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# State dependent vagus nerve stimulation for targeted plasticity therapy: challenges and considerations

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Targeted plasticity therapy (TPT) utilizes vagus nerve stimulation (VNS) to promote improvements in function following neurological injury and disease. During TPT, a brief burst of VNS induces neuromodulator release, which when paired with relevant behavioral events can influence functionally relevant neuroplasticity. Functional improvements following TPT are therefore in part mediated by neuromodulator signaling. Unfortunately, comorbidities associated with neurological disease often result in altered cognitive states that can influence neuromodulator signaling, potentially impeding neuroplasticity induced by TPT. Aside from altered cognitive states, cardiorespiratory rhythms also affect neuromodulator signaling, due to the vagus nerve's role in relaying visceral sensory information from the cardiovascular and respiratory systems. Moreover, precise VNS delivery during specific periods of the cardiorespiratory rhythms may further improve TPT. Ultimately, understanding the impact of patient-specific states on neuromodulator signaling may likely facilitate optimized VNS delivery, paving the way for personalized neuromodulation during TPT. Overall, this review explores challenges and considerations for developing advanced TPT paradigms, focusing on altered cognitive states and cardiorespiratory rhythms. We specifically discuss the possible impact of these cognitive states and autonomic rhythms on neuromodulator signaling and subsequent neuroplasticity. Altered cognitive states (arousal deficits or pain) could affect VNS intensity, while cardiorespiratory rhythms may further inform optimized timing of VNS. We propose that understanding these interactions will lead to the development of personalized state dependent VNS paradigms for TPT.

KEYWORDS

**vagus nerve stimulation, cognitive state, neuromodulator, cardiorespiratory rhythms, targeted plasticity, neuromodulation, personalized therapy, physiological control systems**

## Introduction

Vagus nerve activity influences central neuromodulator signaling via connections with subcortical structures regulating the release of acetylcholine, norepinephrine, serotonin, and dopamine (Rodenkirch et al., 2022; Hays et al., 2013). This influence impacts synaptic transmission, neuronal excitability, and network activity throughout the nervous system (Lee and Dan, 2012; Brzosko et al., 2019). VNS can activate these neuroanatomical pathways, electrically facilitating neuromodulator release and neuroplasticity. TPT leverages these processes by pairing relevant experiences with VNS in a temporally precise manner, further enhancing activity-dependent neuroplasticity in the central nervous system (Hays, 2016). TPT has been successfully employed across a variety of applications, including stroke (Dawson et al., 2021; Meyers et al., 2018; Badran et al., 2023; Redgrave et al., 2018; Francisco et al., 2023; Khodaparast et al., 2014; Hays et al., 2014), spinal cord injury (Ganzer et al., 2018; Darrow et al., 2020), peripheral nerve injury (Meyers et al., 2019; Darrow et al., 2021; Ruiz et al., 2023a), tinnitus (Engineer et al., 2011; Borland et al., 2016), post-traumatic stress disorder (Noble et al., 2019), as well as learning and memory (Bowles et al., 2022; Altidor et al., 2021; Olsen et al., 2023).

Importantly, the vagus nerve is primarily a conduit for sensory information from end organs to subcortical and cortical areas, facilitating the processing and integration of information related to autonomic function. At the cervical level, ~80% of its fibers are afferent and relay information from organs to the brain, while the remaining ~20% are efferent fibers dedicated to organ control. Given these complex interactions between the organs, the vagus nerve, and the central nervous system, at least two major factors emerge that significantly affect overall neuromodulator signaling: 1) altered cognitive states and 2) ongoing autonomic rhythms. While developments in VNS have led to FDA-approved therapies to treat epilepsy, obesity, stroke, and depression, the responder rates in clinical trials have varied significantly compared to preclinical studies (Dickie et al., 2019; Dawson et al., 2021; Morris et al., 1999; Tyler et al., 2017). This could, in part, be due to variability in patient-specific physiology impacting VNS-induced neuromodulator release.

Recent developments in bioelectronic medicines have interestingly begun using stimulation paradigms based on specific physiological states, cardiorespiratory rhythms, and altered cognitive states, representing a possible avenue for optimizing VNS paradigms and TPT. Studies are now exploring the use of closed-loop adaptive neuromodulation systems to optimally deliver stimulation based on the sleep-wake cycle in patients with Parkinson's disease (Gilron et al., 2021). Algorithms that consider patient-specific circadian rhythms are also now being utilized to optimize adaptive stimulation systems for treating epilepsy (Fleming et al., 2022). Brain-computer interfaces rely on neural signals to decode intent and re-establish control of the impaired end effector (Ethier et al., 2015). These neural signals are often influenced by altered states, such as shifts in attention or arousal (Hennig et al., 2021), motivation (Kleih-Dahms et al., 2021), and neuropathic pain (Vuckovic et al., 2015). Therefore, identifying the influence of non-motor cognitive states in neural decoding could further improve the performance of BCI-FES systems for movement control (Gallego et al., 2022). Moreover, regulating arousal levels via neurofeedback may also improve BCI performance, highlighting the importance of cognitive states (Faller et al., 2019). Overall, evidence suggests that personalized optimization of stimulus programming in neuromodulation systems can importantly improve patient outcomes (Moro et al., 2006). For example, a recent clinical study found that personalized chronic adaptive deep brain stimulation (DBS) outperformed conventional DBS for improving motor symptoms (Oehrn et al., 2024). Optimizing stimulus programming has also been useful in managing speech impairments following Parkinson's disease (Swinnen et al., 2024). Furthermore, appropriately timed stimulation synchronized with physiological states affects both functional outcome and neuroplasticity. For example, phase specific thalamic DBS can suppress essential tremor significantly better than traditional high-frequency thalamic DBS (Cagnan et al., 2017). Phase-specific stimulation synchronous with cortical beta oscillations can also lead to bidirectional synaptic plasticity (Zanos et al., 2018), similar to studies using electroencephalography (EEG) guided transcranial magnetic stimulation for learning and memory (Taylor et al., 2008) or movement disorders (Wendt et al., 2022). Recent studies are now using closed-loop neuromodulation approaches for individuals with treatment-resistant depression, utilizing recordings from the amygdala and spectral power in the gamma frequency as an indicator of their cognitive state (Scangos et al., 2021). Lastly, cardiovascular rhythms and state dependent stimulation is now being incorporated into adaptive cardiac pacemakers that adjust stimulation based on exertional state and demand (Świerżyńska et al., 2023).

Taken together, these studies outline a framework for possibly developing a state dependent VNS paradigm for TPT to maximize plasticity and function recovery, considering the influence of altered cognitive states and cardiorespiratory rhythms. Patient-specific cognitive states, such as arousal and pain perception changes, could ultimately influence VNS parameter selection. In addition, cardiorespiratory rhythms may significantly impact the VNS timing needed for optimized TPT. Overall, this review aims to summarize and discuss the influence of altered cognitive states and cardiorespiratory rhythms on neuromodulator release, potentially impacting neuroplasticity associated with TPT. The content throughout aims to be hypothesis generating, hopefully paving the way for the development of personalized VNS and optimized TPT.

## Role of neuromodulator signaling in neuroplasticity associated with TPT

VNS promotes neuromodulator release that significantly affects neuronal excitability, enhancing signal-to-noise ratios and salient events, as well as influencing synaptic modifications in the brain, thereby regulating several aspects of neuroplasticity (Pedrosa and Clopath, 2017; Hirata et al., 2006). Neuroplasticity represents a critical substrate of learning and memory (Serradj et al., 2023), recovery of motor function after neurological injury (Nandakumar et al., 2023; Mohammed and Hollis 2018; Ward et al., 2003), and several other processes. Subcortical structures, namely, the nucleus basalis of Meynert (NB), the locus coeruleus (LC), the dorsal raphe nucleus (DRN), and the ventral tegmental area (VTA), serve as principal sources of key neuromodulators involved in neuroplasticity, including acetylcholine, norepinephrine, serotonin, and dopamine respectively

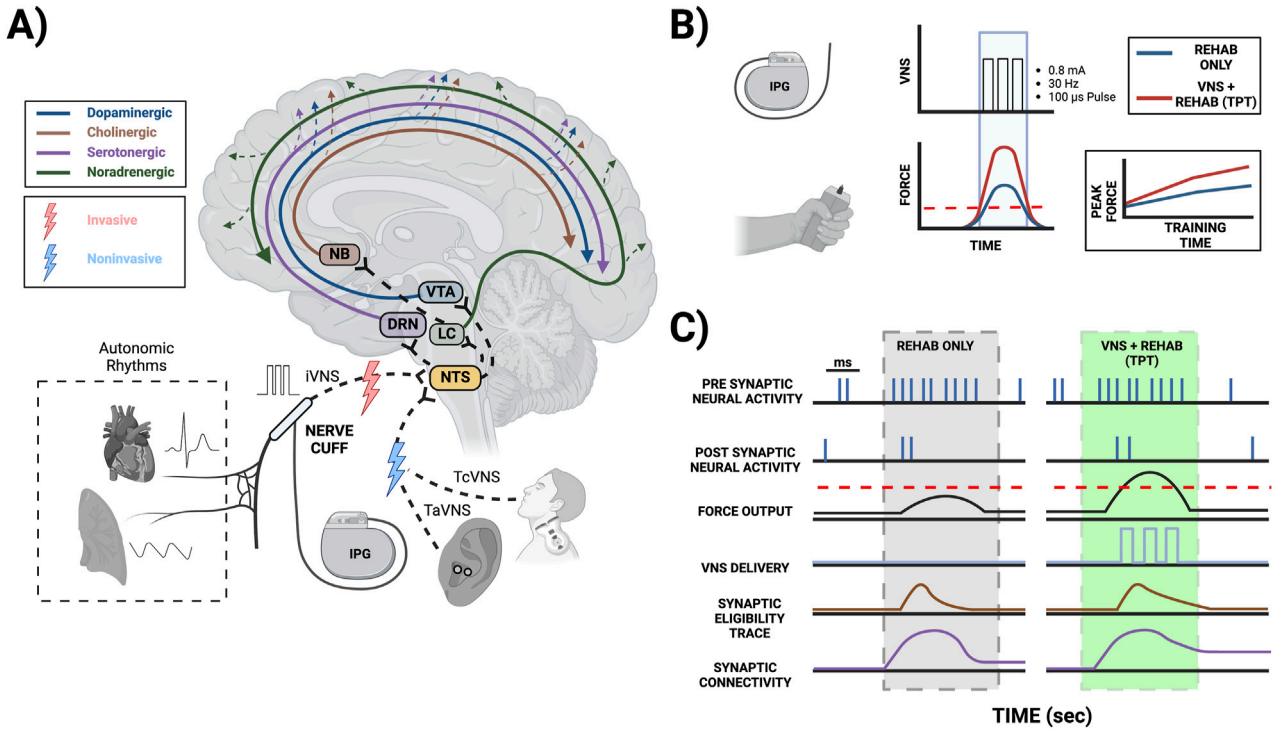


FIGURE 1
Mechanisms of TPT-induced neuroplasticity mediated by neuromodulator signaling. **(A)** TPT commonly involves implanting a VNS cuff (iVNS) at the cervical level along with an implantable pulse generator (IPG), stimulating the ear non-invasively targeting the auricular branch of the vagus (TaVNS), or stimulating the neck non-invasively targeting the cervical vagus (TcVNS). Stimulating the vagus nerve and its branches can activate the nucleus tractus solitarius (NTS) in the brainstem, which has extensive projections to other key brainstem nuclei facilitating neuromodulator release, including the locus coeruleus (LC) for norepinephrine release, the nucleus basalis of Meynert (NB) for acetylcholine release, the dorsal raphe nucleus (DRN) for serotonin release, and the ventral tegmental area (VTA) for dopamine release. Overall, VNS leads to the release of these neuromodulators across multiple brain areas. The vagus nerve also transmits information from the cardiovascular and respiratory tissues to the NTS and higher brain order structures, thereby possibly affecting VNS-induced neuromodulator signaling. **(B)** TPT for upper limb rehabilitation commonly uses a brief burst of iVNS (0.8 mA, 30 Hz, 100 µs pulse width, and a 0.5 s train duration) that can be paired with successful movements to improve motor performance (e.g., where the achieved force exceeds a given threshold). **(C)** Coincident activity of presynaptic and postsynaptic neurons during rehabilitation creates a transient synaptic tag, commonly referred to as the synaptic eligibility trace. These traces can be converted to long-term changes in synaptic strength mediated by VNS-induced neuromodulator release local to the synapse (please note the specific time scales in panel C; red dashed lines **(B, C)**: VNS thresholds during successful force events).

(for an extensive review refer to (Gu, 2002)). Dysregulation of these neuromodulators has been associated with deficits in learning, impaired memory consolidation, and behavioral dysfunction following neurological injury (Li and Hollis, 2023; Ramanathan et al., 2015; Conner et al., 2010; Monk and Hussain Shuler, 2019; Wachtel et al., 1975).

VNS engages these neuromodulatory transmission systems via the nucleus tractus solitarius (NTS) in the brainstem, subsequently promoting neuronal activation in the NB (Bowles et al., 2022; Collins et al., 2021; Mridha et al., 2021), the LC (Hulsey et al., 2016b), the DRN (Manta et al., 2012; 2013; Dorr and Guy, 2006), and the VTA (Brougher et al., 2021; Fernandes et al., 2020) (Figure 1A). Even a brief burst of VNS releases neuromodulators diffusely throughout the cortex, causing widespread changes in cortical excitability (Collins et al., 2021). Moreover, this neuromodulator release triggered by VNS is essential for TPT-induced neuroplasticity (Kilgard and Merzenich, 1998; Hulsey et al., 2016a; Ramanathan et al., 2009). A reduction in neuromodulator signaling impairs TPT-induced neuroplasticity, while enhancement facilitates neuroplasticity and behavioral outcomes (Hulsey et al., 2016a; Hulsey et al., 2019; Nichols et al., 2011; Meyers et al., 2019; Bowles et al., 2022).

TPT commonly uses a brief burst of VNS (e.g., 0.5 s in duration). Importantly, these brief bursts of stimulation alone are insufficient to strengthen synapses and facilitate TPT-induced neuroplasticity, as they must be paired with a given event in a temporally precise manner to promote enhanced function (Hays, 2016; Hays et al., 2014). Aside from TPT, other applications of VNS commonly use longer stimulation trains that can facilitate some degree of neuroplasticity (Furmaga et al., 2012; Biggio et al., 2009; Olsen et al., 2022). Typical plasticity mechanisms follow Hebbian rules requiring the coincident activity of presynaptic and postsynaptic neurons, with the temporal differences in spiking dictating synaptic strengthening via long-term potentiation (LTP) or weakening via long-term depression (LTD), known as spike timing dependent plasticity (STDP) (Urbin et al., 2017; Kleim and Jones, 2008; Ziemann et al., 2004). These synaptic modifications are often transient, and the rules of STDP can be dramatically influenced by the presence of neuromodulators (Brzosko et al., 2019; Pawlak et al., 2010; Gerstner et al., 2018). Recent studies suggest that most

synaptic plasticity is heterotypic, involving the reinforcement of neuromodulators seconds after Hebbian conditioning leveraging the synaptic eligibility trace (He et al., 2015; Bailey et al., 2000; Froemke et al., 2007) (Figures 1B,C). Neuromodulator release associated with TPT generally acts as a reinforcer (Bowles et al., 2022) when paired with behavioral events and modifies the STDP window further affecting neuroplasticity (Hays et al., 2013). There are a number of possible behavioral events for triggering VNS during TPT, ultimately depending on the therapeutic application (e.g., VNS paired with a motor event during upper limb rehabilitation, VNS paired with a somatosensory event during tactile rehabilitation, or VNS paired with an auditory event during therapy for tinnitus).

Importantly, VNS activates the NTS, a critical structure receiving ongoing neural signaling from the visceral tissues (e.g., neural signals from the cardiovascular and respiratory systems). Hence, this visceral input likely affects VNS-induced neuronal transmission within the NTS (Beaumont et al., 2017) and subsequent downstream neuromodulator release. Overall, these intricate brain-body interactions and the role of visceral input affecting TPT-induced neuroplasticity are incompletely understood. This emphasizes the need for further inquiry, particularly given the vagus nerve's connection to the viscera, the brainstem, and higher-order structures.

## Role of stimulation dose in modifying neuromodulator signaling

The stimulation dose is a critical concept when considering neuromodulator release and overall neuromodulatory signaling. The stimulation dose for VNS involves a number of factors governing the amount of electrical energy being applied to the vagus (Peterchev et al., 2012). Stimulation dose can be adjusted by varying the amplitude of stimulation, location, modality of stimulation, waveform characteristics (pulse width, frequency, or inter-trial interval), stimulation timing, and the overall therapy duration. Overall, TPT has used several VNS approaches, including invasive VNS at the cervical level using an implantable cuff (iVNS) (Khodaparast et al., 2014; Borland et al., 2016; Noble et al., 2017; Ganzer et al., 2018; Meyers et al., 2018; Meyers et al., 2019; Darrow et al., 2020; Tseng et al., 2020; Dawson et al., 2021), noninvasive trans-auricular stimulation (TaVNS) targeting the auricular branch of the vagus nerve located on the ear (Redgrave et al., 2018; Badran et al., 2023; Chen et al., 2023; Rufener et al., 2023; Thompson et al., 2021), and transcutaneous VNS at the cervical level (TcVNS) (Gurel et al., 2020; Jigo et al., 2024; McIntire et al., 2021). Each stimulation approach could differentially engage important neuromodulatory systems and hence likely requires unique stimulation dosing strategies. iVNS, TaVNS, and TcVNS are exclusively used in this section to better differentiate the various VNS approaches.

Parametric characterization of the optimal stimulation dose for TPT has been most extensively studied in animal models using iVNS. Increasing the stimulus intensity and pulse width leads to increased activity in the noradrenergic LC (Hulsey et al., 2016a), as well as increased cholinergic transmission from NB to the cortex (Mridha et al., 2021). However, increasing the pulse frequency alters the timing, but not the total amount, of VNS-driven neuronal activity in the LC (Hulsey et al., 2016a) and cholinergic activity from NB (Mridha et al., 2021). Moreover, extensive characterization of plasticity as a function of iVNS dose has revealed a non-monotonic inverted U relationship between frequency, stimulus intensity, and plasticity across several preclinical TPT studies (Hays et al., 2023; Borland et al., 2016; Buell et al., 2019; Souza et al., 2021b; Hays et al., 2023; Loerwald et al., 2018). Additionally, the number of overall VNS event pairings (Hays et al., 2014), as well as the interval between VNS event pairings within sessions (Borland et al., 2018) and across sessions/weeks (Ruiz et al., 2023b), influences neuroplasticity and recovery. An optimal stimulation dose, usually consisting of a specific set of VNS parameters (0.8 mA, 30 Hz, 100 μs pulse width, 0.5 s train duration, and biphasic pulses), generally enhances neuroplasticity and improvements following TPT across a variety of applications (Hays et al., 2023).

There is now increasing interest in using noninvasive TaVNS for TPT, also known to activate subcortical structures such as the NTS and LC (Frangos et al., 2015; Sclocco et al., 2019). TPT paradigms that utilize TaVNS are now being applied to stroke rehabilitation (Badran et al., 2023; Redgrave et al., 2018; Wu et al., 2020) and have shown promise in smaller cohorts of patients. More extensive large-scale clinical trials can be pursued to assess whether TaVNS is a reliable means of providing TPT and enhancing recovery. TPT using noninvasive TcVNS at the cervical level has also shown promise (Jigo et al., 2024; McIntire et al., 2021). Overall, new data indicates that the effects of TaVNS outcomes may be variable compared to iVNS (Thompson et al., 2021; Verma et al., 2021; Badran et al., 2018; Warren et al., 2019; Keute et al., 2019; Gadeyne et al., 2022). This variability could partly be due to differences in fiber recruitment and subsequent activation of the associated neuromodulatory centers, which often results in differential brain network modulation when comparing iVNS and TaVNS (Schuerman et al., 2021). Moreover, these noninvasive studies are commonly done in human subjects, where the variability across investigations could be due to several factors, including patient-specific pathophysiology. Further assessing both TaVNS and TcVNS clinically, and its specific mechanisms preclinically, should allow for a sufficient characterization of the stimulation parameter space and optimization of outcomes as needed following non-invasive TPT.

Overall, there are a number of aspects to consider when optimizing the stimulation dose for TPT. Regardless, the possible effects of altered cognitive states and cardiorespiratory rhythms on TPT-induced plasticity and recovery remain poorly understood. Both of these processes affect neuromodulator signaling. Altered cognitive states may likely affect several required stimulation dose components, including stimulus intensity, pulse width, and duration, while cardiorespiratory rhythms may ultimately impact the timing required for optimized VNS delivery.

## Role of altered cognitive states in modifying neuromodulator signaling

While the stimulation dose for maximizing plasticity is robust and generalizable in preclinical models (Hays et al., 2023; Souza et al., 2021a; Tyler et al., 2017), the responder rates in clinical trials

have varied (e.g., 47% in the VNS-REHAB pivotal trial for stroke and 50% using VNS paired with tone therapy for tinnitus). This emphasizes a need to possibly optimize the stimulation dose further and specifically consider patient-specific states for improving responder rates and recovery.

Patients with neurological injuries or diseases often have comorbidities, leading to altered cognitive states such as enhanced pain perception, arousal deficits, and lack of motivation. For instance, spinal cord injuries may result in neuropathic pain (Henderson et al., 2011; Blumenthal et al., 2021), while parkinsonism can alter arousal levels (Verma et al., 2024) and induce sudden daytime sleepiness (Verma et al., 2023). Stroke patients also often exhibit apathy (Marin and Wilkosz, 2005). These physiological changes impact neuromodulator transmission and cortical excitability and can therefore potentially modify the effects of TPT.

Recent preclinical studies have highlighted that TPT may fail to improve motor recovery in the presence of neuropathic pain (Adcock et al., 2022). In this study, neuropathic pain may have also contributed to the animal's overall behavioral engagement in the task. Regardless, pain alters cholinergic signaling in the basal forebrain, potentially affecting TPT-induced neuroplasticity (Oswald et al., 2022; Paquette et al., 2019; Piché et al., 2010). Moreover, neuropathic pain can have effects on noradrenergic signaling in the LC, manifesting as an exacerbation of noradrenergic transmission when co-occurring with chronic depression (Bravo et al., 2014). This suggests that considering the subject's pain perception may be crucial when optimizing the stimulation dose for TPT. Scoring methodologies, such as a visual analog scale for pain perception, can quantify the patient's pain perception level (Bodian et al., 2001). Machine learning algorithms can likely use these features to modify stimulus intensity adaptively based on the patient's pain state, optimizing VNS-mediated neuromodulator release.

Arousal state can also influence learning (Song, 2019), recovery of function after injury (Goldfine and Schiff, 2011), and performance (Yerkes and Dodson, 1908). It is well known that alterations in neuromodulator signaling mediate arousal's impact on behavior (Joshi et al., 2016; Reimer et al., 2016; Murphy et al., 2014) and cortical excitability, both of which are essential for synaptic plasticity (Lee and Dan, 2012). Recent studies indicate that VNS modulates pupil dilation, a biomarker of arousal, primarily through noradrenergic signaling in the LC and cholinergic signaling in the NB (Mridha et al., 2021; Collins et al., 2021). Moreover, the basal arousal state before VNS delivery differentially impacts cortical excitability and behavioral responses in preclinical models (Collins et al., 2021). Hence, correlates of neuromodulator signaling assessed using pupillometry can possibly be used to measure basal arousal state and inform the efficacy of VNS delivery. Measuring the high-frequency to low-frequency activity ratios derived from EEG is another possible avenue for assessing arousal levels (Putman et al., 2014). In addition, the P300 signal derived from EEG can also be utilized to quantify correlates of attention and noradrenergic signaling (D'Agostini et al., 2023; Gurtubay et al., 2023; Riccio et al., 2013). While these findings are promising, they await testing in human subjects to understand the complex interaction between arousal states and responses to VNS.

Conventionally, when examining the relationship between arousal and behavior, the Yerke-Dodson law (Yerkes and Dodson, 1908) reveals a non-monotonic inverted U relationship, with moderate arousal being the most optimal and a hyper-aroused state (e.g., stress or pain) being detrimental to performance. Interestingly, it has been hypothesized that hyperarousal resulting from a higher stimulation dose could impede TPT (Hays et al., 2023), potentially explaining the inverted U relationship between stimulation dose and TPT. The relationship between neuromodulator signaling and stimulation parameter optimization has also been modeled previously (Buell et al., 2019). Based on these findings, arousal is likely to significantly modify neuromodulator signaling. Overall, these findings suggest that the arousal levels during TPT sessions likely influences the relationship between stimulation dose, plasticity, and performance. Overall, further studies are needed to elucidate the intricate relationship between arousal states and performance during TPT.

In addition to arousal deficits, diminished motivation is a common comorbidity following brain injury, such as stroke (Marin and Wilkosz, 2005; Verrienti et al., 2023). Lack of motivation adversely impacts rehabilitation therapy efficacy (Yoshida et al., 2023), as well as BCI performance (Kleih-Dahms et al., 2021). This is partly due to impaired endogenous dopaminergic engagement, where the energetic cost of effort often outweighs the reward value (Neuser et al., 2020). Notably, VNS therapy can improve the motivation to work for rewards (Neuser et al., 2020). However, to optimize therapy outcomes, it is necessary to understand how this improvement in motivation interacts with and affects functional outcomes in VNS-based TPT studies.

Medication taken by patients that affects neuromodulator signaling likely also affects VNS mediated neuromodulator release and may limit TPT efficacy (for a more detailed review, refer to (Hays et al., 2023)). In a recent preclinical study, preliminary findings support using beta blockers to alter the inverted U relationship between stimulus intensity and neuroplasticity (Neifert et al., 2023). Moreover, alpha-blockers also attenuated activity-dependent plasticity during rehabilitation (Sawaki et al., 2003). These studies highlight the need to carefully consider the pharmacological agents administered when designing therapeutic strategies that rely on neuromodulator systems such as TPT. In summary, there is a critical need to further assess how altered cognitive states discussed above may interact with VNS-induced neuromodulator signaling, TPT, and recovery.

## Role of cardiorespiratory rhythms in modifying neuromodulator signaling

In addition to cognitive states, cardiorespiratory rhythms also robustly modulate neuromodulator signaling. Sensory afferents from the vagus nerve terminate within the NTS, carrying information related to a number of visceral processes including cardiovascular and respiratory states (e.g., via baroreceptors and pulmonary stretch receptors). Cardiorespiratory afferents arise from several locations, including mechanoreceptors signaling changes in blood pressure and pulmonary stretch (primarily located in the

aortic arch, the carotid sinus, and the pulmonary tissues), as well as peripheral chemoreceptors signaling changes in blood gas content (primarily located in the carotid body and aortic body) (Zyuzin and Jendzjowsky, 2022). These systems interact with each other and modulate overall NTS activity (Spyer, 1982; Rogers et al., 1993; Hayward and Felder, 1995; Zoccal et al., 2014; Mifflin, 1993; Beaumont et al., 2017). Hence, it's likely that neuromodulator release induced by VNS may be differentially modulated across the ongoing phases of the cardiovascular (systole or diastole) and respiratory rhythms (inspiration or expiration).

Neural activity in the LC is differentially modulated during ongoing phases of the cardiovascular and respiratory rhythms (Biancardi et al., 2014; Biancardi et al., 2008; Iwamoto et al., 2023; Magalhães et al., 2018; Morilak et al., 1986; Patrone et al., 2014; Carvalho et al., 2017). For example, neurons in the LC are more likely to be activated during the diastolic phase rather than the systolic phase of the cardiovascular rhythm (Morilak et al., 1986; Morilak et al., 1987). Respiratory rhythms also entrain the neuronal activity of LC, making it more responsive to specific phases of the respiratory cycle (Magalhães et al., 2018; Huangfu et al., 1992; Iwamoto et al., 2023). This was recently assessed using fMRI, demonstrating a greater activation of the LC when VNS was delivered during exhalation compared to inhalation (Sclocco et al., 2019). Overall, studies have used VNS delivered during expiration demonstrating that the NTS may be more sensitive to afferent input during this phase of the respiratory cycle (Garcia et al., 2017; Sclocco et al., 2019). Neuronal activity in the LC also processes information related to blood oxygenation. In fact, studies have shown that the firing frequency of LC is heightened during conditions of hypoxia and hypercapnia (Magalhães et al., 2018; Biancardi et al., 2008). Hence, conditions of altered chemoreceptor signaling (Plataki et al., 2013) may potentially impact neuromodulator signaling in the LC during TPT.

Aside from subcortical structures, cortical excitability in response to sensory stimuli is also preferentially modulated depending on the phase of the cardiovascular cycle (Park et al., 2018; Gray et al., 2010). A recent study demonstrated that both somatosensory evoked potentials and pain perception were higher during the diastolic phase than the systolic phase of the cardiovascular rhythm (Al et al., 2020). Interestingly, this phenomenon also exists across different modalities of sensory stimuli (for an extensive review, refer to Critchley and Garfinkel (2015)).

Lastly, cardiovascular measures such as heart rate variability have been used as a marker of sympathetic and parasympathetic balance (Bravi et al., 2013), usually quantified as the ratio of low frequency (0.04–0.15 Hz) to high frequency (0.15–0.4 Hz) activity. Overall, these measures are sensitive to recording length, signal processing method, breathing, body position, and emotional state (Shaffer and Ginsberg, 2017). Longer recording times pose an additional challenge for precise spectral estimation, making it possibly suboptimal for adaptive TPT paradigms requiring shorter timescales (i.e., seconds). Additionally, recent studies demonstrate that direct recordings of cardiac vagal activity correlate with a subset of heart rate variability parameters (Laborde et al., 2017; Marmerstein et al., 2021; Billman, 2013). Nevertheless, HRV could be useful for quantifying arousal levels (Huo et al., 2023).

Taken together, these studies demonstrate the extensive influence of cardiovascular and respiratory factors on neuromodulator signaling and the sensitivity of inputs originating from both VNS and other sensory stimuli (both factors critically involved in several forms of TPT). Given the impact of cardiorespiratory rhythms on neuromodulator signaling, it is tempting to speculate that VNS during diastole may better facilitate neuromodulator release. Additionally, VNS during expiration may also be beneficial in driving neuroplasticity. Appropriately timing VNS during TPT, considering both the targeted event and the optimal phase(s) of the cardiorespiratory rhythms, may likely further enhance neuroplasticity and behavioral outcomes after TPT. Regardless, extensive work is needed to address these hypotheses.

## Discussion and future directions

Altered cognitive states and cardiorespiratory rhythms affect neuromodulator tone, potentially significantly impacting TPT. To assess the possibility of optimizing TPT for personalized use, it is important to consider not only the individual impacts of each state and autonomic rhythm on neuromodulator signaling, but also their complex interactions that could ultimately affect plasticity (Mylavarapu et al., 2023). Given the nature of these interactions, machine learning frameworks may be needed to both fine-tune VNS parameters and further identify relationships between signals (Ganzer et al., 2022; Ganzer and Sharma, 2019). Overall, the performance of any state dependent TPT system is dependent on several factors, including system controller inputs and overall system design. Table 1 summarizes a number of existing neuromodulation devices and their associated stimulation control schemes. These systems have the following stimulation control schemes: 1) open-loop control consisting of a static control algorithm, where stimulation parameters are fixed regardless of the given state; 2) closed-loop feedforward control triggering stimulation delivery via a change in a monitored variable alone; 3) closed-loop feedback control monitoring a variable that needs to be modified in order to alleviate symptoms, therefore optimizing the stimulation dose in an adaptive and closed-loop manner.

A state dependent TPT system (schematized in Figure 2) can possibly leverage a number of technology attributes listed in Table 1. As previously discussed, altered cognitive states and cardiorespiratory rhythms may affect neuromodulator signaling and ultimately TPT efficacy. Fortunately, most of these factors, with the exception of pain, have viable biomarkers that can be used for decoding (Figure 2). Spectral analysis of electrocorticography (ECoG) signals have been integrated into responsive neurostimulation systems for epilepsy (Table 1). Similar to ECoG, EEG is also a valuable electrophysiological signal and can be used to assess a patient's arousal levels and attention (Figure 2A; e.g., via a decrease in the ratio of high-frequency to low-frequency spectral power in the EEG). Additionally, a correlate of basal neuromodulator signaling can be extracted from pupillometry as a complimentary feature for arousal, with additional potential use as a biomarker of VNS-induced neuromodulator release (Figure 2A). For measuring the phases of ongoing cardiovascular and respiratory rhythms, wearable sensors can be utilized similar to other existing

TABLE 1 Overview of selected neuromodulation devices and their control system attributes. Abbreviations: iVNS (implanted vagus nerve stimulation), TPT (targeted plasticity therapy), ECG (electrocardiography), DBS (deep brain stimulation), ECoG (electrocorticography), SCS (spinal cord stimulation), ECAP (evoked compound action potential), LFP (Local field potential), and TcVNS (transcutaneous vagus nerve stimulation).

| Therapeutic application | Medical device | Stimulation approach | General control scheme | Controller input (if closed-loop) |
|---|---|---|---|---|
| Tinnitus | Lenire® | Tongue stimulation | Open-loop | N/A |
| Stroke | Vivistim® (MicroTransponder) | iVNS (TPT) | Open-loop or closed-loop feedforward | N/A or therapist assessing movement quality |
| Multiple sclerosis | PoNS™ (Helius Medical Technologies) | Tongue stimulation | Open-loop | N/A |
| Epilepsy | SenTiva™ (LivaNova) | iVNS | Open-loop or closed-loop feedforward | N/A or ECG (heart rate) |
| | RNS® system (NeuroPace) | DBS | Closed-loop feedforward | ECoG |
| Pain | Evoke® system (Saluda Medical) | SCS | Closed-loop feedback | ECAP |
| | Intellis™ AdaptiveStim™ (Medtronic) | SCS | Closed-loop feedforward or closed-loop feedback | Pain level or body position |
| | RestoreSensor™ (Medtronic) | SCS | Closed-loop feedforward or closed-loop feedback | Pain level or accelerometer |
| Heart failure | Barostim™ (CVRx) | Carotid sinus stimulation | Open-loop | N/A |
| Obesity | Maestro® System (EnteroMedics) | iVNS | Open-loop | N/A |
| Parkinson's disease | Percept™ PC (Medtronic) | DBS | Open-loop | N/A (LFP recordings only) |
| Headache | gammaCore™ (electroCore) | TcVNS | Open-loop or closed-loop feedforward | N/A or pain level |
| Obstructive sleep apnea | Inspire® Upper Airway Stimulation system (Inspire Medical Systems) | Hypoglossal nerve stimulation | Closed-loop feedforward | Respiratory sensor |

technologies (Figure 2B; e.g., via electrocardiography and pneumography) (Bayoumy et. al., 2021). Functional improvements over longer time scales may also be used to potentially adjust stimulation dose and enhance outcomes (Mylavarapu et al., 2023; Epperson et al, 2024), as further recovery of function may require modification of stimulation parameters across time during TPT. Overall, these are a number of hypothesis generating considerations and challenges related to state dependent TPT that require further investigation.

Simple or complex stimulation control algorithms can be used for decoding and triggering optimized VNS. Ultimately, advanced machine learning techniques may be required to effectively integrate these multifactorial inputs and enhance VNS control (Ganzer et al., 2022; Ganzer and Sharma, 2019). Bayesian optimization represents one option. This approach iteratively refreshes assessment of the response surface by utilizing a probabilistic model that effectively converges on ideal settings, while maintaining a balance between exploration and exploitation (Shahriari et al., 2016). Bayesian optimization has also been extensively used in neurostimulation (Choinière et al., 2024). Furthermore, bayesian optimization may be especially effective for individualizing therapy, as it can adapt to each patient's unique physiological profile. In addition, deep neural networks and ensemble learning are likely viable options for optimizing VNS control. Deep learning algorithms can handle large datasets that may be required for deciphering the complex relationship between state dependent signals and their role in optimized neuroplasticity. In the context of movement disorders, these models can discern subtle changes in the states mentioned above, potentially maximizing the effectiveness of VNS during TPT. Furthermore, these models may also be able to relate physiological states to optimized VNS control in ways that are not self-evident to humans. Lastly, ensemble learning can combine decisions from multiple models, where simple and complex algorithms are being used in combination (Dietterich, 2000) (e.g., complex arousal state detection using EEG combined with simpler cardiac cycle detection using electrocardiography). Ultimately, future studies will need to consider the combinatorial characterization of physiological states and autonomic rhythms on neuromodulator signaling, plasticity, and functional improvement during TPT, paving the way towards state dependent VNS and enhanced TPT.

## Author contributions

BN: Conceptualization, Formal Analysis, Investigation, Methodology, Project administration, Validation, Visualization, Writing–original draft, Writing–review and editing. RM: Conceptualization, Investigation, Methodology, Visualization, Writing–original draft, Writing–review and editing. RH: Conceptualization, Formal Analysis, Investigation, Validation, Writing–original draft, Writing–review and editing. EA: Methodology, Resources, Validation, Writing–original draft, Writing–review and editing. ZY: Resources, Validation, Writing–original draft, Writing–review and editing. CH: Resources, Validation, Writing–original draft, Writing–review and editing. DM: Writing–original draft, Writing–review and editing. VK: Resources, Validation, Writing–original draft, Writing–review and editing. PG: Conceptualization, Funding acquisition, Investigation, Methodology,

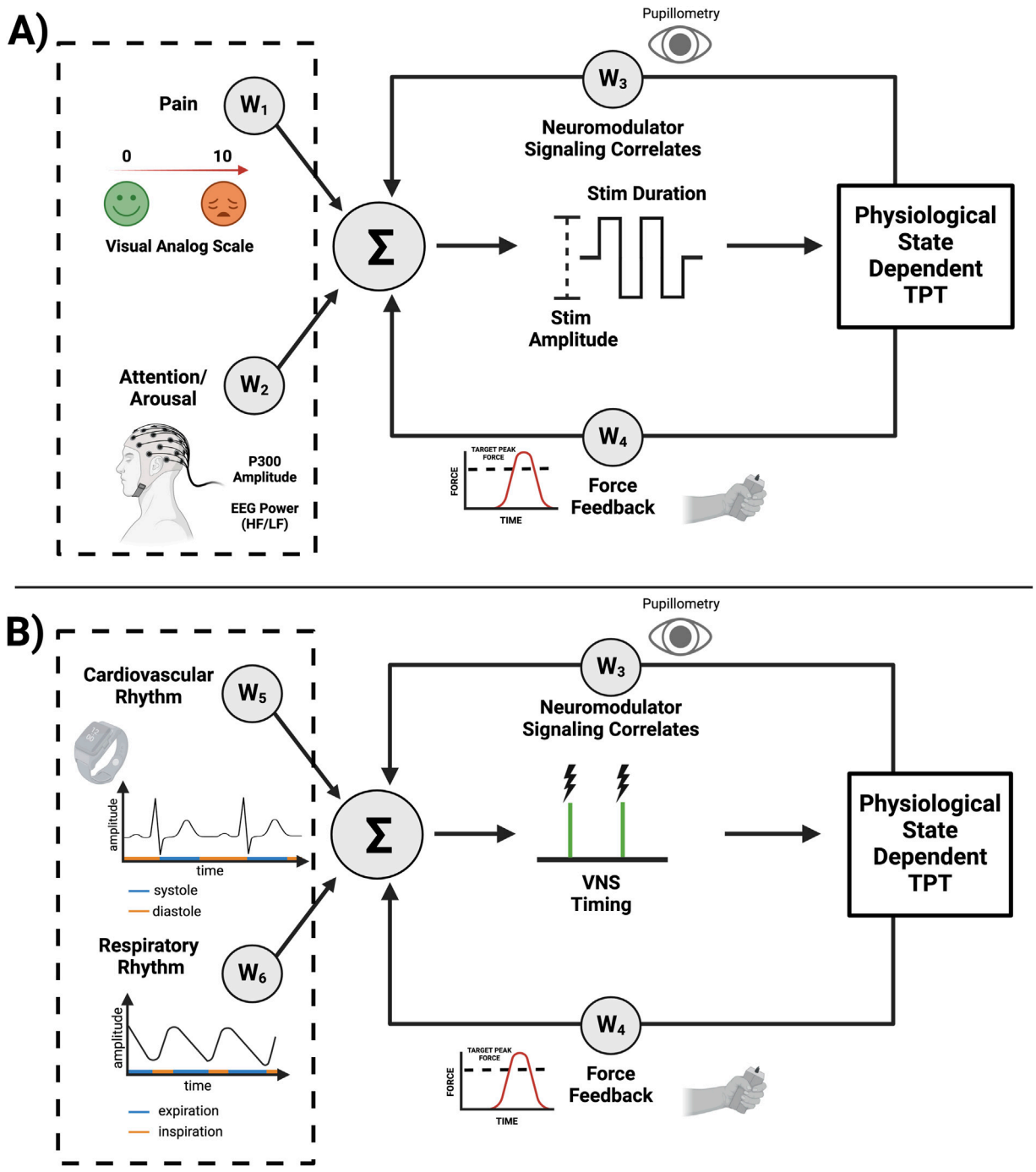


FIGURE 2
System design considerations for state dependent TPT. The following information is applied to upper limb TPT as an example. **(A)** Altered states such as pain and arousal deficits can alter neuromodulator signaling. Increased pain perception may require reducing VNS intensity (e.g., via amplitude or pulse width) characterized by negative weights ($W_1 < 0$), while arousal deficits may require compensation ($W_2$) by increasing stimulus intensity to achieve the desired neuromodulator signaling. Pupillometry can also be used to extract an indirect fast measure of neuromodulator signaling ($W_3$), with force feedback during upper limb rehabilitation measuring a slower and long-term biomarker of functional improvement ($W_4$), all allowing for further adjustment of VNS parameters and possible optimization of recovery. **(B)** The specific timing of VNS during TPT may also play a significant role in improving neuroplasticity and recovery of function. For example, force feedback during upper limb TPT can be used as a fast read-out of successful movement trials. TPT during diastole ($W_5 = 1$, if diastole) may further improve neuromodulator signaling. VNS during the expiratory phase of the respiratory cycle ($W_6 = 1$, if expiration) may also lead to optimized neuromodulator release and, hence, enhanced neuroplasticity. Overall, this *a priori* knowledge can be used to modify the given weights of the schematized control system with further fine-tuning via adaptive machine-learning algorithms.

Project administration, Resources, Supervision, Validation, Writing–original draft, Writing–review and editing.

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## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

## Publisher's note



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