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ORIGINAL ARTICLE

Effects of non-invasive vagus nerve stimulation on cognitive and autonomic correlates of perseverative cognition

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Abstract

Perseverative cognitions can provoke psychophysiological stress in the absence of an actual stressor and are considered important transdiagnostic vulnerability factors for several (mental) health issues. These stress-related cognitive processes are reflected by both cognitive (assessed by self-reports) and autonomic inflexibility (assessed by heart rate variability; HRV), with a key role attributed to the vagus nerve. Interestingly, modulation of the afferent branches of the vagus can be achieved with transcutaneous auricular vagus nerve stimulation (taVNS), a non-invasive technique that employs a low-intensity electrical current applied to the ear. In a sample of healthy individuals, we investigated the effects of taVNS of the left concha, compared to sham (earlobe) stimulation, on the cognitive and autonomic correlates of perseverative cognition following a psychosocial stress task. Interestingly, taVNS significantly reduced cognitive rigidity, reflected by reduced subjective perseverative thinking after psychosocial stress. Although there were no direct effects on autonomic correlates of perseverative cognition, individual differences in perseverative thinking after the stressor significantly affected the effects of taVNS on HRV. Specifically, more autonomic inflexibility during the stress task (i.e., reduced HRV) was associated with increases in perseverative thinking afterward for the sham condition, but not the active taVNS condition. Additional exploratory analyses revealed no significant moderation of stimulation intensity. Overall, the study findings endorse the association between perseverative cognitions and vagus nerve functioning.

KEYWORDS

cognitive rigidity, heart rate variability (HRV), perseverative cognition, stress, transcutaneous auricular vagus nerve stimulation

1 | INTRODUCTION

Every time we perceive something as stressful, our bodies respond with a well-coordinated stress response eliciting a cascade of psychological and physiological changes (Chrousos, 2009). The natural stress-induced physiological action tendency, promoting adaptation and energy mobilization, has been postulated to be a default response to uncertainty, novelty, and threat (Brosschot et al., 2017), which is under continuous inhibition by the ventromedial prefrontal cortex (vmPFC; Motzkin et al., 2015). When this default stress response becomes disinhibited, and prefrontal inhibition of amygdalar activity decreases (Motzkin et al., 2015; Thayer & Lane, 2000), changes in autonomic nervous system activity arise (Thayer & Lane, 2000). As such, parasympathetic activation swiftly decreases (i.e., parasympathetic withdrawal) and, relatively slower, sympathetic activity increases (i.e., sympathetic arousal) resulting in, for instance, increased heart rate and skin conductance (i.e., fight-flight response, Gaab et al., 2003; Kemeny, 2003). Crucially, however, as soon as the source of stress has disappeared, and the situation is perceived as safe, we should be able to inhibit this response allowing for physiological stress recovery (Brosschot et al., 2017; Thayer, 2006). Yet, stressful events might trigger perseverative cognitions, referring to negative thoughts that mentally represent such event and that are difficult to suppress (Brosschot et al., 2005, 2006). Such cognitions promote a prolongation of the psychophysiological stress response—and thereby feelings of stress—in the absence of the actual stressor (Verkuil et al., 2010). Importantly, perseverative cognitions, such as ruminating about past stressful events or worrying about feared future events, keep the psychological, but also the physiological stress response sustained (Brosschot et al., 2005, 2006) and, are considered important transdiagnostic vulnerability factors for several psychological (Ehring & Watkins, 2008; Spinhoven et al., 2018) and somatic (Ottaviani et al., 2016; Verkuil et al., 2010) health issues. Indeed, several longitudinal studies have linked perseverative cognition with the maintenance and recurrence of psychopathological conditions (Spinhoven et al., 2018) as well as with an increased likelihood of developing cardiovascular disease (e.g., Kubzansky et al., 1997). Hence, research investigating ways to reduce perseverative cognition is pivotal.

The vagus nerve, one of the major nerves of the parasympathetic division of the autonomic nervous system, has been suggested to play an important role in perseverative cognition (Ottaviani, 2018; Thayer & Lane, 2002). It is indeed plausible that peripheral processes (physiological states of the body) that are monitored by the sensory pathways of the vagus nerve interact with central processes related to perseverative cognition, making it an embodied process. In support of this idea, several studies have demonstrated associations between vagally mediated heart rate variability (HRV), defined as the variability of time periods between two successive heartbeats caused by an energetic interaction between inputs from the sympathetic and parasympathetic branches of the autonomic nervous system (Malik et al., 1996), and neurocognitive processes intrinsic to perseverative cognition (Ottaviani, 2018). Such processes include cognitive control (Beckwé et al., 2014; Gillie & Thayer, 2014; Nasso et al., 2019), intrusive thoughts (Gillie et al., 2015; Rombold-Bruehl et al., 2019), and emotional and cognitive flexibility (Alba et al., 2019; Grol & De Raedt, 2020; Vanderhasselt et al., 2015). Moreover, HRV, a potential non-invasive biomarker of vagus nerve activity (Burger et al., 2020; Laborde et al., 2017; Wolf et al., 2021), has been proposed as a marker of prefrontal cortex-mediated regulatory strength (Holzman & Bridgett, 2017; Thayer & Lane, 2009) and the autonomic inflexibility underlying perseverative cognition (Ottaviani, 2018). High (as compared to low) HRV reflects robust parasympathetic, efferent vagal inhibitory control on the heart, and is considered a substrate of autonomic flexibility, high adaptability, and self-regulatory responses to meet perceived stress (Thayer & Lane, 2000). In contrast, low HRV is reflective of parasympathetic (i.e., vagal) withdrawal, and consequently, the inability of the system to inhibit sympathetic arousal, and thus reflects autonomic rigidity and incapability to adapt to changing environmental demands (Appelhans & Luecken, 2006; Thayer & Lane, 2000). Moreover, an impaired HRV recovery following stress is suggested to indicate poor inhibitory control and sustained representation of the stressor (i.e., perseverative cognition; Ottaviani, 2018; Thayer, 2006). Hence, vagal modulation, indexed with HRV, reflects the association between cognitive and autonomic inflexibility during perseverative cognition (Ottaviani, 2018; Ottaviani et al., 2016; Thayer, 2006).

Interestingly, modulation of vagal nerve activation can be achieved with transcutaneous auricular vagus nerve stimulation (taVNS) (Farmer et al., 2021). taVNS is a safe, non-invasive stimulation technique that employs electrical stimulation of the auricular branches of the vagus nerve via the tragus or cymba conchae of the outer ear (Butt et al., 2019; Peuker & Filler, 2002), thereby generating an afferent signal that propagates from the peripheral vagal nerves toward the brainstem and cerebral cortex (i.e., bottom-up modulation of brain activity; Dietrich et al., 2008; Frangos et al., 2015; Shiozawa et al., 2014). Neuroimaging studies have shown that the stimulation of the afferent branch of the vagus nerve is associated with altered activity in the nucleus tractus solitarii (NTS), hypothalamus, amygdala, hippocampus, anterior cingulate cortex (ACC), insula, and nucleus accumbens (Frangos et al., 2015; Kong et al., 2018; Kraus et al., 2007; Yakunina

et al., 2017; see also Burger & Verkuil, 2018). These neural networks are implicated in the ability to inhibit ongoing physiological and psychosocial stress reactivity, which results in reduced perseverative cognitions. In turn, this neural functional activity has been found to influence the efferent branch of the vagal nerve to innervate peripheral organs, such as the heart, to enable adaptive responding to acute stressors. Overall, taVNS promotes activity in brain areas that modulate perseverative cognitions, including the prefrontal and the anterior cingulate cortices (Makovac et al., 2020 for a meta-analysis; Yakunina et al., 2017 for a review). Furthermore, taVNS increases the functional connectivity between the amygdala and the prefrontal cortex in depressed patients (Liu et al., 2016), neural networks that are also found to be implicated in the cognitive regulation of stress. Crucially, several studies have shown that taVNS enhances core processes related to perseverative cognition, such as inhibitory control (Beste et al., 2016; Fischer et al., 2018) and cognitive flexibility (Borges et al., 2020), hence, suggesting that taVNS might be a promising technique to reduce perseverative cognition. In fact, in a study with chronic worriers, Burger et al. (2019) found positive effects of taVNS on negative thought intrusions (i.e., worrying). Specifically, in their study, the authors assessed spontaneous and induced worries, using a breathing focus task (see also Hirsch et al., 2009), in high worriers during a single session of taVNS applied to the left concha or earlobe (i.e., sham stimulation). Their results showed that taVNS, as compared to sham (earlobe) stimulation, was able to significantly reduce the occurrence of spontaneous (but not induced) intrusive thoughts (Burger et al., 2019). Contrarily, Burger et al. (2019) found no evidence for the modulatory effects of taVNS on the autonomic rigidity that characterized participants' worrying behavior, reflected by a reduced HRV during the worry and post-worry period. Although more research is required, the authors postulated that the lack of cardiac effects could possibly be explained by, among others, an insufficient stimulation intensity (0.5 mA) to adequately stimulate the nerve fibers primarily responsible for vagal cardiac effects (Burger et al., 2019; Yoo et al., 2013; although see also Borges et al., 2019). Indeed, more recent work also suggests that higher taVNS intensities might be required to cause robust neuromodulatory effects (Mertens et al., 2021). Moreover, although evidence is mixed (e.g., Borges et al., 2019), there is some preliminary evidence for a positive linear relationship between taVNS intensity and various indices of HRV (although not for RMSSD; see Machetanz et al., 2021a). To conclude, notwithstanding the preliminary evidence that taVNS may reduce perseverative cognition, the modulatory effects of taVNS on perseverative cognition, and the autonomic and cognitive inflexibility that characterizes perseverative cognition, especially after psychosocial stressors, are still poorly studied.

In this randomized, single-blind, sham-controlled study with healthy individuals, the primary research aim was to investigate the effects of taVNS on the cognitive and autonomic inflexibility that characterizes perseverative cognition following a psychosocial stressor. The perseverative thinking questionnaire (PTQ), a self-report questionnaire assessing an individuals' lack of ability to inhibit or disengage from repetitive negative thoughts, was used as a subjective measure of perseverative cognition and its cognitive rigidity and vagally mediated heart rate variability (HRV) served as a physiological marker of autonomic inflexibility when recovering from psychosocial stress. Given that taVNS modulates the activity of the afferent vagus nerve, which plays an important role in perseverative cognition, we expected taVNS of the concha, as compared to sham (earlobe) stimulation, to decrease cognitive (i.e., reduced subjective perseverative cognition) and autonomic (i.e., increased HRV) inflexibility following psychosocial stress. In addition, we further explored the effects of taVNS on the association between cognitive and autonomic inflexibility, by examining changes in subjective perseverative cognition (i.e., cognitive inflexibility) to be associated with changes in HRV following taVNS. Finally, given (1) the use of an individualized method to set the stimulation intensity based on participants' subjective pain thresholds and (2) the rising number of studies describing a possible association between stimulation intensity and taVNS effects (Borges et al., 2019; Machetanz et al., 2021a; Mertens et al., 2021), we investigated the possible influence of stimulation intensity on all physiological and psychological outcome measures using an exploratory approach.

2 | MATERIAL AND METHOD

The study is carried-out in accordance with the declaration of Helsinki (2018) and approved by the medical ethical committee of the Ghent University Hospital (UZGent). All participants gave written informed consent. This study was part of a larger project investigating the effects of taVNS on cognitive reappraisal as well as perseverative cognition in healthy individuals. TaVNS effects on cognitive reappraisal exceed the scope of this manuscript and are described in De Smet, Baeken, Seminck, et al. (2021).

2.1 | Study sample

Eighty-five healthy participants between 18 and 35 years old were recruited via the Sona research participation system of the Ghent University and via flyers that were

spread across social media platforms. Participants were screened before participation for past or current mental disorders using the semi-structured Mini International Neuropsychiatric Interview (MINI screening version 7.0.2; Sheehan, 2016). For an overview of all inclusion criteria, we refer to the supplementary materials.

Based on power analyses (see data plan), 85 participants were recruited for the study. Two participants did not complete the entire study protocol and were therefore removed from the final sample, resulting in a total study sample of 83 participants (79% female, mean age = 21.10, $SD = 3.11$). Participants were randomly assigned to an active stimulation condition ($n = 42$) or sham stimulation condition ($n = 41$; see results for an overview of the sample characteristics) resulting in a between-subjects study design.

2.2 | Procedure

All experimental sessions took place in a well-controlled laboratory environment at the Ghent University Hospital. Participants were asked to sleep sufficiently, restrain from intense physical activity and alcohol the day before the session. In addition, participants were asked to abstain from strenuous exercise and not to consume any caffeinated beverages, alcohol nor nicotine 2 h prior to the session. During the entire session, participants remained seated on a chair positioning their knees at a 90 degree angle. At the start of the experimental session, several questionnaires were administered and the physiological lab equipment, to record cardiac and electrodermal activity, was set-up. Next, there was a 10-min rest period during which participants had the time to habituate to the laboratory while their cardiac and electrodermal activity was recorded (i.e., baseline, see Figure 1 for an overview of the experimental procedure). Afterward, the taVNS equipment was set-up and stimulation was applied. All participants—naïve to the stimulation condition—received 20 min of active taVNS or sham stimulation. After a 15-min rest period during stimulation (i.e., taVNS-rest), that allowed for a build-up of the neuromodulatory effects of taVNS (e.g., Burger et al., 2018; Frangos et al., 2015), participants performed a surprise 5-min arithmetic task (i.e., taVNS-task) that was used to experimentally induce psychosocial stress. Following this psychosocial stressor (and stimulation), there was a rest period of 10 min (i.e., recovery). For each rest period, participants were instructed to relax and keep their eyes open. During the experimental session, psychological measures (i.e., subjective perseverative cognition and negative affect) were assessed at baseline and after the 10-min recovery period. Besides HRV assessments (i.e., to index autonomic inflexibility during perseverative cognition), heart rate and skin conductance were measured throughout the session to assess physiological changes in response to the psychosocial stressor. At the end of the session, participants were asked about possible adverse effects of the stimulation and, as a manipulation check, participants were asked whether they believed they received sham or active stimulation. Participants were debriefed about the purpose of the study and received a monetary compensation for their participation.

2.3 | Transcutaneous vagus nerve stimulation (tVNS)

Stimulation was performed using a NEMOS® tVNS device (Cerbomed, Erlangen, Germany; CE-certified for treatment-resistant epilepsy, Yap et al., 2020) that

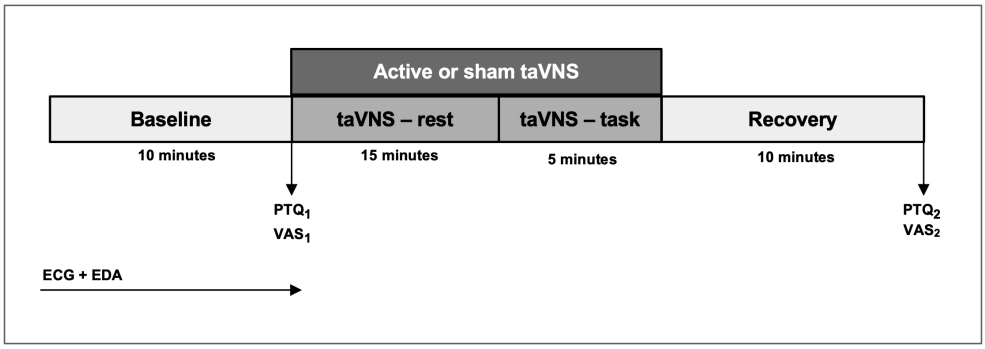

FIGURE 1 Experimental procedure. Participants received 20 min of active taVNS or sham stimulation. Physiological recordings, to measure cardiac and electrodermal activity, were taken throughout the session. At the end of baseline and after the recovery, participants' subjective perseverative cognition and negative affect levels were assessed using the perseverative thinking questionnaire (PTQ) and Visual Analogue Scales (VAS), respectively. ECG, electrocardiogram; EDA, electrodermal activity; taVNS, transcutaneous auricular vagus nerve stimulation.

provided electrical stimulation through two titanium ball-point electrodes (positioned on top of an adjustable silicon earpiece) that were connected to the stimulator with a wire. The following stimulation parameters were used: monophasic square wave pulses with a pulse width of 250 μs and frequency set at 25 Hz and, on and off duty cycles of 30 seconds for 20 min. To reduce impedance and warrant optimal electrical conductivity (Yap et al., 2020), the skin at the stimulation sites was prepared beforehand with abrasive gel (Nuprep™ abrasive skin gel; Weaver and Company, Aurora, CO, USA) and isopropyl alcohol. For active taVNS, the stimulation was applied to the cymba concha of the left ear, an area known to be innervated by the afferent auricular branch of the vagus nerve (Frangos et al., 2015; Peuker & Filler, 2002). Stimulation of this area is suggested to result in the strongest activation of afferent vagal pathways as compared to other taVNS stimulation locations (Yakunina et al., 2017). For sham stimulation, the electrodes were placed at the center of the left ear lobe, an area that is free of cutaneous vagal innervation (Kraus et al., 2013; Peuker & Filler, 2002), and fixated with medical tape. To ensure activation of the afferent vagal nerve fibers, stimulation intensity was set above the individual detection level and just below the individual pain threshold (i.e., the pain threshold minus 0.1 mA, see also Ellrich, 2011; $M_{active} = 1.37$, $SD_{active} = 0.81$, $M_{sham} = 1.89$, $SD_{sham} = 0.89$, $t(79.98) = 2.75$, $p = .007$, $d = 0.60$). Adverse events resulting from the stimulation were systematically evaluated using six self-report items addressing feelings of headache, neck pain, nausea, muscle contractions, prickling sensations under the electrodes and burning sensations (responses ranging from "1 = not at all" to "5 = very much").

2.4 | Psychosocial stressor

To induce stress in the participants, we used an arithmetic task adapted from the Trier Social Stress Test (TSST; Kirschbaum et al., 1993). During the task, participants were asked to count backward from 2083 in steps of 13 as fast as possible. When a mistake was made, participants had to restart from 2083. Without being informed about the duration of the task, participants were asked to stop after 5 min. To maximize the aspect of social evaluation and psychosocial stress elicited by the negative event, the experimenter was seated in front of the participants to provide them with direct negative feedback during incorrect responses. In addition, a video camera recorded the arithmetic session. As a cover story, participants were informed that an external panel would analyze their performance during the arithmetic task and that the task gave a strong indication of their overall intelligence.

2.5 | Psychological measures

2.5.1 | Baseline questionnaires

To ensure that there were no prior differences between taVNS conditions in depressive symptoms, ruminative tendencies and stress resilience, variables known to be associated with cognitive and autonomic flexibility (e.g., An et al., 2020; Carnevali et al., 2018; Grol & De Raedt, 2020), we collected participants' responses to the Beck Depression Inventory (BDI-II; Beck et al., 2011; Dutch translation by Van der Does, 2002), Ruminative Response Scale (RRS; Nolen-Hoeksema & Morrow, 1991; Dutch version by Raes et al., 2003) and Connor-Davidson Resilience Scale (CD-RISC; Connor & Davidson, 2003), respectively.

2.5.2 | Negative affect

Throughout the session, participants were repeatedly asked to rate their current emotional state using Visual Analogue Scales (VAS). Each scale consisted of a 100 millimeters straight line with captions at both sides of the continuum indicating the extremes of an emotional experience (e.g., "I do not feel angry at all", "I feel very angry"). Participants had to mark the point of the continuum that corresponded to their current affective state. VAS were used to detect changes in feelings of anger, tension, sadness, happiness, stress, and anxiety (McCormack et al., 1988). From these scales, a compounded negative affect score was calculated (i.e., the sum of all VAS scores divided by the number of VAS, with the VAS scores for "happy" being reversed). Higher scores indicate higher levels of negative affect.

2.5.3 | Perseverative thinking questionnaire

Repetitive negative thinking, a form of perseverative cognition, was assessed using the Dutch version of the Perseverative Thinking Questionnaire (PTQ-NL; Ehring et al., 2011, 2012). The PTQ is a content-independent measure of repetitive negative thinking and consists of 15 self-report items that assess participants' preservative thoughts about negative experiences or problems (e.g., "my thoughts consumed me," 'the same thoughts kept going through my mind again and again'). Given that this study focuses on temporal changes in perseverative cognition following a psychosocial stressor, the original instructions of the PTQ ("in this questionnaire you are asked to indicate how you normally think about negative experiences or problems") were adapted to assess changes in state perseverative cognition during the

experimental session ("in this questionnaire you are asked to indicate how you have thought in the past rest period about negative experiences or problems," see also Allaert et al., 2019). Responses were made on a 5-point Likert-like scale, ranging from "0 = not at all" to "4 = very much." As recommended (Ehring et al., 2011), a total PTQ score was calculated by summing all individual items, with higher scores indicating higher levels of subjective perseverative cognition and cognitive rigidity. With the current study sample, the state PTQ measure showed an internal consistency of alpha = .95.

2.6 | Psychophysiological measures

All physiological measures were acquired using the Biopac MP150 and Biopac Acqknowledge software 4.3 (Biopac Systems Inc., USA). The Biopac ECG100C and EDA100C-MRI amplifiers were used to measure cardiac and electrodermal activity, respectively. For the ECG amplifier, the gain was set at 5000, a high pass filter of 0.05 Hz and a low pass filter of 35 Hz was used. The EDA parameters included: gain set to 5 μʊ/V, no high pass filter, and a low pass filter of 10 Hz. For both amplifiers, the sampling rate was set at 1000 Hz.

2.6.1 | Heart rate and heart rate variability

The electrocardiogram (ECG) was set-up using a lead I ECG configuration (Francis, 2016), with two Ag/Agcl electrodes attached below the left and right clavicle and a third reference electrode placed under the ribs. The ECG data were analyzed with PhysioData Toolbox version 0.5 (Sjak-Shie, 2019) which allows for automated R-peak detection and inter-beat-interval (IBI) extraction. Misidentified R-peaks were manually corrected after a visual inspection of the data. Missing or incorrect IBIs were corrected using cubic spline interpolation (Lippman et al., 1994). Mean heart rate (HR; beats per minute) was computed through shape-preserving piecewise cubic interpolation of the IBIs. Heart rate variability (HRV; milliseconds) was assessed by calculating the Root Mean Squared of Successive Differences (RMSSD) of the detrended IBI data (Shaffer & Ginsberg, 2017; Tarvainen et al., 2002). RMSSD is ought to reflect vagally mediated changes in HRV (Laborde et al., 2017; Shaffer & Ginsberg, 2017) and, compared to other HRV indices, is less sensitive to movement artifacts or respiratory influences (Laborde et al., 2017; Penttila et al., 2001). As recommended, RMSSD was calculated for time epochs of 5 min (Malik et al., 1996). Consistent with HRV, mean HR was computed for epochs of 5 min. In line with prior work, the HRV and mean HR epochs, with expectation of the taVNS-task measurement, were averaged resulting in one measure per period per participant (e.g., the baseline and recovery period both resulted in 2 epochs of 5 min that were averaged resulting in one mean value per period, see also De Smet, Baeken, De Raedt, et al., 2021; Pulopulos et al., 2020).

2.6.2 | Electrodermal activity

Throughout the experimental session, skin conductance (μS) was measured using two velcro finger electrodes (prepped with Biopac GEL101, an isotonic electrode gel) strapped around the distal phalanges of the index and middle finger of the non-dominant hand. All EDA data were processed using Ledalab, a MATLAB toolbox (version 3.4.9, www.ledalab.be). The data were down sampled to 50 Hz. In addition, adaptive smoothing and a Butterworth filter were applied to remove any noise from the data before it was manually corrected for artifacts (Boucsein, 2012). Feature extraction was performed using Continuous Decomposition Analysis (CDA; Benedek & Kaernbach, 2010) with a detection threshold of 0.03 μS (Boucsein, 2012; Braithwaite et al., 2013). In line with the cardiac data, skin conductance levels (SCL) were calculated for epochs of 5 min and averaged resulting in one SCL value per participant for each of the different time periods (i.e., baseline, taVNS-rest, taVNS-task, recovery).

2.7 | Data plan

Sample size calculation using G*Power 3.1 software (Faul et al., 2009) resulted in a required sample size of 75 participants to obtain a power of 0.80 to detect a low to medium effect size (F-test for repeated measures with 2 groups and 2 measurements with a correlation of 0.5, $f = 0.165$, alpha error probability = .05). Considering possible data losses or dropouts of 10% to 15%, 85 participants were recruited. However, two participants did not complete the full study protocol and were therefore removed from the sample, resulting in a final sample of 83 participants. Due to technical issues with the physiological recording equipment, less participants were included in the analyses of HRV ($n = 79$), mean HR ($n = 79$) and SCL ($n = 76$).

All statistical analyses were performed with R version 4.1.2 (R Core Team, 2021). The "lmerTest" (Kuznetsova et al., 2017) and "lme4" (Bates et al., 2015) packages were used for fitting models within the linear mixed effects framework. In all reported models, we employed gaussian error distributions and allowed for intercepts to vary randomly over subjects, whereas other independent variables (such as condition and time) and their interactions

were included as fixed effects. Continuous predictors (i.e., changes in perseverative thinking and stimulation intensity) were centered and model contrasts were set using sum (i.e., effect) coding schemes. χ^2 goodness-of-fit tests showed that adding random slopes to the random intercept models did not significantly improve the model fit and were therefore not included in the final models. Hence, all reported models were built as follows: values of the dependent variable ~ fixed effects + (1 | subject). Due to skewed residual distributions, natural logarithmic transformations were performed for all physiological measures and self-reported negative affect. The *F*-statistics and *p*-values were reported using the Kenward-Roger degrees of freedom approximation and, where applicable, the Tukey correction was used for multiple comparisons. Post-hoc tests for interaction effects consisted of pairwise comparisons of the estimated marginal means of factors or pairwise comparisons of the estimated marginal means of linear trends (i.e., comparisons of the slopes of the continuous variable for each factor level) that were obtained from the mixed effects models, using the "emmeans" and "emtrends" functions of the "emmeans" package (Lenth, 2021), respectively. Partial eta squared (i.e., η_p^2) and Cohen's *d* were used to report effect sizes of *F* and *t* test statistics, respectively, using the "effectsize" package that allows for effect size calculations of linear mixed models (Ben-Shachar et al., 2020). The significance level was set at alpha = .05.

First, independent sample t-tests, chi-squared and exact binomial tests were used to examine differences between the two conditions in age, sex, baseline questionnaires, belief in the manipulation, self-reported adverse events to the stimulation and performance on the task. Additionally, Pearson's product–moment correlations were used to examine if task performance was associated with perseverative thinking.

To evaluate the effectiveness of the psychosocial stressor (i.e., changes in physiological arousal following the arithmetic task), depending on the stimulation condition, 4 (time: baseline, taVNS-rest, taVNS-task, recovery) by 2 (condition: sham vs. active stimulation) linear mixed models were used for the mean HR and SCL data. In addition, to investigate changes in negative affect during the session, and effects of taVNS on negative affect, a 2 (time: baseline, recovery) by 2 (condition: sham vs. active stimulation) linear mixed model was fitted with negative affect as the outcome measure.

To examine the effects of taVNS on subjective levels of perseverative cognition following stress, a 2 (time: baseline, recovery) by 2 (condition: sham vs. active stimulation) linear mixed model was fitted with the PTQ scores as outcome measure. With regard to autonomic inflexibility, a 4 (time: baseline, taVNS-rest, taVNS-task, recovery) by 2 (condition: sham vs. active stimulation) linear mixed model was fitted to investigate the direct effects of taVNS on HRV.

Considering the association between cognitive and autonomic inflexibility during stress recovery and, the significant effect of taVNS on subjective perseverative cognition (i.e., PTQ scores) but lack of evidence for direct effects of taVNS on HRV (see below in the results section), an additional exploratory analysis was performed to investigate the relation between changes in subjective perseverative cognition (i.e., changes in PTQ scores, $\Delta PTQ = PTQ_{T2} - PTQ_{T1}$, see also Figure 1) and HRV following taVNS. As such, the ΔPTQ scores were added as a continuous predictor to the HRV model.

Given the use of individualized stimulation intensities based on subjective pain thresholds (see Ellrich, 2011), exploratory analyses were performed to investigate possible influences of stimulation intensity on the different psychological and physiological measures. Thus, using an exploratory approach, stimulation intensity was included as a continuous predictor in all above-mentioned models.

3 | RESULTS

3.1 | Descriptive statistics

Table 1 gives an overview of the study characteristics, there were no significant baseline differences between conditions. An exact binomial test showed that the success probability of participants guessing the correct stimulation condition was not significantly different from chance level ($p = .741$). Hence, participant blinding was considered successful as they were not able to discriminate between the active taVNS and sham condition.

3.2 | Adverse effects

Table 2 gives an overview of the mean responses to the six self-report items examining adverse events following sham or active taVNS. With exception of higher levels of reported burning sensations under the electrodes following active taVNS, there were no significant differences in reported adverse events between the two types of stimulation (i.e., active vs. sham stimulation).

3.3 | Task performance

There were no significant differences in task performance between the sham ($M = 5.27$, $SD = 2.29$) and active taVNS condition ($M = 4.57$, $SD = 2.24$), $t(80.83) = 1.40$, $p = .165$, $d = 0.31$. In the sham condition, there was a significant

TABLE 1 Characteristics of the study sample

	Sham taVNS ($n = 41$)	Active taVNS ($n = 42$)	Statistics
Age	21.34 (3.53)	20.86 (2.67)	$t(81) = 0.71$, $p = .482$, $d = 0.16$
Sex	78% female	83% female	$\chi^2(1, 83) = 0.372$, $p = .542$, $\varphi = 0.07$
BDI-II	4.66 (5.48)	5.74 (5.73)	$t(81) = 0.88$, $p = .383$, $d = 0.19$
RRS	15.10 (7.99)	16.26 (10.34)	$t(77.02) = 0.58$, $p = .567$, $d = 0.13$
CD-RISC	69.10 (9.97)	69.07 (12.18)	$t(81) = 0.01$, $p = .992$, $d = 0.01$
Baseline NA	15.59 (6.67)	15.26 (6.83)	$t(81) = 0.22$, $p = .828$, $d = 0.04$

Note: Mean (*SD* i.e., standard deviation) for age, scores on the Beck Depression Inventory (BDI-II), Ruminative Response Scale (RRS), Connor-Davidson Resilience Scale (CD-RISC), and the scores on the Visual Analogue Scale (VAS) assessing participants' negative affect (NA) levels at baseline. Sex is described as the percentage of female participants in each condition. Overall, no significant differences in sample characteristics were found between the active taVNS and sham stimulation condition.

Abbreviation: taVNS, transcutaneous auricular vagus nerve stimulation.

TABLE 2 Self-reported adverse events to the different stimulation conditions

	Sham taVNS ($n = 41$)	Active taVNS ($n = 42$)	Statistics
Headache	1.20 (0.40)	1.12 (0.40)	$t(80) = 0.83$, $p = .411$, $d = 0.18$
Neck pain	1.46 (0.81)	1.17 (0.54)	$t(70) = 1.92$, $p = .059$, $d = 0.42$
Nausea	1.07 (0.35)	1.15 (0.57)	$t(65.7) = 0.70$, $p = .486$, $d = 0.15$
Muscle contractions	1.32 (0.57)	1.37 (0.77)	$t(73.71) = 0.33$, $p = .744$, $d = 0.07$
Prickling sensation	2.07 (1.03)	2.00 (1.07)	$t(79.9) = 0.31$, $p = .754$, $d = 0.07$
Burning feeling	1.44 (0.78)	1.90 (1.02)	$t(74.69) = 2.32$, $p = .023$, $d = 0.51$

Note: Mean (*SD* i.e., standard deviation) for each of the items examining adverse effects following active taVNS or sham stimulation.

Abbreviation: taVNS, transcutaneous auricular vagus nerve stimulation.

positive association between task performance and perseverative thinking, with participants performing worse (i.e., making more mistakes) showing higher levels of subjective perseverative cognition afterward, $t(39) = 2.52$, $p = .016$, $r = 0.37$. No such association was found for active taVNS, $t(39) = 0.01$, $p = .992$, $r < 0.01$.

3.4 | Stress-induced physiological arousal

3.4.1 | Mean heart rate

The results of the analysis revealed a significant main effect of time for the linear mixed model with mean HR, $F(3, 229.06) = 88.17$, $p < .001$, $\eta_p^2 = 0.54$. Post-hoc analyses showed a significantly higher mean HR during the confrontation with the psychosocial stressor ($M = 89.23$, $SD = 13.37$) as compared to baseline ($M = 81.53$, $SD = 12.98$), $t(229) = 9.76$, $p < .001$, $d = 1.55$. After the stress test (i.e., during the recovery period), mean HR was significantly lower ($M = 77.53$, $SD = 10.88$) compared to during the arithmetic task (i.e., taVNS-task), $t(229) = 14.42$, $p < .001$, $d = 2.31$, and compared to baseline, $t(229) = 4.70$, $p < .001$, $d = 0.75$. There was no effect of condition, $F(1, 77) = 0.25$, $p = .616$, $\eta_p^2 < 0.01$, nor significant interaction between time and condition, $F(3, 229.06) = 0.53$, $p = .659$, $\eta_p^2 < 0.01$.

The exploratory analysis showed no significant effects of taVNS stimulation intensity on mean heart rate during the different phases of the experimental session, F's < 1.14, p's $> .332$, η_p^2's < 0.02.

3.4.2 | Skin conductance levels

The results of the linear mixed effects analysis revealed a significant main effect of time for the SCL data, $F(3, 221.02) = 113.66$, $p < .001$, $\eta_p^2 = 0.61$. During the stress task, SCL was significantly higher ($M = 11.83$, $SD = 4.22$) compared to baseline ($M = 8.06$, $SD = 3.96$), $t(221) = 17.79$, $p < .001$, $d = 2.89$. During the recovery period, as compared to during the stress task, SCL was significantly reduced ($M = 10.41$, $SD = 3.90$), $t(221) = 5.08$, $p < .001$, $d = 0.83$. The SCL level during the recovery was significantly higher

than baseline, $t(221) = 12.64$, $p < .001$, $d = 2.06$. There was no effect of condition, $F(1, 74) = 0.02$, $p = .982$, $\eta_p^2 < 0.01$, nor significant interaction between time and condition, $F(3, 221.01) = 1.30$, $p = .276$, $\eta_p^2 = 0.02$.

We found no evidence for any effects of stimulation intensity on skin conductance levels, F's < 1.72, p's $> .185$, η_p^2's < 0.03.

3.5 | Negative affect

Results showed a significant main effect of time, with overall higher levels of negative affect post recovery ($M = 17.41$, $SD = 8.84$) compared to baseline ($M = 15.42$, $SD = 6.71$), $F(1, 80.28) = 6.40$, $p = .013$, $\eta_p^2 = 0.07$. There was no significant main effect of condition, $F(1, 80.97) = 0.19$, $p = .661$, $\eta_p^2 < 0.01$. Although the levels of negative affect at the end of the recovery period were higher for the sham condition ($M = 18.27$, $SD = 10.27$) compared to the active taVNS condition ($M = 16.56$, $SD = 7.16$), there was no significant interaction between time and condition, $F(1, 80.28) = 0.49$, $p = .486$, $\eta_p^2 < 0.01$.

Exploratory analysis did not reveal any significant effects of stimulation intensity on negative affect levels during the session, F's < 2.02, p's $> .159$, η_p^2's < 0.03.

3.6 | Effects of taVNS on perseverative cognition

3.6.1 | Perseverative thinking questionnaire

For the subjective measure of perseverative cognition, the linear mixed effects analyses showed a significant interaction between time and condition, $F(1, 80.14) = 5.59$, $p = .021$, $\eta_p^2 = 0.07$. For the sham condition, there were no significant changes in PTQ scores during the session, $t(80) = 0.10$, $p = .920$, $d = 0.02$. In the active taVNS condition, however, PTQ levels were significantly decreased at the end of the recovery period, $t(80.3) = 3.24$, $p = .002$, $d = 0.72$, as compared to baseline (see Figure 2). Results also showed a lower-order significant main effect of time, $F(1, 80.14) = 4.94$, $p = .030$, $\eta_p^2 = 0.06$, but no main effect of condition, $F(1, 80.99) = 0.19$, $p = .666$, $\eta_p^2 < 0.01$.

Results of the exploratory analysis revealed no significant effects of stimulation intensity on subjective perseverative cognition, F's < 0.81, p's $> .370$, η_p^2's < 0.01.

3.6.2 | Heart rate variability

Results of the linear mixed effects analyses evaluating the direct effects of taVNS on HRV revealed no significant interaction between time and condition (see Figure 3), $F(3, 229.11) = 0.33$, $p = .806$, $\eta_p^2 < 0.01$, nor a significant main effect of condition, $F(1, 76.99) = 0.06$, $p = .810$, $\eta_p^2 < 0.01$. There was a significant main effect of time, $F(1, 229.11) = 3.94$, $p = .009$, $\eta_p^2 = 0.05$. During the recovery period, HRV was significantly higher as compared to baseline, $t(229) = 3.09$, $p = .012$, $d = 0.49$. In addition, there was a marginal statistical difference between the HRV levels during the tVNS-rest and baseline period, $t(229) = 2.60$, $p = .049$, $d = 0.42$, with an overall higher HRV during tVNS-rest compared to baseline. The HRV levels during the arithmetic task (i.e., taVNS-task) were not significantly different from the HRV levels during the taVNS-rest, $t(229) = 1.41$, $p = .493$, $d = 0.23$, or recovery period, $t(229) = 1.91$, $p = .227$, $d = 0.31$.

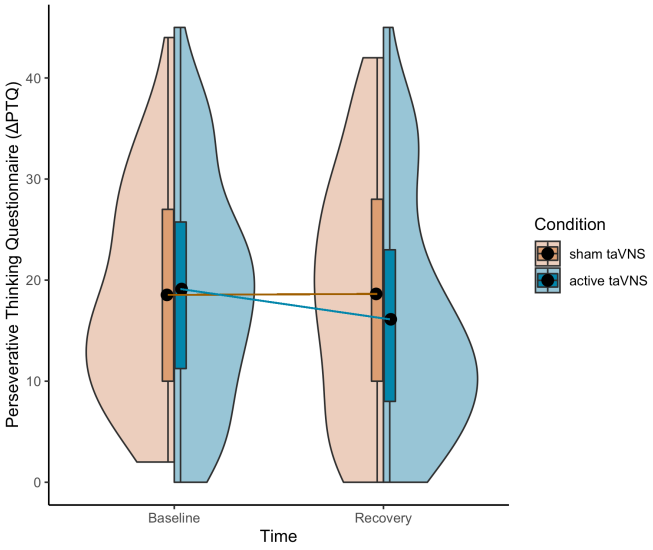

FIGURE 2 Violin plots representing the subjective perseverative cognition values during the session for the active taVNS and sham stimulation condition. taVNS, transcutaneous auricular vagus nerve stimulation.

Results of the exploratory analysis showed no significant effects on stimulation intensity on HRV, F's < 0.91, p's $> .344$, η_p^2's < 0.01.

3.6.3 | Influence of individual differences in cognitive inflexibility on the effects of taVNS on HRV

Considering the association between cognitive and autonomic inflexibility and, the significant effect of taVNS on subjective perseverative cognition (i.e., PTQ scores) but lack of evidence for direct effects of taVNS on HRV, we further explored how individual differences in PTQ scores are related to the effects of taVNS on HRV.

Specifically, when investigating the role of changes in subjective perseverative cognition (i.e., changes in PTQ

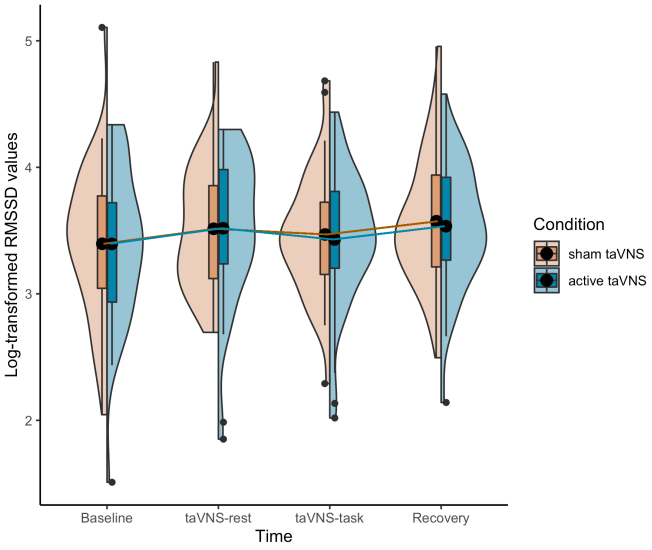

FIGURE 3 Log-transformed vagally-mediated HRV (i.e., RMSSD) values across participants throughout the experimental session for the active taVNS and sham condition. Error bars depict standard error to the mean. HRV, heart rate variability; RMSSD, Root Mean Square of Successive Differences; taVNS, transcutaneous auricular vagus nerve stimulation.

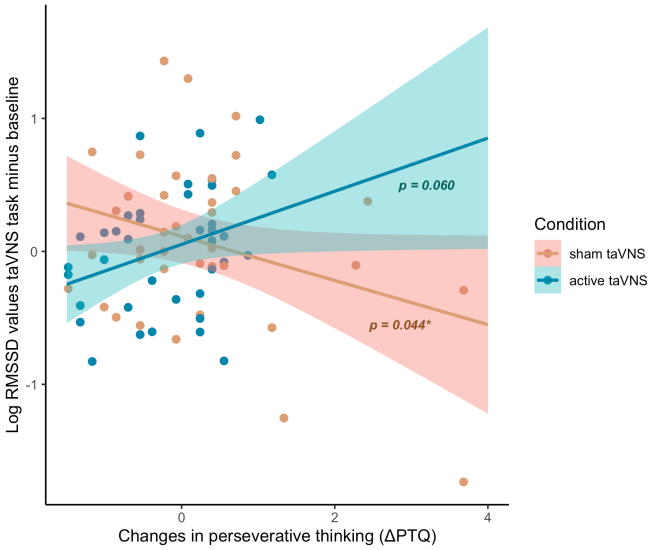

FIGURE 4 Scatterplot representing the relationship between participants' HRV (i.e., log-transformed RMSSD) values during the taVNS task as compared to baseline (i.e., taVNS task minus baseline) and changes in perseverative thinking (ΔPTQ scores) for the active taVNS and sham condition. Lower HRV levels during the stress task as compared to baseline (i.e., smaller $RMSSD_{taVNStask\text{-}baseline}$ values) indicate higher autonomic inflexibility and, more perseverative thinking after stress recovery (i.e., larger ΔPTQ scores) reflect higher cognitive inflexibility. Confidence interval bands are set at a 95% confidence level. HRV, heart rate variability; PTQ, Perseverative Thinking Questionnaire; RMSSD, Root Mean Square of Successive Differences; taVNS, transcutaneous auricular vagus nerve stimulation.

scores, ΔPTQ) on the effects of taVNS on HRV, results showed a significant three-way interaction between time, condition and ΔPTQ scores, $F(3, 221) = 4.04$, $p = .008$, $\eta_p^2 = 0.05$. Specifically, in the sham taVNS condition, there was a marginally significant interaction between time and ΔPTQ scores, $F(3, 107.00) = 2.70$, $p = .049$, $\eta_p^2 = 0.07$, whereas no such effect was found in the active stimulation condition, $F(3, 114) = 2.38$, $p = .073$, $\eta_p^2 = 0.06$. In particular, in the sham taVNS condition, lower HRV levels during the arithmetic task (i.e., taVNS-task), as compared to baseline, were significantly associated with increases in PTQ scores after the recovery period (i.e., higher ΔPTQ scores), $t(107) = 2.66$, $p = .044$, $d = 0.23$. Although not statistically significant, an opposite pattern was present in the active taVNS condition (i.e., a positive association between HRV levels during the task, as compared to baseline, and ΔPTQ scores, see Figure 4), $t(114) = 2.53$, $p = .060$, $d = 0.06$. Besides this higher-order significant interaction, the model also showed a significant main effect of time, $F(3, 221.05) = 4.54$, $p = .004$, $\eta_p^2 = 0.06$.

The additional exploratory analysis with stimulation intensity revealed no significant moderation of stimulation intensity, F's < 1.18, p's $> .282$, η_p^2's < 0.02.

4 | DISCUSSION

Despite its role in perseverative cognition (Ottaviani, 2018; Thayer & Lane, 2002), research investigating the causal modulation of the vagus nerve, using non-invasive vagal nerve stimulation techniques such as taVNS, to affect perseverative cognition is scarce. To fill this gap, this study investigated the effects of taVNS of the left concha, compared to sham (earlobe) stimulation, on the cognitive (i.e., self-reported perseverative thinking) and autonomic (i.e., vagally mediated HRV) inflexibility that characterizes perseverative cognition following psychosocial stress in a sample of healthy individuals.

The stressor caused, in both stimulation conditions, a significant peak in heart rate and skin conductance, indicative of an acute physiological stress response during the arithmetic task adapted from the TSST. In terms of subjective levels of negative affect, independent of the stimulation (intensity) they received, participants reported higher levels of negative affect at the end of the stress recovery period compared to the baseline assessment. Whereas the electrodermal activity remained significantly higher during stress recovery compared to baseline, no such sustained activation was found for the cardiac measures. These results show that our manipulation induced stress, measured with psychological and physiological indices, indicative of sympathetic reactivity throughout the experiment.

The effects of the activation of the auricular branch of the vagus nerve (vs. sham) will be described separately for the psychological (i.e., subjective self-reports) and physiological (i.e., HRV) measures. With regard to the subjective measurements of perseverative cognition, the study results showed that taVNS significantly affected preservative thinking after psychosocial stress. Specifically, in this sample, taVNS of the left concha, as compared to sham (earlobe) stimulation, led to a significant reduction of perseverative thinking following stress recovery. This is in line with past research showing a reduction of spontaneous worrying behavior during taVNS of the left cymba concha (Burger et al., 2019), and endorses the causal role of the vagus nerve in perseverative cognition (Ottaviani, 2018).

With regard to HRV, the study results showed no direct effects of taVNS on this autonomic correlate of perseverative cognition, which, though in contrast to our a priori hypotheses, is in line with the findings of Burger et al. (2019) on the autonomic correlates of negative thought intrusions in high worriers. Moreover, although positive taVNS effects have been reported (e.g., Höper et al., 2022; Keute et al., 2021; Machetanz et al., 2021a, 2021b), the current study findings (in a well-powered sample) are in accordance with the findings of the interactive Bayesian random effects meta-analysis by Wolf et al. (2021), which provides strong evidence for the lack of effects of active taVNS, compared to sham, on vagally mediated HRV. Interestingly, however, individual differences in the subjective changes in perseverative cognition before versus after the stressor significantly affected the effects of taVNS on HRV. In particular, for the sham condition, a significant association was found between self-reported perseverative thinking and HRV levels during the arithmetic task as compared to baseline. In line with previous research demonstrating a negative relationship between cognitive rigidity and HRV (Ottaviani et al., 2016), the current results demonstrate that higher autonomic inflexibility during the stressor was linked with increases in perseverative thinking after the recovery period. A trending but non-significant finding, and therefore interpreted with caution, was that for the active taVNS condition an opposite pattern was found in which higher levels of HRV during the task as compared to baseline (i.e., indicating more autonomic flexibility) were associated with more cognitive rigidity. To speculate, this contrary trend could possibly result from a dissociation between psychological and physiological changes following taVNS. Hence, although participants might show more physiological flexibility following taVNS, compared to sham, they might not experience reduced perseverative cognition on a subjective level. Indeed, a dissociation between cognitive, behavioral, and physiological measures has also been reported in previous work investigating perseverative cognitions following inhibitory neurostimulation of the prefrontal cortex (Era et al., 2021). Notably, although some studies have reported taVNS-induced decreases in heart rate (e.g., Höper et al., 2022; Keute et al., 2021; Yokota et al., 2022) and electrodermal activity (e.g., Lamb et al., 2017; although see also Burger et al., 2017, 2018), no such effects were found in the current study. Notwithstanding, the present findings are in line with previous work using similar stimulation parameters (De Smet, Baeken, Seminck, et al., 2021).

Overall, the exploratory analyses revealed no significant effects of taVNS intensity, individually determined based on the subjective pain threshold, on the psychological and physiological measures used in this study. This is in contrast with past research demonstrating a positive association between stimulation intensity and various outcome measures including cortical excitability (Mertens et al., 2021) and HRV (Machetanz et al., 2021a). Interestingly, Mertens et al. (2021), report relatively higher mean stimulation currents (3.35 mA) as compared to the current study (mean taVNS intensity = 1.37 mA), suggesting that higher intensities might be required to facilitate neuromodulatory effects. However, Machetanz et al. (2021a) used stimulation intensities that were relatively lower than the above-mentioned studies (max 0.4, 0.77, and 2 mA), contradicting this idea. Moreover, in a series of experiments in which Borges et al. (2019) systematically evaluated the effects of stimulation intensity on vagally mediated HRV (i.e., RMSSD), the authors found an overall positive association between taVNS intensity and HRV in their second experiment. Yet, this effect could not be replicated in a later experiment in which the taVNS intensity was significantly higher (mean intensity taVNS of 2.50 and 1.78 mA, respectively, Borges et al., 2019). Hence, more research systematically investigating the effects of taVNS stimulation intensity, and which intensities might result in the most optimal results, on cognitive, affective, and psychophysiological processes is warranted (see also Burger et al., 2020; Farmer et al., 2021). Notably, although Wolf et al. (2021) made use of a Shiny web app that is frequently updated with newly published findings to keep the evidence of their interactive Bayesian random effects meta-analysis up to date, the moderating role of stimulation intensity (e.g., using meta regressions with stimulation intensity as a continuous predictor) has not yet been explored. However, it is important to note that this type of analysis requires participant-level data which is often not shared or publicly available. Hence, past and future studies are highly encouraged to share participant-level data which facilitates the process for future meta-analyses to investigate the moderating role of stimulation intensity.

Given that stimulation was applied during the task, but not during the 10-min recovery period thereafter, the significant taVNS effects on correlates of perseverative cognition provide evidence for the continuation of taVNS effects beyond the period of stimulation. Although replication in (non-)clinical samples is warranted, these findings provide promising implications for the use of taVNS in clinical settings, in which the duration of effects is pivotal. Indeed, as our findings suggest that a single session of taVNS can reduce perseverative thinking in healthy individuals, taVNS might hold potential as a (adjuvant) intervention in psychopathologies characterized by perseverative cognition. For instance, the tendency to engage in repetitive negative thinking about past events (i.e., rumination) is suggested to be one of the most important risk factors for the development, maintenance, and recurrence of stress-related disorders such as major depressive disorder (MDD; Ehring & Watkins, 2008; Nolen-Hoeksema et al., 2008). Interestingly, studies have revealed positive effects of taVNS on depressive symptoms in patients suffering from MDD (Hein et al., 2013; Kong et al., 2018; Rong et al., 2016). Hence, the effects of taVNS on perseverative cognition might serve as one of the underlying working mechanisms of the antidepressant effects of taVNS. Though, well-powered randomized controlled trials, including neuroimaging assessments, are warranted to further gain insights into taVNS working mechanisms and to optimize its therapeutic potential.

Although this study has several methodological strengths, such as its rigorous set-up and sham-controlled design, some important limitations need to be discussed. First, given the lack of subjective stress measure directly after the task (we only measured negative affect at baseline and after the recovery period), it remains unclear whether the physiological changes during the arithmetic task (i.e., the peak in heart rate and skin conductance during the task) were accompanied by an acute subjective (i.e., psychological) stress response. Hence, future studies are endorsed to assess such measures directly following the stressor, as these can inform us on the acute psychological changes associated with stress-induced physiological responses. Second, although the data showed a slight drop in HRV during the actual confrontation with the stressor, compared to the time period before the task, this reduction in HRV was not significant. Hence, this indicates that the manipulation (i.e., arithmetic task) was not effective in decreasing HRV. A reduction in HRV, however, is ought to represent parasympathetic (i.e., vagal) withdrawal when confronted with a stressor (Ottaviani, 2018). Due to the lack of a control task, it remains unclear whether or not this is due to the specific type of task used in this study. In the literature, different methods have been described to induce perseverative cognition including more direct induction methods, asking participants to directly engage in perseverative cognitions (e.g., Borkovec et al., 1983), but also stressful tasks that provoke ruminative thinking (Ottaviani et al., 2016). Moreover, in terms of heart rate responses, a meta-analysis in healthy individuals showed that only studies employing stressful tasks, compared to other induction methods, showed significant effects of perseverative cognition (Ottaviani et al., 2016). With regard to HRV, however, meta-analytic findings showed an association between perseverative cognition and reduced HRV, but no significant moderation effects of the type of induction (Ottaviani et al., 2016). Crucially though, only studies employing within-subjects designs, compared to between-subjects designs, showed significant HRV responses to perseverative cognition. Hence, implementing a within-subjects design, and control task, might be crucial for future taVNS studies to detect robust changes in HRV responses to perseverative cognition. Third, given our interest in physiological changes over the different phases of the experiment (e.g., stress reactivity and recovery), and not in the temporal changes within a phase, we a priori decided to average HRV over phases. However, the aggregation of data results in a loss of information. Hence, future studies may instead consider binning the data by time. Last, solely HRV was used as a physiological marker of vagal activation. Due to the inconsistency of reported findings (Wolf et al., 2021), the reliability of HRV as taVNS biomarker has been questioned. Although no robust biomarkers have yet been identified (Burger et al., 2020), several potentials candidates have been put forward, including pupil dilation and salivary alpha-amylase (Burger et al., 2020; although evidence is mixed e.g., D'Agostini et al., 2021; Warren et al., 2019), which are advised to be implemented in future research investigating taVNS effects.

To conclude, this study in healthy individuals investigated the effects of a single session of taVNS on cognitive and autonomic correlates of perseverative cognition following a psychosocial stressor. Our results demonstrated that taVNS significantly reduced cognitive rigidity, as reflected by lower levels of subjective perseverative cognition after a stressor. Vagally mediated HRV was not directly affected by taVNS. However, individual differences in perseverative thinking modulated the effects of taVNS on HRV, with a negative association between autonomic and cognitive inflexibility for the sham but not for the active taVNS condition. In addition, although more systematic research is warranted, exploratory analyses presented no evidence for a relationship between taVNS intensity and the psychophysiological measures used in this study, including HRV and perseverative

thinking. Overall, our findings provide evidence for the association between the vagus nerve and preservative cognitions, which might be important information for the treatment of stress-related mental health problems (Verkuil et al., 2010).

AUTHOR CONTRIBUTIONS

Stefanie De Smet: Conceptualization; data curation; formal analysis; funding acquisition; investigation; methodology; project administration; software; visualization; writing – original draft; writing – review and editing. **Cristina Ottaviani:** Writing – review and editing. **Bart Verkuil:** Writing – review and editing. **Mitchel Kappen:** Writing – review and editing. **Chris Baeken:** Writing – review and editing. **Marie-Anne Vanderhasselt:** Conceptualization; funding acquisition; methodology; resources; supervision; validation; writing – review and editing.

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DATA AVAILABILITY STATEMENT

The data and R script that support the findings of this study are openly available via the Open Science Framework at https://doi.org/10.17605/OSF.IO/NKDFQ.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

Appendix S1

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