

General information

1. Research idea, design, and impact

1a. NWO Domain

I submit this proposal within the domain Social Sciences and Humanities (SSH/SGW): Yes

This proposal involves scientific disciplines related to other NWO domains: No

1b. Titles and abstract

a. Title of the research proposal

Neurocognitive effects of noninvasive vagus nerve stimulation

b. Title of the [public summary](#) in English

Neurocognitive effects of vagus nerve stimulation

c. Title of the [public summary](#) in Dutch

Neurocognitieve effecten van vagale zenuwstimulatie

d. Abstract

Transcutaneous vagus nerve stimulation (tVNS) is a noninvasive method for stimulating the vagus nerve, the long nerve that connects several vital organs with the brainstem. Scientists and commercial sellers of tVNS devices have stressed the potential of tVNS to enhance cognitive functions in healthy individuals. Furthermore, cognitive neuroscientists believe tVNS may offer a unique tool for stimulating neuromodulatory arousal systems. However, many of these scientific claims lack robust empirical support, suggesting the need for rigorous tests. In the proposed research, we will (1) examine the acute and cumulative effects of tVNS on cognitive functions in younger and older adults; and (2) use sophisticated pupil, EEG and fMRI methods to test whether pulsed tVNS activates neuromodulatory arousal systems. Importantly, unlike previous research, we will examine both auricular and cervical tVNS. The results will inform the potential of tVNS for cognitive enhancement in healthy individuals and reveal the neuromodulatory arousal systems involved.

1c. Research idea

SCIENTIFIC BACKGROUND

~ Invasive vagus nerve stimulation (VNS) ~

The vagus nerve can be considered a “superhighway”: as the longest nerve in the human nervous system it serves a major role in carrying signals from various organs to the brain and back. Vagus nerve stimulation (VNS) is a medical treatment that involves sending electrical impulses to the vagus nerve using an implanted device similar to a pacemaker. VNS is currently used for treating pharmacoresistant epilepsy, refractory depression, migraine and cluster headaches, and examined as a potential treatment for a wide range of other neurological and psychiatric disorders¹. The biological mechanisms underlying the beneficial effects of VNS on brain diseases are only partially understood. However, animal work has established that through its direct projections to the (brainstem) nucleus tractus solitarius, the vagus nerve modulates activity of several neuromodulatory arousal nuclei², including the noradrenergic locus coeruleus (Figure 1). Moreover, there is growing evidence that these neuromodulatory systems mediate the beneficial medical effects of VNS¹.

~ Transcutaneous vagus nerve stimulation (tVNS) ~

Because VNS is costly and invasive, limiting novel therapeutic applications, transcutaneous (= passing through the skin) VNS (tVNS) was developed as a noninvasive, less expensive, and easily applicable alternative: it consists of a small stimulation device that is connected with electrodes placed on the ear or the neck, where it can deliver mild electrical currents to the auricular (ear) or cervical (neck) branch of the vagus nerve. Over the past ten years neurologists and psychiatrists have started examining the clinical potential of tVNS for a wide range of disorders¹. When the first promising effects on headaches and epilepsy were published, this drew the attention of medical technology companies, cognitive psychologists and neuroscientists, who envisioned two potentially powerful, non-medical applications of tVNS: the medical technology companies and cognitive psychologists saw tVNS as a possible way to enhance cognitive functions in healthy adults; cognitive neuroscientists saw it as a means of stimulating and studying neuromodulatory arousal systems. Ten years later, commercial sellers of tVNS devices are still popping up like mushrooms, and the number of neuroscientific studies on tVNS is rapidly growing. However, the scientific evidence supporting the two non-medical applications is still far from clear.

Therefore, the general aim of the proposed research is to validate the effectiveness of tVNS at enhancing cognitive functions (WP1) and activating neuromodulatory arousal systems (WP2).

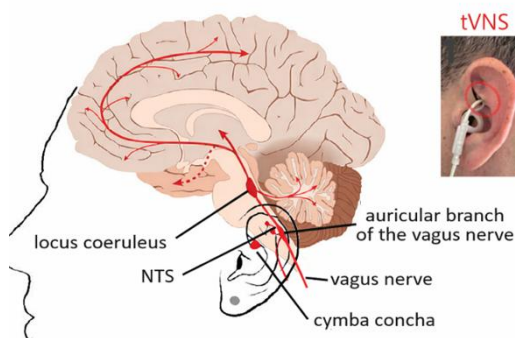


Figure 1. Auricular tVNS involves electrical stimulation of the cymba concha, a part of the outer ear that is innervated by the auricular branch of the vagus nerve. Successful stimulation of this nerve is assumed to activate the nucleus tractus solitarius (NTS) in the brainstem, which in turn activates the locus coeruleus and other neuromodulatory arousal systems. [Figure adapted from ref. 17]

~ Enhancement of cognitive functions ~

It is far from obvious that a method with proven clinical potential for certain types of neurological patients enhances cognitive function in healthy individuals. For example, despite popular belief, the effects of the ADHD drug methylphenidate on cognition in healthy individuals are minimal. Yet, companies are selling tVNS devices to the general public as a means for stress relief and other mental benefits, claiming that it "... supports enhanced learning, sharper memory, and improved focus, promoting overall cognitive wellness" (Nurosym), "... optimizes mental state, improving accuracy of hearing, vision, and touch" (SharperSense), and leads one to "feel calmer, think clearer, sleep better" (Truvaga). Indeed, these strong claims are rarely backed up by solid scientific evidence.

On their websites, commercial parties advertize the tVNS devices by citing positive but anecdotal reports from individual consumers, who may simply experience a placebo effect or cognitive dissonance, having just bought an expensive device (~€300-€800). The companies also cite scientific evidence, but tend to cherry-pick from the scientific literature. For example, they often claim that tVNS relieves stress because it increases heart-rate variability; but when all studies on tVNS and heart-rate variability are taken into account, the null results outweigh the positive results³. Commercial claims also tend to imply that positive effects outlast the stimulation period, but scientific studies often do not examine whether cognitive effects remain after the (e.g., 30 minutes of) stimulation ends.

However, scientists should not only blame commercial companies for their practices; they should also reflect on themselves. Although recent years have seen a steady increase in high-quality tVNS studies on cognitive enhancement^{4-7,53}, the field also suffers from limitations. For example, many tVNS studies include relatively few participants, which increases the chance of false positives or negatives and limits generalizability. Researchers also tend to emphasize the significant (positive) findings, even if these are limited to one cell of the study design, and disregard the negative findings. Replication studies are rare. Further complicating things, there is still a limited understanding of the optimal stimulation parameters (e.g., intensity and frequency^{8,9}). Moreover, critical comments about the default sham location¹⁰ (earlobe) appear to be largely ignored.

The field needs more systematic, pre-registered studies to establish which claims about tVNS and cognitive enhancement are true and which are false. The proposed research aims to contribute to that aim.

~ Activation of neuromodulatory arousal systems ~

Neuromodulatory arousal systems, including the noradrenergic, cholinergic, dopaminergic and serotonergic systems, play a crucial role in regulating cognitive and brain function¹¹⁻¹³. These systems originate from small, localized nuclei (locus coeruleus, basal forebrain, ventral tegmental area, substantia nigra, raphe nuclei) but send diffuse projections throughout the cortex, hippocampus, thalamus, basal ganglia, and cerebellum. This architecture allows them to coordinate activity across large-scale brain networks, and thus help switch the brain between distinct functional modes such as cognitive flexibility/stability, exploration/exploitation, and learning slow/fast. These fundamental processes allow the brain to adapt cognition to environmental demands, such as novelty, uncertainty, and reward availability. Unfortunately, these crucial functions of neuromodulatory arousal systems are notoriously hard to study in humans. MRI of small subcortical nuclei is challenging, owing to their anatomical complexity and deep location in the brain⁵². Fortunately, researchers have validated pupil size and EEG desynchronization as indirect measures of neuromodulatory arousal¹⁴⁻¹⁶. However, aside from (invasive) pharmacological interventions, there used to be no options to directly manipulate human neuromodulatory arousal systems and examine the causal effects on brain and cognition.

Given that invasive VNS is known to modulate activity of several neuromodulatory arousal systems², tVNS may offer a long-awaited non-invasive instrument for stimulating these systems, transiently or over longer periods of time. Validating this application of tVNS is proving hard¹⁷, so new attempts using more powerful methods are needed. One of these methods is cervical tVNS.

~ Auricular versus cervical tVNS ~

Although both auricular (in-ear stimulation) and cervical tVNS (on the neck) are safe and well-tolerated¹⁸, over 95% of fundamental research on tVNS effects on healthy human brain and cognition has used auricular tVNS (taVNS). This is likely due to the device's ease of use; the electrodes are worn as earphones, while until recently cervical tVNS (tcVNS) was almost exclusively administered using a handheld device. However, from a scientific perspective, the almost exclusive focus on auricular tVNS is odd because (i) unlike auricular tVNS, cervical tVNS targets the same (cervical) branch of the vagus nerve that is stimulated by the implanted VNS devices that we know have widespread neural and clinical effects; (ii) pharmacoresistant cluster headaches and migraine are exclusively treated with cervical tVNS; (iii) a considerable portion of studies on auricular tVNS and cognitive function have yielded null effects; and (iv) the only two studies that directly compared cognitive effects of (sham-controlled) auricular and cervical tVNS found that cervical but not auricular tVNS enhanced language acquisition¹⁹ and sensory performance⁵. So, fundamental research should examine the effects of both auricular and cervical tVNS.

~ Key research objectives ~

In WP1, we will examine whether auricular and cervical tVNS enhance cognitive functions, focusing in particular on perception, working memory and cognitive control. We will study the acute effects of tcVNS in younger adults and the cumulative effects of a two-week taVNS intervention in older adults.

In WP2, we will investigate whether pulsed auricular and cervical tVNS activate neuromodulatory arousal systems, using pupillometry, EEG and ultra-high-field fMRI.

Both work packages will start with a **theoretical review and critical reflection** on existing literature.

METHODOLOGY

WP1: Does tVNS enhance cognitive functions in younger and older adults? (PhD student)

Although plenty of studies have reported beneficial effects of auricular tVNS on cognitive functions²⁰, recent null findings^{21,22} and non-replications^{4,6,23} show that the picture is less clear-cut than initially thought. Importantly, many early studies were not preregistered, opening the door for publication bias. Furthermore, over 90% of published studies on cognitive functions used auricular tVNS; the number of tcVNS studies is very small^{5,6,19}. Studies that examined the effect of a longer tVNS intervention on cognitive function in non-clinical samples have also been very rare^{6,24}. The goal of WP1 is to address these limitations.

WP1a. A review and *p*-curve analysis of tVNS effects on cognition

To start this project and chart existing work on tVNS and cognitive enhancement in healthy younger and older adults, we will write a comprehensive review, in which we pay special attention to replication studies and the limited number of tcVNS studies, as a prelude to WP1b. Another important component will be the choice of stimulation parameters, a critical moderating factor²⁵. As part of this review, we will carry out a *p*-curve analysis²⁶, a statistical method used in psychology to detect practices like publication bias and *p*-hacking²⁷. Instead of looking at effect sizes or meta-analytic averages, a *p*-curve analysis examines the distribution of statistically significant *p*-values reported across a set of studies that test the same hypothesis.

WP1b. Effects of cervical tVNS on perception, working memory and cognitive control

Given the current scarcity of empirical evidence on tcVNS and cognitive enhancement, WP1b aims to help establish a robust and methodologically sound literature base, which will also provide an evidence-based foundation for evaluating scientific claims made in the marketing of tcVNS devices. In three large experiments, we will assess the effects of continuous tcVNS on perception, working memory, and cognitive control in groups of healthy young adults. We choose these three cognitive functions because they are known to be modulated by neuromodulatory arousal^{54,55}. Cognitive performance will be tested on two separate occasions, once during tcVNS and once during sham stimulation. The two interventions will be delivered in counterbalanced order, at least 7 days apart to avoid carry-over effects. Stimulation will be administered during task blocks (total 40-45 mins) with 5-minute breaks in between.

~ Cognitive tasks ~

Experiment 1 will focus on perception. Participants will perform difficult auditory and visual detection and discrimination tasks²⁸. Staircase procedures will be used to titrate each task to ~75% response accuracy. Experiment 2 will focus on working memory: Participants will perform an n-back task and a delayed matching-to sample task in the continuous color domain²⁹, focusing on the updating and maintenance components of working memory, respectively. A mathematical model will allow us to distinguish between tcVNS effects on memory accuracy versus memory precision²⁹. Experiment 3 will examine tcVNS effects on cognitive control, and in particular on Stroop performance and cued task switching²². In all three experiments we will, where possible, use dependent measures based on psychophysics (e.g., *d*-prime, accuracy), to mitigate tVNS effects on response speed and the speed-accuracy tradeoff²². In addition, we will use computational models to isolate the latent cognitive processes that are modulated by tVNS.

~ tcVNS ~

To apply tcVNS, we will use a pair of DS7A Digitimers, one for active and one for sham stimulation, paired with cervical electrodes. Sham stimulation will be applied to an appropriate (i.e. non-vagal and safe) control location in the neck⁵. Given the deep location of the cervical vagus nerve (~3 cm beneath the skin), a sufficient

stimulation intensity is crucial for tcVNS. Indeed, clinical studies and a biophysical model of tcVNS³⁰ show that effective tcVNS typically requires much higher currents than taVNS. We will take into account these considerations in selecting an intensity that is perceptible, tolerable, and does not induce muscle activation^{5,31}. The subjective intensities of tcVNS and sham will be carefully matched and recalibrated after each task block to avoid habituation³².

~ Statistics and sample size ~

To answer the key question whether cognitive performance is enhanced in the tcVNS condition, we will submit the task performance measures to frequentist and Bayesian paired-samples *t*-tests (or ANOVAs that also include task variables), with stimulation condition (tcVNS vs. sham) as the critical independent variable. Given that we will be covering new ground, we assume a medium effect size (Cohen's $d = .4$) as the most reasonable estimate for a practically and theoretically meaningful effect. A power analysis for a paired-samples *t*-test (G*Power 3.1, Cohen's $d = .4$, one-tailed $\alpha = .05$, power = .80) indicated that a sample of 42 participants is required per experiment.

WP1c. Effects of a two-week auricular tVNS intervention on cognitive function in older adults

Recent reviews have stressed the potential benefits of tVNS in promoting healthy cognitive aging^{33,34}. Accordingly, a leading manufacturer that sells tVNS devices directly to customers (Nurosym) claims that 15-30 minutes of daily stimulation "strengthens cognitive performance to counteract the effects of aging". Importantly, these claims suggest that the beneficial cognitive effects of tVNS outlast the stimulation period. However, the scientific literature is limited to two studies that examined the effects of a single session of taVNS on memory in older age and the results are inconsistent^{35,36}. In WP1c we will examine the cumulative effects of a two-week sham-controlled taVNS intervention²⁴ on perception, working memory and cognitive control in a large group of carefully screened, healthy older (70-80 years) adults. This study will provide an important test of whether a longer taVNS intervention can produce cumulative cognitive benefits in a group with slightly impaired cognitive function, offering room for cognitive enhancement.

Older participants will come to the lab for a cognitive testing session on the days before (day 1) and after (day 16) a two-week intervention. On both days they will perform a diverse battery of cognitive tasks assessing perception, working memory and cognitive control, three domains that show clear aging effects³⁷. The task battery consists of shortened versions of the tasks described under WP1b, and will be administered over the course of a half-day, with plenty of breaks in between. No tVNS will be delivered during these sessions. In between these sessions (days 2-15), the participants self-administer taVNS (active group) or sham (control group) once a day for 30 minutes. To examine if the effects of the intervention outlast the intervention period, the post-intervention session will be held 24 hours after the last stimulation.

~ taVNS ~

All participants will be trained on day 1 to self-administer taVNS or sham to their left ear using the NEMOS/tVNS® device, following the standard settings of the manufacturer (e.g., 30 sec on/off cycle). A daily dose of 30 minutes is the most commonly used taVNS duration in clinical treatment protocols for epilepsy, chronic pain and other medical conditions. Clinical studies support the feasibility, acceptability, and safety of home-based, self-administered taVNS for 30 mins/day – an important reason why we opt for auricular tVNS in this subproject. Common side effects are mild and transient, and can include local skin irritation at the electrode site and mild headache. Participants in the active group will be instructed to start their daily stimulation procedure by setting the stimulation intensity to a level above their sensory thresholds, causing a light tingling yet comfortable feeling in the ear. Participants in the sham group will be asked to select an ineffective, low and fixed intensity (0.2 mA) before starting the 30 minutes of stimulation.

~ Statistics and sample size ~

To address the key question whether the taVNS intervention enhances cognitive task performance, we will submit the task performance measures to 2×2 mixed (frequentist and Bayesian) ANOVAs with group (taVNS vs. sham) and time point (before vs. after the intervention) as critical independent variables. A power analysis assuming a 'clinically relevant' medium effect size and a moderate correlation ($r \approx .50$) between pre- and post-intervention task performance measures indicated a required sample size of 34 participants per group (G*Power 3.1, Cohen's f for critical interaction effect = .25, two-tailed $\alpha = .05$, power = .80). To anticipate drop-outs, we will recruit 40 participants per group.

WP2: Does pulsed tVNS activate neuromodulatory arousal systems? (postdoc)

Subcortical nuclei of the ascending arousal system play an important role in regulating brain and cognition. As argued above, understanding these neuromodulatory arousal systems belongs to the most fundamental goals of cognitive neuroscience. While it is already possible, using pharmacology, to change activity of neuromodulatory arousal systems for a longer period of time (on the order of hours), there currently exists no adequate method for briefly (on the order of seconds) stimulating these systems in humans. Having such a method would allow cognitive neuroscientists to vary stimulation from trial to trial during cognitive tasks, and test hypotheses about the effects of phasic neuromodulatory arousal changes on brain and cognition. Importantly, tVNS, as a non-invasive method that can deliver pulsed (i.e., brief bursts of) stimulation, promises to offer this opportunity: Animal studies have shown that invasive VNS activates the noradrenergic and cholinergic arousal systems^{38,39}, possibly explaining its therapeutic effects in human patients with psychiatric or neurological disorders.

Assessing whether taVNS affects neuromodulatory arousal systems in humans is highly challenging¹⁷, primarily because of the difficulties in neuroimaging of the tiny subcortical nuclei that form the core of these systems. The goal of WP2 is to accelerate research on this topic through a critical literature review and addressing important but unanswered empirical questions.

WP2a. Review of effects of tVNS on EEG and fMRI measures

To start this project we will review fMRI studies on the neural effects of auricular and cervical tVNS, with an emphasis on reports of taVNS-specific BOLD activation in neuromodulatory nuclei. Measuring BOLD activation of these tiny nuclei, such as the locus coeruleus, requires dedicated fMRI acquisition and analysis methods, including methods to delineate these nuclei and correct for physiological sources of noise (see below). Therefore, we will scrutinize the extent to which previous tVNS studies have used these dedicated fMRI methods. In addition, we will review tVNS-EEG studies, focusing in particular on studies that examined EEG desynchronization: a shift from slow, rhythmic brain waves to faster, lower-amplitude activity, indicating increased neuromodulatory arousal¹⁵. In reviewing this fMRI and EEG literature, we will take into account the choice of tVNS stimulation parameters, including whether stimulation was pulsed or continuous.

WP2b. Effects of pulsed cervical and auricular tVNS on pupil dilation and EEG

Do short bursts of tVNS activate neuromodulatory arousal systems? As mentioned above, EEG desynchronization is an important index of neuromodulatory arousal. Evidence for an effect of pulsed taVNS and tcVNS on EEG desynchronization is mixed^{31,40-42}, but we do not understand why. But an even more important overt index of neuromodulatory arousal is pupil size¹⁶ and event-related pupil dilation¹⁴. A recent meta-analysis of 18 taVNS/pupillometry studies found that pulsed taVNS, but not continuous taVNS, has a strong effect on pupil dilation⁴³. Surprisingly, not a single study has examined the effect of tcVNS on pupil size.

The goal of WP2b is to examine the effects of pulsed cervical and auricular tVNS on pupil size and EEG desynchronization in a group of healthy young adults. In half of the experiment (30 mins), we will administer auricular tVNS vs. sham, in the other half (30 mins) cervical tVNS vs. sham, with the order counterbalanced across participants. Resting-state pupil size and EEG will be simultaneously recorded. Importantly, previous studies reporting taVNS effects on pupil dilation have delivered taVNS and sham stimulation in separate blocks of trials or in separate sessions, hindering the integration of taVNS into the rapid, event-related task designs of cognitive neuroscientists. In WP2b we will intermix pulsed tVNS and sham in the same blocks of trials. If tVNS effects are preserved, this will provide an important step toward validating tVNS as a manipulation of phasic neuromodulatory arousal during task performance.

~ tVNS ~

To administer pulsed tcVNS and taVNS, we will use two DS7A Digitimers, paired with cervical or auricular electrodes. Cervical sham stimulation will be applied to an appropriate (i.e., non-vagal and safe) control location in the neck; auricular sham to the scapha⁴⁴, a part of the outer ear that is possibly a more appropriate control location than the earlobe¹⁰. Stimulation intensity will be calibrated separately for tcVNS, taVNS and the corresponding sham locations (see WP1b), and recalibrated halfway through the tcVNS and taVNS halves of the experiment³². The stimulation frequency and pulse width will be carefully chosen based on previous work^{8,45} and piloting. Note that we do not intend to directly compare effects of tcVNS and taVNS, given that the nerves targeted by these two methods differ fundamentally⁴⁰, and cervical and auricular stimulation intensities cannot

be compared. Instead, our goal is to find a form of stimulation that reliably targets neuromodulatory arousal systems.

~ Statistics and sample size ~

To answer the key question whether pulsed tcVNS and taVNS affect pupil dilation and EEG desynchronization, we will carry out four frequentist and Bayesian paired-samples *t*-tests with stimulation type (tVNS vs. sham) as the independent variable. Furthermore, we will characterize the time course of pupil and EEG frequency modulations, using nonparametric permutation testing with corrections for multiple comparisons. Previous pulsed taVNS/pupillometry | EEG desynchronization studies^{42,43} suggest that a sample size of 32 participants provides sufficient statistical power.

WP2c. Effects of pulsed tVNS on ultra-high-field fMRI

Another way to examine whether short bursts of tVNS activate neuromodulatory arousal systems is through the use of fMRI. However, as noted above, measuring BOLD activation of these tiny nuclei, such as the locus coeruleus, is challenging and requires dedicated fMRI acquisition and analysis methods. These may include ultra-high-field MRI, multi-echo imaging to increase signal-to-noise ratio in subcortical structures, neuromelanin-weighted T1 imaging for delineation of the locus coeruleus, optimized brainstem co-registration, and physiological noise regression to suppress respiratory and cardiac artifacts^{16,46}. Several high-quality studies combining tVNS with fMRI have reported that tVNS activates the human locus coeruleus⁴⁷⁻⁵⁰. However, most did not use brainstem-dedicated fMRI methods and did not examine other neuromodulatory arousal systems, including the dopamine nuclei, raphe nuclei and basal forebrain. Furthermore, most studies applied tVNS continuously or repeatedly over long periods of time. We are aware of only two auricular taVNS studies that used pulsed stimulation, ultra-high-field (7T) MRI, and brainstem-dedicated methods^{49,50}. However, taVNS and sham were not intermixed. Importantly, we are not aware of any cervical tVNS-MRI studies that were equipped to reliably assess neuromodulatory arousal systems.

In WP2c we will use ultra-high-field (7T) fMRI and other sophisticated imaging methods to examine if pulsed auricular and cervical tVNS, intermixed with their corresponding sham stimulation, activate neuromodulatory arousal systems in healthy young adults.

~ tVNS and MRI ~

We will use the same pulsed and intermixed tcVNS/taVNS/sham stimulation protocol as in WP2b. MRI-compatible wires and electrodes will be used to connect the tVNS device with the participant. For (f)MRI data acquisition and analysis we will use the brainstem-dedicated methods mentioned above and described in detail in my previous work^{14,16,46}. Anatomical MRI scans will be collected before the task-related fMRI scans to allow participants to acclimatize to the scanner and loud scanner noise, and hence mitigate novelty-related arousal from confounding the fMRI data. Respiration data will be collected to determine if we can replicate evidence that taVNS effects on brainstem nuclei are larger when tVNS is delivered during exhalation^{45,50}.

~ Sample size ~

Recent brainstem fMRI studies reporting widespread event-related activation of neuromodulatory nuclei were based on sample sizes of 16-32 participants^{46,50,51}. To stay on the safe side, we opt for a final sample size of 36.

1d. Scientific and/or societal impact

Chosen impact focus: Both scientific and societal impact

WP1 can have important societal impact, WP2 will have significant scientific impact.

~ Societal impact (WP1) ~

The outcomes of WP1 have clear translational relevance, given the rapidly growing public and commercial interest in tVNS-based interventions. If WP1 yields positive findings, these results are likely to attract immediate attention from commercial stakeholders. In that case, I will proactively engage with the media through carefully framed press releases to ensure that potential applications, limitations, and uncertainties are communicated accurately and responsibly. Conversely, if WP1 yields null or mixed findings, these results will be disseminated with equal transparency, together with a balanced and evidence-based evaluation of existing commercial claims, to help prevent misinformation and premature adoption by the public.

Beyond academic dissemination, sharing these findings with the general public is essential to promote informed decision-making and public trust in neuroscience. To this end, I will communicate the results in accessible formats, including a popular science article in *Skepter*, a magazine dedicated to the critical examination of extraordinary claims and controversial methods, and follow-up contributions to national public media (e.g., NTR Focus¹). In parallel, the results will be actively shared within the *European Research Network on tVNS* and presented at the biannual *International Brain Stimulation Conference*, ensuring rapid knowledge transfer to both the scientific community and translational stakeholders.

~ Scientific impact (WP 2) ~

The potential scientific impact of WP2 is substantial. If pulsed tVNS is validated as a reliable method for transiently engaging neuromodulatory arousal systems, it would represent a major addition to the cognitive neuroscientist's experimental toolkit. In contrast to pharmacological manipulations—which often have delayed onsets, systemic side effects, and broad, difficult-to-control effects across the brain—tVNS offers a relatively inexpensive, noninvasive, and temporally precise means of modulating neuromodulatory activity. This makes it particularly well suited for hypothesis-driven experiments targeting the functional role of arousal systems in brain, cognition and behavior, a set of questions that lies at the core of contemporary cognitive neuroscience.

Collectively, WP2a, WP2b, and WP2c will constitute one of the most rigorous validation efforts to date for auricular tVNS, and the first such validation for cervical tVNS. Beyond its immediate scientific contributions, the impact of WP2 will be amplified through targeted community-building activities. In particular, I will organize dedicated symposia on tVNS and neuromodulatory arousal systems at the annual meetings of the *Cognitive Neuroscience Society* and the *Society for Neuroscience*, facilitating cross-disciplinary exchange and accelerating the responsible adoption of these methods within the broader neuroscience community.

~ Open science statement ~

All empirical studies (WP1 and WP2) will be preregistered to promote transparency and counteract publication bias. Analysis code and data sets will be shared through publication in the open repository DataverseNL.

¹ I recently shared my skeptical views on commercial tVNS initiatives in a popular science podcast on national public radio (NTR Focus⁵⁶), and aim to follow up on this.

1e. Literature references

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