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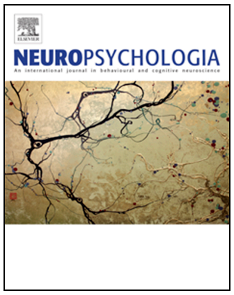

Transcutaneous vagus nerve stimulation improves interoceptive accuracy

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Abstract

How can interoceptive accuracy, i.e. the objective ability to identify interoceptive signals, be improved? In the present study, we investigated whether non-invasive stimulation of the auricular branch of the vagus nerve (taVNS) modulates cardiac interoceptive accuracy, interoceptive sensibility, i.e. confidence in the identification of bodily signals, and interoceptive awareness, i.e. the capacity to evaluate one's ability in the objective task. Using a single-blind within-subjects design we compared participants' performance on the heartbeat counting task and on the heartbeat discrimination task during active and sham taVNS stimulation. Results revealed improved accuracy during active taVNS on the heartbeat discrimination task but not on the heartbeat counting task. Participants were also more confident during active stimulation, but interoceptive awareness was not modulated by taVNS. These findings show that taVNS can modulate interoceptive processing and suggest its potential as a tool to investigate body-brain interactions.

Impact Statement (max words: 100)

The vagus nerve is a major component of the parasympathetic system and one of the most important pathways between the internal body organs and the brain. However, evidence of its role in the conscious perception of interoceptive sensations is still lacking. Here, we show that the non-invasive stimulation of the auricular branch of the vagus nerve (taVNS) increases the ability to correctly identify own heartbeats. These findings enhance our understanding of the mechanisms underlying the conscious perception of heartbeats and demonstrate the potential of taVNS as an important tool to manipulate interoceptive processing and investigate brain-body interactions.

1. Introduction

Interoception refers predominantly to the processing and central representation of signals arising from within the body. The term was first introduced by Sherrington in 1906 and the concept of interoception has been developing ever since with different authors arguing for a more inclusive definition, while others remain focused on visceral signals only (e.g., Ceunen, Vlaeyen, & Van Diest, 2016; Craig, 2002; Critchley & Garfinkel, 2017). There is, however, a generalized consensus that interoception should be perceived as a multi-dimensional phenomenon (Garfinkel, Seth, Barrett, Suzuki & Critchley 2015; Khalsa et al., 2018; A. Schulz & Vögele, 2015). For example, Garfinkel and colleagues (2015) distinguished three dimensions of interoception: accuracy, sensibility, and awareness. Interoceptive accuracy (IAcc) refers to the ability to accurately detect internal bodily sensations and represents an objective measure of behavioural performance; interoceptive sensibility refers to self-evaluated, dispositional tendencies to interpret interoceptive sensations and thus represents a subjective dimension; interoceptive awareness refers to a metacognitive ability and reflects the correspondence between objective and subjective measures.

The cardiovascular system has been the main target to gauge interoception by focusing on interoceptive accuracy (IAcc). There are two widely used methods to measure cardiac IAcc, the heartbeat counting task (HCT; Schandry, 1981) and heartbeat discrimination tasks (HDT; Whitehead, Drescher, Heiman, & Blackwell, 1977; Ring & Brener, 2018). Both involve the perception of heartbeats as discrete interoceptive events. During the HCT participants are asked to silently count individual heartbeats for predetermined time-intervals and without taking their pulse. The number of counted heartbeats is compared with the actual number of heartbeats they had to form an accuracy index. Performance in this task has been shown to correlate with several dimensions of human cognition, ranging from the intensity of emotional experience and psychopathology (Dunn, Dalgleish, Ogilvie, & Lawrence, 2007; Ehlers & Breuer, 1992) to decision-making (Dunn et al., 2010;

Lenggenhager, Azevedo, Mancini, & Aglioti, 2013). The HCT presents some advantages over other methods, such as easiness of administration, but it has been subject to important criticisms (Murphy, Brewer, Hobson, Catmur, & Bird, 2018; Ring, Brener, Knapp, & Mailloux, 2015; Zamariola, Maurage, Luminet, & Corneille, 2018). The fact that performance in this task does not require actual online heartbeat perception and that it may be influenced by previous knowledge of one's own heart rate are among the limitations. However, performance in the task has theoretical and predictive validity in domains where interoceptive accuracy is thought to play a role, such as emotion processing and various sub-clinical and clinical conditions (Badoud & Tsakiris, 2017; Herbert & Pollatos, 2012; Khalsa et al., 2018; Quadt, Critchley, & Garfinkel, 2018).

For the HDT, the second most used IAcc measure, participants are asked to judge if a train of ten auditory tones are delivered in synchrony (200ms after the ECG's R-peak) or asynchrony (500ms after the ECG's R-peak) with their own heartbeats. Performance in the HDT has been shown to be associated, among other things, with the intensity of emotional experience (Barrett, Quigley, Bliss-Moreau, & Aronson, 2004; Katkin, Wiens, & Öhman, 2001; Wiens, Mezzacappa, & Katkin, 2000) and anxiety (Critchley, Wiens, Rotshtein, Öhman, & Dolan, 2004). Because accurate responding in the HDT requires online heartbeat perception and is not influenced by previous beliefs and expectations, it has been suggested that this task, or variations of this task (e.g., Ring & Brener, 2018), constitute a more valid method to assess cardiac IAcc (Kleckner, Wormwood, Simmons, Barrett, & Quigley, 2015; Ring & Brener, 2018; Ring et al., 2015).

At the neural level, the cortical correlates of cardioception have been linked to the insula, the anterior cingulate and the prefrontal and somatosensory cortices (Critchley et al., 2004; Pollatos, Gramann, & Schandry, 2007; S. M. Schulz, 2016). Nonetheless, and while the anatomical afferent pathways conveying visceral information to the brain are fairly well understood, the neurophysiological mechanisms underlying the conscious perception of cardiac signals remain subject to debate. The most prominent hypothesis posits that cardiac sensations depend on the stimulation of mechanoreceptors (i.e., baroreceptors) in the heart or in the surrounding major arteries, such as the aortic arch, by the pressure wave generated by the blood ejected at each heartbeat (Cameron, 2002; Critchley & Harrison, 2013). These signals are carried by the cranial nerves X (i.e., vagus nerve) and IX (i.e., glossopharyngeal nerve) to the Nucleus Tractus Solitarius (NTS) in the brainstem from where they are relayed, through thalamocortical projections, to higher order structures such as the insula, a structure well known for its role in the processing of interoceptive sensations (Craig, 2002; Critchley et al., 2004).

The vagus nerve, i.e. the X cranial nerve, is part of the parasympathetic division of the autonomic nervous system and one of the most important communication pathways between the body and the brain (Cameron, 2002; Critchley & Harrison, 2013) conveying afferent signals from the major internal organs, including the heart. This information is funnelled into the NTS of the brainstem, a major interoceptive hub for homeostatic control with direct ascending projections to the monoaminergic neuromodulatory system (Critchley & Harrison, 2013). Capitalising on these projections, direct stimulation of the vagus nerve (VNS), through an electrical device implanted in the upper chest, has been used as a treatment for a wide range of neurologic and psychiatric disorders, such as refractory epilepsy and depression (Beekwilder & Beems, 2010). In 2000, Ventureyra developed taVNS, an alternative, non-invasive approach, consisting in the application of mild electrical current to the auricular branch of the vagus nerve whose fibres are found in the tragus and the cymba conchae of the auricle (Peuker & Filler, 2002). Since then, several fMRI studies confirmed that taVNS modulates brain activity in those areas identified by VNS, such as brainstem regions, thalamus, amygdala and insula (Badran, Dowdle, et al., 2018; Dietrich et al., 2008; Frangos, Ellrich, & Komisaruk, 2015; Kraus et al., 2007; Kraus et al., 2013), many of them known to be involved in the regulation of autonomic activity.

Research on taVNS initially focused on investigating the possible clinical applications of this stimulation, but there is now a growing interest in taVNS as a tool to modulate cognitive and emotional processes (Colzato, Sellaro, & Beste, 2017; Keute, Ruhnau, Heinze, & Zaehle, 2018, Ventura-Bort et al., 2018). For instance, a recent study found that taVNS modulates flow absorption (Colzato, Wolters & Peifer, 2018), a psychophysiological state related to sustained attention to external tasks and diminished self-awareness (Sheldon, Prentice & Halusic, 2014). Other studies have shown that taVNS enhances emotion recognition of others' faces and bodies (Colzato et al., 2017; Sellaro, de Gelder, Finisguerra, & Colzato, 2018) and may accelerate fear extinction (Burger et al., 2016; but see Genheimer, Andreatta, Asan, & Pauli, 2017). However, it is still unclear whether these effects are mediated by changes in the representation of physiological activity. Research investigating the impact of taVNS on autonomic activity has presented, so far, conflicting evidence. Some studies found taVNS modulation of physiological indices, such as heart rate and heart rate variability and blood pressure (Antonino et al., 2017; Badran, Mithoefer, et al., 2018; Clancy et al., 2014) while other studies failed to observe such effects (e.g., Burger et al., 2016; Colzato et al., 2017). Indeed, despite the fundamental role of the vagus nerve in the communication and regulation of physiological activity, little attention has been given to its effects in the processing of the actual physiological signals and how this may be linked to their awareness.

The main purpose of this study was to test the potential of taVNS in the modulation of interoceptive processing. To that end, we used a within-subjects design to compare participants' accuracy in the HCT and HDT during active and sham taVNS. Since tavNS modulates activity within the interoceptive neural network (Badran et al., 2018), we predicted that taVNS would lead to increased accuracy in both tasks. We also tested participants' interoceptive sensitivity and interoceptive (meta-) awareness, but had no specific prediction regarding the effect of taVNS on these dimensions. Finally, we measured several physiological indices, such as heart rate variability, heart rate and blood pressure. Given the contrasting findings observed in the literature, we had no specific predictions regarding the effects of taVNS in autonomic activity. However, these variables were collected to be used as covariates in our main analyses looking at changes in IAcc as a function of stimulation type.

2. Methods

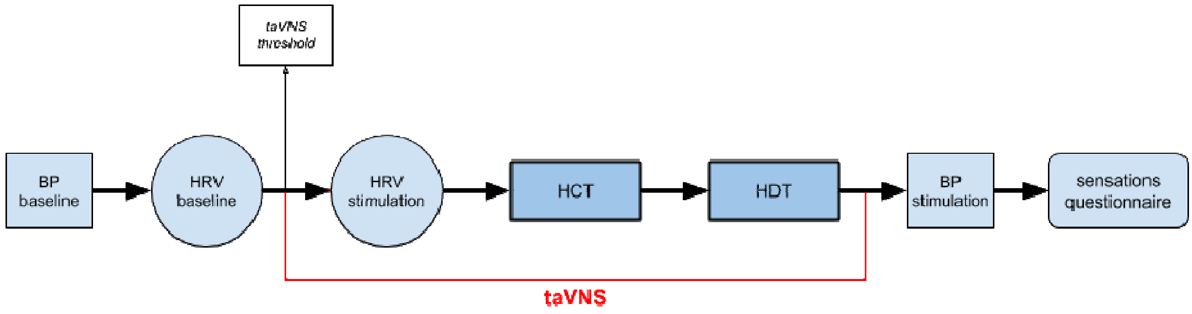
2.1 Participants

Following recent recommendations to achieve sufficient reliability ($r_{true} > 0.35$) in the HDT (Kleckner et al., 2015), the task consisted of 50 trials and the sample size was set to 45. A power analyses (G* Power – Faul, Edgar Erdfelder, & Buchner, 2007; www.gpower.hhu.de/), based on a previous report (Colzato et al., 2018) of taVNS modulation on the experience of flow absorption (effect size: η2p=0.191), estimated the need for 37 participants to detect a significant effect (α=0.05) with 80% power. Fifty-one volunteers (17 males; mean age=21.1, sd=3.1) were recruited for the present study. Data from five participants were excluded due to noisy ECG (n=3) or technical difficulties with the stimulation (n=2). Thus, the final sample consisted of 46 subjects (14 males; mean age=21.2, sd=3.1). A screening form was administered to all participants to assess their eligibility to undergo taVNS. Only volunteers who met the following inclusion criteria were tested: no personal/familiar history of neuro-psychiatric, cardiovascular and/or respiratory disorders; no metal/implants fitted into the body; not currently pregnant; no alcohol/drugs taken 24 h prior to the experiment. Eligible participants were given oral and written explanation about the study procedure and were informed about the possible taVNS-induced adverse side effects, i.e. itching, burning sensations under the electrodes and mild headache. All participants gave written informed consent prior to the experiment and received £20 as compensation for their time. The study was approved by the University's Ethical Committee at Royal Holloway University of London.

2.2 Transcutaneous auricular vagus nerve stimulation

A single blind, sham-controlled, within-subjects design was used to assess the effects of online taVNS on the ability to attend cardiac bodily signals. All participants carried out two identical experimental sessions, at least one week apart, differing only in the stimulation type: active or sham taVNS (see Figure 1). The session order was randomized. Stimulation was delivered using the Transcutaneous

Electrical Nerve Stimulation device (V-TENS Plus; https://bodyclock.co.uk/) with a custom-built clip electrode (cf. Clancy et al., 2014). During active taVNS, the electrode was placed on the anterior wall of the external ear canal corresponding to the participant's tragus. Sham taVNS was performed by placing the electrode on the left earlobe, an area of the auricle which is known to be free of vagal endings (Peuker & Filler, 2002). Current was applied continuously with the following parameters: pulse width=250µs, frequency=25Hz. The intensity of stimulation was individually tailored to a level just above the participant's perceptual threshold. To achieve this, the experimenter slowly increased the amplitude until the participant reported some sensations (e.g., tingling), which could be barely detected and did not cause neither pain nor discomfort. The same procedure was adopted for active and sham stimulation. Once initiated, the stimulation was applied throughout the session for an average duration of 37min (sd=3min)[1]. At the end of each session, participants completed a questionnaire, consisting of 8 items to be rated on a Likert scale (1 – not at all; 5 – extremely), to assess sensations and adverse effects they might have felt due to the stimulation (cf. Colzato et al., 2017). Average ratings for each session were compared with Wilcoxon signed rank test with continuity correction revealing significantly (W=350.5, p=0.043) higher average discomfort ratings during active taVNS (mean=1.26, sd=0.23) than during sham (mean=1.18, sd=0.18). However, reported sensations were rather mild and none of the participants reported major complaints or discomfort during or after taVNS. Average sensation scores were tested as covariates in the regression models (see below).



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[1] Variations in total time of stimulation depended on participant's HR and response speed, which was constrained to a fixed duration for both tasks (up to 20 seconds in the HCT and up to 7 seconds in the HDT).

Figure 1. Experimental procedure carried out for both active and sham taVNS sessions (counterbalanced).

2.3 Physiological measures

In order to record participants' ECG, two electrodes were attached under the left and right clavicle and one on the left lower back, within the ribcage frame. The ECG signal was recorded using a Powerlab 8/35 box (Bio Amp 132) and LabChart 8 software (https://www.adinstruments.com). The sampling rate was 1 kHz and a hardware band-pass filter between 0.3 and 1,000 Hz was applied as well as a 50 Hz notch filter to reduce electrical noise. During the HDT, heartbeats were detected online with the LabChart's fast response output function, a hardware-based function that identifies, with minimal delays (~1ms), the R-wave each time the ECG amplitude exceeds an individually-tailored threshold. We also collected blood pressure (BP), heart rate (HR) and heart rate variability (HRV) before and during stimulation. HR and HRV were calculated offline with a LabChart dedicated toolbox (maximum frequency = 0.5 Hz, number of frequencies = 500; VLF = 0-0.04 Hz, LF = 0.04-0.15, HF = 0.15-0.45 Hz) over 5-minute recordings of rest-ECG immediately before (baseline) and immediately after stimulation start (stimulation). The main index of interest was high frequency HRV (HF-HRV) because it is generally regarded a proxy of vagal tone. However, the ratio between low and high frequencies HRV (LF/HF-HRV) was also used because it has been previously found to be modulated by taVNS (Clancy et al., 2014). BP was measured using an Omron BP629N monitor (www.omronhealthcare.com) wrapped around the left wrist[2]. The average of two measurements taken before stimulation (BP-baseline) and two taken immediately after stimulation completion (BP-stimulation) were used to test for taVNS-induced changes in BP (data from 4 participants was lost due to equipment failure).

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[2] this type of device may not be ideal to detect small variations in BP, continuous beat-to-beat BP measurements should be used to adequately assess the effect of taVNS on BP.

2.4 Interoceptive accuracy tasks

Two methods were used to assess interoceptive accuracy: the heartbeat counting task (HCT; Schandry, 1981) and the heartbeat discrimination task (HDT; Whitehead et al., 1977). In the HCT, participants were instructed to silently count their heartbeats over six trials of different duration (21s, 25s, 33s, 47s, 55s, and 74s). An auditory tone signalled the beginning of the trial and a second one signalled its end. Participants were then asked to input the number of counted heartbeats. The order of each trial was randomised and an accuracy score was computed according to the equation below:

$$\frac{1}{6}\sum 1 - \frac{(|HB_{counted} - HB_{recorded}|)}{HB_{recorded}}$$

In the HDT, participants listened to sequences of ten auditory tones. The sequences could be either synchronous (200ms after R wave) or asynchronous (500ms after R wave) with the participants' heartbeats. Participants were instructed to focus on their cardiac sensations and asked to discriminate between synchronous and asynchronous sequences by pressing one of two keys on a keyboard. After that, they were asked to rate their confidence about their response on a visual analogue scale (1 – not confident at all; 100 – extremely confident). The procedure was repeated fifty times (25 synchronous and 25 asynchronous trials) to ensure sufficient reliability (Kleckner et al., 2015) and the order of trials was fully randomised. The accuracy score for this task was computed as the percentage of correctly identified trials. Confidence ratings were collected after each trial to estimate interoceptive sensibility and meta-awareness.

During both tasks, participants sat upright in a dimly lit room to avoid distractions and were not allowed to take their pulse throughout the experiment. All subjects did one practice trial for the HCT and three practice trials for the HDT. The HCT was always carried out before the HDT to prevent that knowledge about own-heart rhythm gathered during the HDT from biasing performance on the HCT

(Ring & Brener, 2018). We have no reasons to believe that carrying out the HCT may contaminate performance on the HDT. The HCT lasted approximately 10 minutes and the HDT lasted approximately 20 minutes.

2.5 Data analyses

Interoceptive accuracy – data from both tasks was analysed with mixed-model regressions using the lme4 v1.1 -17 package (Bates, Mächler, Bolker, & Walker, 2014) available for R software (R Core Team, 2013) with participant's ID as a priori random factor, i.e. the model allowed subject-specific intercepts, and stimulation type (1=taVNS; 0=sham) as a dummy predictor. The covariates – session (1=first session; 2=second session), HF-HRV (during stimulation), HR, BMI, age, gender (1=male; 2=female) and average reported stimulation sensations – were sequentially entered in the model as fixed factors (and random slopes) and retained whenever improving model fit ($p<0.05$). Model comparisons and statistical significance of each predictor of the final model were carried out through loglikelihood ratio statistics asymptotically approximated to a χ^2 distribution (Barr, 2013), using the *anova* and *drop1* functions, respectively. Shapiro-Wilk test was used to test the normality of the DVs. When data was not normally distributed, the function *descdist* of the *fitdistrplus* package (Delignette-Muller & Dutang, 2015) was used to select the distribution that better fitted the data.

Interoceptive sensibility – Average confidence ratings given in each session were estimated to create an index of interoceptive sensibility. It should be noted that this measure is independent of the actual (trial-by-trial) accuracy and reflects the participant's beliefs about their ability to perform the task.

Interoceptive awareness – Trial-by-trial confidence ratings were combined with objective (type-I) performance to estimate participant's metacognitive ability (type-II performance). A close correspondence between accuracy and confidence (e.g., incorrect trials with low confidence and correct trials with high confidence), indicates good knowledge of the ability to perform the task, i.e. a high metacognitive ability. To estimate this type-II performance index we used a measure (meta-d';

sum-square error approach) developed by Maniscalco and Lau (2012, http://www.columbia.edu/~bsm2105/type2sdt/; see also Fleming & Lau, 2014; Azevedo, Aglioti, & Lenggenhager, 2016). This method is conceptually similar to other approaches, such as the type 2 Receiver Operator Curve (cf. Garfinkel et al., 2015), but is more robust to variations in type-I performance and to response biases (Fleming & Lau, 2014).

The final model for IAcc on the HDT was:

HDT_final = glmer(IAcc_HDT ~ stimulation + HF-HRV_stimulation + (1 + HF-HRV_stimulation|participant), data=HDT, family=gaussian(link="log"))

The final model for IAcc on the HCT was:

HCT_final = lmer(IAcc_HCT ~ stimulation+ HR_stimulation + (1|participant), data=HCT)

The final model for interoceptive sensibility on the HDT was:

Sensibility_HDT_final = glmer(Confidence ~ stimulation + (1 |participant), data=HDT, family=gaussian(link="log"))

The final model for interoceptive awareness on the HDT was:

Meta_HDT_final = lmer(Meta_HDT ~ stimulation + BMI + (1|participant), data=HDT)

Physiological measures – To test potential effects of taVNS on HRV, HR and BP, we divided the values acquired during stimulation with those measured during the baseline period, and compared the resulting indices for each stimulation type with paired t-tests or Wilcoxon signed rank tests when the variables were not normality distributed.

3. Results

Heartbeat discrimination task. Results showed improved accuracy during active taVNS (mean=0.58; sd=0.11) compared to sham (mean=0.55; sd=0.091) stimulation (χ^2=6.86, p=0.009; see Figure 2A)[3]. None of the covariates, nor their interaction with stimulation type, were found to significantly predict accuracy in HDT. A significant difference was also found for interoceptive sensibility (χ^2=10.34, p=0.0013), reflecting higher confidence during active (mean=32.55; sd=6.26) than sham (mean=31.80; sd=7.05) stimulation. None of the covariates were significant. Conversely, stimulation type was not associated with changes in metacognitive awareness (χ^2=0.063, p=0.80; active: mean=0.25; sd=0.8; sham: mean=0.22; sd=0.48). Only a negative relationship between BMI and interoceptive awareness was found (χ^2=7.48, p=0.006).

Heartbeat counting task. Accuracy on the HCT did not differ (χ^2=0.75, p=0.39) between taVNS (mean=0.64, sd=0.18) and sham (mean=0.65, sd=0.18) stimulation. HR during stimulation (χ^2=4.74, p=0.03) was found to be negative predictor of accuracy.

Physiological measures. No significant differences between stimulation types were observed in any of the physiological measures: HF-HRV (active: mean=1.16, sd=0.48; sham: mean=1.19, sd=0.50; W=528, p=0.90); LF/HF-HRV (active: mean=0.95, sd=0.63; sham: mean=0.94, sd=0.49; W=556, p=0.87) , HR (active: mean=0.97, sd=0.03; sham: mean=0.97, sd=0.04; t(45)=0.03, p=0.97); systolic BP (active: mean=0.96, sd=0.06; sham: mean=0.96, sd=0.06; t(40)=-0.18, p=0.86) and diastolic BP (active: mean=0.99, sd=0.09; sham: mean=0.99, sd=0.09; t(40)=-0.14, p=0.89).

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[3] Equivalent results are observed (χ^2=5.17, p=0.023) when replacing the covariate HF-HRV index with LF/HF-HRV or when excluding data from 4 outliers (χ^2=4.81, p=0.028), defined as those in which the difference of accuracy scores between the two session exceeded ± 2.5 standard deviations from the mean difference.

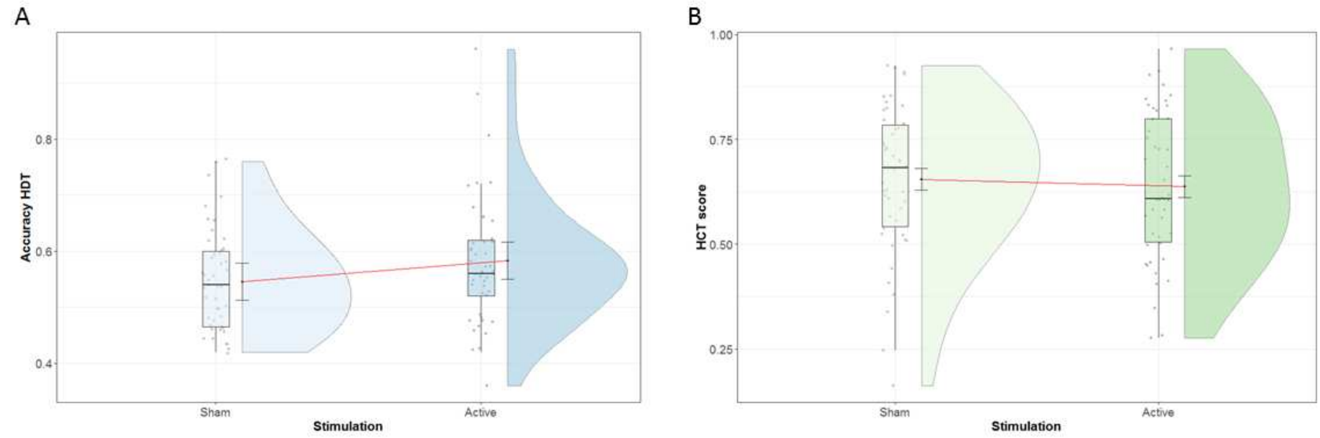

Figure 2. Accuracy in the A) heartbeat discrimination task (HDT) and in the B) heartbeat counting task (HCT) as a function of stimulation type. The raincloud plots (Allen, Poggiali, Whitaker, Marshall, & Kievit, 2018) provide a comprehensive descriptive representation of accuracy scores during sham (lighter colour) and active (darker colour) stimulation. The red lines correspond to the fitted values, with error bars, and represent the main effect of stimulation that was found to be significant in the HDT but not in the HCT.

4. Discussion

We investigated the effects of taVNS on the ability to accurately detect and report heartbeats. Active and sham taVNS stimulation were applied on different sessions while participants performed the two most widely used tasks to measure cardiac IAcc: the heartbeat counting task (HCT) and the heartbeat detection task (HDT). Confidence ratings were also collected during the HDT to assess the potential impact of taVNS on interoceptive meta-awareness. The pattern of results observed here partially supports our predictions, given that accuracy during active (vs sham) stimulation was higher on the HDT, but not on the HCT. Additionally, while participants tended to be more confident in their synchrony judgments (i.e. interoceptive sensibility), no significant differences were found on interoceptive awareness scores as a function of stimulation. Importantly, we adopted a within-subjects design and controlled for several variables known to impact performance on both tasks, such as HRV, HR, BMI and gender (Grabauskaitė, Baranauskas, & Griškova-Bulanova, 2017; Herbert & Pollatos, 2014; Rouse, Jones, & Jones, 1988). We also measured several indices of autonomic activity before and after stimulation but found no significant differences as a function of stimulation type. Together, these findings demonstrate the potential of taVNS on the modulation of interoceptive processing.

The fact that we found improved accuracy during active taVNS in the HDT but not in the HCT is likely due to methodological differences between these two tasks. The HCT can be influenced by higher-order factors, such as the previous knowledge of one's own heart-rate, and does not necessarily require online conscious perception of heartbeats. At least some of our participants may partially rely on strategies unrelated to online heartbeat perception to count heartbeats, making the HCT less sensitive to manipulations that induce changes in the processing of visceral signals. In contrast, in the HDT, both synchronous and asynchronous conditions reflect the participant's actual online heart rhythm and, therefore, accurate performance on this task requires actual perception of ongoing heartbeats. The HDT is also thought to be more immune to top-down influences than the HCT. There are also conceptual differences between these two tasks. While the latter consist only in the monitoring of heartbeats, the former also requires the matching between the interoceptive sensations and auditory tones. Thus, it is possible that taVNS also facilitated the integration of signals originating within and outside the body, an ability known be to be associated with insula activity (Critchley et al., 2004; Ronchi et al., 2015).

Several fMRI studies have shown that taVNS modulates activity in several brain regions related with the processing of afferent vagal signals and interoception, such as the NTS, thalamus, precentral gyrus and insular cortex (e.g., Badran, Dowdle, et al., 2018; Dietrich et al., 2008; Yakunina, Kim, & Nam, 2017). Interestingly, grey matter volume and activation of the insula during the HDT have been shown to correlate with accuracy in the task (Critchley et al., 2004). Similarly to other non-invasive brain stimulation techniques, taVNS effects might be explained by modulation of neural activity and consequent shifts in the signal-to-noise ratio in the system (Miniussi, Harris, & Ruzzoli, 2013). Importantly, the effects of the stimulation depend on the state of the recruited neural populations (i.e., state dependency) and thus on the task's characteristics. Here, it is likely that taVNS modulation of brain activity within vagal and interoceptive regions, e.g. NTS or insula, increased the signal-to-noise ratio enhancing the sensitivity to heartbeat sensations during the HDT, which necessarily relies on online heartbeat perception, but not during the HCT, for which the possible endorsement of ancillary strategies may be associated with poorer signal-to-noise relation.

We also measured several physiological indices (HR, HRV and BP) but found no differences as a function of stimulation type. We note that there is currently no consensus on the direct impact of taVNS on autonomic activity and therefore we had no specific predictions in this regard. It is possible that the contrasting findings observed so far in literature reflect the different experimental procedures and stimulation parameters, e.g. right vs left ear stimulation or continuous vs phasic stimulation, adopted in these studies (e.g., Badran, Mithoefer, et al., 2018; Burger et al., 2016; Clancy et al., 2014; Colzato et al., 2017). Importantly, however, in the present study we included these variables as covariates and found that they did modulate accuracy on the HDT as a function of stimulation type. This suggests that taVNS effects on IAcc are not driven by substantial changes in autonomic activity and are more likely to occur at the representational level in the central nervous system.

Interestingly, even if participants were more confident (interoceptive sensibility) in their ability to perform the task during active stimulation, such confidence was unrelated to their actual accuracy, as no differences were found on interoceptive awareness, i.e. the meta-ability to evaluate one’s own accuracy. This is possible if participants report higher confidence even when their answer is not accurate. Indeed, while these three dimensions are related, research has shown that they are also partially dissociable (Azevedo, Aglioti, & Lenggenhager, 2016; Garfinkel et al., 2015) and rely on partially distinct neural networks (Barttfeld et al., 2013; García-Cordero et al., 2016; Rouault, McWilliams, Allen, & Fleming, 2018). Interoceptive sensibility reflects processes such as subjective interpretation of bodily sensations, attention and cognitive biases. Conversely, interoceptive awareness is likely to reflect higher-order processes that integrate sensory information with other, domain-specific and domain-general, decision-making variables (Rouault et al., 2018). It may be that taVNS modulates interoceptive-sensory processing (IAcc) and appraisal of bodily sensations or cognitive states (interoceptive sensibility) but not processes related to meta-evaluation. Nevertheless, such interpretation should be taken with caution. A recent study found increases in metacognitive performance but not in objective performance in a visual perception task after pharmacological blockage of noradrenaline (Hauser et al., 2017), which is known to be modulated by stimulation of the vagus nerve (Ruffoli et al., 2011). Thus, future studies using other interoceptive tasks, arousal-inducing paradigms or probing other sensory modalities may shed further light into the possible effects of taVNS on metacognitive processes.

Although the HDT is, arguably, the most reliable method to assess IAcc, it has some limitations, such as the task's difficulty. In fact, it is generally accepted that the HDT has limited sensitivity at the lower end of the accuracy spectrum with participants performing at chance levels (Khalsa, Rudrauf, Sandesara, Olshansky, & Tranel, 2009). Thus, it is possible that stimulation had no influence on those with particularly low accuracy and a minimal level of interoceptive representation is required to benefit from it. It is also believed that extent to which taVNS impacts behaviour and physiological activity may partially depend on inter-individual differences, as exemplified by the finding that older participants tend to show greater stimulation induced changes in HRV (Clancy et al, 2014). Thus, it might be that variability along physiological and performance-related factors might account for inter-individual differences in taVNS responsivity in the present study. Moreover, it would also be important to test whether different stimulation sites, e.g. cymba conchae, and different stimulation parameters have different effect on IAcc. While stimulation in these two sites produce equivalent patterns of cortical activity (Badran et al, 2018), there is currently a debate on whether these are fully equivalent (Badran, Brown, et al., 2018; Burger & Verkuil, 2018). A recent study compared several stimulation parameters and found that some specific stimulation frequencies (e.g., 10Hz) and pulse with (e.g., 500 µs) have stronger effects on HR (Badran, Mithoefer, et al., 2018). Formal investigations using different parameters, e.g. ON-OFF 30-second cycles vs continuous stimulation, applied on either the tragus or the cymba conchae would be required to elucidate this further. Pupil size, which is thought to be closely related to noradrenaline release by the locus coeruleus (Aston-Jones & Cohen, 2005), might be a good index of autonomic activity to establish the effectiveness of taVNS. Finally, future studies may also be designed to test how taVNS modulates responses to manipulations of the interoceptive system and how these are reflected in changes in IAcc (Khalsa, Rudrauf, Sandesara, et al., 2009; Schandry, Bestler, & Montoya, 1993). Peripheral perturbations of the cardiovascular system might increase the salience of interoceptive signals and reveal increased accuracy also in the HCT when paired with taVNS.

While interoceptive accuracy, as measured with tasks such as the HCT and the HDT, is typically regarded as a trait measure, several studies have shown state-dependent changes (Ainley, Tajadura-Jiménez, Fotopoulou, & Tsakiris, 2012; Canales-Johnson et al., 2015; Khalsa, Rudrauf, Sandesara, et al., 2009; Schandry et al., 1993). For example, experimental manipulations targeting top-down processes, such as psychological stress (Fairclough & Goodwin, 2007) or attention towards one's own body (Ainley et al., 2012), may modulate IAcc. At the physiological level, procedures inducing changes on cardiovascular parameters, such as physical exercise and postural manipulations (Schandry et al., 1993) or bolus infusions of isoproterenol (Khalsa, Rudrauf, Sandesara, et al., 2009), can also induce transient changes in IAcc. Here, we introduce a new procedure to manipulate interoceptive processing with large potential for experimental research and clinical practice. The non-invasiveness of this method and the fact that it is does not seem to rely on higher-order cognitive factors, such as attention or psychological stress, makes it a valuable tool for the study of body-brain interactions and, potentially, the impact of afferent cardiac signals in healthy and clinical populations. Recent proposals argue for a central role of dysfunctional interoceptive processing in certain psychiatric disorders, e.g. anxiety and eating disorders. Specifically, it is argued that the inability to correctly perceive inner bodily states or the mismatch between this ability and subjective believes may be important for the development of psychopathological states (Khalsa et al., 2018; Palser, Fotopoulou, Pellicano, & Kilner, 2018; Quadt et al., 2018). Thus, clinical interventions targeting dysfunctional bodily awareness should include protocols to improve participants' IAcc and align this ability with their meta-cognitive beliefs about bodily states. Future studies may be designed to investigate how taVNS can promote interoceptive learning (IAcc) or be integrated with other therapeutic techniques, e.g. mindfulness, to improve interoceptive awareness for the treatment of metal health conditions. The findings reported here enhance our understanding of the mechanisms underlying the conscious perception of heartbeats and demonstrate the potential of taVNS as an important tool to investigate brain-body interactions.

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Highlights

taVNS improved interoceptive accuracy in the heartbeat detection task

taVNS increased confidence in interoceptive performance but not in meta-awareness

It can be used to modulate interoceptive processing and study body-brain interactions

Credit statement

RTA, VV and MT designed the study. VV collected the data. RTA and VV analysed the data. RTA, VV and MT interpreted the results and prepared the manuscript.