical vagus nerve stimulation
DA	Dopamine
DMN	Dorsal motor nucleus
EAT	Effort allocation task
FCR	Food cue reactivity
MDD	Major depression disorder
NAcc	Nucleus accumbens
OFC	Orbitofrontal cortex
NTS	Nucleus tractus solitarii
SN	Substantia nigra
taVNS	Transcutaneous auricular vagus nerve stimulation
VAS	Visual analogue scale
vmPFC	Ventromedial prefrontal cortex
VNS	Vagus nerve stimulation
VTA	Ventral tegmental area
WtHR	Waist-to-height-ratio

Statistic abbreviation	Meaning
BF_{10}	Bayes factor for the alternative hypothesis
M	Mean
CI	Confidence interval
SEM	Standard error of the mean
±	Standard deviation

1. Introduction

Note: Parts of the results presented in this manuscript have already been published (Müller, Teckentrup, Kühnel, Ferstl, & Kroemer, 2022).

In our modern world with food available at almost all time, individuals tend to consume beyond their needs. This seems to conflict with our society's ideal of beauty: being skinny. Not surprisingly, dietary topics are ever-present in our daily life. We are facing commercials that suggest how to lose weight and hear people discussing about which diet works best. Conversely, "most attempts to lose weight are not successful because it is hard to resist food that we like (de Araujo, Schatzker, & Small, 2019; Lowe et al., 2009)." (Müller et al., 2022, p. 1). How is it that the desire to consume certain foods is strong enough to let us forget about the adverse consequences, to let us ignore the knowledge that we will feel guilty after having given up on our dietary intentions? Considering the development of disproportionate food intake and a worldwide drastically increased prevalence of obesity (Collaborators, 2017; Val-Laillet et al., 2015), there has been increasing interest in the physiological mechanisms underlying eating behavior.

"Intriguingly, the vagus nerve has been shown to play an essential role in the regulation of food intake by facilitating gut-brain interactions (Berthoud, 2008; Breit, Kupferberg, Rogler, & Hasler, 2018; Cork, 2018; de Araujo, Ferreira, Tellez, Ren, & Yeckel, 2012; de Lartigue, 2016)" (Müller et al., 2022, p. 1). For instance, vagal signaling provides information about gastric stretch and digested nutrients to the brain (Williams et al., 2016). In this context, a desensitization of vagal fibers due to a high caloric diet is thought to result in further overeating as physiological satiating feedback signals are disturbed (de Lartigue, 2016). Apart from mere homeostatic regulation, vagal transmission was found to more broadly affect motivational behavior (Neuser et al., 2020) and reward reinforcement learning (Kühnel et al., 2020), indicating a vital modulatory role of the vagus nerve in (food) reward systems.

Interestingly, vagus nerve stimulation (VNS) has been shown to modulate food intake and body weight in both humans (Abubakr & Wambacq, 2008; Burneo, Faught, Knowlton, Morawetz, & Kuzniecky, 2002; Pardo et al., 2007) and

animal models (Bugajski et al., 2007; Gil, Bugajski, & Thor, 2011; Roslin & Kurian, 2001; Sobocki, Krolczyk, Herman, Matyja, & Thor, 2005; Yao et al., 2018). However, it remains unclear how exactly vagal stimulation causes the observed changes in food intake and body weight. “To close this gap, we examined subjective cue-induced food liking and wanting [during transcutaneous auricular vagus nerve stimulation (taVNS)] in healthy participants. Cue-induced ratings reflect the rewarding properties of food which has been repeatedly shown to be associated with food intake (Parker et al., 2004; Rogers & Hardman, 2015). […] To measure the effects of taVNS on food liking and wanting, we used a food cue reactivity (FCR) task including subjective ratings of food pictures. We hypothesized that taVNS might reduce cue-induced wanting for food since vagal afferent signals contribute to a physiological feedback loop terminating intake after a meal (de Lartigue, 2016)“ (Müller et al., 2022, p. 2).

1.1 The vagus nerve is deeply involved in homeostatic food intake regulation

The vagus nerve is the tenth and longest cranial nerve, given its name (“wandering nerve”) due to its vast dispersion (Yuan & Silberstein, 2016). Vagal neurons arise from the brainstem and spread through the head, neck, chest, and abdomen (Breit et al., 2018; see Müller et al., 2022). Intriguingly, information is conveyed bidirectionally through the vagus nerve. Efferent fibers promote digestion whereas afferent fibers are part of a feedback loop that “provides information about meal sizes and digested nutrients to appetite and satiety centers in the brain (Berthoud, 2008; Bonaz, Picq, Sinniger, Mayol, & Clarençon, 2013; Breit et al., 2018; Browning, Verheijden, & Boeckxstaens, 2017; Kaniusas et al., 2019)” (Müller et al., 2022, p. 1).

1.1.1 Efferent vagal signaling

Efferent vagal signals from the brain to the peripheral organs mostly interface with the parasympathetic nervous system and contribute to the

autonomic control of heart, lungs and part of the gastrointestinal tract including the stomach, the intestines, and the hindgut until descending colon. Besides, vagal motoneurons innervate muscles in the pharynx and larynx with origin in the nucleus ambiguous (Kaniusas et al., 2019). Parasympathetic neurons arise from the dorsal motor nucleus (DMN) in the brainstem (Bonaz et al., 2013; Breit et al., 2018) innervating heart, lungs, and the gastrointestinal tract (Kaniusas et al., 2019). Although the enteric nervous system works autonomically, the central nervous system has a strong modulatory impact. Vagal efferent fibers densely innervate the stomach and become less numerous in more distal parts of the gastrointestinal tract (Browning et al., 2017). Their activation leads to a broad range of physiological alterations in preparation for food intake and digestion. Here, a cholinergic release in vagal neurons promotes the contraction of gastric and intestinal smooth muscles (Travagli & Anselmi, 2016) as well as the secretion of gastric acid and other digestive liquids like pancreatic juice and bile acids (Pelot & Grill, 2018). Furthermore, the intestinal blood flow is increased due to vessel dilatation and glandular secretion is stimulated (Breit et al., 2018).

1.1.2 Afferent vagal signaling

Although the vagus nerves are predominantly known for their contribution to the parasympathetic nervous system, over 90% of the vagal fibers are afferent (Breit et al., 2018), conveying information from peripheral organs to the central nervous system. For instance, fibers originating in the abdomen provide information about digested nutrients as a feedback signal to the brain, routed via the inferior (nodose) ganglia to the nuclei tractus solitarii (NTS) in the brainstem (Berthoud & Neuhuber, 2000; Bonaz et al., 2013; Cork, 2018; de Lartigue, 2016). Numerous connections between the NTS and further brain regions are implicated in digestion, energy homeostasis and appetite such as the DMN (de Lartigue, 2016), the arcuate nucleus (Breit et al., 2018; Palmiter, 2007; Volkow, Wang, & Baler, 2011), the lateral hypothalamus (Dagher, 2012; Hopkins, Blundell, Halford, King, & Finlayson, 2000; Palmiter, 2007; Volkow et al., 2011) and the amygdala (Breit et al., 2018; Howland, 2014). Beside the NTS, there are vagal afferent

projections to the area postrema and trigeminal nuclei (Berthoud & Neuhuber, 2000).

Two functional phenotypes of vagal afferent fibers can be distinguished that either promote or inhibit food intake depending on the expressed receptors and neuropeptides (de Lartigue, 2016). Given the enormous plasticity of this system, the expression of receptors and neuropeptides changes based on the feeding status whereby vagal activation can have both orexigenic or anorexigenic effects. In lean individuals, after a meal, the expression of anorexigenic neuropeptides in vagal afferent fibers is increased (de Lartigue, 2016; de Lartigue, Dimaline, Varro, & Dockray, 2007). Vagal anorexigenic fibers are activated mechanically by stomach distension and chemo-sensitively by the digested nutrients (Berthoud & Neuhuber, 2000). This feedback information is conveyed to the brain and leads to an inhibition of food intake. Remarkably, chronic high-caloric diets can result in a disturbance of these feedback mechanisms which might contribute to obesity by further enhancing overeating (de Lartigue, 2016). Moreover, post-ingestive (vagally-transmitted) homeostatic signals have been found to modulate food preferences (de Araujo, Lin, Veldhuizen, & Small, 2013; Tan et al., 2020). Taken together, these findings strongly indicate that vagal afferent signaling crucially contributes to homeostatic eating behavior.

1.1.3 Interactions of vagal signaling and metabolic hormones

Beyond mere neural transmission, vagal afferent signaling is modulated by various metabolic hormones which contributes to a finely tuned homeostatic regulation of food intake (de Lartigue, 2016; Morton, Cummings, Baskin, Barsh, & Schwartz, 2006; Palmiter, 2007).

For instance, Cholecystochinine (CCK) is produced by endocrinologically active cells in the duodenum’s mucosa that are sensitive to digested nutrients, mainly fatty acids (Hopkins et al., 2000). Its release jolts several physiological processes to support digestion such as the contraction of gallbladder (Roslin &

Kurian, 2001). Furthermore, CCK stimulates vagal afferents in the stomach and thereby seems to drive satiation (de Lartigue, 2016; Roslin & Kurian, 2001). Effects of CCK on vagal afferents are promoted by leptin, another satiating hormone (Baskin et al., 1999; de Lartigue, 2016). Leptin is released by adipose tissue and provides information about the body's fat stores (Hopkins et al., 2000; Palmiter, 2007). Moreover, leptin was shown to be short-term responsive to food intake. More precisely, after underfeeding periods, leptin levels were found to be diminished. Conversely, after overfeeding, leptin levels were found to be increased, suggesting that leptin provides a short-term feedback of the body's energy balance (Chin-Chance, Polonsky, & Schoeller, 2000). In lean individuals, both leptin and CCK seem to suppress food intake via vagal feedback pathways routed by nodose ganglia and NTS, subsequently affecting further relevant brain regions that are involved in homeostasis, appetite and digestion (de Lartigue, 2016). Notably, disturbances in leptin and CCK vagal signaling are thought to drive overeating and obesity (de Lartigue, Ronveaux, & Raybould, 2014). Accordingly, congenital leptin deficiency leads to enormous obesity (Montague et al., 1997). Interestingly, in these patients, leptin substitution was shown to be sufficient to induce a loss of body weight (Farooqi et al., 1999; Licinio et al., 2004). Analogously, in animal models, leptin injection to the ventral tegmental area (VTA; Hommel et al., 2006) as well as in the caudal brainstem (Grill et al., 2002) lead to decreased food intake whereas a leptin receptor knockout resulted in increased food intake (Hommel et al., 2006).

In contrast, ghrelin is produced in the fasting state and drives food intake by reducing the vagal stimulating effect of CCK as well as vagal sensitivity to stomach distension (de Lartigue, 2016). In the presence of ghrelin, vagal afferents predominantly express the orexigenic rather than the anorexigenic phenotype subsequently leading to a prolonged duration of food intake as well as increased meal sizes (de Lartigue, 2016). Accordingly, ghrelin receptor knockout in the vagal nodose ganglia of rats resulted in reduced meal sizes probably due to prolonged gastric emptying (Davis et al., 2020). In healthy humans, ghrelin administration has been shown to drastically increase food intake (Wren et al.,

2001) and food cue reactivity, i.e. brain responses to food pictures (Malik, McGlone, Bedrossian, & Dagher, 2008). High fasting ghrelin levels were found to be correlated with increasing cue-induced appetite ratings and brain responses as well (Kroemer, Krebs, Kobiella, Grimm, Pilhatsch, et al., 2013). To conclude, anorexigenic leptin and CCK as well as orexigenic ghrelin are well known to modulate vagal signaling. Conversely, chronic VNS was shown to affect serum levels of leptin as well as ghrelin in rodents (Gil et al., 2011), indicating that this interaction might partly mediate the effects of vagal signaling on eating behavior.

Beyond leptin and ghrelin, vagal signaling has been shown to affect insulin levels. In line with its parasympathetic function to prepare the body for digestion (Breit et al., 2018), efferent vagal signaling promotes glucose responsive insulin release from the pancreas (Meyers, Kronemberger, Lira, Rahmouni, & Stauss, 2016). In contrast, during afferent vagal stimulation, pancreatic insulin secretion was found to be suppressed, resulting in increased blood glucose levels (Meyers et al., 2016; Stauss, Stangl, Clark, Kwitek, & Lira, 2018). In general, insulin is known to provide anorexigenic feedback signals to the central nervous system (Baskin et al., 1999; Morton et al., 2006). Accordingly, intraventricular insulin injection was shown to reduce food intake as well as body weight (Baskin et al., 1999; Brief & Davis, 1984). Moreover, in animal models, disrupted insulin signaling due to dysfunctional insulin receptors resulted in increased food intake and body weight (Brüning et al., 2000). In line with this, serum insulin levels in healthy humans after an oral glucose challenge are negatively correlated with cue-induced appetite (Kroemer, Krebs, Kobiella, Grimm, Vollstädt-Klein, et al., 2013). As insulin is known to affect central nervous appetite homeostatic centers in the hypothalamus (Pardini et al., 2006) with further connections to the vagal NTS (Baskin et al., 1999), insulin actions are highly likely to contribute to vagal modulation of food intake regulation.

To conclude, metabolic hormones as well as vagal afferent signaling both collaborate to ensure a finely tuned homeostatic regulation. Interestingly, apart from mere homeostatic circuitries, another intersection of vagal and metabolic

food intake regulation is given by their close link to motivational and reward-evaluating brain networks where neural computations related to dietary decision-making take place (de Araujo et al., 2012; de Araujo et al., 2019; Palmiter, 2007).

1.2 Implications of vagal signaling and reward networks

Concerning reward evaluation and dietary decision-making, dopaminergic (DA) signaling plays an important role. Two different functional dopaminergic neural circuitries, both implicated in feeding behavior, can be distinguished (Palmiter, 2007). On the one hand, DA levels seem to track caloric intake like a sensor in order to tune food intake according to physiological needs (de Araujo et al., 2012; Tellez et al., 2016). Here, the arcuate nucleus, lateral hypothalamus and periventricular nucleus have been identified as hotspots to integrate peripheral signals in food intake regulation (Baik, 2013; Palmiter, 2007). On the other hand, mesencephalic DA release is known to be essential for reward and behavioral reinforcement (Baik, 2013; Berridge, 2009; Palmiter, 2007; Tellez et al., 2016). Even though implications of DA signaling in reward are highly complex and not fully understood up to date, the role of dopamine to provide a reward prediction error signal is well established (Schultz, 2016). More precisely, dopaminergic activity encodes whether rewards, including food, occur as predicted based on previous associations with certain cues (Schultz, 2016).

From an anatomical perspective, there are two main mesolimbic dopaminergic pathways. Firstly, DA neurons in the ventral tegmental area (VTA) project to the nucleus accumbens (NAcc) and limbic areas. This pathway is implicated in motivational processes (Baik, 2013) and reinforcement learning as well as learned appetitive behavior (Fields, Hjelmstad, Margolis, & Nicola, 2007).

Secondly, DA transmission in the nigrostriatal pathway from the substantia nigra to the dorsal striatum was shown to be essential for goal-directed behavior including feeding (Baik, 2013) as L-DOPA application selectively in the dorsal striatum in aphagic dopamine-deficient rodents sufficed to restore feeding and other goal-directed behaviors (Palmiter, 2008; Szczypka et al., 2001). In line with

this, DA release in the dorsal striatum has been shown to be associated with the desire to eat in healthy humans (Volkow et al., 2002). Moreover, DA signaling in the dorsal striatum was found to track the nutritional value of sugar, indicating that the dorsal striatum provides energetic evaluations of food opportunities to neural appetite networks (Tellez et al., 2016). Accordingly, the dorsal striatum has been shown to be activated during the sight of high-caloric food pictures in obese humans (Rothemund et al., 2007). Possibly, the nutritional value of food cues encoded in DA striatal signaling is passed on to cortical regions such as the the orbitofrontal cortex (OFC) and ventromedial prefrontal cortex (vmPFC) where potential reward is calculated from various inputs and food choices are made (Dagher, 2012).

Different central nervous dopaminergic pathways, however, cannot be considered independent but rather seem to be interwoven as physiological signals affect both homeostatic as well as reward circuitries (Palmiter, 2007). Vagal signaling from the gut was found to elicit an activation of both described mesolimbic DA pathways. Recently, Fernandes et al. (2020) showed that post-ingestive sugar-sensing routed via the hepatic branch of the vagus nerve to dopaminergic neurons in the VTA modulated food-seeking behavior. Apart from that, Han et al. (2018) presented a neural pathway connecting vagal neurons in the gut with the substantia nigra, subsequently the dorsal striatum. Interestingly, this pathway was found to be linked to l activation of the right but not left nodose ganglion (Han et al., 2018).

Moreover, hunger and satiation hormones such as insulin, leptin and ghrelin were shown to activate receptors in the VTA (Figlewicz, Evans, Murphy, Hoen, & Baskin, 2003; Hommel et al., 2006; King, Isaacs, O'farrell, & Abizaid, 2011; Pardini et al., 2006) and the substantia nigra (Figlewicz et al., 2003), subsequently affecting DA signaling in the NAcc or the dorsal striatum (Fulton et al., 2006; Palmiter, 2007). Thus, homeostatic as well as reward centers likely collaborate and interact to affect dietary choices (Morton et al., 2006) and vagal signaling might be a crucial link between those two functional circuitries.

Consequently, it does not seem surprising that in obesity alterations of dopaminergic signaling occur. DA function has been found to be decreased as a consequence of chronic overeating and a high-fat diet (Val-Laillet et al., 2015). Possibly, DA deficiency further drives a disproportionately high-caloric intake to compensate for the extenuated dopaminergic response (P. M. Johnson & Kenny, 2010; Tellez et al., 2013; Wang et al., 2001). Vagal neuromodulation that subsequently affects dopaminergic brain networks might therefore help to restore physiological feeding behavior and maintaining a healthy body weight (Kaniusas et al., 2019; Palmiter, 2007).

1.3 Vagus nerve stimulation (VNS) affects body weight

In line with its implications in physiological feedback loops as well as reward circuitries, VNS has been shown to affect body weight in several preclinical and clinical studies, indicating a potential therapeutical option to treat metabolic disorders such as obesity (R. L. Johnson & Wilson, 2018).

1.3.1 taVNS: A novel tool to non-invasively stimulate the vagus nerve

There are diverse approaches to target the vagal circuit for neuromodulation in humans. Originally, implanted electrodes were used to invasively stimulate the cervical vagal trunk. Since 1997, cervical vagus nerve stimulation (cVNS) is an FDA-approved treatment for drug-resistant epilepsy, followed by another approval in 2005 for drug-resistant depression in adult patients (Bonaz et al., 2013; Howland, 2014; R. L. Johnson & Wilson, 2018). Apart from these established therapeutic purposes, VNS might also provide a potent treatment in chronic inflammatory diseases and pain disorders and metabolic disorders including obesity (Bonaz et al., 2013; R. L. Johnson & Wilson, 2018).

Transcutaneous auricular vagus nerve stimulation (taVNS) was developed as a useful tool to non-invasively target the auricular branch of the vagus nerve (ABVN) which innervates the cymba conchae of the external ear (Ellrich, 2011;

Peuker & Filler, 2002). taVNS, like invasive cVNS, has been proven to improve symptoms in patients with epilepsy (Bauer et al., 2016; Stefan et al., 2012) or major depression disorder (MDD; Fang et al., 2016; Liu et al., 2016; Trevizol et al., 2015). Moreover, the NEMOS taVNS device (see 2.3; Figure 1) is certified for the treatment of chronic pain as well as anxiety (Farmer et al., 2021). Notably, auricular electroacupuncture has been shown to reduce body weight in obese females (Schukro, Heiserer, Michalek-Sauberer, Gleiss, & Sator-Katzenschlager, 2014), indicating that taVNS might show an impact on body weight as well.

1.3.2 taVNS targets brain regions that are implicated in eating behavior

Comparable effects of taVNS and cVNS can be explained by the activation of similar brain networks such as the NTS and subsequent projections (Frangos, Ellrich, & Komisaruk, 2015; Yakunina, Kim, & Nam, 2017). Interestingly, several brain regions targeted by cVNS as well as taVNS are deeply involved in appetite and feeding behavior (Frangos et al., 2015). External cues such as the sight or smell of food lead to an activation of the amygdala and insula (Dagher, 2012; Tang, Fellows, Small, & Dagher, 2012). Additionally, interoceptive cues affecting appetite such as hunger or nausea are routed via the insula as well (Dagher, 2012). Moreover, the hypothalamus and dopaminergic neurons in the midbrain are implicated in the integration of internal cues as they express receptors for blood circulation neuropeptides and hormones (Dagher, 2012; de Araujo et al., 2013; Palmiter, 2007; Volkow et al., 2011). Exteroceptive and interoceptive information is transferred to the OFC and vmPFC and taken into consideration when the motivational value to consume a certain food is computed and food choices are being made (Dagher, 2012).

For dietary decision-making, dopaminergic signaling seems to be essential, given that brain regions implicated in appetite and feeding behavior are interconnected with dopaminergic midbrain neurons originating in the VTA and the SN (Dagher, 2012). Consistent with these findings, it has been shown that taVNS alters firing of dopaminergic midbrain neurons (Alicart et al., 2020) as well as activity in the amygdala, insula, hypothalamus and OFC (Alicart et al.,

2020; Frangos et al., 2015; T. Kraus et al., 2007; Liu et al., 2016) indicating that it may modulate food cue processing and reward-based (dietary) decision-making.

1.3.3 Animal models support weight-decreasing effects of VNS

In line with the vital role of the vagus nerve in the regulation of food intake, it does not seem surprising that VNS was shown to affect body weight. Interestingly, most animal studies delivered clear results in favor of weight loss due to VNS. Accordingly, rodents treated with low-frequency VNS presented weight loss or decreased weight gain, decreased food intake and a loss of body fat stores (Bugajski et al., 2007; Gil et al., 2011; Yao et al., 2018). Likewise, dogs showed weight loss and a drastically reduced food intake (Roslin & Kurian, 2001). Obese minipigs presented reduced food consumption and decreased craving for sweet foods as well (Val-Laillet, Biraben, Randuineau, & Malbert, 2010). Intriguingly, another study on pigs reported an alteration in body composition after VNS with decreased body fat stores although metabolism remained unaffected (Sobocki et al., 2005). Even during a high- caloric diet, VNS reduced body weight and visceral fat in rats (Bugajski et al., 2007; Gil et al., 2011; Li et al., 2015).

1.3.4 Equivocal research on VNS effects in humans

In contrast to preclinical work, human research into effects of VNS on food intake and body weight is inconclusive to date. Interestingly, both low frequency VNS as well as vagal blockade due to high frequency stimulation were shown to affect body weight (de Lartigue, 2016; Pelot & Grill, 2018). A subdiaphragmatically implanted high frequency VNS device (VBLOC) that likely blocks the conduction of action potentials was FDA-approved for obesity in 2015 (Food and Drug Administration, 2015). VBLOC was shown to induce weight loss in obese participants even though it was less effective compared to bariatric surgery (Apovian et al., 2017; Ikramuddin et al., 2014; Sarr et al., 2012).

Regarding low frequency VNS in humans, the clinical studies' results vary considerably (Pelot & Grill, 2018). "Inconclusive results in humans might be

explained by differences in stimulation protocols (Bugajski et al., 2007; Gil et al., 2011; Roslin & Kurian, 2001; Sobocki et al., 2005; Val-Laillet et al., 2010), differences in the anatomical location the stimulation is applied to (Bodenlos et al., 2014; Ikramuddin et al., 2014), or sample characteristics (Bodenlos et al., 2007; Bodenlos et al., 2014; Pardo et al., 2007)" (Müller et al., 2022, p. 2). Several retrospective studies observed weight loss during chronic VNS in patients with depression (Pardo et al., 2007) or epilepsy (Burneo et al., 2002), whereas others found VNS to be rather ineffective in causing weight changes. "One study reported altered wanting for sweet foods due to acute cervical VNS in depressed patients (Bodenlos et al., 2007)" (Müller et al., 2022, p. 2). Intriguingly, whether the stimulation leads to an increase or decrease in craving, seemed to be determined by modulating factors, e.g. lower BMI was associated with an increase in craving for sweet foods (Bodenlos et al., 2007).

However, recent studies observed no alteration of food consumption during acutely applied taVNS (Alicart et al., 2020; Obst, Heldmann, Alicart, Tittgemeyer, & Münte, 2020; Öztürk, Büning, Frangos, De Lartigue, & Veldhuizen, 2020). Interestingly, even though food intake remained unaffected, Öztürk et al. (2020) reported increased liking of low-fat in comparison to high-fat pudding samples, indicating an alteration of food hedonics. Moreover, Alicart et al. (2020) and Obst et al. (2020) provided evidence that taVNS affects the processing of visual (food) cues, indicating an impact on FCR and food reward in humans.

1.4 Food reward predicts feeding behavior

Given the described implications of vagal signaling on reward systems, one likely mechanism to mediate the reported weight loss during VNS is reduced food intake due to reduced food reward. Food reward has been shown to predict food intake and subsequently body weight (Boswell & Kober, 2016). To examine food reward in humans, FCR measurements provide a useful method. As individuals are continuously exposed to the sight of foods, feeding choices are mostly made based on visual cues (van der Laan, De Ridder, Viergever, &

Smeets, 2011). In line with this, the mere sight of foods already leads to a range of physiological processes in preparation for subsequent food intake and activates brain regions that are involved in eating behavior (Dagher, 2012; Tang et al., 2012; van der Laan, De Ridder, Viergever, & Smeets, 2011). Moreover, visual food cues such as pictures were found to have a similar predictive impact on food intake and body weight compared to real food stimuli (Boswell & Kober, 2016). Beyond that, food cues elicit comparable neural responses as triggers for addictive behaviors such as cigarettes in smokers (Tang et al., 2012). Consequently, visual food cues entail the potential to elicit food cravings that are associated with respective intake of the craved types of food (Chao, Grilo, White, & Sinha, 2014).

To measure food reward, it is important to assess *wanting* as well as *liking* for food as the two terms represent separable neural constructs that are both necessary for reward (Berridge, 2009; Nicola, 2016). Liking describes the hedonic value or pleasure of food, whereas wanting is referred to as the *incentive salience* to consume certain food, closely linked to mesolimbic processes in the brain (Berridge, 2009). Even if wanting and liking are usually intertwined, they are encoded in different brain regions and can occur independently (Berridge, 2009).

More precisely, wanting, referred to as a motivational process, was shown to strongly depend on dopaminergic brain activity (Berridge, 2009; Palmiter, 2007; Robinson, Sandstrom, Denenberg, & Palmiter, 2005). Accordingly, genetically engineered mice lacking dopamine were aphagic without showing any motivational behavior culminating in starvation unless they were continuously treated with L-DOPA to reestablish activity and feeding (Palmiter, 2008). In contrast, hyperdopaminergic mice showed higher food intake and stronger goal-directed behavior (Pecina, Cagniard, Berridge, Aldridge, & Zhuang, 2003).

Instead, liking is thought to persist in the complete absence of dopamine (Berridge & Robinson, 1998; Robinson et al., 2005). This was demonstrated by dopamine-depleted mice that still showed preference for sucrose (Palmiter, 2008) as well as hyperdopaminergic mice that failed to show stronger liking compared to wildtype animals (Pecina et al., 2003).

As they are both necessary for food reward and subsequently affect feeding behavior (Nicola, 2016; Parker et al., 2004; Rogers & Hardman, 2015), wanting and liking ratings of presented food pictures can be used to measure the effects of taVNS on perceived food reward. In this context, it is particularly interesting to look at differences of taVNS effects on food wanting compared to food liking since vagal signaling is known to interfere with dopaminergic motivational brain networks (de Araujo et al., 2012; Fernandes et al., 2020; Han et al., 2018; Neuser et al., 2020).

1.5 How does taVNS affect cue-induced subjective food reward?

To summarize, vagal afferent signaling has consistently been shown to modulate eating behavior. However, the acute impact of VNS on food intake in humans is mostly inconclusive (Pelot & Grill, 2018) and the mechanisms leading to weight loss during chronic VNS remain elusive (Burneo et al., 2002; Pardo et al., 2007). To close this gap, we investigated the impact of acute taVNS on cue-induced food reward in healthy participants by measuring subjective liking and wanting ratings of food and non-food pictures in a FCR task.

First, we aimed to investigate the effects of taVNS on wanting and liking ratings of food items compared to non-food pictures as a control condition. In line with a previous study reporting an effect of VNS on food craving (Bodenlos et al., 2007), we expected an alteration of food wanting as an indicator of food craving. We hypothesized that taVNS might diminish food wanting ratings, since vagal afferent signals contribute to a feedback loop terminating food intake after a meal (de Lartigue, 2016). Such anorexigenic effects could be imitated by the stimulation. In this regard, we expected food wanting ratings to be affected during taVNS given its close link to mesolimbic dopaminergic brain networks. “In contrast, we did not expect taVNS-induced changes in anticipatory liking ratings due to the absence of post-ingestive feedback signals in our design (Öztürk et

al., 2020)" (Müller et al., 2022, p. 2). Neither were liking and wanting for non-food items expected to show any taVNS-induced alterations.

Second, we aimed to assess time effects of taVNS as stimulation protocols in previous studies vary considerably (Farmer et al., 2021) and there is little knowledge about the dynamics of acute taVNS effects. Thus, we compared wanting and liking rating differences (taVNS vs. sham) over time.

Third, we aimed to identify potential modulators of taVNS-induced alterations such as different categories of food as within-subject factors. In line with a recent study suggesting an alteration of food preferences during taVNS (Öztürk et al., 2020), we assumed that taVNS may lead to decreased food reward of "unhealthy" sweet and high-caloric food items. Healthier dietary choices during taVNS might be a mechanism to induce weight loss as previously reported. Moreover, as potential between-subject modulating factors of eating behavior, we examined whether taVNS effects were dependent on the participants` BMI (as proposed by: Bodenlos et al., 2007; Bodenlos et al., 2014; Pardo et al., 2007), sex (Herman & Polivy, 2010), or the stimulated side (Han et al., 2018).

2. Methods

2.1 Participants

We collected data from a sample of 85 healthy participants who were invited for two measurement sessions in a single-blind randomized cross-over design (taVNS vs. sham). Parts of the presented study in this manuscript have been published in Müller et al. (2022) and sections of this paper are cited here.
"The study was approved by the local ethics committee according to the Declaration of Helsinki (reference number 235/2017BO1) and each participant gave written informed consent. Participants were included if they were between 18 and 40 years old, right-handed, and German speaking. Participants were excluded if they suffered from diabetes, severe brain injuries, schizophrenia, bipolar disorder, major depression disorder, a moderate or severe substance use disorder as well as any anxiety disorder (except specific phobia), obsessive compulsive disorder, posttraumatic stress disorder, somatic symptom disorder or any eating disorder within the past 12 months. To verify the participant's eligibility for the study, we conducted screenings by phone. The participants were compensated with either €32 or partial course credits plus additional money and breakfast as well as snacks depending on their performance in two other tasks that followed the FCR task. For the reported analyses, we excluded three participants because they did not complete the second session. Consequently, we analyzed data from 82 participants […]. Out of this sample, one group of participants (n = 42) received taVNS at the left ear, whereas a separate group of participants (n = 40) received taVNS at the right ear. This sample size (n = 82) allows to assess small to medium-sized effects (Cohen's d_z ~ .36) with a power of 1-β = .90" (Müller et al., 2022, p. 2).

Overall, our sample (n = 82) consisted of 36 men and 46 women (M_{age} = 24.4 ± 3.4; M_{BMI} = 23.07 ± 3.0; see Table 1). In addition to BMI, we calculated the participants' Waist-to-Height-Ratio (WtHR) as it is more related to the body's fat stores and therefore a more suitable predictive marker of cardiovascular disease

risk than the BMI (Schneider et al., 2010). In our sample, the WtHR was between 0.37 and 0.57 (M_{WtHR}= 0.45 ± 0.04, see Table 1).

Sample and stimulation characteristics

	Range	Mean (± standard deviation)
Age	19 – 37 years	24.4 ± 3.4 years
BMI	17.9 – 30.9 kg/m^2	23.07 ± 3.0 kg/m^2
WtHR	0.37 – 0.57	0.45 ± 0.04
Stimulation intensity taVNS	0.2 - 2.5 mA	1,2 mA
Stimulation intensity sham	0.5 - 3.1 mA	1,8 mA

Table 1: **Sample and stimulation characteristics.**Range, mean and standard deviation of age, BMI, Waist-to-Height-Ratio (WtHR) as well as stimulation intensities for transcutaneous auricular vagus nerve stimulaton (taVNS) and sham stimulation in our sample (*n* = 82)

2.2 Experimental procedure

The study's aim was to investigate effects of taVNS on subjectively rated food reward. In a single-blind randomized cross-over study, we collected wanting and liking ratings for food cues as well as non-food pictures (control condition) during taVNS vs. sham ("food cue reactivity" task). Apart from the stimulation condition, each of the two experimental sessions followed the same protocol. The order of the stimulation conditions was randomized, and the second session was planned to take place at approximately the same time during the day as the first one with a washout period of two to seven days in between. Participants were instructed to fast over night before coming to the lab, where the sessions took place between morning and noon. For breakfast, participants received cereal in a break during the experimental procedure. Water was provided ad libitum during the sessions.

After giving written informed consent at the beginning of the first session, the participants were asked to choose one amongst four different kinds of cereals that they would later receive as breakfast together with milk (almond milk was offered as a replacement). Here, participants were instructed that the snack points they earned during an effort allocation task (EAT, followed the FCR during the session) would be converted into the caloric amount of their breakfast and

possibly additional snacks. We continued with measuring anthropometric data such as height, weight, hip, and waist circumference as well as pulse rate and documented the last food and drink intake. To detect possible bradycardic taVNS effects (De Couck et al., 2017), pulse rate was measured once more after the taVNS or sham stimulation had been running for approximately 60 min. After the physiological measurements, participants were asked to do several visual analogue scale (VAS) ratings concerning their metabolic and affective state (reported in: Ferstl et al. (2020)). The same rating questions were repeated before (approximately 90 min after the baseline) and after breakfast (approximately 110 min after the baseline).

Next, the stimulation electrode was placed at the left or right ear and stimulation strength was adjusted with the help of a pain VAS (see 2.3). During the stimulation (taVNS or sham), participants did three tasks. To estimate food reward, participants had to rate their wanting and liking for various food pictures (Charbonnier, van Meer, van der Laan, Viergever, & Smeets, 2016) in a FCR task. Pictures of neutral objects such as office items (Charbonnier et al., 2016) were used as control condition. The FCR task started approximately 10 min after stimulation onset. Two other subsequent tasks investigating the motivation to work for reward (EAT; see Neuser et al., 2020) and reinforcement learning (see Kühnel et al., 2020) have been reported before. By doing the tasks, the participants could win monetary and caloric reward points. “After the tasks [and the second VAS questionnaire], there was a 10 min break when participants received their breakfast (cereal) based on ‘energy points’ in the second task” (Müller et al., 2022, p. 2). Moreover, in case of a sufficient number of energy points, participants could choose a chocolate bar to either eat it immediately or take it with them. In the end of each session, participants received additional cash based on their performance in the tasks. Furthermore, after having conducted both sessions, the participants received their compensatory fixed amount of money or course credits, respectively.

2.3 Vagus nerve stimulation device

Figure 1: **NEMOS Vagus nerve stimulation device** that we used for transcutaneous auricular vagus nerve stimulation.

taVNS was conducted using NEMOS by Cerbomed GmbH (Erlangen, Germany, see Figure 1). The device is CE approved and used for treating epilepsy and depression (Ellrich, 2011) as well as chronic pain and anxiety (Farmer et al., 2021). Vagal stimulation was performed with the electrodes placed on the cymba conchae of the external ear that is innervated by the ABVN (Peuker & Filler, 2002). For sham stimulation, the device was positioned upside down (see Figure 2), placing the electrodes at the ear lobe as proposed by previous studies (Frangos et al., 2015; T. Kraus et al., 2007; Öztürk et al., 2020) since the lobule of the auricle is not innervated by the vagus nerve (Peuker & Filler, 2002).

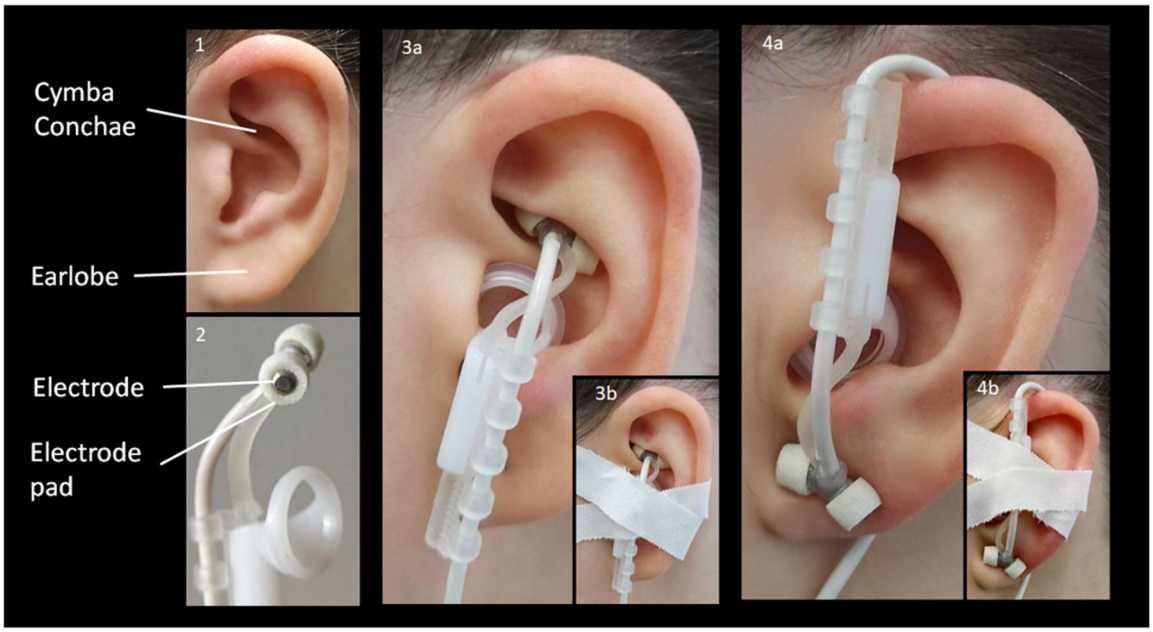

Figure 2**: Electrode placement for the two stimulation conditions.** 1: Important anatomical regions. 2: NEMOS stimulation device electrodes. 3: Electrode placement for transcutaneous auricular vagus nerve stimulation (taVNS). 4: Electrode placement for sham stimulation. (Müller et al., 2022)

"To ensure adequate skin contact, we rubbed the skin with alcohol and placed medical tape to secure the electrodes in place. For both conditions, the stimulation strength was individually adjusted. To this end, we used a pain VAS to track the participant's sensations during the stepwise increase of the stimulation strength (steps of 0.1 or 0.2 mA) starting at 0.1 mA. The individual intensity for each participant then corresponded to a "tingling" sensation below the pain threshold (Frangos et al., 2015). The stimulation strength for taVNS was M_{taVNS} [range] = 1.2 [0.2–2.5] mA and sham stimulation was M_{sham} [range] = 1.8 [0.5–3.1] mA" (Müller et al., 2022, p. 3; see Table 1).

As provided by NEMOS, the stimulation protocol was preset with a biphasic alternating current with a pulse width of 200-300 µs at 25 Hz resulting in stimulation phases of 30 s on – 30 s off (Farmer et al., 2021).

2.4 Food cue reactivity task

“Here, we investigated the effect of taVNS on cue-induced food liking (hedonic evaluation) and wanting (desire to eat) as both constructs capture the rewarding properties of food (Berridge, 2009; Finlayson, King, & Blundell, 2007) as a proxy of future food intake (Parker et al., 2004; Rogers & Hardman, 2015; Spence et al., 2016; Temple et al., 2009). To this end, we used a food cue reactivity task [..] with visual food cues. Participants viewed pictures of food and stationery non-food control pictures and rated their liking and wanting of these items” (Müller et al., 2022, p. 4).

The image set we used was provided by Charbonnier, van Meer, van der Laan, Viergever, and Smeets (2016), including 80 standardized pictures of food and 40 pictures of office supplies. The images were chosen by Charbonnier et al. (2016) from a larger group of pictures based on recognizability ratings from 449 adult volunteers originating in four different countries. To guarantee a consistent presentation, all pictures were taken in a photo studio from a defined distance and angle with every item placed on a homogenous white plate on a grey background (Charbonnier et al., 2016). Furthermore, Charbonnier et al. (2016) provided additional information on the food pictures, such as the caloric content, mean liking, perceived healthiness and estimated caloric content ratings from the volunteers in their study.

To compare wanting and liking of food with neutral objects, we selected 60 food images and 20 non-food images for each participant from the provided set of 120 pictures. Each image was presented twice during two separate runs (once per run). In half of the trials, participants had to rate their liking of the depicted item whereas in the other half, they had to rate their wanting. “To avoid systematic order confounds, we randomized the order of the ratings and images. Due to a minor error in the randomization script, the ratings were not fully balanced (one wanting, one liking rating per image) for all participants. However, since we are primarily interested in the contrast between taVNS and sham sessions, this error does not systematically affect the comparisons between sessions. The FCR task started approximately 5–10 min after stimulation onset. The images were shown for 1.5 s each. Then, participants viewed a black fixation

cross on a white screen (inter-stimulus interval) before the rating scale appeared on the screen for a maximum of 2 s. After the rating was submitted, another fixation cross was shown (inter-trial interval). To keep the rate of stimuli the same, the inter-trial interval was extended by the time that participants saved by pressing the button before the allotted 2 s had passed. Ratings were submitted by moving the left thumb joystick on an Xbox 360 controller. If participants did not submit the rating by pressing the (right thumb) A-button on the controller within 2 s, the last position on the scale was saved as rating. However, if participants did not move the joystick at all, such an unsubmitted rating was considered as invalid and removed from the analysis" (Müller et al., 2022, p. 4; see Figure 3).

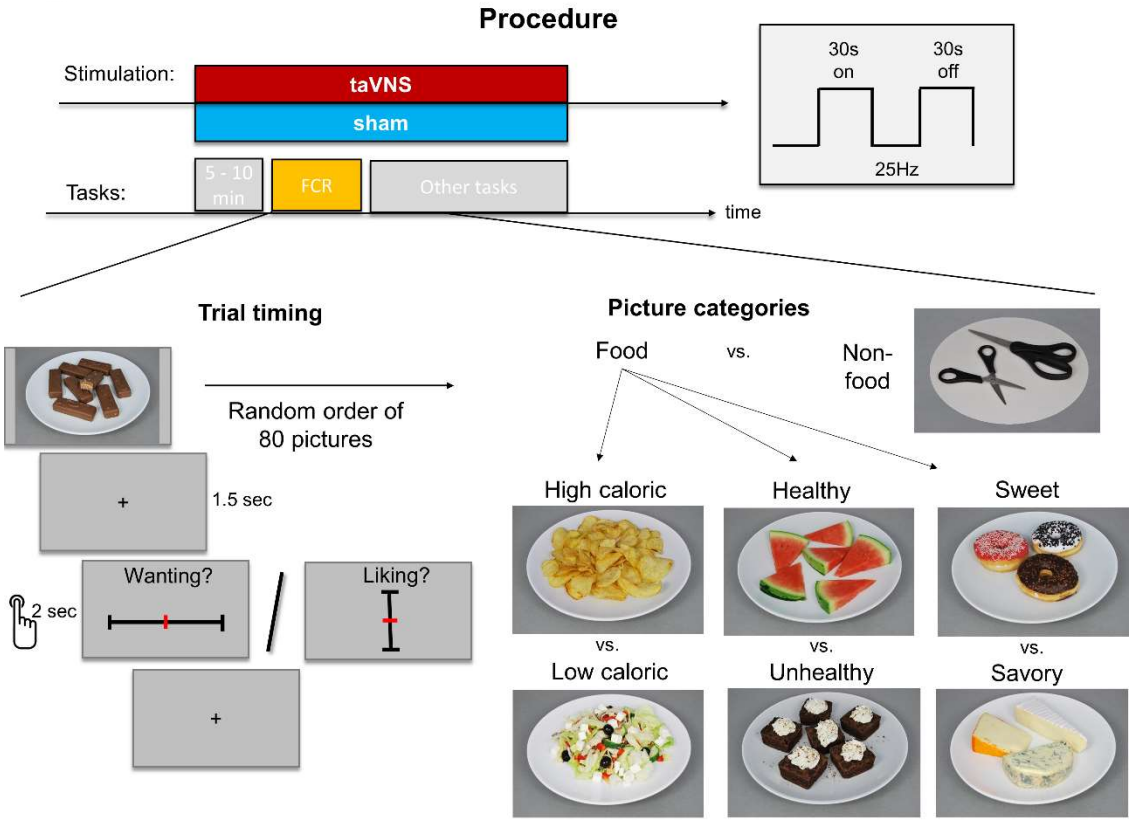

Figure 3: **Experimental procedure and task design.** "Experimental procedure and duty cycle. As part of the experimental sessions, participants completed a food cue reactivity (FCR) task, where they viewed pictures of various food and non-food items. Examples for the categories are provided that were used for further subgroup analyses. After participants viewed the pictures, they either rated their liking or wanting (each cue was shown twice [ensuring one liking and wanting rating for each picture]) on vertical and horizontal visual analog scales, respectively" (Müller et al., 2022, p. 3).

“To measure liking ratings, we used a vertically labeled hedonic (visual analogue) scale. Liking ratings ranged from - 100 (strongest disliking imaginable) to +100 (strongest liking imaginable; Lim, Wood, and Green (2009)). The participants were asked to ‘rate in the context of the full range of sensations that they have experienced in their life’ and were provided with five gradual anchors on the scale’s axis from which the two extremes were labeled” (Müller et al., 2022, p. 4).

To acquire wanting ratings, participants were asked to rate how much they wanted to obtain the shown item as a reward. To better differentiate the demanded constructs (liking versus wanting) we used a horizontal instead of a vertically labeled scale for wanting ratings allowing to rate between 0 (label at the very left side: “I did not want the item at all”) and 100 (label at the very right side: “I wanted the item really badly”) as negative values are not reasonable in the context of reward wanting.

2.5 Food items classifications

“To analyze a variation of stimulation effects on different kinds of food, we introduced several food classifications. Information about caloric content of the depicted items was provided by Charbonnier et al. (2016). For one picture (#50, Grissini bread sticks), the caloric density was not provided by the authors, so we calculated 418 kcal/100 g based on similar items” (Müller et al., 2022, p. 4).
Moreover, Charbonnier et al. (2016) provided ratings on mean liking, estimated caloric content and perceived healthiness on a 1-to-9-point hedonic scale by adults in four different countries. This information was used as a basis of the food classifications that we introduced for more fine-grained analyses.

First, we calculated the mean liking, estimated caloric content, and perceived healthiness for each food picture across countries. Next, we introduced the categories high- and low-caloric food as well as high and low perceived healthiness based on correlations of mean ratings and the mean estimated caloric content (see Figures 4 and 5).

Food with more than 180 kcal/100g was considered “high-caloric” whereas food with less than or equal to 180 kcal/100g was considered “low-caloric” (see Figure 5A). Moreover, food with a perceived healthiness rating higher than 5.5 was declared as “healthy”, respectively with a rating lower or equal to 5.5 as “unhealthy” (see Figure 5B). Furthermore, we created the food categories sweet and savory. By considering different properties of the depicted items, we aimed to assess whether taVNS modulates food preferences.

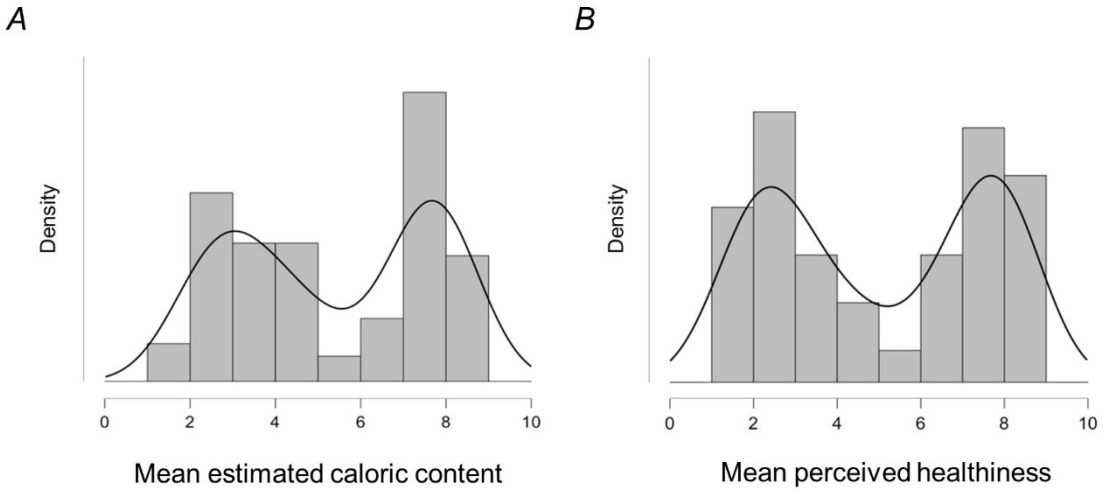

Figure 4: **Bimodal distribution of mean estimated caloric content and mean perceived healthiness of the study’s food picture set.** Charbonnier et al. (2016) provided rating data concerning the estimated caloric content (A) and perceived healthiness (B) of the study’s picture set. The bimodal mean rating distribution of food pictures indicates the classification in low- and high-caloric density as well as in high and low perceived healthiness.

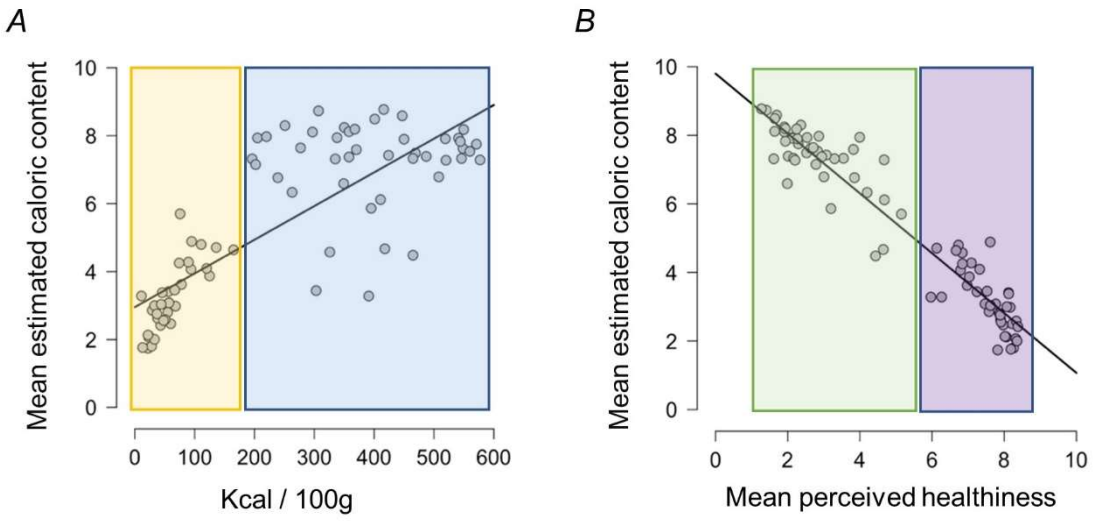

Figure 5: **Correlation of mean estimated caloric content with actual caloric content and mean perceived healthiness.** A: Correlation of actual caloric content and mean estimated caloric content of the study's food picture set (Charbonnier et al, 2015) indicates a cut-off of 180 kcal/100g to classify the categories "low-caloric" (yellow) and "high-caloric" food (blue). B: Correlation of mean perceived healthiness and mean caloric content of the study's food picture set (Charbonnier et al, 2015) indicates a cut-off of mean perceived healthiness = 5.5 to classify the categories "unhealthy" (green) vs. "healthy" (purple).

2.6 Behavioral data analyses

For the analyses presented in this manuscript, we used the same statistical methods and software as already published in Müller et al. (2022).

"To assess taVNS-induced changes in food wanting and liking, we ran one-sample t-tests on individual differences in average ratings between taVNS and sham sessions using both frequentist and Bayesian inference (i.e., equivalent to a paired t-test)" (Müller et al., 2022, p. 4). P-values ≤.05 were considered statistically significant.

As a measure of within-subject effect size, we calculated d_z:

$$dz = \frac{\text{mean difference between condtions}}{\text{standard deviation of mean difference scores}}$$ (Lakens, 2013)

"We used Bayesian inference to estimate the likelihood of the alternative hypothesis (taVNS changes cue-induced ratings) versus the null hypothesis (Quintana & Williams, 2018). Bayesian testing combines a prior distribution of the expected effect with a measured data distribution ("likelihood"). As a result, we obtained a posterior distribution that integrates the prior and the observed data.

Depending on the specification of the prior, a Bayes factor (BF) can be calculated. BF_{10} is defined as the ratio of the marginal likelihoods of the alternative hypothesis compared to the null hypothesis. Thus, a BF_{10} greater than one favors the alternative hypothesis whereas a BF_{10} lower than one favors the null hypothesis. Logically, the more extreme the BF is, the more conclusive is the evidence regarding the hypotheses that were defined a priori and BFs ~1 indicate that more data is necessary to provide conclusive evidence (Quintana & Williams, 2018)" (Müller et al., 2022, p. 4). Considering that the posterior distribution is dependent on the predefined prior, it is helpful to execute a Bayes factor robustness check that illustrates the Bayes factor as a function of the prior widths.

To conclude, Bayesian hypothesis testing can be conducted to evaluate whether non-significant effects based on classical significance testing favor the null hypothesis or whether there were too few data to detect an effect. Hence, Bayesian hypothesis testing provides a valuable tool in addition to classical significance testing (Quintana & Williams, 2018). To report relationships, we conducted Bayesian correlation analyses.

"We used two-sided tests for all effects of interest. Additionally, to test the directed hypothesis that food wanting would be decreased during active taVNS, we used a one-sided t-test. To ensure that our results are robust across different specifications of the analysis such as testing effects only in subsets of the data depending on the picture category, stimulation side, or sex, we performed multiverse analysis (Orben, Dienlin, & Przybylski, 2019). Multiverse analyses increase transparency of typically hidden data analysis choices (Lonsdorf et al., 2019) and therefore help evaluate the robustness of reported findings. To this end, we performed 80 post hoc analyses where we split the collected ratings according to stimulation side and sex (between-subject factors) as well as caloric density, perceived healthiness, and sweet versus savory foods (within-subject factors). Crucially, this approach prevents over-interpreting few significant results in very specific partitions of the data by comparing it with the distribution of other plausible specifications. Thereby, it becomes apparent whether such a significant result is an outlier compared to similar specifications or if the distribution across

many specifications supports a finding, making it more robust against minor changes in the analysis pipeline. Nonetheless, this approach still enables identification of robust effects that depend on one condition (e.g., many significant effects when only including women (Orben et al., 2019))" (Müller et al., 2022, p. 4).

2.7 Statistical software

"We collected data using Psychtoolbox v3 (Kleiner, Brainard, & Pelli, 2007) and preprocessed it in MATLAB v2018a. We conducted statistical tests and plotted results with JASP v0.09 – v.0.11 (JASP team, 2019) and R v3.6.0 (R Core Team, 2019). As predefined by JASP, we set the prior of the Cauchy scale parameter to 0.707. To avoid that the inference is strongly dependent on the scaling parameter, we ran a prior robustness check as well, testing plausible narrower and wider prior settings" (Müller et al., 2022, p. 4).

3. Results

Parts of the results presented in this manuscript have been published in Müller et al. (2022) and sections as well as figures of this paper are cited here.

3.1 No main effect of taVNS on liking and wanting

To examine taVNS main effects on food liking and wanting, we calculated mean ratings during taVNS and sham stimulation for each participant and used non-food pictures as a control condition. An overview of the results presented in this chapter has been published in Müller et al. (2022).

We found that mean liking ratings of food pictures were slightly higher during taVNS ($M_{taVNS\ (food\ liking)}$ = 19.42, $SEM_{taVNS\ (food\ liking)}$ = 1.42) compared to sham stimulation ($M_{sham\ (food\ liking)}$ = 18.44, $SEM_{sham\ (food\ liking)}$ = 1.68; see Figure 6). However, a one-sample Student's t-test performed in JASP (see Table 2) revealed that the mean food liking rating differences of taVNS compared to sham stimulation (*mean difference* $_{taVNS\ vs.\ sham\ (food\ liking)}$ = 0.98, *95%CI* [-2.00, 3.97]) were not significant (t = 0.657, df = 81, p = .513) with a small effect size (d_z = 0.073).

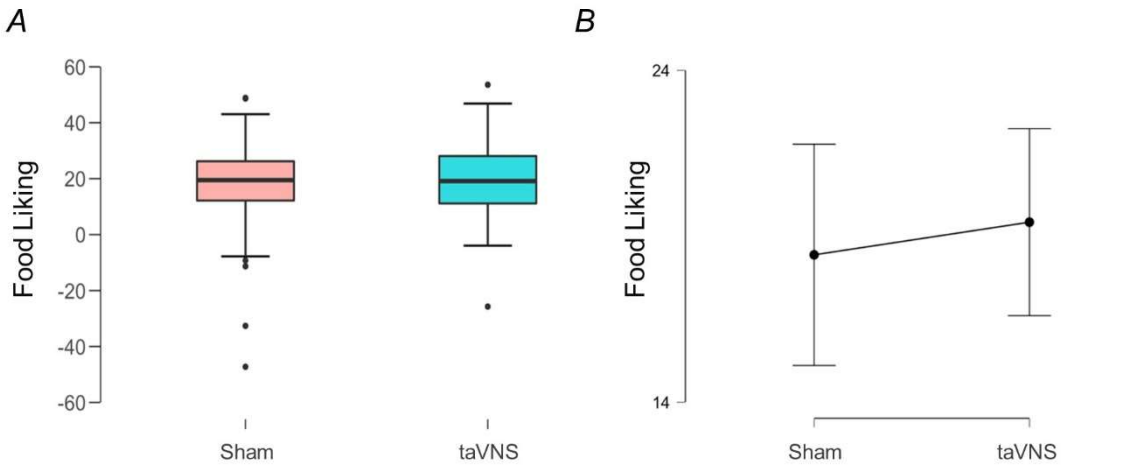

Figure 6: **No effect of taVNS on subjective cue-induced food liking.** A: Boxplots illustrate individual averages of food liking ratings during sham stimulation and transcutaneous auricular vagus nerve stimulation (taVNS; Müller et al., 2022) B: 95% confidence interval of average ratings during sham and taVNS.

taVNS-induced changes (taVNS – sham)

	t	df	p	Mean Difference	Lower 95% CI	Upper 95% CI	d_z	BF_{10}
Food liking	0.657	81	.513	0.98	-2.00	3.97	0.073	0.15
Food wanting	1.601	81	.113	1.75	-0.43	3.93	0.177	0.41
Non-food liking	1.501	81	.137	1.95	-0.64	4.53	0.166	0.36
Non-food wanting	0.211	81	.833	0.26	-2.18	2.69	0.023	0.12
Food vs. non-food liking difference	-0.615	81	.540	-0.96	-4.08	2.15	-0.068	0.15
Food vs. non-food wanting difference	0.979	81	.330	1.49	-1.54	4.52	0.108	0.19

Table 2**: No main effect of taVNS on cue induced liking and wanting ratings.** ”Results of a Student’s one-sample t-test as well as Bayesian inference evaluating the mean differences between taVNS [transcutaneous auricular vagus nerve stimulation] and sham stimulation and Bayes factor (BF_{10}) for food liking, food wanting, non-food liking and non-food wanting as well as food versus non-food wanting and liking differences” (Müller et al., 2022, p. 5, table modified)

To estimate the evidence for the alternative hypothesis that mean liking taVNS ratings were different compared to ratings during sham stimulation, we further conducted a Bayesian one-sample t-test. The corresponding BF_{10}= 0.15 suggests moderate evidence against an acute effect of taVNS on food liking. More precisely, the posterior distribution of the effect size δ showed a median of δ = 0.07 and a 95% credible interval [-0.14, 0.28] (see Figure 7, A). Moreover, the Bayes factor robustness check revealed that, even when the prior distribution is set more widely, evidence for the null hypothesis remained moderate to strong (see Figure 7, B). Thus, we conclude that taVNS does not acutely affect food liking.

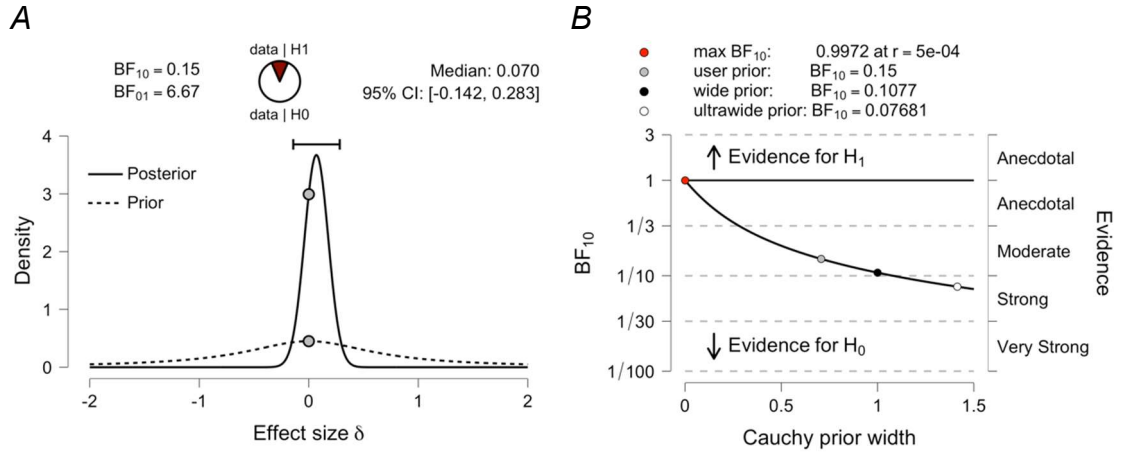

Figure 7: **Moderate evidence against an effect of taVNS on food liking.** A: Prior and posterior distribution of effects sizes of food liking rating differences during transcutaneous auricular vagus nerve stimulation (taVNS) compared to sham stimulation. B: The Bayes factor robustness check indicates moderate to strong evidence that there is no effect of taVNS on food liking (Müller et al., 2022).

We further compared food wanting ratings during taVNS and sham stimulation as well. Here, we found that mean wanting ratings were slightly higher during taVNS ($M_{taVNS\ (food\ wanting)}$ = 60.74, $SEM_{taVNS\ (food\ wanting)}$ = 1.13) compared to sham stimulation ($M_{sham\ (food\ wanting)}$ = 58.99, $SEM_{sham\ (food\ wanting)}$ = 1.33). However, mean food rating differences of taVNS compared to sham stimulation (*mean difference* $_{taVNS\ vs.\ sham\ (food\ wanting)}$ = 1.75, 95%CI [-0.43, 3.93]; see Figure 8) were not significant (t = 1.601, df = 81, p = .113) with a small effect size (d_z = 0.177; see Table 2). In a Bayesian one-sample t-test of mean food wanting rating differences between taVNS and sham stimulation, we observed BF_{10}= 0.41 given the default prior. This corresponds to anecdotal support for the null hypothesis that there is no acute effect of taVNS on food wanting. The posterior distribution of the effect size showed a median of δ = 0.17 and a *95% CI* [-0.04, 0.39] (see Figure 9, A). Moreover, the Bayes factor robustness check showed that with a very small Cauchy prior width, BF_{10} is close to one and even greater (see Figure 9, B). This indicates that data provided by the study is not conclusive to detect an effect or refute its presence. However, a very tight Cauchy prior width is not realistic in the context of our experiment. When we apply the default prior or wider priors, the evidence for the null hypothesis is anecdotal to moderate.

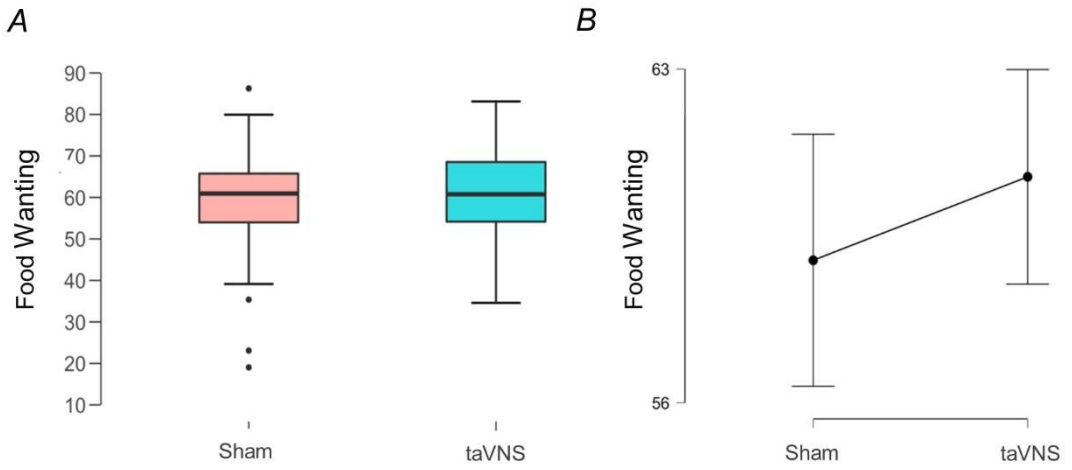

Figure 8**: No effect of taVNS on subjective cue-induced food wanting.** A: Boxplots illustrate individual averages of food wanting ratings during sham stimulation and transcutaneous auricular vagus nerve stimulation (taVNS; Müller et al., 2022) B: 95% confidence interval of average ratings during sham and taVNS.

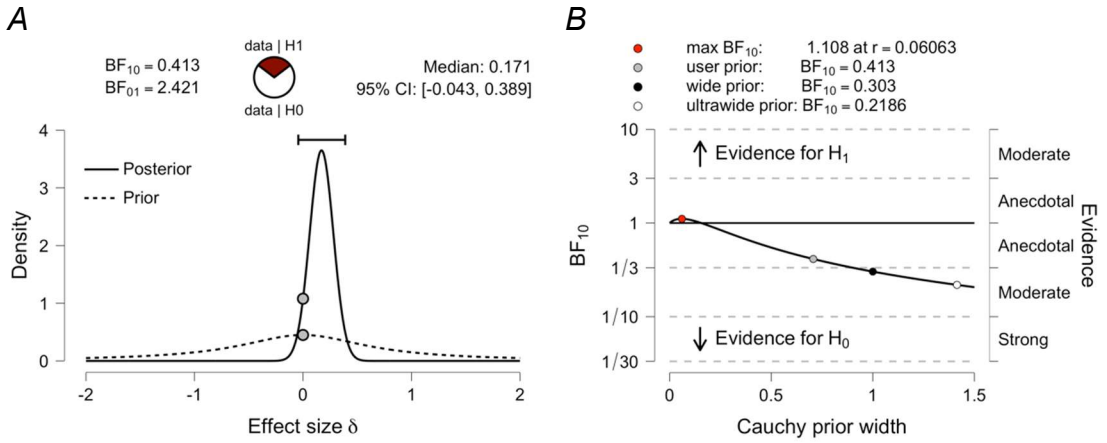

Figure 9: **Anecdotal evidence against an effect of taVNS on food wanting.** A: Prior and posterior distribution of effect sizes of food wanting rating differences during transcutaneous auricular vagus nerve stimulation (taVNS) compared to sham stimulation. B: The Bayes factor robustness check indicates anecdotal to moderate support against an effect of acute taVNS on food wanting (Müller et al., 2022).

As we hypothesized taVNS-induced decreases of subjective food wanting, we tested the directional alternative hypothesis that mean wanting ratings during taVNS were minor compared to sham stimulation. Contradictory, the $BF\text{-}_0 = 0.05$ indicated strong support for the null hypothesis (posterior distribution of effect size *δ* = -0.04, *95% CI* [-0.15, -0.00]; see Figure 10, A). Given that prior robustness analyses indicated strong or very strong evidence in favor of the null

hypothesis even with priors set otherwise (see Figure 10, B), we can confidently conclude that taVNS did not acutely decrease food wanting ratings.

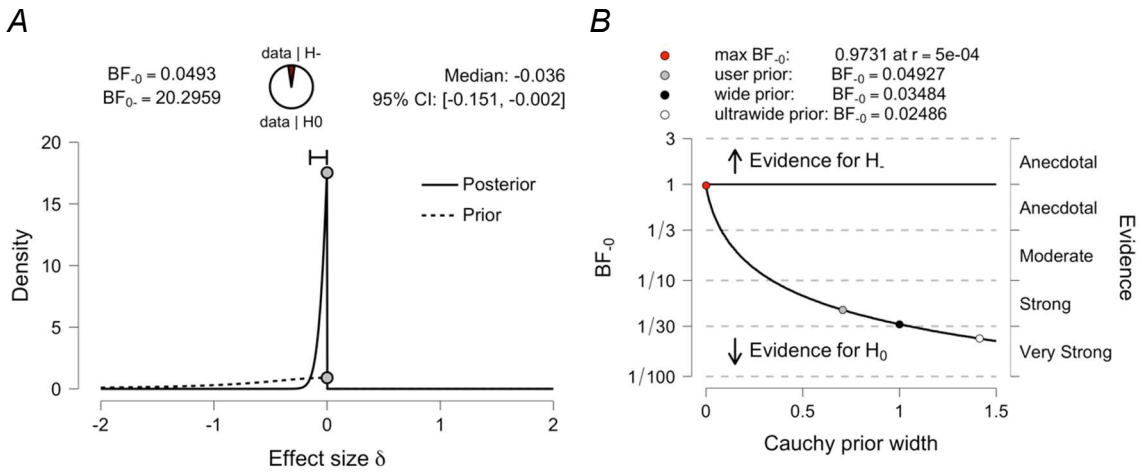

Figure 10: **Strong evidence that acute taVNS does not decrease food wanting** A: Prior and posterior distribution of effect sizes of food wanting ratings during transcutaneous auricular vagus nerve stimulation (taVNS) compared to sham stimulation considering a directional alternative hypothesis that taVNS decreases wanting ratings. B: Bayes factor robustness check indicates strong evidence against a decrease of food wanting during acute taVNS (Müller et al., 2022).

Collectively, our results indicate that there was no acute effect of taVNS on food wanting and liking. To compare food liking and wanting to liking and wanting of neutral objects as a control condition, we calculated each participant's mean ratings for non-food items as well.

When we analyzed food versus non-food rating differences independently of the stimulation condition (ratings during taVNS and sham stimulation combined; see Figure 11), we found that the differences between mean food and non-food ratings were significant for liking as well as wanting (*mean difference* $_{food\ vs.\ non\text{-}food\ liking}$ = 24.61, t = 10.923, df = 81, p < 0.001 and *mean difference* $_{food\ vs.\ non\text{-}food\ wanting}$ = 29.68, t = 12.547 df = 81, p <.001).

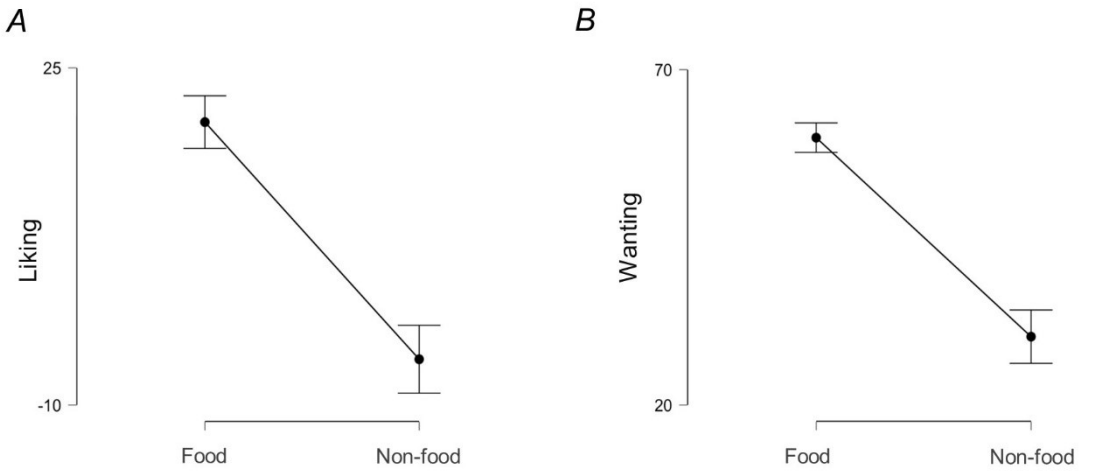

Figure 11: **Food pictures elicit greater liking and wanting compared to non-food pictures**. Individual averages and 95% confidence interval of food vs. non-food liking (A) and wanting (B) ratings for both stimulation conditions (transcutaneous auricular vagus nerve stimulation and sham stimulation) combined

To test whether mean rating differences of food versus non-food pictures were affected by the stimulation condition, we calculated mean differences (food – non-food ratings) during taVNS and sham stimulation (see Figure 12). We found that taVNS-induced alterations of the difference between food and non-food liking or wanting were not significant (*mean difference* $_{taVNS\ vs.\ sham\ (food\ -\ non\text{-}food\ liking)}$ = -0.96, t = -0.615, df = 81, p = .540 and *mean difference* $_{taVNS\ vs.\ sham\ (food\ -\ non\text{-}food\ wanting)}$ = 0.98, t = 0.979 df = 81, p = .330).

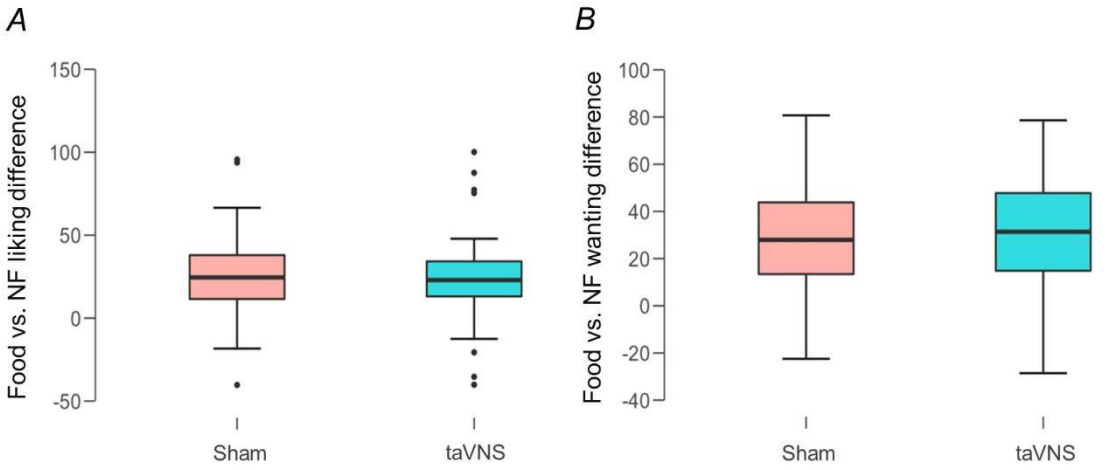

Figure 12: **Food vs. non-food rating differences do not considerably differ during taVNS compared to sham stimulation.** Boxplots illustrate individual averages of differences between food and non-food (NF) liking (A) and wanting (B) during sham stimulation and transcutaneous auricular vagus nerve stimulation (Müller et al., 2022).

Next, to analyze taVNS effects on non-food liking and wanting, we calculated each participant's mean ratings of non-food items. We found that non-food ratings were slightly higher during taVNS compared to sham stimulation for both liking and wanting ($M_{taVNS\ (non\text{-}food\ liking)}$ = -4.69, $SEM_{taVNS\ (non\text{-}food\ liking)}$ = 1.87, $M_{sham\ (non\text{-}food\ liking)}$ = -6.64, $SEM_{sham\ (non\text{-}food\ liking)}$ = 1.91, $M_{taVNS\ (non\text{-}food\ wanting)}$ = 30.39, $SEM_{taVNS\ (non\text{-}food\ wanting)}$ = 2.11, $M_{sham\ (non\text{-}food\ wanting)}$ = 30.14, $SEM_{sham\ (non\text{-}food\ wanting)}$ = 2.06; see Figure 13). However, mean non-food rating differences during taVNS versus sham stimulation were not significant (*mean difference* $_{taVNS\ vs.\ sham\ (non\text{-}food\ liking)}$ = 1.95, *95%CI* [-0.64, 4.53], t = 1.501, df = 81, p = .137 and *mean difference* $_{taVNS\ vs.\ sham\ (non\text{-}food\ wanting)}$ = 0.26, *95%CI* [-2.18, 2.69], t = 0.211, df = 81, p = .833) and presented a small size effect of d_z = 0.166 for non-food liking and d_z = 0.023 for non-food wanting.

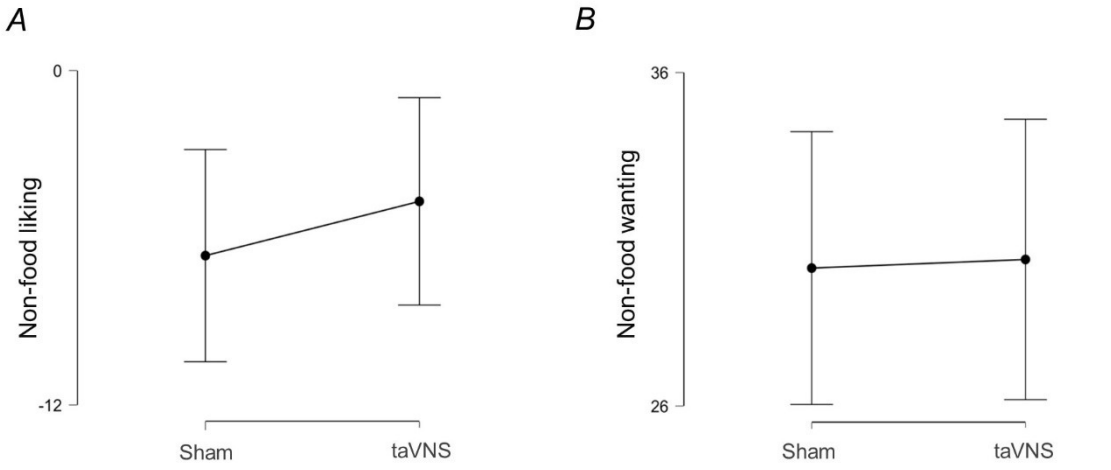

Figure 13: **No effect of taVNS on non-food liking or wanting.** Individual averages and 95% confidence interval of non-food liking (A) and non-food wanting (B) ratings during sham stimulation compared to transcutaneous auricular vagus nerve stimulation (taVNS)

Furthermore, we calculated a BF_{10} = 0.36 for liking of non-food pictures with a median posterior effect size of δ = 0.16 and a *95% CI* [-0.05, 0.38] (see Figure 14, A). For wanting rating differences of non-food pictures, we calculated a BF_{10} = 0.12 and a median posterior effect size of δ = 0.02 with a 95% *CI* of [-0.19, 0.23] (see Figure 14, C). These results indicate anecdotal to moderate evidence against an acute effect of taVNS on non-food liking (see Figure 14, B)

as well as moderate to strong support against an acute effect of taVNS on non-food wanting (see Figure 14, D).

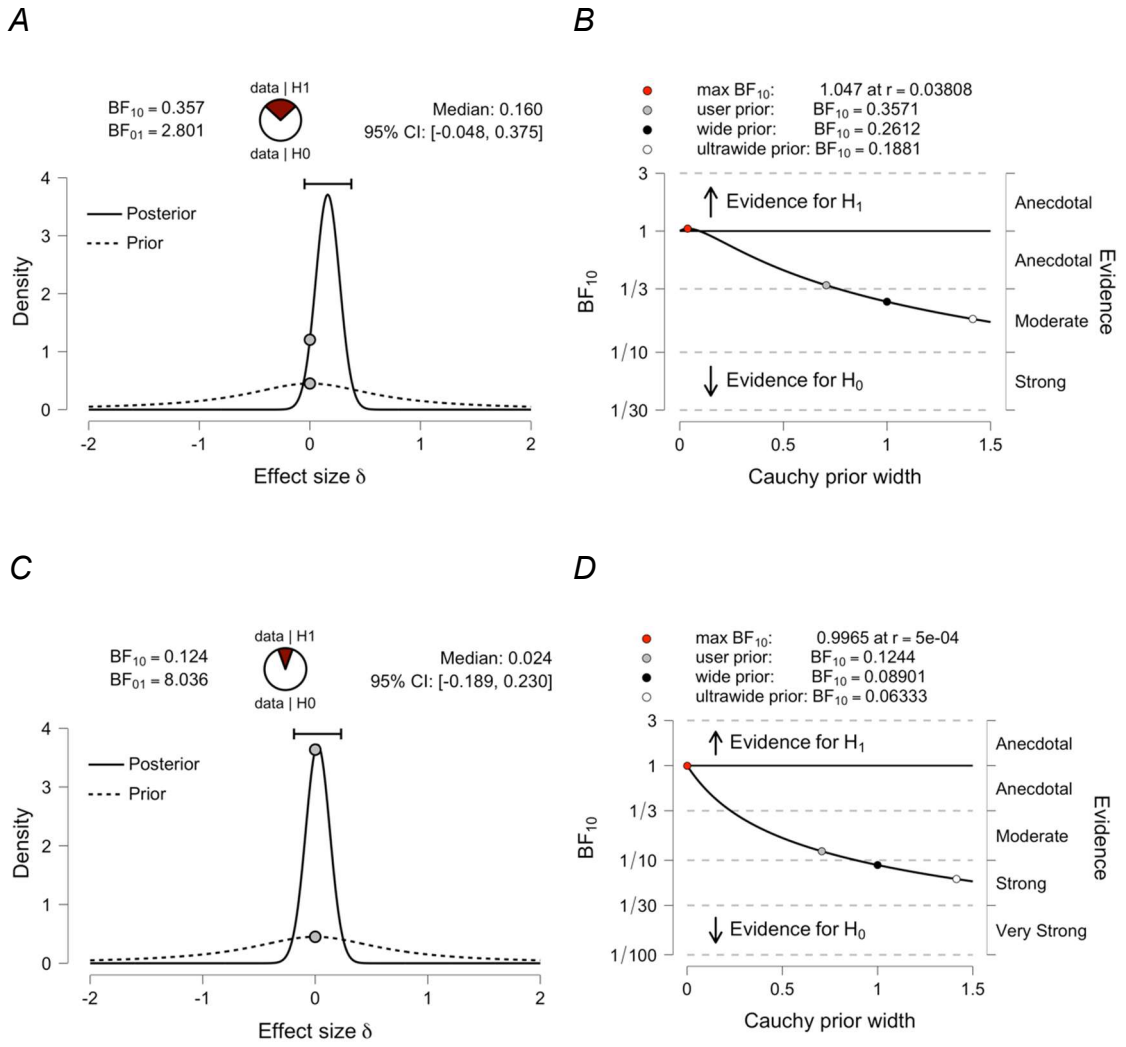

Figure 14: **Anecdotal to moderate evidence against taVNS effects on non-food liking and wanting.** A & C: Prior and posterior distribution of effect sizes of non-food liking (A) and wanting (B) rating differences during transcutaneous auricular vagus nerve stimulation (taVNS) compared to sham stimulation. B & D: Bayes factor robustness check for taVNS-induced alterations in non-food liking (B) and wanting (D).

Collectively, we see that acute taVNS in healthy participants most likely does not alter subjective liking and wanting of neither food, nor non-food items. Moreover, “estimated effect sizes were low (d_z < 0.18 [; see Table 2]) suggesting limited practical relevance of any potential effect induced by acute taVNS” (Müller et al., 2022, pp. 4-5).

3.2 No alteration of taVNS effects over time

To examine whether taVNS effects on food wanting and liking evolve over time during the stimulation, we separately calculated each participant's mean ratings during the first and the second run for taVNS as well as for sham stimulation.

We found that taVNS-induced changes (taVNS – sham stimulation ratings; "taVNS effects") in food liking were lower during the first run compared to the second run ($M_{taVNS\ effects\ (R1)}$ = -0.39, $SEM_{taVNS\ effects\ (R1)}$ = 1.65, $M_{taVNS\ effects\ (R2)}$ = 2.30, $SEM_{taVNS\ effects\ (R2)}$ = 1.84; see Figure 15). However, the mean difference of taVNS effects on food liking between the two runs was not significant ($M_{taVNS\ effects\ (R2-R1)}$ = 2.69, t = 1.454, df = 81, p = .150) with a small effect size d_z = 0.161. The corresponding BF_{10} = 0.34 suggested as well that there was no difference of taVNS-induced changes between the first and the second run.

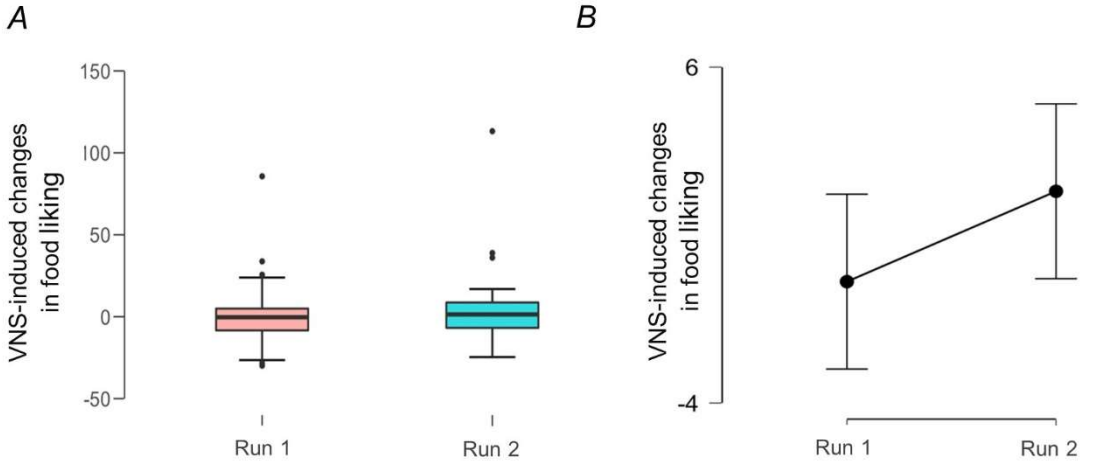

Figure 15: **taVNS effects on food liking do not evolve over time.** A: Boxplots illustrate individual averages of food liking rating differences between transcutaneous auricular vagus nerve stimulation (taVNS) and sham stimulation ("VNS-induced changes") during Run 1 and Run 2. B: 95% confidence interval of average VNS-induced changes during Run 1 and Run 2

In contrast to liking, we found that mean taVNS-induced changes in food wanting were greater in the first run compared to the second run ($M_{taVNS\ effects\ (R1)}$ = 2.27, $SEM_{taVNS\ effects\ (R1)}$ = 1.32, $M_{taVNS\ effects\ (R2)}$ = 1.30, $SEM_{taVNS\ effects\ (R2)}$ = 1.14, see Figure 16). However, the difference between Run 1 and Run 2 was not

significant either (t = -0.837, df = 81, p = .405, d_z = 0.092) and the corresponding BF_{10} = 0.17 indicated strong evidence against a difference of taVNS effects on food wanting between the first and second run.

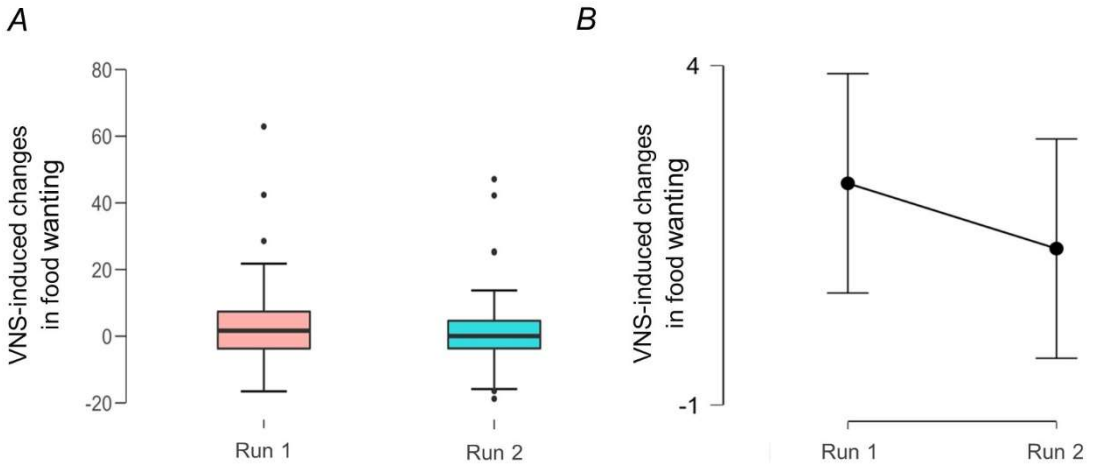

Figure 16: **taVNS effects on food wanting do not evolve over time.** A: Boxplots illustrate individual averages of food wanting rating differences between transcutaneous auricular vagus nerve stimulation (taVNS) and sham stimulation ("VNS-induced changes") during Run 1 and Run 2. B: 95% confidence interval of average VNS-induced changes during Run 1 and Run 2

To further expel that significant taVNS effects occurred exclusively during the second run, we ran Student's t-tests of taVNS vs. sham rating differences in the subgroup of Run 2. We found that differences in food liking as well as food wanting between taVNS and sham stimulation during the second run were not significant (*mean difference* $_{taVNS\ vs.\ sham\ (food\ liking,\ R2)}$ = 2.30*, 95%CI* [-1.36, 5.97], *t* = *1.251* , *df* = 81*, p* = .215 and *mean difference* $_{taVNS\ vs.\ sham\ (food\ wanting,\ R2)}$ = 1.30*, 95%CI* [-0.96, 3.57], *t* = 1.145*, df* = 81*, p* = .255) with a small effect size d_z= 0.138 for food liking and d_z= 0.126 for food wanting. The corresponding BF_{10}= 0.26 for food liking and BF_{10}= 0.23 for food wanting indicate evidence that within the subgroup of ratings during Run 2, taVNS showed no impact on food liking and wanting.

Taken together, our results indicate that taVNS effects on subjective liking and wanting ratings did not differ during the first or the second run of the paradigm. This strengthens the evidence for the absence of a taVNS effect on subjective food reward ratings.

3.3 No effects of taVNS on liking and wanting in different subgroups

To test whether taVNS selectively alters ratings for certain kinds of food, we investigated taVNS effects on six various food categories: high- or low-caloric food, food with high or low perceived healthiness as well as sweet or savory food.

First, to compare liking and wanting for the oppositional categories, we calculated mean ratings for both conditions (taVNS and sham stimulation) combined. We found that liking and wanting were significantly different for high- versus low-caloric food (*mean difference* $_{high\text{- vs. low-caloric liking}}$ = -11.50, t = -5.410, df = 81, p <.001 and *mean difference* $_{high\text{- vs. low-caloric wanting}}$ = -9.18, t = -5.749, df = 81, p <.001), as well as for food with high versus low perceived healthiness (*mean difference* $_{healthy\ vs.\ unhealthy\ liking}$ = 8.40, t = 3.822, df = 81, p <.001 and *mean difference* $_{healthy\ vs.\ unhealthy\ wanting}$ = 6.90, t = 4.27, df = 81, p <.001) and sweet versus savory food (*mean difference* $_{sweet\ vs.\ savory\ liking}$ = 8.14, t = 5.10, df = 81, p <.001 and *mean difference* $_{sweet\ vs.\ savory\ wanting}$ = 9.20, t = 6.825, df = 81, p <.001). These results indicate that the categorization reflected differences between the food items that led to differential ratings of liking and wanting by the participants (see Figure 17).

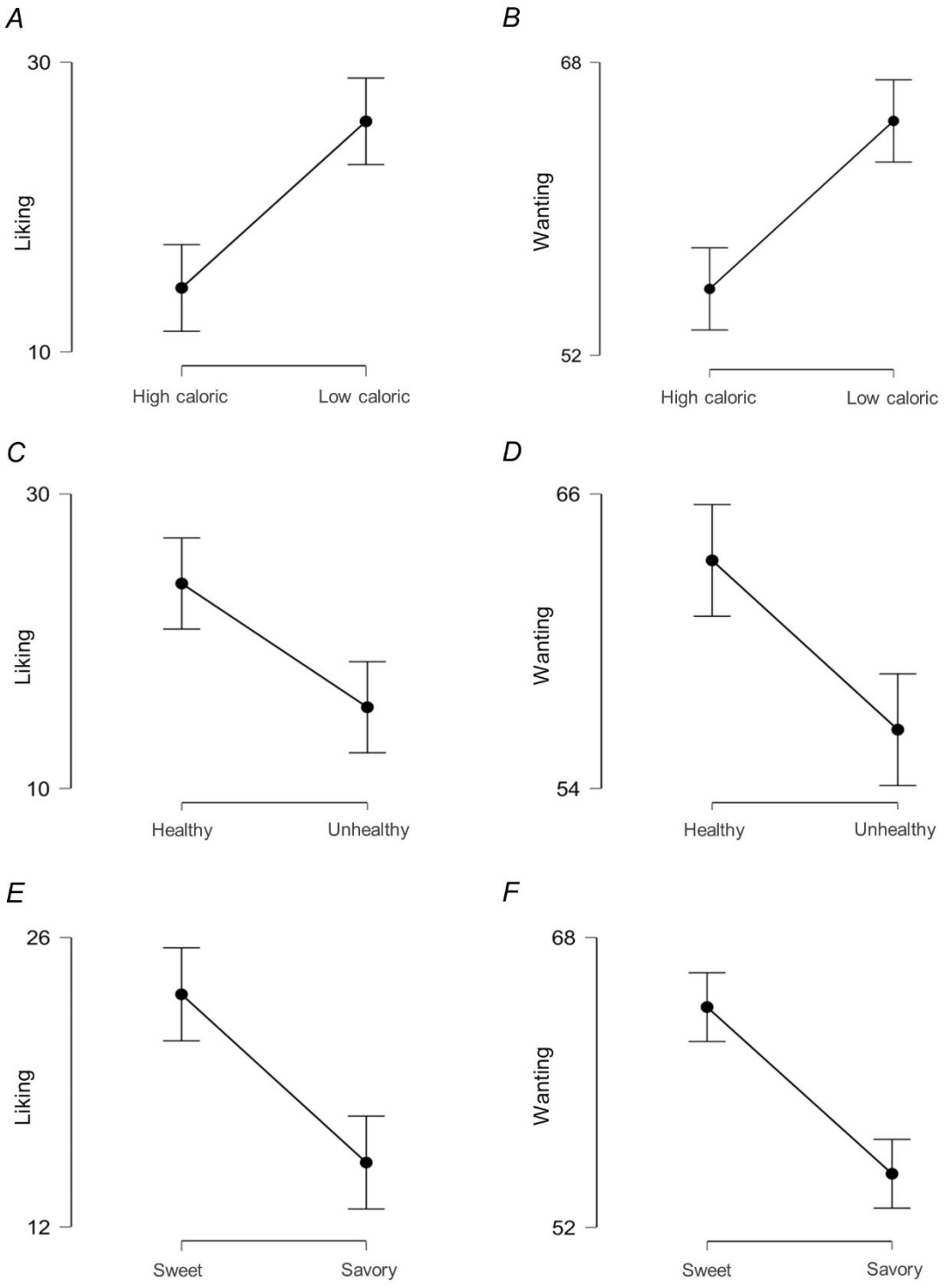

Figure 17: **Oppositional food categories elicit differential liking and wanting.** Individual averages as well as 95% confidence interval of liking and wanting ratings in the food categories high- versus low-caloric density (A & B), high versus low perceived healthiness (C & D) and sweet versus savory taste (E & F) for both stimulation conditions (transcutaneous auricular vagus nerve stimulation and sham) combined

Next, to assess specific taVNS effects, we analyzed taVNS versus sham stimulation liking and wanting ratings in different categories of food as within-subject factors. As part of a multiverse analysis (see Müller et al., 2022), we additionally introduced sex as a between-subject factor and partitioned the data into subgroups including exclusively women (*n* = 46) or men (*n* = 36).

For differences in liking ratings between taVNS and sham stimulation, we found no significant effect of taVNS on different food categories (all *p* > .275; see Table 3; Figure 18, A), but an isolated significant taVNS effect on non-food liking (control condition) in men (*n* = 36, *p* = .026). For differences in wanting ratings between taVNS and sham stimulation in the subgroups (see Table 3; Figure 18, B), we found an effect on savory food wanting in the full sample without correction for multiple comparisons (*n* = 82, *p* = .045). Beyond these two significant differences in ratings, there were no other significant taVNS effects in the respective subgroups indicating that these isolated findings could be simply due to chance due to the high number of 44 tests.

taVNS-induced changes (taVNS – sham)

Rating	Sex	Caloric content	Perceived healthiness	Flavor	n	Mean Difference	p
Liking	All	High caloric	-	-	82	0.374	0.798
Liking	All	Low caloric	-	-	82	1.654	0.327
Liking	All	-	Healthy	-	82	1.652	0.322
Liking	All	-	Unhealthy	-	82	0.194	0.896
Liking	All	-	-	Sweet	82	1.745	0.312
Liking	All	-	-	Savory	82	0.195	0.887
Liking	Female	All	All	All	46	1.907	0.432
Liking	Female	Non-food	Non-food	Non-food	46	-0.278	0.864
Liking	Female	High caloric	-	-	46	1.026	0.657
Liking	Female	Low caloric	-	-	46	2.891	0.295
Liking	Female	-	Healthy	-	46	2.973	0.275
Liking	Female	-	Unhealthy	-	46	0.700	0.768
Liking	Female	-	-	Sweet	46	3.050	0.279
Liking	Female	-	-	Savory	46	0.762	0.719
Liking	Male	All	All	All	36	-0.195	0.897

taVNS-induced changes (taVNS – sham)

Rating	Sex	Caloric content	Perceived healthiness	Flavor	n	Mean Difference	p
Liking	**Male**	**Non-food**	**Non-food**	**Non-food**	**36**	**4.792**	**0.026**
Liking	Male	High caloric	-	-	36	-0.459	0.775
Liking	Male	Low caloric	-	-	36	0.074	0.963
Liking	Male	-	Healthy	-	36	-0.036	0.982
Liking	Male	-	Unhealthy	-	36	-0.453	0.771
Liking	Male	-	-	Sweet	36	0.077	0.963
Liking	Male	-	-	Savory	36	-0.529	0.742
Wanting	All	High caloric	-	-	82	2.075	0.051
Wanting	All	Low caloric	-	-	82	1.464	0.262
Wanting	All	-	Healthy	-	82	1.596	0.195
Wanting	All	-	Unhealthy	-	82	1.983	0.073
Wanting	All	-	-	Sweet	82	1.389	0.259
Wanting	**All**	**-**	**-**	**Savory**	**82**	**2.304**	**0.045**
Wanting	Female	All	All	All	46	2.077	0.245
Wanting	Female	Non-food	Non-food	Non-food	46	-0.617	0.704
Wanting	Female	High caloric	-	-	46	2.055	0.221
Wanting	Female	Low caloric	-	-	46	2.156	0.315
Wanting	Female	-	Healthy	-	46	2.189	0.276
Wanting	Female	-	Unhealthy	-	46	2.021	0.255
Wanting	Female	-	-	Sweet	46	2.247	0.264
Wanting	Female	-	-	Savory	46	2.132	0.231
Wanting	Male	All	All	All	36	1.332	0.229
Wanting	Male	Non-food	Non-food	Non-food	36	1.377	0.469
Wanting	Male	High caloric	-	-	36	2.101	0.069
Wanting	Male	Low caloric	-	-	36	0.581	0.63
Wanting	Male	-	Healthy	-	36	0.840	0.481
Wanting	Male	-	Unhealthy	-	36	1.934	0.09
Wanting	Male	-	-	Sweet	36	0.292	0.802
Wanting	Male	-	-	Savory	36	2.523	0.059

Table 3: **Isolated significant differences between taVNS and sham stimulation liking and wanting ratings in various subgroups** Results of one-sample t-tests testing rating differences between transcutaneous auricular vagus nerve stimulation (taVNS) and sham stimulation in various subgroups concerning picture category (non-food, food split by caloric density, perceived healthiness, and flavor as within-subject factors) as well as sex (between-subject factor). Significant results (not corrected for multiple comparisons) are set in boldface (Müller et al., 2022, table modified).

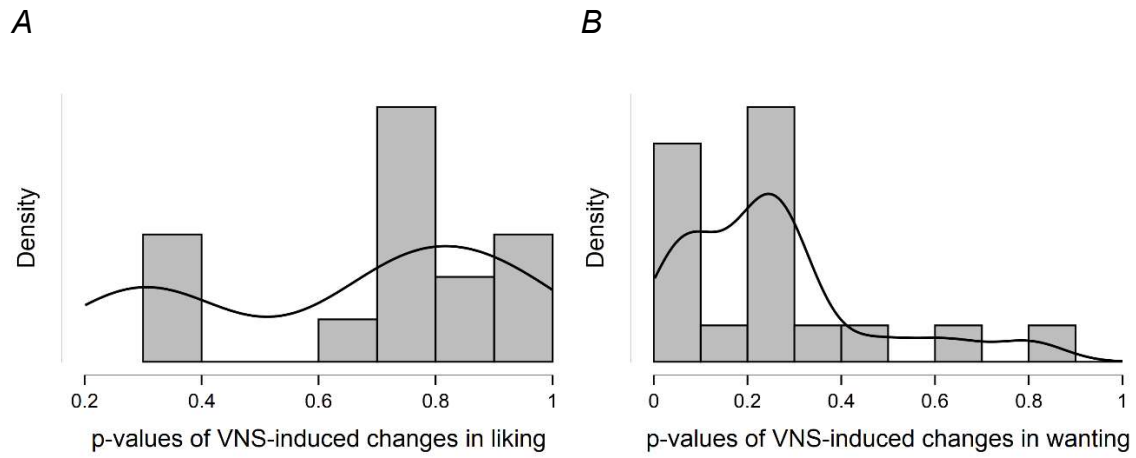

Figure 18: **Distribution of p-values indicates that there is no effect of taVNS on food liking or wanting.** Distribution of p-values for food liking (A) and wanting (B) rating differences between transcutaneous auricular vagus nerve stimulation (taVNS) and sham stimulation ("VNS-induced changes") in different subgroups concerning picture category (high- and low-caloric density, high and low perceived healthiness, sweet and savory taste as within-subject factors) as well as sex (between-subject factor)

To further estimate the likelihood of a stimulation effect on savory food wanting, we ran a Bayesian one-sample t-test where we yielded a $BF_{10} = 0.87$ (posterior distribution median effect size of $\delta = 0.22$, 95% credible interval [0.00; 0.43]; see Figure 19, A). This indicates anecdotal evidence for the null hypothesis that ratings are not altered by taVNS (see Figure 19, B). Thus, the significant effect of taVNS on savory food wanting should rather be attributed to chance than to a stimulation effect.

In summary, our results suggest that taVNS does not change liking and wanting preferences for certain kinds of food. Moreover, there is no taVNS effect exclusively observed in women or men.

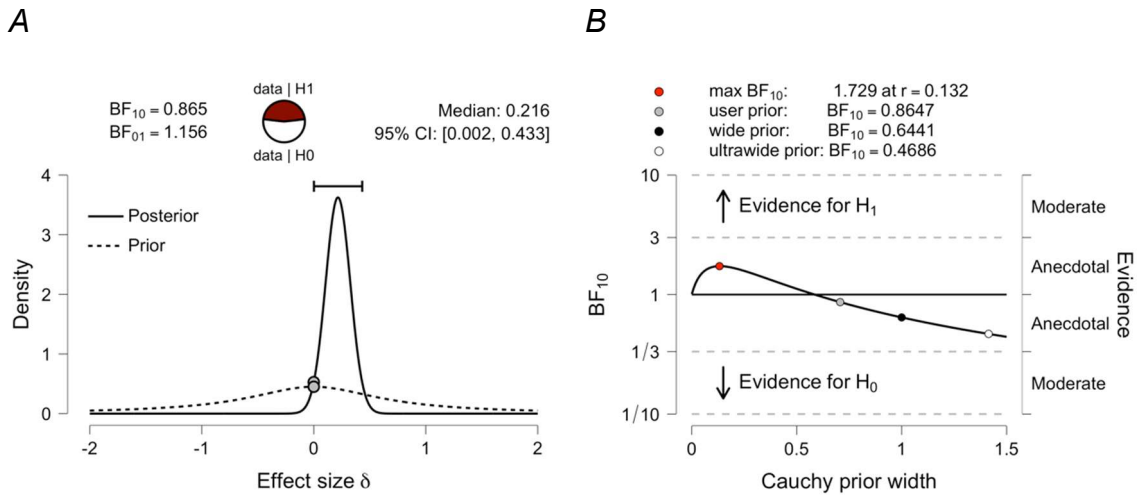

Figure 19: **Anecdotal evidence against an effect of taVNS on wanting of savory food**. A: Prior and posterior distribution of savory food wanting rating differences during transcutaneous auricular vagus nerve stimulation (taVNS) compared to sham stimulation. B: The Bayes factor robustness check indicates anecdotal evidence against an acute effect of taVNS on savory food wanting.

3.4 No modulating impact of body composition

"Due to previously reported associations between BMI and sensitivity to homeostatic feedback signals (Schwartz & Porte, 2005), we reasoned that body composition may modulate the effects of taVNS on food picture wanting and liking. Again, using Bayesian inference, we observed no significant association between BMI and taVNS-induced changes in liking ratings (r = - 0.111, BF_{10} = 0.22) or wanting ratings for food (r = - 0.074 with a BF_{10} = 0.17; [see Figure 20])" (Müller et al., 2022, p. 6).

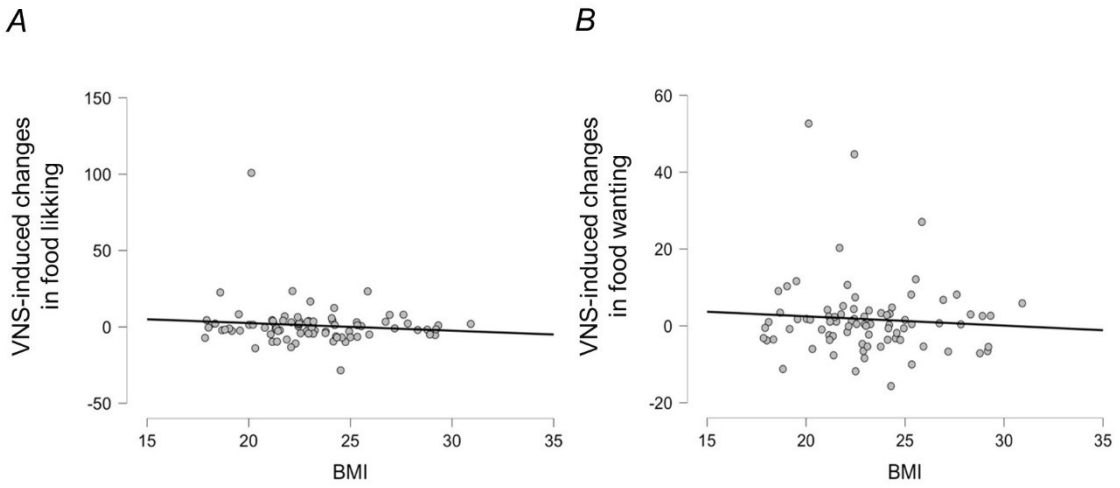

Figure 20: **No association between BMI and taVNS effects on food liking or wanting.** Correlation between BMI and rating differences of transcutaneous auricular vagus nerve stimulation (taVNS) compared to sham stimulation ("VNS-induced changes") for cue-induced liking (A) and wanting (B) of food (Müller et al., 2022)

Additionally, when we ran a Bayesian Pearson's correlation of mean taVNS-induced rating differences and the WtHR, we observed comparable results (r = -0.107, BF_{10} = 0.22 for food liking and r = -0.001, BF_{10} = 0.14 for food wanting). This is well in line with the WtHR found to be clearly associated with the BMI in our sample (r = 0.846).

Hence, there is moderate evidence against an association between taVNS effects on food liking and wanting and the body composition measures BMI and WtHR. To better evaluate these results, we further looked at an association of the BMI and general liking and wanting independently of the stimulation condition (taVNS and sham ratings combined). Here as well, we found that the BMI was neither correlated with food liking (r = 0.158, BF_{10} = 0.37) nor with food wanting (r = 0.048, BF_{10} = 0.15). Moreover, the BMI was not associated with liking or wanting in any of the categories high- and low-caloric food, healthy and unhealthy food, sweet and savory food as well as non-food pictures ($-0.084 \leq r \leq 0.259$, $0.14 \leq BF_{10} \leq 2.09$).

Regarding the potential use of (ta)VNS in treatments of overweight or obesity, we calculated mean taVNS-induced alterations in a subset of overweight or obese

participants (BMI ≥ 25, n = 19) and conducted a one-sample t-test to test whether taVNS affected subjective cue-induced food reward exclusively in overweight/ obese participants. Again, we found no indication that taVNS alters liking or wanting in overweight/obese participants (all *p*s ≥ .159; see Table 4).

taVNS-induced changes (taVNS – sham) in overweight/obese participants

Rating	Stimulus	Caloric content	Perceived healthiness	Flavor	n	Mean Difference	p
Liking	Non-food	-	-	-	19	0.916	0.571
Liking	Food	-	-	-	19	1.091	0.654
Liking	Food	High-caloric			19	1.334	0.437
Liking	Food	Low-caloric	-	-	19	0.349	0.847
Liking	Food	-	Healthy	-	19	0.206	0.910
Liking	Food	-	Unhealthy	-	19	1.470	0.378
Liking	Food	-	-	Sweet	19	1.624	0.349
Liking	Food	-	-	Savory	19	0.022	0.991
Wanting	Non-food				19	2.014	0.322
Wanting	Food				19	1.652	0.571
Wanting	Food	High-caloric	-	-	19	2.740	0.169
Wanting	Food	Low-caloric	-	-	19	1.413	0.546
Wanting	Food	-	Healthy	-	19	1.608	0.483
Wanting	Food	-	Unhealthy	-	19	2.717	0.168
Wanting	Food	-	-	Sweet	19	1.042	0.623
Wanting	Food	-	-	Savory	19	3.235	0.159

Table 4: **No significant effect of taVNS on liking and wanting ratings in a subset of overweight/obese participants.** Results of one-sample t-tests testing the differences between transcutaneous auricular vagus nerve stimulation (taVNS) and sham stimulation in various subgroups concerning picture category (non-food, caloric density, perceived healthiness, and flavor as within-subject factors) for all participants with BMI ≥ 25 (*n* = 19)

3.5 No lateralization of taVNS effects on liking or wanting

To assess possible lateralization effects, our participants received taVNS either the left (n = 42) or the right auricle (n = 40). To analyze whether taVNS effects were different at the left compared to the right side (between-subject factor), we calculated differences between taVNS and sham stimulation ratings for each participant in the left- and right-side subgroups.

We found that taVNS effects (taVNS – sham stimulation ratings) on food liking were slightly higher for left-sided ($M_{\text{taVNS effects on food liking (left)}}$ = 1.24, $SEM_{\text{taVNS effects on food liking (left)}}$ = 2.75) compared to right-sided stimulation ($M_{\text{taVNS effects on food liking (right)}}$ = 0.71, $SEM_{\text{taVNS effects on food liking (right)}}$ = 1.11; see Figure 21, A&B). However, an independent samples t-test showed that differences in taVNS effects on food liking between left and right stimulation side were not significant (*mean difference* $_{\text{left vs. right (taVNS effects on non-food liking)}}$ = 0.53, t = 0.176, df = 80, p = .861) with a small effect size of *Cohen's d* = 0.039. The corresponding BF_{10} = 0.23 provided moderate support in favor of the null hypothesis (posterior effect size median δ = 0.03, *95% CI* [-0.37, 0.44]) even with alternative priors (see Figure 22).

In contrast, non-food liking differences of taVNS vs. sham stimulation were higher at the right ($M_{\text{taVNS effects on non-food liking (right)}}$ = 3.45, $SEM_{\text{taVNS effects on non-food liking (right)}}$ = 2.1) compared to the left side ($M_{\text{taVNS effects on non-food liking (left)}}$ = 0.52, $SEM_{\text{taVNS effects on non-food liking (left)}}$ = 1.51; see Figure 21, C&D). Here as well, differences between the left vs. right side on taVNS effects of non-food liking were not significant (*mean difference* $_{\text{left vs. right (taVNS effects on non-food liking)}}$ = -2.94, t = -1.132, df = 80, p = .261, *Cohen's d*= -0.250). Hence, we conclude that neither food nor non-food liking taVNS effects were modulated by the stimulation side.

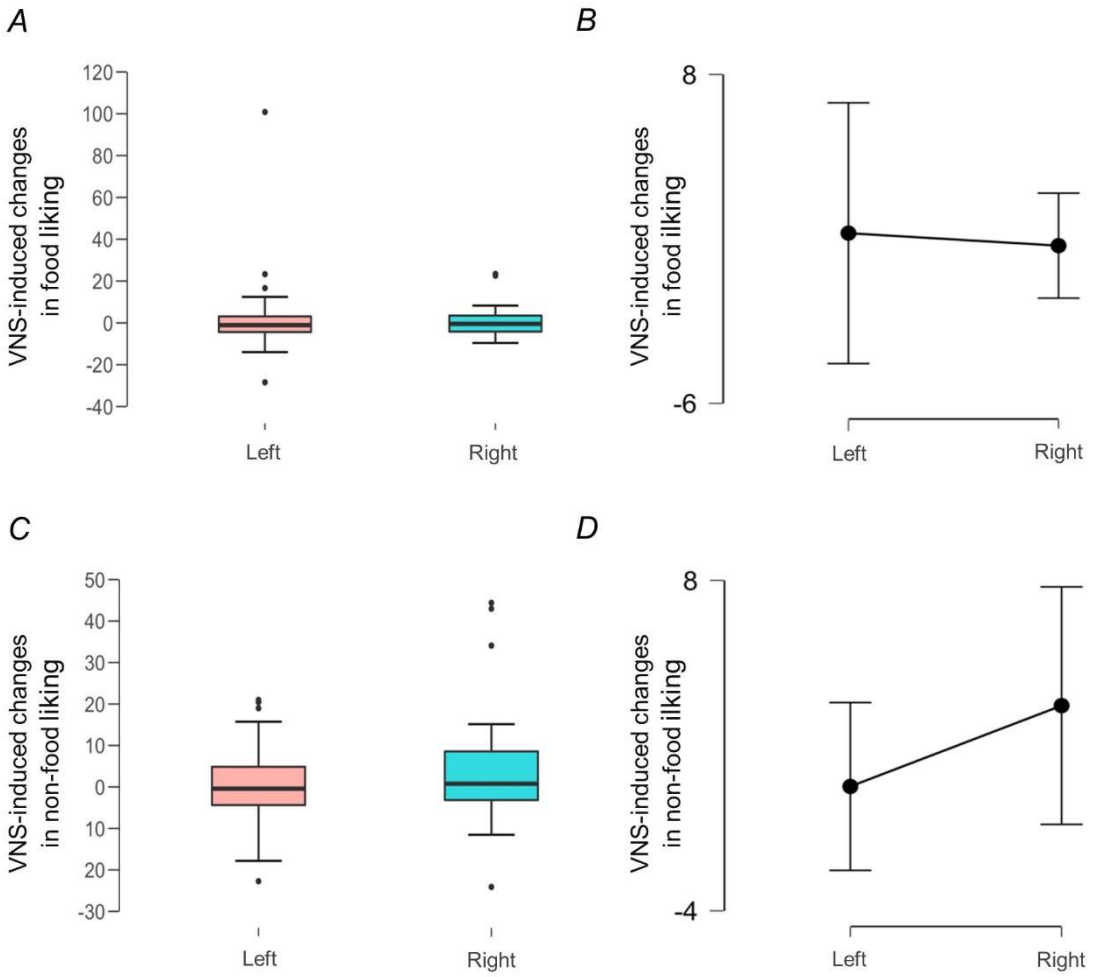

Figure 21: **No modulation of taVNS effects on food and non-food liking by the stimulated side.** A & C: Boxplots illustrate individual averages of food and non-food liking rating differences between transcutaneous auricular vagus nerve stimulation (taVNS) and sham stimulation ("VNS-induced changes") at the left versus the right side. B & D: 95% confidence interval of mean left- and right-sided VNS-induced changes in food and non-food liking

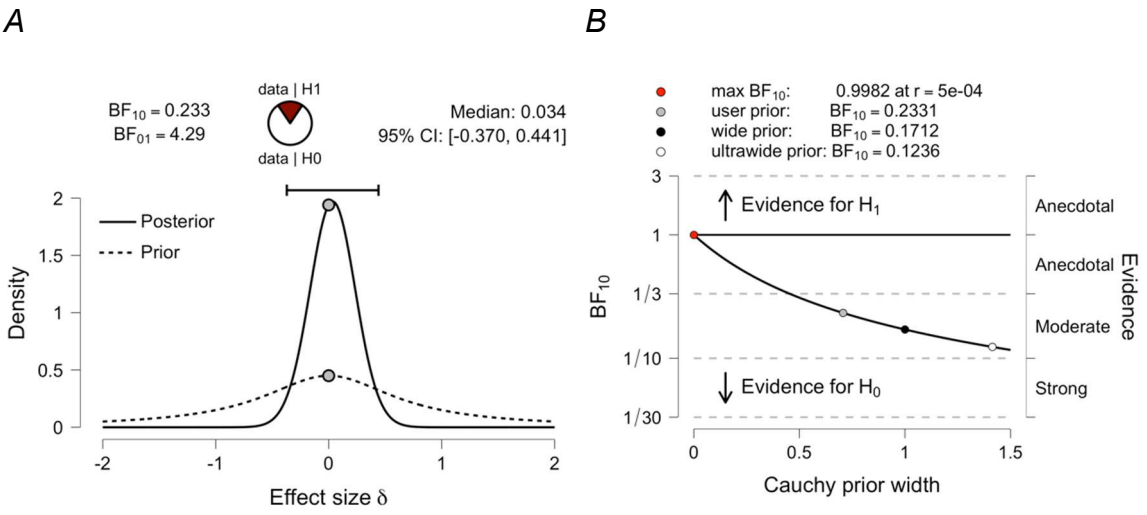

Figure 22: **Moderate evidence against lateralization of taVNS effects on food liking**. A: Prior and posterior distribution of effect sizes on transcutaneous auricular vagus nerve stimulation (taVNS) effect differences between the left and right side. B: The Bayes factor robustness check indicates moderate support that food liking taVNS effects are not altered as a function of the stimulated side.

For food wanting ratings, we found that rating differences between taVNS and sham stimulation were slightly higher at the right side ($M_{\text{taVNS effects on food wanting (right)}}$ = 1.82, $SEM_{\text{taVNS effects on food wanting (right)}}$ = 0.98) compared to the left side ($M_{\text{taVNS effects on food wanting (left)}}$ = 1.68, $SEM_{\text{taVNS effects on food wanting (left)}}$ = 1.93; see Figure 23, A&B). However, mean wanting rating differences between left- and right-sided stimulation effects were not significant (*mean difference* $_{\text{left vs. right (taVNS effects on food wanting)}}$ = -0.139, t = -0.063, df = 80, p = .950) with a small effect size of *Cohen's d*= -0.014. In Bayesian statistics of food wanting stimulation effect differences between left and right side taVNS, we observed a BF_{10} = 0.23 and a posterior effect size distribution with a median of δ = -0.01 and a *95% CI* of [-0.41, 0.40] indicating moderate evidence against a lateralization of food wanting stimulation effects (see Figure 24).

Looking at non-food wanting, mean taVNS-induced changes were higher at the right side ($M_{\text{taVNS effects on non-food wanting (right)}}$ = 2.66, $SEM_{\text{taVNS effects on non-food wanting (right)}}$ = 1.83) compared to the left side ($M_{\text{taVNS effects on non-food wanting (left)}}$ = -2.09, $SEM_{\text{taVNS effects on non-food wanting (left)}}$ = 1.57; see Figure 23, C&D). Nevertheless, the difference (*mean difference* $_{\text{left vs. right (taVNS effects on non-food wanting)}}$ = -4.69) was not significant either (t = -1.949, df = 80, p = .055, *Cohen's d* = -0.431).

Thus, we conclude that neither liking nor wanting taVNS effects are altered as a function of the stimulated side.

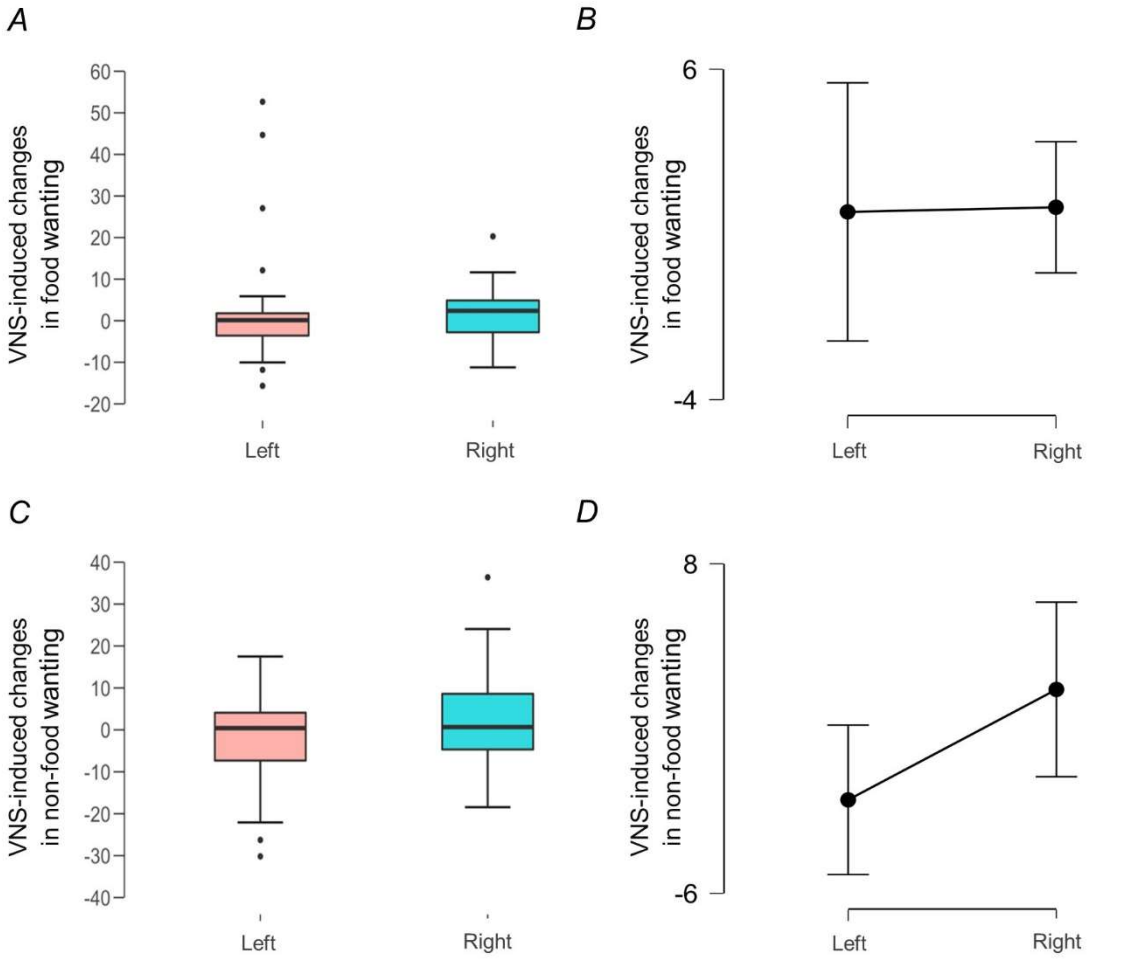

Figure 23: **No modulation of taVNS effects on food and non-food wanting by the stimulated side.** A & C: Boxplots illustrate individual averages of food and non-food wanting rating differences between transcutaneous auricular vagus nerve stimulation (taVNS) and sham stimulation ("VNS-induced changes") at the left versus the right side. B & D: 95% confidence interval of mean left- and right-sided VNS-induced changes in food and non-food wanting

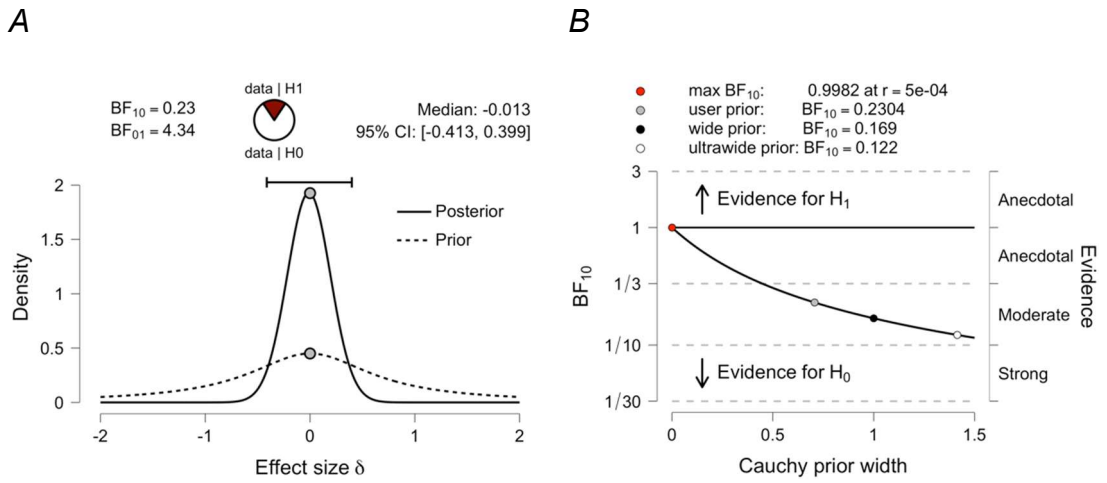

Figure 24: **Moderate evidence against lateralization of food wanting taVNS effects**. A: Prior and posterior distribution of effect sizes on mean transcutaneous auricular vagus nerve stimulation (taVNS) effect differences between the left and right side. B: The Bayes factor robustness check indicates moderate support that food wanting taVNS effects are not altered as a function of the stimulated side.

To detect taVNS effects that possibly exclusively occur during left- or right-sided taVNS, we further analyzed taVNS-induced changes within our left- or right-sided subset. Here as well, we conducted various post hoc analyses (liking and wanting ratings in the picture item categories food, non-food, high-caloric food, low-caloric food, food with high and low perceived healthiness, sweet and savory food).

In the left-sided sample (n = 42), we found that liking rating differences between taVNS and sham stimulation were not significant in any of the eight categories (all p > .433; see Table 5). Moreover, BF_{10} was between 0.17 and 0.22 and thus provided moderate evidence against left-sided taVNS effects on liking ratings.

Furthermore, wanting rating differences between taVNS and sham stimulation in the left-sided subset were not significant either (all p > .204; see Table 5). Corresponding BF_{10} between 0.21 and 0.36 indicated anecdotal to moderate support that mean wanting ratings were not different during left-sided taVNS compared to sham stimulation. Thus, we conclude that left-sided taVNS shows no effect on wanting or liking.

Left-sided taVNS-induced changes (taVNS – sham)

Rating	Stimulus	Caloric content	Perceived healthiness	Flavor	n	Mean Difference	p
Liking	Non-food	-	-	-	42	0.516	0.734
Liking	Food	-	-	-	42	1.243	0.653
Liking	Food	High-caloric			42	0.453	0.863
Liking	Food	Low-caloric	-	-	42	2.380	0.433
Liking	Food	-	Healthy	-	42	2.024	0.50
Liking	Food	-	Unhealthy	-	42	0.538	0.837
Liking	Food	-	-	Sweet	42	1.582	0.622
Liking	Food	-	-	Savory	42	1.030	0.664
Wanting	Non-food				42	-2.029	0.204
Wanting	Food				42	1.682	0.389
Wanting	Food	High-caloric	-	-	42	1.364	0.439
Wanting	Food	Low-caloric	-	-	42	2.266	0.337
Wanting	Food	-	Healthy	-	42	2.077	0.347
Wanting	Food	-	Unhealthy	-	42	1.447	0.437
Wanting	Food	-	-	Sweet	42	1.570	0.47
Wanting	Food	-	-	Savory	42	2.019	0.286

Table 5 : **No significant differences between left-sided taVNS and sham stimulation liking and wanting ratings in various subgroups.** Results of one-sample t-tests testing the differences between left-sided transcutaneous auricular vagus nerve stimulation (taVNS) and sham stimulation in various subgroups concerning picture category (non-food, food split by caloric density, perceived healthiness, and flavor as within-subject factors) as within-subject factors (Müller et al., 2022, table modified)

Analogously, in the right-sided stimulation subset (n = 40), we analyzed whether there were taVNS effects in the eight categories food, non-food, high- and low-caloric food, high and low perceived healthiness and sweet as well as savory.

Here, we found that liking rating differences between taVNS and sham stimulation were not significant (all p > .107; see Table 6). BF_{10} was between 0.17 and 0.59. Thus, there seems to be no acute taVNS effect on liking ratings during stimulation at the right ear.

In contrast, if we analyze wanting rating differences between taVNS and sham stimulation within our right-sided sample, three subgroups show p-values below the significance level of .05: high-caloric food pictures (p = .016), food

pictures with low perceived healthiness (p = .031) and pictures of savory foods (p = .046; see Table 6).

Right-sided taVNS-induced changes (taVNS – sham)

Rating	Stimulus	Caloric content	Perceived healthiness	Flavor	n	Mean Difference	p
Liking	Non-food	-	-	-	40	3.451	0.114
Liking	Food	-	-	-	40		0.523
Liking	Food	High-caloric			40	0.291	0.815
Liking	Food	Low-caloric	-	-	40	0.892	0.53
Liking	Food	-	Healthy	-	40	1.262	0.369
Liking	Food	-	Unhealthy	-	40	-0.168	0.903
Liking	Food	-	-	Sweet	40	1.916	0.107
Liking	Food	-	-	Savory	40	-0.681	0.613
Wanting	Non-food				40	2.660	0.155
Wanting	Food				40	1.822	0.071
Wanting	**Food**	**High-caloric**	**-**	**-**	**40**	**2.822**	**0.016**
Wanting	Food	Low-caloric	-	-	40	0.623	0.559
Wanting	Food	-	Healthy	-	40	1.091	0.304
Wanting	**Food**	**-**	**Unhealthy**	**-**	**40**	**2.546**	**0.031**
Wanting	Food	-	-	Sweet	40	1.198	0.289
Wanting	**Food**	**-**	**-**	**Savory**	**40**	**2.603**	**0.046**

Table 6**: Isolated significant differences between right-sided taVNS and sham stimulation liking and wanting ratings in various subgroups.** Results of one-sample t-tests testing the differences between right-sided transcutaneous auricular vagus nerve stimulation (taVNS) and sham stimulation in various subgroups concerning picture category (non-food, food split by caloric density, perceived healthiness, and flavor as within-subject factors) as within-subject factors (Müller et al., 2022, table modified)

To estimate the evidence for effects of right-sided taVNS on wanting ratings in the categories high-caloric food, food with low perceived healthiness and savory food, we additionally ran Bayesian one-sample t-tests of wanting rating differences between taVNS and sham stimulation.

When we analyzed taVNS effects on high-caloric food wanting during right-sided stimulation (taVNS – sham stimulation ratings), Bayesian statistics resulted in a BF_{10} of 2.68 (see Table 7) with a posterior median effect size of δ = 0.37 and a *95% CI [*0.06, 0.69] which provided anecdotal support in favor of an

effect of right-sided taVNS on high-caloric food wanting. Moreover, the Bayes factor robustness check revealed that, with wider priors, evidence for the alternative hypothesis remained anecdotal (see Figure 25).

Looking at food pictures with low perceived healthiness within the right-sided subset, our data provided anecdotal support in favor of a right-sided taVNS effect as well (BF_{10} = 1.56, posterior median effect size of δ = 0.33 within a *95% CI* of [0.01, 0.64]).

In the subset of savory food pictures within the right-sided sample, the corresponding BF_{10} = 1.15 with posterior median effect size of δ = 0.30, *95%* CI [-0.00, 0.62] indicated that our data was not sensitive enough to detect a taVNS effect (see Table 7). Thus, the isolated significant taVNS effects in data subsets during right-sided stimulation are not supported by Bayesian statistics as our data provided anecdotal evidence at best.

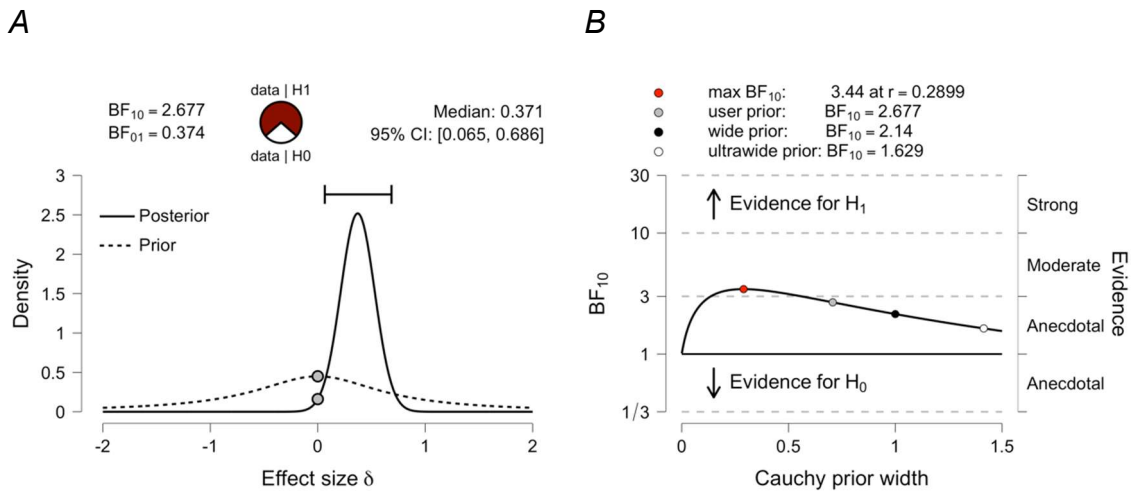

Figure 25: **Anecdotal evidence that right-sided taVNS affects high-caloric food wanting.** A: Prior and posterior distribution of effect sizes of high-caloric food wanting differences between transcutaneous auricular vagus nerve stimulation (taVNS) and sham stimulation. B: The Bayes factor robustness check indicates anecdotal evidence in support of an effect of right-sided taVNS on high-caloric food wanting (Müller et al., 2022).

Collectively, we conclude that taVNS at the left side does not alter food wanting or liking. At the right side, our data provided anecdotal support in favor of condition-specific taVNS effects, whereas liking seemed to be unaffected.

3.6 Multiverse analyses support absence of taVNS effects on food liking or wanting

To summarize, when we analyzed taVNS effects on subjective liking and wanting ratings, we ran a multiverse of 80 post hoc tests, using within-subject (different food categories) and between-subject factors (sex, stimulation side; see Müller et al. (2022)). Looking at food rating differences between taVNS and sham stimulation, we found four isolated significant results in our subgroup analyses (savory food wanting in the full sample as well as high-caloric, unhealthy, and savory food wanting in right-sided subset). “Still, evidence in support of a taVNS effect was merely at an anecdotal level [at best] […] and the distribution across the multiverse of tests did not show robust significant effects across analyses specifications [see Figure 26]. […] Thereby, our results provide mostly conclusive evidence for the absence of acute taVNS-induced effects on ratings of wanting and liking” (Müller et al., 2022, p. 6).

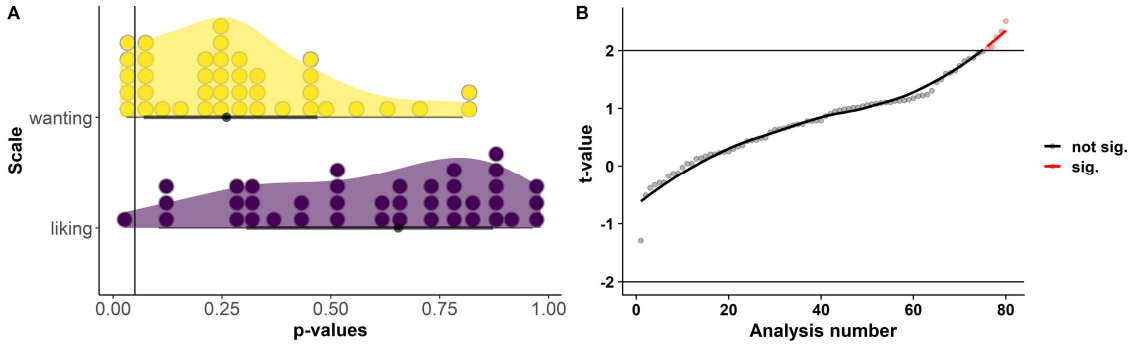

Figure 26**: Multiverse of post hoc subgroup analyses support absence of taVNS effects on food liking or wanting.** “A: Distribution of *p*-values for a stimulation main effect on ratings of liking and wanting within different subgroups defined by between-subject and within-subject factors. B: Corresponding distribution of t-values. The line denotes the uncorrected p-threshold for the 80 separate analyses. No result exceeded p-thresholds corrected for multiple comparisons or provided more than anecdotal evidence in Bayesian analyses for the presence of taVNS-induced changes” (Müller et al., 2022).

4. Discussion

“Vagal afferent signals play a vital role in the regulation of eating behavior by forwarding interoceptive feedback to tune goal-directed behavior. To better understand the contribution of vagal afferent activation in the evaluation of food reward, we investigated the impact of taVNS on cue-induced food wanting and liking. As hypothesized, taVNS did not alter ratings of liking for food in the absence of food intake (Öztürk et al., 2020) or ratings of liking and wanting for non-food items. However, in contrast to previous reports, wanting ratings for food were also not affected by acute taVNS, which is in accordance with an absence of taVNS effects on wanting ratings in an effort allocation task within the same study (Neuser et al., 2020). We conclude that effects on conscious ratings of liking and wanting elicited by acute taVNS are unlikely to account for previously reported weight loss due to chronic invasive VNS (Burneo et al., 2002; Pardo et al., 2007). These results call for further research on subacute and subconscious motivational effects of taVNS (Kühnel et al., 2020; Neuser et al., 2020) that may help elucidate the potential of taVNS for future eating-related interventions” (Müller et al., 2022, p. 6).

4.1 Data reliability

The present study provides the largest data set to investigate the impact of taVNS on subjective food reward in healthy humans so far. In contrast to preliminary retrospective studies examining the effect of VNS on body weight and food intake (Abubakr & Wambacq, 2008; Burneo et al., 2002; Koren & Holmes, 2006; Pardo et al., 2007), we applied a randomized placebo-controlled cross-over design that maximizes power by reducing between-subject variance in taVNS effects. Moreover, our large sample size of 82 participants enabled more reliable analyses than recent studies with a smaller sample size (Alicart et al., 2020; Obst et al., 2020; Öztürk et al., 2020). Beyond the powerful study design, we used Bayesian analyses in addition to classical statistics that allowed us to calculate

the likelihood of the null hypothesis (i.e., that there is no effect of taVNS on food liking or wanting ratings). “Still, our results provide mostly moderate evidence for the null hypothesis that conscious ratings of food are not acutely affected by taVNS. Moreover, since we observed non-significant increases in wanting and liking, our data provides strong evidence against the directed hypothesis that taVNS may acutely decrease food reward in healthy participants“ (Müller et al., 2022, p. 6).

4.2 Evidence against a general effect of taVNS on subjective food liking and wanting in healthy humans

Overall, we showed that acute taVNS does not affect subjective food liking or wanting in healthy participants. The discrepancy between our results and observed taVNS-induced alterations of food liking in a recent study by Öztürk et al. (2020) might be explained by differential taVNS effects on anticipatory reward and taste. Hence, whereas we measured anticipatory subjective reward elicited by visual cues, Öztürk et al. (2020) used taste samples to assess liking and wanting, which incorporates feedback signals due to the consumption of food (Rogers & Hardman, 2015). A modulatory effect of taVNS on liking linked to consumption is consistent with the role of the vagus nerve in providing homeostatic feedback signals to the central nervous system (Williams et al., 2016).

Concerning food wanting ratings, our results are not consistent with the hypothesis of a decrease during taVNS. However, “these findings are well in line with recent smaller studies that reported no changes in food consumption or wanting ratings during acute taVNS in healthy participants (Alicart et al., 2020; Obst et al., 2020; Öztürk et al., 2020). Notably, the absence of taVNS-induced changes in ratings of cue-induced […] wanting is also in line with the previously reported absence of taVNS effects on wanting in an effort allocation task despite a taVNS-induced increase in the invigoration to work for rewards at stake (Neuser et al., 2020)” (Müller et al., 2022, p. 6).

A lack of taVNS effects on food liking and wanting was further supported by separate analyses of differences in liking and wanting during the first and second run. Given that taVNS protocols in preliminary human studies varied considerably (Farmer et al., 2021), little is known about the dynamics of (acute) stimulation effects. To refute that the absence of a general taVNS effect was due to a long duration until the stimulation kicked in, we showed that taVNS-induced changes in liking and wanting were not different between the runs, nor did any effects occur exclusively during the second run. Still, the stimulation duration of approximately 30 min (start of FCR task approximately 10 min after stimulation onset, FCR task duration 20 min, i.e., 10 min per run) was shorter than in other recent taVNS studies (~45 min in Öztürk et al. (2020), 1.9 h in Obst et al. (2020)). Alicart et al. (2020), on the contrary, did not even stimulate during measurements but started their tasks after a prior taVNS period of one hour. However, in our study, taVNS did neither show an effect on wanting ratings in the EAT task that started ~30 min after stimulation onset and lasted another 40 min (Neuser et al., 2020). We conclude that a missing effect of acute taVNS on conscious food reward is likely not due to a slow evolution of the effect.

Beyond a general effect of taVNS, we introduced various food categories as preliminary studies suggested specific (ta)VNS effects on wanting for sweets (Bodenlos et al., 2007) or liking of low-fat food (Öztürk et al., 2020). In our study, all three opponent pairs (high- versus low-caloric, high versus low perceived healthiness and sweet versus savory) showed differences in liking and wanting ratings over both conditions (taVNS and sham stimulation combined), indicating that the categories reflected differences in ratings. Still, our data provided support for the absence of category-specific taVNS effects. Moreover, regarding sex differences in eating behavior (Herman & Polivy, 2010), we split our data set according to sex, without revealing any specific taVNS effects on food liking or wanting for either women or men. Collectively, this extensive set of post hoc subgroup analyses corroborates the absence of an effect of taVNS on subjective food liking and wanting.

4.3 Anecdotal evidence in favor of right-sided taVNS effects on condition-specific food wanting

In general, there was no evidence for taVNS-induced changes of subjective liking or wanting. Still, right-sided taVNS increased wanting for high-caloric as well as unhealthy or savory food items at an uncorrected threshold. Regarding the regulation of food wanting, central-nervous dopamine plays an essential role (Berridge, 2009). taVNS has been shown to elicit activation in the NTS (Frangos et al., 2015; Yakunina et al., 2017) that further induces enhanced activity in dopaminergic hotspots such as the substantia nigra (SN) and the NAcc (Frangos et al., 2015; Han et al., 2018), indicating a taVNS-induced increase in dopamine signaling. Crucially, Han et al. (2018) showed that stimulating the right but not the left vagus nerve activated the SN which might be well in line with our findings specifically for the right side (Frangos et al., 2015; Han et al., 2018). Moreover, dopaminergic release is well known to be essential for food wanting whereas acute liking seems to be mostly independent of dopamine (Berridge, 2009; Berridge & Robinson, 1998; Robinson et al., 2005). Consequently, dopamine release induced by right-sided taVNS might boost food wanting.

However, it remains uncertain whether comparable pathways as described by Han et et (2018) exist during taVNS in humans as well given that the proposed vagal-nigrostriatal pathway arose from observations in rodents (Han et al., 2018). Differences between Han's (2018) observations and taVNS in humans are strikingly demonstrated by Polak et al. (2009) who reported that there was no effect of the stimulated side on vagus sensory evoked potentials in the brainstem during left- and right-sided taVNS.

Moreover, Bayesian evidence that right-sided taVNS increases condition-specific food wanting was at an anecdotal level at best. Given the comparably large sample testing within-person effects, the small effect sizes and the exploratory nature of the subgroup analyses necessitate more research in independent samples to improve confidence in these subgroup effects. Interestingly, when we repeated the same FCR task with another independent sample including right-sided taVNS in 32 healthy participants (Koepp et al.,

2021), we did not replicate condition-specific significant changes in food wanting ratings for taVNS compared to sham stimulation (see Müller et al., 2022).

Taken together, the data suggest that the anecdotal evidence for taVNS effects for wanting of high-caloric (as well as unhealthy or savory) food is not robust so far and future research is necessary to evaluate potential stimulation protocols that may elicit stronger effects on wanting.

4.4 No modulation of taVNS effects by body composition

Since VNS has been shown to reduce food intake, taVNS is currently discussed as a potential treatment for obesity (de Lartigue, 2016; Kaniusas et al., 2019). Interestingly, de Lartigue (2016) showed that overconsumption of food leads to a desensitization of anorexigenic vagal fibers which further promotes overfeeding. As already portrayed, taVNS holds the potential to induce recovery of vagal signaling by substituting impaired anorexigenic feedback loops (Kaniusas et al., 2019). In this matter, we hypothesized that vagal stimulation effects might be stronger in participants with a higher BMI.

First, when we analyzed the impact of BMI and WtHR on food liking and wanting across stimulation conditions (i.e., sham and taVNS ratings collapsed), there was no association. This is in line with previous studies reporting that obesity is not positively correlated with food pleasantness (Wall et al., 2020).

Importantly, taVNS effects on food liking and wanting were not dependent on BMI either. At first sight, this contrasts with preliminary evidence that food intake or weight loss due to VNS in humans might be correlated with pre-treatment BMI (Bodenlos et al., 2007; Pardo et al., 2007). However, our sample mostly consisted of participants within a normal weight range (72%, 18.5 < BMI < 25), while 6% were underweight (BMI < 18,5) and 22% overweight (BMI > 25). Only one participant was obese with a BMI of 30.9. In contrast, Bodenlos et al. (2007) reported BMI-dependent alterations in sweet food wanting due to VNS in a sample of patients with depression with a mean BMI of 30.94. Still, preliminary research does not provide unequivocal evidence. For example, subsequent findings by Bodenlos et al. (2014) indicated an impact of acute VNS on food

intake in lean but not in overweight humans receiving VNS for depression or epilepsy. Thus, possible (ta)VNS effects on food reward and body weight in individuals with obesity remain largely elusive.

4.5 Differences to preliminary work reporting VNS-induced weight loss

In addition to body composition in the sample, there are further crucial differences between our study and preliminary work reporting moderate-to-large effects of VNS on body weight.

First, many of the previous studies that reported weight loss or reduced food intake due to VNS were based on animal models (Bugajski et al., 2007; Gil et al., 2011; Li et al., 2015; Roslin & Kurian, 2001; Yao et al., 2018). Here, the anatomical stimulation location likely plays a role, as in animals VNS is often applied close to the stomach (subdiaphragmal) by stimulating the celiac branches of the vagus (Bugajski et al., 2007; Sobocki, Fourtanier, Estany, & Otal, 2006). Instead, invasive VNS in humans commonly targets the cervical branch of the vagus and non-invasive stimulation is either applied to the cervical or the auricular vagal branch (Alicart et al., 2020; Bodenlos et al., 2014; Obst et al., 2020; Öztürk et al., 2020). On the contrary, the only vagal neuromodulation device approved for obesity treatment in humans works via subdiaphragmal high-frequency blockade of vagal signaling (Ikramuddin et al., 2014; Sarr et al., 2012). Thus, stimulation close to the gastric system might have a more pronounced effect on eating behavior (Bodenlos et al., 2014; Ikramuddin et al., 2014). Beyond stimulation location, research in animals predominantly focused on overweight animals losing weight or preventing weight gain. There is preliminary evidence that weight loss after VNS in humans might be positively correlated with pre-treatment BMI (Bodenlos et al., 2007; Bodenlos et al., 2014; Pardo et al., 2007) which might explain some of the conflicting results based on the respective sample included in each study.

Second, we examined acute effects of taVNS while other animal and human studies investigated chronic VNS effects (Abubakr & Wambacq, 2008; Burneo et al., 2002; Pardo et al., 2007). Vijgen et al. (2013) used invasive VNS in humans

and found an increase in energy expenditure when the device was on vs. off whereas we observed no effect of acute taVNS on energy expenditure (Teckentrup et al., 2020). This supports the idea that changes in metabolism only take place over longer periods of time. Moreover, in mongrel dogs, Roslin and Kurian (2001) observed that chronic but not acute stimulation led to reduced food intake and a loss of body weight. These chronic anorexigenic effects of VNS might be explained by the role of the vagus nerve in post-digestive processes, where it initiates conditioning and reward-based learning (de Araujo et al., 2019). The vagus nerve has been shown to convey information about digested nutrients to the brain, functioning as a central caloric sensor (de Araujo et al., 2012; de Araujo et al., 2013; Tellez et al., 2016). In this context, vagal activation during and after the consumption of calories is thought to be necessary to create associations of flavors and their nutritional value, subsequently initiating flavor preferences (Uematsu, Tsurugizawa, Uneyama, & Torii, 2010). Food cues that have previously been paired with nutrients were shown to elicit an activation in the hypothalamus and the NAcc, whose activation encodes the expected rewarding value of foods according to a metabolic signal (de Araujo et al., 2013).

In line with the role of nutrients in conditioning, the neural response to food cues as well as the willingness to pay for foods was shown to be associated with their caloric content (Tang, Fellows, & Dagher, 2014). Activation of reward-related brain regions by vagal stimulation linked to consumption of healthy food might help to its upgrade its nutritional value, thereby enhance its rewarding potential, and possibly leads to alterations in eating behavior. Therefore, it might be plausible that chronic VNS reduces food intake, while taVNS does not reduce food reward acutely.

In addition to the difference in the timeframe of stimulation (e.g. chronic vs. acute), our study differed in the sample, as we investigated healthy participants, while previous work was often done in patients with epilepsy (Abubakr & Wambacq, 2008; Burneo et al., 2002) and depression (Pardo et al., 2007). In depression as well as in epilepsy, alterations in dopaminergic (Salamone, Correa, Farrar, & Mingote, 2007) and other monoaminergic brain transmitter systems occur (Ben-Menachem, 2002; Manta, El Mansari, Debonnel,

& Blier, 2013). As portrayed, there is strong evidence that VNS modulates various monoaminergic systems in the brain (Manta et al., 2013; Van Leusden, Sellaro, & Colzato, 2015), possibly by normalizing impaired feedback loops, thereby inducing regeneration (Kaniusas et al., 2019). Consequently, in a state of unimpaired vagal signaling in healthy participants, vagal stimulation may not have comparable effects. In line with this, findings by Bodenlos et al. (2007) showed that decreased food wanting during VNS was associated with higher levels of depression, indicating that stimulation effects might be greater in highly affected individuals. Thus, food reward could be more affected by taVNS in patients compared to healthy participants.

4.6 Alternative mechanisms to mediate previously reported weight loss

Given our findings, acutely decreased subjective food reward is unlikely to mediate previously reported VNS-induced weight loss. Thus, there is a need to explain how VNS might lead to weight loss if it is not due to reduced conscious food reward evaluation.

First, taVNS might modulate food reward on an unconscious level. Interestingly, Neuser et al. (2020) found that taVNS increased the motivation to work for reward without respective alternation of conscious wanting ratings. “This dissociation between taVNS effects on subjective motivation to pursue food (wanting) and objectively measured motivation to work for rewards might indicate that taVNS acutely modulates motivation on the subconscious level, [possibly] via reward learning (Kühnel et al., 2020), probably based on vagal projections to dopaminergic areas in the midbrain (Fernandes et al., 2020; Han et al., 2018). Collectively, these findings provide further support for the theorized subconscious role of reward signals originating from the gut (de Araujo et al., 2019)” (Müller et al., 2022, p. 6).

Second, a boost of motivation during VNS (Neuser et al., 2020) indicates that VNS-induced weight loss might partly be mediated by enhanced physical activity. Crucially, body weight was shown to be associated with time spent on sedentary activities (Mitchell, Pate, Beets, & Nader, 2013; Prentice-Dunn &

Prentice-Dunn, 2012). Consistently, individuals with obesity tend to be less willing to invest physical effort to receive snack food rewards compared to lean individuals (Mathar, Horstmann, Pleger, Villringer, & Neumann, 2016). Thus, increased willingness to work for reward and increased physical activity provide a promising mode of action of VNS to reduce body weight in humans with obesity.

Third, “Vijgen et al. (2013) showed that chronic VNS increased energy expenditure in humans. Likewise, Li et al. (2015) found that chronic taVNS led to decreased body weight due to alterations in energy expenditure in obese rats. In contrast to this, we observed no effect of acute taVNS on energy expenditure but found a reduction in gastric myoelectric frequency (Teckentrup et al., 2020). This change in gastric frequency may not be instantaneously reflected in ratings but could conceivably alter eating and expected satiety (Janssen et al., 2011). Since other vagally-mediated mechanisms contribute to weight loss, slower food intake (Roslin & Kurian, 2001) and stronger subjective satiation after consumption of food (Pardo et al., 2007) could contribute to practically relevant effects of (ta)VNS on body weight” (Müller et al., 2022, p. 6).

4.7 Limitations, remaining questions, and future directions

Despite its notable strengths, our study is not without several limitations. While our results provide clear evidence across left- and right-sided stimulation that taVNS does not affect food reward, results are less clear for exclusively right-sided stimulation. Possible right-sided taVNS effects on food reward should be targeted in studies including a higher number of participants to collect more data and thus provide conclusive evidence.

Beyond equivocal results during right-sided taVNS, we note that our study captures behavioral effects only. However, taVNS might have subconscious effects on food reward and thus alter eating behavior without alterations in subjective food liking or wanting. To better disentangle subconscious neural modifications, central-nervous activation elicited by VNS could be assessed in fMRI or PET scans. Besides neuroimaging, metabolic measurements might be useful to examine subconscious effects of taVNS on eating behavior since

metabolic signals are well known to be integrated in food cue reactivity responses (Smeets, Erkner, & De Graaf, 2010). We recommend investigating the role of metabolic endocrine signals such as insulin, blood glucose, ghrelin, and leptin. In rats, cervical afferent vagal stimulation resulted in impaired glucose metabolism by suppressing insulin release (Meyers et al., 2016; Stauss et al., 2018). Interestingly, ghrelin levels were found to be elevated, whereas leptin serum levels were decreased in humans during cervical VNS (Gil et al., 2011). Thus, it would be interesting to assess ghrelin, leptin, insulin as well as blood glucose levels before, during and after taVNS in humans to examine whether VNS effects might depend on these markers. Beyond serum marker investigations, it might be interesting to compare VNS-induced changes in food reward at different metabolic states, i.e. in fasted versus satiated or in a neither hungry nor full state.

Moreover, our sample with a restricted BMI range does not allow conclusions on taVNS effects in individuals with obesity. To evaluate taVNS as a potential treatment option in obesity, future studies should include an obese cohort as well in addition to lean participants. In particular, it might be interesting to compare food reward and weight effects in healthy humans to participants with obesity as observed differences might lead to a better understanding of the pathomechanisms underlying obesity.

Finally, we only looked at acute taVNS effects. As stimulation effects might need a longer time to develop, chronic taVNS effects should be taken into consideration in future studies.

4.8 Broader conclusions

In sum, our data provided strong evidence that taVNS in healthy humans does not acutely decrease subjective food reward as measured by ratings of wanting and liking. “Still, given the reported moderate-to-large effects of chronic invasive VNS on body weight in animals and humans, more mechanistic research is necessary to unravel subacute or subconscious effects of taVNS that could be used to improve future treatments of pathological alterations in eating behavior and food choice. Implicit liking and wanting as assessed using reaction times

(Cowdrey, Finlayson, & Park, 2013; Dalton & Finlayson, 2014; Finlayson, Arlotti, Dalton, King, & Blundell, 2011), approach-avoidance tasks (Piqueras-Fiszman, Kraus, & Spence, 2014), implicit association tests (Connell, Finkelstein, Scott, & Vallen, 2018; A. A. Kraus & Piqueras-Fiszman, 2018), or effort allocation tasks (Neuser et al., 2020), or combined physiological and behavioral measures (Mueller, Teckentrup, Rebollo, Hallschmid, & Kroemer, 2021), may reflect such subconscious preferences that conscious choices are operating on (Finlayson, Bryant, Blundell, & King, 2009; Finlayson et al., 2007; Rogers & Hardman, 2015) and, thus, could be acutely modulated by taVNS more rapidly compared to consciously reported liking and wanting. In general, our results support the idea that vagal afferent activation elicits unconscious effects on food choice, which is in line with the theorized role of the “low road” to food choice (de Araujo et al., 2019).” (Müller et al., 2022, p. 7).

5. Summary / Zusammenfassung

Excessive food intake is associated with metabolic health conditions such as obesity which has become more prevalent in modern times. The vagus nerve plays an important role in food intake regulation. Accordingly, vagus nerve stimulation (VNS) has been shown to affect body weight in animals and humans possibly due to experiencing less reward when encountering food during stimulation (food reward reduction). Transcutaneous vagus nerve stimulation at the auricle (taVNS) provides a non-invasive opportunity to stimulate the vagus nerve, yet, the acute effects of taVNS on eating behavior in humans have not been examined so far. In this study, we used a food cue reactivity paradigm to assess food reward during left- and right-sided taVNS versus sham stimulation in a randomized cross-over design including 82 healthy participants (46 women, 36 men, M_{BMI} = 23.1 kg/m^2, $n_{left\text{-}sided\ stimulation}$ = 42, $n_{right\text{-}sided\ stimulation}$ = 40). During stimulation, the participants rated their subjective liking and wanting of presented food and non-food (control condition) pictures.

We found that food picture wanting and liking ratings were not significantly different during taVNS compared to sham stimulation (*t* = *0*.657*, df* = 81*, p* = .513 for food liking and *t* = 1.601*, df* = 81*, p* = .113 for food wanting*)*. Neither was the difference of VNS-induced changes between food and non-food liking or wanting at a significant level (*t* = -0.615*, df* = 81*, p* = .540 for liking and *t* = *0.979, df* = *81, p* = *.33* for wanting). To further test whether there was a specific taVNS effect, we conducted various subgroup analyses by splitting our data according to stimulation side and sex (as between-subject factors) as well as caloric content, perceived healthiness and sweet versus savory flavor (as within-subject factors). In most subgroups, our data support the absence of taVNS-induced changes in liking and wanting. The strongest taVNS effect was merely at an anecdotal evidence level (high-caloric food wanting rating differences for right-side taVNS vs. sham stimulation: *mean difference* = 2.82*, t* = 2.508*, df* = 39*, p* = .016, BF_{10} = 2.677).

Collectively, our results suggest that acute taVNS does not decrease subjective food reward in healthy humans. We conclude that previous reported weight loss due to vagal stimulation might be mediated by other mechanisms than acutely reduced food reward such as chronically reduced food intake or an increase in energy expenditure.

Zusammenfassung

Im Angesicht weltweit stetig steigender Prävalenz von Übergewicht und damit einhergehenden Gesundheitsschäden ist es wichtig, neue effektive Therapiemethoden zu entwickeln. Nachweislich ist der Vagusnerv maßgeblich an der Regulierung von Nahrungsaufnahme beteiligt. Bereits in mehreren Tier- und Humanstudien wurde eine Gewichtsabnahme durch Vagusnervstimulation (VNS) beobachtet. Ein möglicher Mechanismus hierbei ist eine Reduktion von Belohnungserfahrungen durch Essen („Food reward“). Dies wurde allerdings bisher noch nicht hinreichend erforscht.

Vorliegende Studie untersucht die akuten Auswirkungen einer nicht-invasiven transkutanen aurikulären Vagusnervstimulation (taVNS) auf die subjektive Beurteilung von Food reward. Hierbei bewerteten 82 gesunden Probanden (46 Frauen, 36 Männer, M_{BMI} = 23.1 kg/m^2, $n_{linksseitige\ Stimulation}$ = 42, $n_{rechtsseitige\ Stimulation}$ = 40) an zwei Studienterminen (einmal taVNS und einmal eine Scheinstimulation) Bilder von Essen sowie von Bürogegenständen (als Kontrollbedingung). Gefragt wurde hierbei sowohl, wie sehr das Gezeigte allgemein gemocht wird, als auch, wie sehr man das Gezeigte momentan als Belohnung erhalten wollen würde.

Unsere Analysen haben keinen signifikanten Unterschied der Durchschnittsratings von Essensbildern zwischen taVNS und Scheinstimulation ergeben (t = 0.657, df = 81, p = .513 für “Mögen” and t = 1.601, df = 81, p = .113 für “momentanes Wollen”). taVNS-induzierte Ratingunterschiede für Bürogegenstände waren ebenfalls nicht signifikant (t = -0.615, df = 81, p = .540 für “Mögen” und $t = 0.979$, $df = 81$, $p = .33$ für “momentanes Wollen”). Um darüber hinaus zu testen, ob taVNS-Effekte nur spezifisch in verschiedene Subgruppen auftreten, haben wir unseren Datensatz in weiterführenden Analysen in Subgruppen aufgeteilt nach Geschlecht, rechts- oder linksseitiger Stimulation sowie nach verschiedenen Essenskategorien (hoch- oder niedrigkalorisch, gesund oder ungesund, süß oder herzhaft). Auch hierbei ergaben sich in fast allen Subgruppen keine signifikanten Stimulationseffekte. Den stärksten Stimulationseffekt fanden wir bei “Wollen” von hochkalorischen Lebensmitteln

während rechtsseitiger Stimulation (Durchschnitt der Ratingunterschiede zwischen taVNS und Scheinstimulation = 2.82, t = 2.508, df = 39, p = .016), dieser zeigte allerdings in Bay'scher Statisik ein nicht ausreichend hohes Evidenzlevel (BF_{10} = 2.677).

Zusammenfassend konnten wir zeigen, dass taVNS nicht akut zu einem verminderten subjektiven Verlangen nach Essen führt. Daraus lässt sich schlussfolgern, dass eine bisher berichtete VNS-induzierte Gewichtsabnahme vermutlich durch andere Mechanismen ausgelöst wird, wie beispielsweise eine nicht akut, sondern nur chronisch auftretende Reduktion der Nahrungsaufnahme oder durch unbewusste Veränderungen wie beispielsweise einen erhöhten Grundumsatz.

6. Literaturverzeichnis

Abubakr, A., & Wambacq, I. (2008). Long-term outcome of vagus nerve stimulation therapy in patients with refractory epilepsy. *Journal of Clinical Neuroscience, 15*(2), 127-129.

Alicart, H., Heldmann, M., Göttlich, M., Obst, M. A., Tittgemeyer, M., & Münte, T. F. (2020). Modulation of visual processing of food by transcutaneous vagus nerve stimulation (tVNS). *Brain Imaging and Behavior*, 1-12.

Apovian, C. M., Shah, S. N., Wolfe, B. M., Ikramuddin, S., Miller, C. J., Tweden, K. S., . . . Shikora, S. A. (2017). Two-year outcomes of vagal nerve blocking (vBloc) for the treatment of obesity in the ReCharge trial. *Obesity surgery, 27*(1), 169-176.

Baik, J.-H. (2013). Dopamine signaling in food addiction: role of dopamine D2 receptors. *BMB reports, 46*(11), 519.

Baskin, D. G., Lattemann, D. F., Seeley, R. J., Woods, S. C., Porte Jr, D., & Schwartz, M. W. (1999). Insulin and leptin: dual adiposity signals to the brain for the regulation of food intake and body weight. *Brain research, 848*(1-2), 114-123.

Bauer, S., Baier, H., Baumgartner, C., Bohlmann, K., Fauser, S., Graf, W., . . . Lerche, H. (2016). Transcutaneous vagus nerve stimulation (tVNS) for treatment of drug-resistant epilepsy: a randomized, double-blind clinical trial (cMPsE02). *Brain stimulation, 9*(3), 356-363.

Ben-Menachem, E. (2002). Vagus-nerve stimulation for the treatment of epilepsy. *The Lancet Neurology, 1*(8), 477-482.

Berridge, K. C. (2009). 'Liking'and 'wanting'food rewards: brain substrates and roles in eating disorders. *Physiology & behavior, 97*(5), 537-550.

Berridge, K. C., & Robinson, T. E. (1998). What is the role of dopamine in reward: hedonic impact, reward learning, or incentive salience? *Brain research reviews, 28*(3), 309-369.

Berthoud, H.-R. (2008). Vagal and hormonal gut–brain communication: from satiation to satisfaction. *Neurogastroenterology & Motility, 20*, 64-72.

Berthoud, H.-R., & Neuhuber, W. L. (2000). Functional and chemical anatomy of the afferent vagal system. *Autonomic Neuroscience, 85*(1-3), 1-17.

Bodenlos, J. S., Kose, S., Borckardt, J. J., Nahas, Z., Shaw, D., O'Neil, P. M., & George, M. S. (2007). Vagus nerve stimulation acutely alters food craving in adults with depression. *Appetite, 48*(2), 145-153.

Bodenlos, J. S., Schneider, K. L., Oleski, J., Gordon, K., Rothschild, A. J., & Pagoto, S. L. (2014). Vagus nerve stimulation and food intake: effect of body mass index. *Journal of diabetes science and technology, 8*(3), 590-595.

Bonaz, B., Picq, C., Sinniger, V., Mayol, J.-F., & Clarençon, D. (2013). Vagus nerve stimulation: from epilepsy to the cholinergic anti-inflammatory pathway. *Neurogastroenterology & Motility, 25*(3), 208-221.

Boswell, R. G., & Kober, H. (2016). Food cue reactivity and craving predict eating and weight gain: a meta-analytic review. *Obesity reviews, 17*(2), 159-177.

Breit, S., Kupferberg, A., Rogler, G., & Hasler, G. (2018). Vagus nerve as modulator of the brain–gut axis in psychiatric and inflammatory disorders. *Frontiers in psychiatry, 9*, 44.

Brief, D. J., & Davis, J. D. (1984). Reduction of food intake and body weight by chronic intraventricular insulin infusion. *Brain research bulletin, 12*(5), 571-575.

Browning, K. N., Verheijden, S., & Boeckxstaens, G. E. (2017). The vagus nerve in appetite regulation, mood, and intestinal inflammation. *Gastroenterology, 152*(4), 730-744.

Brüning, J. C., Gautam, D., Burks, D. J., Gillette, J., Schubert, M., Orban, P. C., . . . Kahn, C. R. (2000). Role of brain insulin receptor in control of body weight and reproduction. *Science, 289*(5487), 2122-2125.

Bugajski, A., Gil, K., Ziomber, A., Żurowski, D., Zaraska, W., & Thor, P. (2007). Effect of long-term vagal stimulation on food intake. *Journal of physiology and pharmacology, 58*(1), 5-12.

Burneo, J., Faught, E., Knowlton, R., Morawetz, R., & Kuzniecky, R. (2002). Weight loss associated with vagus nerve stimulation. *Neurology, 59*(3), 463-464.

Chao, A., Grilo, C. M., White, M. A., & Sinha, R. (2014). Food cravings, food intake, and weight status in a community-based sample. *Eating behaviors, 15*(3), 478-482.

Charbonnier, L., van Meer, F., van der Laan, L. N., Viergever, M. A., & Smeets, P. A. M. (2016). Standardized food images: A photographing protocol and image database. *Appetite, 96*, 166-173. doi:10.1016/j.appet.2015.08.041

Chin-Chance, C., Polonsky, K. S., & Schoeller, D. A. (2000). Twenty-four-hour leptin levels respond to cumulative short-term energy imbalance and predict subsequent intake. *The Journal of Clinical Endocrinology & Metabolism, 85*(8), 2685-2691.

Collaborators, G. O. (2017). Health effects of overweight and obesity in 195 countries over 25 years. *New England Journal of Medicine, 377*(1), 13-27.

Connell, P. M., Finkelstein, S. R., Scott, M. L., & Vallen, B. (2018). Negative associations of frozen compared with fresh vegetables. *Appetite, 127*, 296-302.

Cork, S. C. (2018). The role of the vagus nerve in appetite control: Implications for the pathogenesis of obesity. *Journal of neuroendocrinology, 30*(11), e12643.

Cowdrey, F. A., Finlayson, G., & Park, R. J. (2013). Liking compared with wanting for high-and low-calorie foods in anorexia nervosa: aberrant food reward even after weight restoration. *The American journal of clinical nutrition, 97*(3), 463-470.

Dagher, A. (2012). Functional brain imaging of appetite. *Trends in Endocrinology & Metabolism, 23*(5), 250-260.

Dalton, M., & Finlayson, G. (2014). Psychobiological examination of liking and wanting for fat and sweet taste in trait binge eating females. *Physiology & behavior, 136*, 128-134.

Davis, E. A., Wald, H. S., Suarez, A. N., Zubcevic, J., Liu, C. M., Cortella, A. M., . . . Grill, H. J. (2020). Ghrelin signaling regulates feeding behavior, metabolism, and memory through the vagus nerve. *bioRxiv*.

de Araujo, I. E., Ferreira, J. G., Tellez, L. A., Ren, X., & Yeckel, C. W. (2012). The gut–brain dopamine axis: a regulatory system for caloric intake. *Physiology & behavior, 106*(3), 394-399.

de Araujo, I. E., Lin, T., Veldhuizen, M. G., & Small, D. M. (2013). Metabolic regulation of brain response to food cues. *Current Biology, 23*(10), 878-883.

de Araujo, I. E., Schatzker, M., & Small, D. M. (2019). Rethinking Food Reward. *Annu Rev Psychol*. doi:10.1146/annurev-psych-122216-011643

De Couck, M., Cserjesi, R., Caers, R., Zijlstra, W., Widjaja, D., Wolf, N., . . . Gidron, Y. (2017). Effects of short and prolonged transcutaneous vagus nerve stimulation on heart rate variability in healthy subjects. *Autonomic Neuroscience, 203*, 88-96.

de Lartigue, G. (2016). Role of the vagus nerve in the development and treatment of diet-induced obesity. *The Journal of physiology, 594*(20), 5791-5815.

de Lartigue, G., Dimaline, R., Varro, A., & Dockray, G. J. (2007). Cocaine-and amphetamine-regulated transcript: stimulation of expression in rat vagal afferent neurons by cholecystokinin and suppression by ghrelin. *Journal of Neuroscience, 27*(11), 2876-2882.

de Lartigue, G., Ronveaux, C. C., & Raybould, H. E. (2014). Deletion of leptin signaling in vagal afferent neurons results in hyperphagia and obesity. *Molecular metabolism, 3*(6), 595-607.

Ellrich, J. (2011). Transcutaneous vagus nerve stimulation. *Eur Neurol Rev, 6*(4), 254-256.

Fang, J., Rong, P., Hong, Y., Fan, Y., Liu, J., Wang, H., . . . Wang, L. (2016). Transcutaneous vagus nerve stimulation modulates default mode network in major depressive disorder. *Biological psychiatry, 79*(4), 266-273.

Farmer, A. D., Strzelczyk, A., Finisguerra, A., Gourine, A. V., Gharabaghi, A., Hasan, A., . . . Majid, A. (2021). International consensus based review and recommendations for minimum reporting standards in research on transcutaneous vagus nerve stimulation (version 2020). *Frontiers in human neuroscience, 14*, 409.

Farooqi, I. S., Jebb, S. A., Langmack, G., Lawrence, E., Cheetham, C. H., Prentice, A. M., . . . O'Rahilly, S. (1999). Effects of recombinant leptin therapy in a child with congenital leptin deficiency. *New England Journal of Medicine, 341*(12), 879-884.

Fernandes, A. B., da Silva, J. A., Almeida, J., Cui, G., Gerfen, C. R., Costa, R. M., & Oliveira-Maia, A. J. (2020). Postingestive modulation of food seeking depends on vagus-mediated dopamine neuron activity. *neuron, 106*(5), 778-788. e776.

Ferstl, M., Teckentrup, V., Lin, W. M., Kräutlein, F., Kühnel, A., Klaus, J., . . . Kroemer, N. B. (2020). Non-invasive vagus nerve stimulation boosts mood recovery after effort exertion. *bioRxiv*.

Fields, H. L., Hjelmstad, G. O., Margolis, E. B., & Nicola, S. M. (2007). Ventral tegmental area neurons in learned appetitive behavior and positive reinforcement. *Annu. Rev. Neurosci., 30*, 289-316.

Figlewicz, D., Evans, S., Murphy, J., Hoen, M., & Baskin, D. (2003). Expression of receptors for insulin and leptin in the ventral tegmental area/substantia nigra (VTA/SN) of the rat. *Brain research, 964*(1), 107-115.

Finlayson, G., Arlotti, A., Dalton, M., King, N., & Blundell, J. E. (2011). Implicit wanting and explicit liking are markers for trait binge eating. A susceptible phenotype for overeating. *Appetite, 57*(3), 722-728.

Finlayson, G., Bryant, E., Blundell, J. E., & King, N. (2009). Acute compensatory eating following exercise is associated with implicit hedonic wanting for food. *Physiology & behavior, 97*(1), 62-67.

Finlayson, G., King, N., & Blundell, J. E. (2007). Liking vs. wanting food: importance for human appetite control and weight regulation. *Neuroscience & Biobehavioral Reviews, 31*(7), 987-1002.

Food and Drug Administration, U. (2015). *FDA approves first-of-kind device to treat obesity*.

Frangos, E., Ellrich, J., & Komisaruk, B. R. (2015). Non-invasive access to the vagus nerve central projections via electrical stimulation of the external ear: fMRI evidence in humans. *Brain stimulation, 8*(3), 624-636.

Fulton, S., Pissios, P., Manchon, R. P., Stiles, L., Frank, L., Pothos, E. N., . . . Flier, J. S. (2006). Leptin regulation of the mesoaccumbens dopamine pathway. *neuron, 51*(6), 811-822.

Gil, K., Bugajski, A., & Thor, P. (2011). Electrical vagus nerve stimulation decreases food consumption and weight gain in rats fed a high-fat diet. *Journal of physiology and pharmacology, 62*(6), 637.

Grill, H. J., Schwartz, M. W., Kaplan, J. M., Foxhall, J. S., Breininger, J., & Baskin, D. G. (2002). Evidence that the caudal brainstem is a target for the inhibitory effect of leptin on food intake. *Endocrinology, 143*(1), 239-246.

Han, W., Tellez, L. A., Perkins, M. H., Perez, I. O., Qu, T., Ferreira, J., . . . Gao, X.-B. (2018). A neural circuit for gut-induced reward. *Cell, 175*(3), 665-678. e623.

Herman, C. P., & Polivy, J. (2010). Sex and gender differences in eating behavior. In *Handbook of gender research in psychology* (pp. 455-469): Springer.

Hommel, J. D., Trinko, R., Sears, R. M., Georgescu, D., Liu, Z.-W., Gao, X.-B., . . . DiLeone, R. J. (2006). Leptin receptor signaling in midbrain dopamine neurons regulates feeding. *neuron, 51*(6), 801-810.

Hopkins, M., Blundell, J., Halford, J., King, N., & Finlayson, G. (2000). The Regulation of Food Intake in Humans. In K. R. Feingold, B. Anawalt, A. Boyce, G. Chrousos, K. Dungan, A. Grossman, J. M. Hershman, G. Kaltsas, C. Koch, P. Kopp, M. Korbonits, R. McLachlan, J. E. Morley, M. New, L. Perreault, J. Purnell, R. Rebar, F. Singer, D. L. Trence, A. Vinik, & D. P. Wilson (Eds.), *Endotext*. South Dartmouth (MA).

Howland, R. H. (2014). Vagus nerve stimulation. *Current behavioral neuroscience reports, 1*(2), 64-73.

Ikramuddin, S., Blackstone, R. P., Brancatisano, A., Toouli, J., Shah, S. N., Wolfe, B. M., . . . Que, F. G. (2014). Effect of reversible intermittent intra-abdominal vagal nerve blockade on morbid obesity: the ReCharge randomized clinical trial. *Jama, 312*(9), 915-922.

Janssen, P., Vanden Berghe, P., Verschueren, S., Lehmann, A., Depoortere, I., & Tack, J. (2011). the role of gastric motility in the control of food intake. *Alimentary pharmacology & therapeutics, 33*(8), 880-894.

JASP team. (2019). JASP (Version 0.9.0)[Computer software].

Johnson, P. M., & Kenny, P. J. (2010). Dopamine D2 receptors in addiction-like reward dysfunction and compulsive eating in obese rats. *Nature neuroscience, 13*(5), 635.

Johnson, R. L., & Wilson, C. G. (2018). A review of vagus nerve stimulation as a therapeutic intervention. *Journal of inflammation research, 11*, 203.

Kaniusas, E., Kampusch, S., Tittgemeyer, M., Panetsos, F., Gines, R. F., Papa, M., . . . Tanghe, E. (2019). Current directions in the auricular vagus nerve stimulation I-a physiological perspective. *Frontiers in neuroscience, 13*, 854.

King, S., Isaacs, A., O'farrell, E., & Abizaid, A. (2011). Motivation to obtain preferred foods is enhanced by ghrelin in the ventral tegmental area. *Hormones and behavior, 60*(5), 572-580.

Kleiner, M., Brainard, D., & Pelli, D. (2007). What's new in Psychtoolbox-3?

Koepp, V., Klaus, J., Ferstl, M., Müller, F. K., Kühnel, A., & Kroemer, N. B. (2021, November 9). *Non-invasive Vagus Nerve Stimulation Normalizes Food Liking and Improves Liking Ratings in Depression.* PsyArXiv.

Koren, M. S., & Holmes, M. D. (2006). Vagus nerve stimulation does not lead to significant changes in body weight in patients with epilepsy. *Epilepsy & Behavior, 8*(1), 246-249.

Kraus, A. A., & Piqueras-Fiszman, B. (2018). Measuring implicit associations in food-related consumer research. In *Methods in Consumer Research, Volume 2* (pp. 203-230): Elsevier.

Kraus, T., Hösl, K., Kiess, O., Schanze, A., Kornhuber, J., & Forster, C. (2007). BOLD fMRI deactivation of limbic and temporal brain structures and mood enhancing effect by transcutaneous vagus nerve stimulation. *Journal of neural transmission, 114*(11), 1485-1493.

Kroemer, N. B., Krebs, L., Kobiella, A., Grimm, O., Pilhatsch, M., Bidlingmaier, M., . . . Smolka, M. N. (2013). Fasting levels of ghrelin covary with the brain response to food pictures. *Addiction biology, 18*(5), 855-862.

Kroemer, N. B., Krebs, L., Kobiella, A., Grimm, O., Vollstädt-Klein, S., Wolfensteller, U., . . . Smolka, M. N. (2013). (Still) longing for food: insulin reactivity modulates response to food pictures. *Human brain mapping, 34*(10), 2367-2380.

Kühnel, A., Teckentrup, V., Neuser, M. P., Huys, Q. J., Burrasch, C., Walter, M., & Kroemer, N. B. (2020). Stimulation of the vagus nerve reduces learning in a go/no-go reinforcement learning task. *European Neuropsychopharmacology, 35*, 17-29.

Lakens, D. (2013). Calculating and reporting effect sizes to facilitate cumulative science: a practical primer for t-tests and ANOVAs. *Frontiers in psychology, 4*, 863.

Li, H., Zhang, J.-B., Xu, C., Tang, Q.-Q., Shen, W.-X., Zhou, J.-Z., . . . Wang, Y.-P. (2015). Effects and mechanisms of auricular vagus nerve stimulation on high-fat-diet—induced obese rats. *Nutrition, 31*(11-12), 1416-1422.

Licinio, J., Caglayan, S., Ozata, M., Yildiz, B. O., De Miranda, P. B., O'Kirwan, F., . . . Bhasin, S. (2004). Phenotypic effects of leptin replacement on morbid obesity, diabetes mellitus, hypogonadism, and behavior in leptin-deficient adults. *Proceedings of the National Academy of Sciences, 101*(13), 4531-4536.

Lim, J., Wood, A., & Green, B. G. (2009). Derivation and evaluation of a labeled hedonic scale. *Chemical senses, 34*(9), 739-751.

Liu, J., Fang, J., Wang, Z., Rong, P., Hong, Y., Fan, Y., . . . Liu, C. (2016). Transcutaneous vagus nerve stimulation modulates amygdala functional connectivity in patients with depression. *Journal of affective disorders, 205*, 319-326.

Lonsdorf, T. B., Klingelhöfer-Jens, M., Andreatta, M., Beckers, T., Chalkia, A., Gerlicher, A., . . . Richter, J. (2019). Navigating the garden of forking paths for data exclusions in fear conditioning research. *Elife, 8*, e52465.

Lowe, M. R., Butryn, M. L., Didie, E. R., Annunziato, R. A., Thomas, J. G., Crerand, C. E., . . . Wallaert, M. (2009). The Power of Food Scale. A new measure of the psychological influence of the food environment. *Appetite, 53*(1), 114-118.

Malik, S., McGlone, F., Bedrossian, D., & Dagher, A. (2008). Ghrelin modulates brain activity in areas that control appetitive behavior. *Cell metabolism, 7*(5), 400-409.

Manta, S., El Mansari, M., Debonnel, G., & Blier, P. (2013). Electrophysiological and neurochemical effects of long-term vagus nerve stimulation on the rat monoaminergic systems. *International Journal of Neuropsychopharmacology, 16*(2), 459-470.

Mathar, D., Horstmann, A., Pleger, B., Villringer, A., & Neumann, J. (2016). Is it worth the effort? Novel insights into obesity-associated alterations in cost-benefit decision-making. *Frontiers in behavioral neuroscience, 9*, 360.

Meyers, E. E., Kronemberger, A., Lira, V., Rahmouni, K., & Stauss, H. M. (2016). Contrasting effects of afferent and efferent vagal nerve stimulation on insulin secretion and blood glucose regulation. *Physiological reports, 4*(4), e12718.

Mitchell, J., Pate, R., Beets, M., & Nader, P. (2013). Time spent in sedentary behavior and changes in childhood BMI: a longitudinal study from ages 9 to 15 years. *International journal of obesity, 37*(1), 54-60.

Montague, C. T., Farooqi, I. S., Whitehead, J. P., Soos, M. A., Rau, H., Wareham, N. J., . . . Hurst, J. A. (1997). Congenital leptin deficiency is associated with severe early-onset obesity in humans. *Nature, 387*(6636), 903-908.

Morton, G., Cummings, D., Baskin, D., Barsh, G., & Schwartz, M. (2006). Central nervous system control of food intake and body weight. *Nature, 443*(7109), 289-295.

Mueller, S. J., Teckentrup, V., Rebollo, I., Hallschmid, M., & Kroemer, N. B. (2021). Vagus nerve stimulation increases stomach-brain coupling via a vagal afferent pathway. *bioRxiv*.

Müller, F. K., Teckentrup, V., Kühnel, A., Ferstl, M., & Kroemer, N. B. (2022). Acute vagus nerve stimulation does not affect liking or wanting ratings of food in healthy participants. *Appetite, 169*, 105813. doi:10.1016/j.appet.2021.105813

Neuser, M. P., Teckentrup, V., Kühnel, A., Hallschmid, M., Walter, M., & Kroemer, N. B. (2020). Vagus nerve stimulation boosts the drive to work for rewards. *Nature communications, 11*(1), 1-11.

Nicola, S. M. (2016). Reassessing wanting and liking in the study of mesolimbic influence on food intake. *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology, 311*(5), R811-R840.

Obst, M. A., Heldmann, M., Alicart, H., Tittgemeyer, M., & Münte, T. F. (2020). Effect of short-term transcutaneous vagus nerve stimulation (tVNS) on brain processing of food cues: an electrophysiological study. *Frontiers in human neuroscience, 14*, 206.

Orben, A., Dienlin, T., & Przybylski, A. K. (2019). Social media's enduring effect on adolescent life satisfaction. *Proceedings of the National Academy of Sciences, 116*(21), 10226-10228.

Öztürk, L., Büning, P. E., Frangos, E., De Lartigue, G., & Veldhuizen, M. G. (2020). tVNS Increases Liking of Orally Sampled Low-Fat Foods: A Pilot Study. *Frontiers in human neuroscience, 14*, 505.

Palmiter, R. D. (2007). Is dopamine a physiologically relevant mediator of feeding behavior? *Trends in neurosciences, 30*(8), 375-381.

Palmiter, R. D. (2008). Dopamine signaling in the dorsal striatum is essential for motivated behaviors: lessons from dopamine-deficient mice. *Annals of the New York Academy of Sciences, 1129*, 35.

Pardini, A. W., Nguyen, H. T., Figlewicz, D. P., Baskin, D. G., Williams, D. L., Kim, F., & Schwartz, M. W. (2006). Distribution of insulin receptor substrate-2 in brain areas involved in energy homeostasis. *Brain research, 1112*(1), 169-178.

Pardo, J. V., Sheikh, S., Kuskowski, M. A., Surerus-Johnson, C., Hagen, M., Lee, J., . . . Adson, D. (2007). Weight loss during chronic, cervical vagus nerve stimulation in depressed patients with obesity: an observation. *International journal of obesity, 31*(11), 1756-1759.

Parker, B. A., Sturm, K., MacIntosh, C., Feinle, C., Horowitz, M., & Chapman, I. (2004). Relation between food intake and visual analogue scale ratings of appetite and other sensations in healthy older and young subjects. *European journal of clinical nutrition, 58*(2), 212-218.

Pecina, S., Cagniard, B., Berridge, K. C., Aldridge, J. W., & Zhuang, X. (2003). Hyperdopaminergic mutant mice have higher "wanting" but not "liking" for sweet rewards. *Journal of Neuroscience, 23*(28), 9395-9402.

Pelot, N. A., & Grill, W. M. (2018). Effects of vagal neuromodulation on feeding behavior. *Brain research, 1693*, 180-187.

Peuker, E. T., & Filler, T. J. (2002). The nerve supply of the human auricle. *Clinical Anatomy, 15*(1), 35-37.

Piqueras-Fiszman, B., Kraus, A. A., & Spence, C. (2014). "Yummy" versus "Yucky"! Explicit and implicit approach–avoidance motivations towards appealing and disgusting foods. *Appetite, 78*, 193-202.

Polak, T., Markulin, F., Ehlis, A.-C., Langer, J. B., Ringel, T. M., & Fallgatter, A. J. (2009). Far field potentials from brain stem after transcutaneous vagus nerve stimulation: optimization of stimulation and recording parameters. *Journal of neural transmission, 116*(10), 1237-1242.

Prentice-Dunn, H., & Prentice-Dunn, S. (2012). Physical activity, sedentary behavior, and childhood obesity: a review of cross-sectional studies. *Psychology, health & medicine, 17*(3), 255-273.

Quintana, D. S., & Williams, D. R. (2018). Bayesian alternatives for common null-hypothesis significance tests in psychiatry: a non-technical guide using JASP. *BMC psychiatry, 18*(1), 178.

R Core Team. (2019). R: A language and environment for statistical computing. (Version 3.6.0). Vienna, Austria: R Foundation for Statistical Computing.

Robinson, S., Sandstrom, S. M., Denenberg, V. H., & Palmiter, R. D. (2005). Distinguishing whether dopamine regulates liking, wanting, and/or learning about rewards. *Behavioral neuroscience, 119*(1), 5.

Rogers, P. J., & Hardman, C. A. (2015). Food reward. What it is and how to measure it. *Appetite, 90*, 1-15.

Roslin, M., & Kurian, M. (2001). The use of electrical stimulation of the vagus nerve to treat morbid obesity. *Epilepsy & Behavior, 2*(3), S11-S16.

Rothemund, Y., Preuschhof, C., Bohner, G., Bauknecht, H.-C., Klingebiel, R., Flor, H., & Klapp, B. F. (2007). Differential activation of the dorsal striatum by high-calorie visual food stimuli in obese individuals. *Neuroimage, 37*(2), 410-421.

Salamone, J. D., Correa, M., Farrar, A., & Mingote, S. M. (2007). Effort-related functions of nucleus accumbens dopamine and associated forebrain circuits. *Psychopharmacology, 191*(3), 461-482.

Sarr, M. G., Billington, C. J., Brancatisano, R., Brancatisano, A., Toouli, J., Kow, L., . . . Shikora, S. (2012). The EMPOWER study: randomized, prospective, double-blind, multicenter trial of vagal blockade to induce weight loss in morbid obesity. *Obesity surgery, 22*(11), 1771-1782.

Schneider, H. J., Friedrich, N., Klotsche, J., Pieper, L., Nauck, M., John, U., . . . Pittrow, D. (2010). The predictive value of different measures of obesity for incident cardiovascular events and mortality. *The Journal of Clinical Endocrinology & Metabolism, 95*(4), 1777-1785.

Schukro, R. P., Heiserer, C., Michalek-Sauberer, A., Gleiss, A., & Sator-Katzenschlager, S. (2014). The effects of auricular electroacupuncture on obesity in female patients–a prospective randomized placebo-controlled pilot study. *Complementary Therapies in Medicine, 22*(1), 21-25.

Schultz, W. (2016). Reward functions of the basal ganglia. *Journal of neural transmission, 123*(7), 679-693.

Schwartz, M. W., & Porte, D. (2005). Diabetes, obesity, and the brain. *Science, 307*(5708), 375-379.

Smeets, P. A., Erkner, A., & De Graaf, C. (2010). Cephalic phase responses and appetite. *Nutrition Reviews, 68*(11), 643-655.

Sobocki, J., Fourtanier, G., Estany, J., & Otal, P. (2006). Does vagal nerve stimulation affect body composition and metabolism? Experimental study of a new potential technique in bariatric surgery. *Surgery, 139*(2), 209-216. doi:10.1016/j.surg.2005.06.025

Sobocki, J., Krolczyk, G., Herman, R., Matyja, A., & Thor, P. (2005). Influence of vagal nerve stimulation on food intake and body weight-results of experimental studies. *Journal of physiology and pharmacology, 56*, 27.

Spence, M., Stancu, V., Dean, M., Livingstone, M. B. E., Gibney, E. R., & Lähteenmäki, L. (2016). Are food-related perceptions associated with meal portion size decisions? A cross-sectional study. *Appetite, 103*, 377-385.

Stauss, H. M., Stangl, H., Clark, K. C., Kwitek, A. E., & Lira, V. A. (2018). Cervical vagal nerve stimulation impairs glucose tolerance and suppresses insulin release in conscious rats. *Physiological reports, 6*(24), e13953.

Stefan, H., Kreiselmeyer, G., Kerling, F., Kurzbuch, K., Rauch, C., Heers, M., . . . Pauli, E. (2012). Transcutaneous vagus nerve stimulation (t-VNS) in pharmacoresistant epilepsies: A proof of concept trial. *Epilepsia, 53*(7), e115-e118.

Szczypka, M. S., Kwok, K., Brot, M. D., Marck, B. T., Matsumoto, A. M., Donahue, B. A., & Palmiter, R. D. (2001). Dopamine production in the caudate putamen restores feeding in dopamine-deficient mice. *neuron, 30*(3), 819-828.

Tan, H.-E., Sisti, A. C., Jin, H., Vignovich, M., Villavicencio, M., Tsang, K. S., . . . Zuker, C. S. (2020). The gut–brain axis mediates sugar preference. *Nature, 580*(7804), 511-516.

Tang, D. W., Fellows, L. K., & Dagher, A. (2014). Behavioral and neural valuation of foods is driven by implicit knowledge of caloric content. *Psychological Science, 25*(12), 2168-2176.

Tang, D. W., Fellows, L. K., Small, D. M., & Dagher, A. (2012). Food and drug cues activate similar brain regions: a meta-analysis of functional MRI studies. *Physiology & behavior, 106*(3), 317-324.

Teckentrup, V., Neubert, S., Santiago, J. C. P., Hallschmid, M., Walter, M., & Kroemer, N. B. (2020). Non-invasive stimulation of vagal afferents reduces gastric frequency. *Brain stimulation, 13*(2), 470-473. doi:10.1016/j.brs.2019.12.018

Tellez, L. A., Han, W., Zhang, X., Ferreira, T. L., Perez, I. O., Shammah-Lagnado, S. J., . . . De Araujo, I. E. (2016). Separate circuitries encode the hedonic and nutritional values of sugar. *Nature neuroscience, 19*(3), 465.

Tellez, L. A., Medina, S., Han, W., Ferreira, J. G., Licona-Limón, P., Ren, X., . . . De Araujo, I. E. (2013). A gut lipid messenger links excess dietary fat to dopamine deficiency. *Science, 341*(6147), 800-802.

Temple, J. L., Bulkley, A. M., Badawy, R. L., Krause, N., McCann, S., & Epstein, L. H. (2009). Differential effects of daily snack food intake on the reinforcing value of food in obese and nonobese women. *The American journal of clinical nutrition, 90*(2), 304-313.

Travagli, R. A., & Anselmi, L. (2016). Vagal neurocircuitry and its influence on gastric motility. *Nature Reviews Gastroenterology & Hepatology, 13*(7), 389.

Trevizol, A. P., Taiar, I., Barros, M. D., Liquidatto, B., Cordeiro, Q., & Shiozawa, P. (2015). Transcutaneous vagus nerve stimulation (tVNS) protocol for the treatment of major depressive disorder: A case study assessing the auricular branch of the vagus nerve. *Epilepsy & Behavior, 53*, 166-167.

Uematsu, A., Tsurugizawa, T., Uneyama, H., & Torii, K. (2010). Brain–gut communication via vagus nerve modulates conditioned flavor preference. *European Journal of Neuroscience, 31*(6), 1136-1143.

Val-Laillet, D., Aarts, E., Weber, B., Ferrari, M., Quaresima, V., Stoeckel, L., . . . Stice, E. (2015). Neuroimaging and neuromodulation approaches to study eating behavior and prevent and treat eating disorders and obesity. *NeuroImage: Clinical, 8*, 1-31.

Val-Laillet, D., Biraben, A., Randuineau, G., & Malbert, C.-H. (2010). Chronic vagus nerve stimulation decreased weight gain, food consumption and sweet craving in adult obese minipigs. *Appetite, 55*(2), 245-252.

van der Laan, L. N., De Ridder, D. T., Viergever, M. A., & Smeets, P. A. (2011). The first taste is always with the eyes: a meta-analysis on the neural correlates of processing visual food cues. *Neuroimage, 55*(1), 296-303.

Van Leusden, J. W., Sellaro, R., & Colzato, L. S. (2015). Transcutaneous Vagal Nerve Stimulation (tVNS): a new neuromodulation tool in healthy humans? *Frontiers in psychology, 6*, 102.

Vijgen, G. H., Bouvy, N. D., Leenen, L., Rijkers, K., Cornips, E., Majoie, M., . . . van Marken Lichtenbelt, W. D. (2013). Vagus nerve stimulation increases energy expenditure: relation to brown adipose tissue activity. *PLoS One, 8*(10).

Volkow, N. D., Wang, G.-J., & Baler, R. D. (2011). Reward, dopamine and the control of food intake: implications for obesity. *Trends in cognitive sciences, 15*(1), 37-46.

Volkow, N. D., Wang, G. J., Fowler, J. S., Logan, J., Jayne, M., Franceschi, D., . . . Ding, Y. S. (2002). “Nonhedonic” food motivation in humans involves dopamine in the dorsal striatum and methylphenidate amplifies this effect. *Synapse, 44*(3), 175-180.

Wall, K. M., Farruggia, M. C., Perszyk, E. E., Kanyamibwa, A., Fromm, S., Davis, X. S., . . . Small, D. M. (2020). No evidence for an association between obesity and milkshake liking. *International journal of obesity*, 1-10.

Wang, G.-J., Volkow, N. D., Logan, J., Pappas, N. R., Wong, C. T., Zhu, W., . . . Fowler, J. S. (2001). Brain dopamine and obesity. *The Lancet, 357*(9253), 354-357.

Williams, E. K., Chang, R. B., Strochlic, D. E., Umans, B. D., Lowell, B. B., & Liberles, S. D. (2016). Sensory neurons that detect stretch and nutrients in the digestive system. *Cell, 166*(1), 209-221.

Wren, A., Seal, L., Cohen, M., Brynes, A., Frost, G., Murphy, K., . . . Bloom, S. (2001). Ghrelin Enhances Appetite and Increases Food Intake in Humans. *The Journal of Clinical Endocrinology & Metabolism, 86*(12), 5992-5992.

Yakunina, N., Kim, S. S., & Nam, E. C. (2017). Optimization of transcutaneous vagus nerve stimulation using functional MRI. *Neuromodulation: technology at the neural interface, 20*(3), 290-300.

Yao, G., Kang, L., Li, J., Long, Y., Wei, H., Ferreira, C. A., . . . Wang, X. (2018). Effective weight control via an implanted self-powered vagus nerve stimulation device. *Nature communications, 9*(1), 1-10.

Yuan, H., & Silberstein, S. D. (2016). Vagus nerve and vagus nerve stimulation, a comprehensive review: part I. *Headache: The Journal of Head and Face Pain, 56*(1), 71-78.

7. Erklärung zum Eigenanteil

Die Arbeit „The impact of acute transcutaneous auricular vagus nerve stimulation on food cue reactivity in healthy humans" wurde an der Universitätsklinik für Psychiatrie und Psychotherapie Tübingen unter Betreuung von PD Dr. Nils Kroemer durchgeführt.

Ein Teil der in dieser Dissertation präsentierten Ergebnisse wurde bereits in einem von mir als Erstautorin verfassten Manuskript in der Zeitschrift *Appetite* veröffentlicht:

Müller, F. K., Teckentrup, V., Kühnel, A., Ferstl, M., & Kroemer, N. B. (2022). Acute vagus nerve stimulation does not affect liking or wanting ratings of food in healthy participants. *Appetite, 169*, 105813. doi:10.1016/j.appet.2021.105813

Übernahmen aus dieser Publikation sind als solche gekenzeichnet.

Die Konzeption der Studie erfolgte durch PD Dr. Nils Kroemer. Sämtliche Versuche wurden (nach Einarbeitung durch Monja Neuser, mich oder durch weitere Labormitglieder) von mir, Monja Neuser, Caroline Burrasch, Moritz Hernker, Irina Herber, Magdalena Ferstl, Sandra Neubert, Leonie Osthof, Maike Klett und Emily Corwin-Renner durchgeführt.

Eine Voranalyse der durch MATLAB generierten Rohdaten wurde durch PD Dr. Nils Kroemer durchgeführt. Die weitere statistische Auswertung erfolgte nach Anleitung von PD Dr. Nils Kroemer durch mich. Übernommene Abbildungen aus meiner Publikation (Müller et al., 2022) sind als solche gekennzeichnet. Alle anderen Abbildungen wurden von mir selbst erstellt.

Ich versichere, das Manuskript selbstständig verfasst zu haben und keine weiteren als die von mir angegebenen Quellen verwendet zu haben.

Tübingen, den 24.03.2022

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