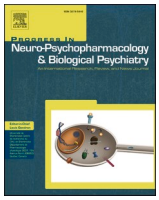
Progress in Neuropsychopharmacology & Biological Psychiatry 137 (2025) 111290

Contents lists available at ScienceDirect

Progress in Neuropsychopharmacology & Biological Psychiatry

journal homepage: www.elsevier.com/locate/pnp



Peripheral transcutaneous electrical stimulation to improve cognition: a review of the main effects in healthy humans and in mildly cognitively impaired patient populations

Giulia Fiorentini [a], Eva Massé [b,c], Stefania C. Ficarella [b], Giulia Torromino [a,*]

[a] Department of Humanistic Studies, University of Naples Federico II, Naples, Italy
[b] Information Processing and Systems, Office National d'Etudes et de Recherches Aérospatiales, Salon de Provence, France
[c] Institut de Neurosciences de la Timone, CNRS & Aix-Marseille Université, Marseille, France

ARTICLE INFO

Keywords:
Transcutaneous electrical stimulation
Peripheral nerve stimulation
Cognitive functions
Non-invasive neuromodulation
Neuroenhancement
Heterosynaptic plasticity
Memory

ABSTRACT

Peripheral nerve stimulation (PNS) is an ancient technique, up to now mainly used for pain management. The least invasive approach for PNS is transcutaneous electrical stimulation (TENS), which is performed by delivering mild electric currents through the skin and, depending on the stimulation pattern, activates the somatosensory Aβ-, Aδ- and C-fibers. In addition to its use for pain relief, accumulating data indicates that TENS can have broad-spectrum cognitive effects through the activation of neuromodulatory brain pathways. This review aims to summarize the current evidence on the cognitive effects of TENS, from healthy participants and mildly cognitively affected patients. Most studies on this topic have investigated the effects of TENS on memory, while fewer studies have explored attention, executive functions, and verbal fluency. Overall, promising evidence suggests that TENS may exert positive effects on specific cognitive functions. Further research is needed to build consensus on the most effective stimulation protocols, for both neurorehabilitation and enhancement, and to better understand the neurobiological mechanisms underlying the cognitive effects of TENS.

1. Introduction

Peripheral nerve stimulation (PNS) is a term generally used to indicate three main approaches for delivering current to peripheral nerves, with similar mechanisms of action but different levels of invasiveness. These range from subcutaneous implants of cuff leads encircling the nerve or paddle leads to less invasive approaches, such as a percutaneous, acupuncture-similar method and transcutaneous electrical stimulation (TENS), which is considered non-invasive. All PNS-mediated techniques can be adjusted by altering intensity, pulse width and frequency of stimulation through external programmable devices (for reviews see Chakravarthy et al., 2016; Deer et al., 2020).

For centuries, PNS has been used to reduce pain by delivering electrical stimulation to peripheral nerves (Ottestad and Orlovich, 2020). The first known application of transcutaneous electricity transmission for pain relief dates back to ancient Egyptians in 2300 BC, and to the Roman physician Scribonius Largus (153 BC), who used electrical currents generated from torpedo fish on patients experiencing pain (Francis and Dingley, 2015; Johnson, 2007). Among all the PNS techniques, TENS is the most interesting in terms of cognitive applications because of its safety (it is contraindicated only in specific cases, such as pregnancy, epilepsy, or the presence of a pacemaker), low cost, and ease of application (Johnson, 2007; Teoli and An, 2023). One of the hypothesized mechanisms of TENS for reducing pain refers to the gate control theory proposed in 1965 by Wall and Melzack (but see also Lin et al., 2020; Ong Sio et al., 2023). This theory posits that low-threshold, large diameter, non-nociceptive sensory Aβ-fibers, when stimulated, convey inhibitory signals to the interneurons in the dorsal horn of the spinal cord. These interneurons play a pivotal role in transmitting nociceptive signals coming from Aδ- and C-fibers (Melzack and Wall, 1965). In this way, stimulation of the somatosensory neurons gates pain signals within the spinal cord and prevents the spread of nociceptive information to the rest of the central nervous system (CNS) (Melzack and Wall, 1965).

While mostly employed for pain management (for reviews see Chakravarthy et al., 2016; Goroszeniuk and Pang, 2014; Teoli and An, 2023), growing evidence suggests that PNS, and TENS in particular, can activate the CNS, modulating the activity of cortical and sub-cortical brain regions involved in various cognitive functions, such as the

* Corresponding author at: Department of Humanistic Studies, University of Naples Federico II, 80133 Naples, Italy.
E-mail address: giulia.torromino@unina.it (G. Torromino).

https://doi.org/10.1016/j.pnpbp.2025.111290
Received 12 September 2024; Received in revised form 6 February 2025; Accepted 7 February 2025
Available online 10 February 2025

lateral prefrontal cortex, the anterior cingulate cortex, the parahippocampal and hippocampal areas, the thalamus and the amygdala (for reviews see Helm et al., 2021; Luckey et al., 2023a; McGinley and Lee, 2022; Strand et al., 2021). Furthermore, several studies have shown that TENS can alter the neurotransmission of noradrenaline, acetylcholine, dopamine and serotonin, primarily *via* the activation of the nucleus tractus solitarius (NTS) (for a review see Luckey et al., 2023b) and modulate neural plasticity pathways (see Bowles et al., 2022). Since these neurotransmitters have widespread influences on the brain, TENS is also likely to have broad effects on brain function, the extent of which remains to be fully understood.

For these reasons, this review article focuses on the cognitive effects of TENS, while extensive reviews on the effects of this technique for pain management can be found elsewhere (Deer et al., 2020).

1.1. The neuroanatomical and functional basis to hypothesize an effect of TENS on cognition

TENS is implemented by applying electrical pads directly to the surface of the skin, allowing a pain-free flow of electrical current to the nerves (for a review see Helm et al., 2021). A wide variability of nerves stimulated by TENS can be found in the scientific literature, ranging from the greater occipital nerve to the facial nerves, the median and peroneal nerves, to the spinal nerves (Fig. 1). Although the rationale behind the choice of specific stimulation sites is not always explicitly stated, studies on humans and animal models have shown that both high- and low-frequency TENS can activate thick-myelinated Aβ-fibers, thin-myelinated Aδ-fibers and unmyelinated C-fibers, depending on the stimulation parameters (Dudar et al., 1979; Dutar et al., 1985; Guo et al., 2002).

These somatosensory fibers reach the brain through a quite well-characterized anatomical pathway that passes through the spinal cord, crosses the midline at the anterolateral funiculus and reaches several brain areas, including the forebrain, pons, midbrain, and medulla (Wang et al., 2022a). Along this path, TENS has been shown to induce the activation of different neuromodulatory systems, including the noradrenergic, cholinergic, dopaminergic and serotoninergic pathways (Fig. 1, Scherder et al., 1995), with the NTS playing a pivotal role in this mechanism (see Luckey et al., 2023a). Indeed, the NTS is a viscerosensitive medullar nucleus that sends direct projections to the reticular formation in the medulla, and ascending projections *via* the parabrachial nucleus and locus coeruleus (LC) to the amygdala, insula, hypothalamus, thalamus, orbitofrontal cortex and other limbic regions (Mohr et al., 2011; Yap et al., 2020).

Based on these neuroanatomical direct and indirect connections with the neuromodulatory systems (Box 1) and the experimental evidence of their TENS-mediated activation (*e.g.* Scherder et al., 1995), TENS has the potential to modulate the activity of different brain pathways relevant to cognition. Indeed, the subcortical and cortical areas included in these pathways are involved in several cognitive functions (for a review, see Avery and Krichmar, 2017). Therefore, TENS effects on cognition might result from heterosynaptic plasticity mechanisms that would strengthen the functional activation of these brain regions.

Understanding the neurobiological mechanisms of TENS-mediated cognitive effects is not only important for its possible applications in neurorehabilitation and neuroenhancement, but more generally because it contributes to the knowledge on the role of the brain-body relationship in cognition, which is one of the pillars of the emerging perspective of Embodied Cognition (Barsalou, 2008; Caramazza et al., 2014; Foglia and Wilson, 2013; Gallese, 2005; Gallese and Lakoff, 2005; Varela et al., 1991). This perspective suggests that human cognitive abilities are mediated by the relationship that our body as a whole – with that intending the brain and the rest of the body – generates with the external world, which starts through the activation of sensory and motor systems (Buzsáki and Tingley, 2023; Ianì, 2022; Ianì, 2019). The relevance of this account lays in a change of paradigm of psychological and

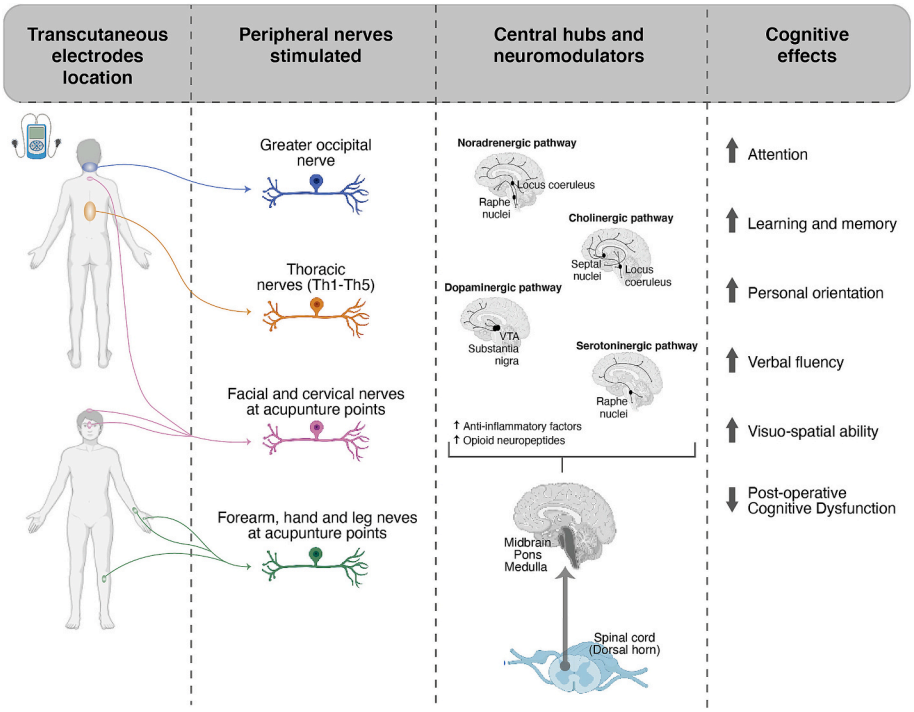


Fig. 1. TENS hypothesized mechanism of action on cognitive functions. The figure shows the different types of peripheral nerves stimulated through TENS to modulate cognition, the implicated neuromodulatory pathways and the cognitive functions affected. Besides the activation of the noradrenergic, cholinergic, dopaminergic and serotoninergic pathways, some of the reviewed studies also report the activation of anti-inflammatory molecules and opioid neuropeptides. All these parallel mechanisms might act in concert or separately to exert the cognitive effects solicited by TENS. VTA = Ventral Tegmental Area. Created with illustrations by https://BioRender.com

neuroscientific studies that challenges classical views of cognitive functions as abstract representation arising from brain activity to functions evolved from brain-body interactions.

In the present context, the potential of PNS techniques, such as TENS, represent another exciting method to achieve non-invasive cognitive enhancement, starting from the stimulation of the peripheral nervous system.

1.2. Aim of the review

While representing an intriguing scientific avenue, the knowledge concerning the cognitive effects of TENS remains limited. The aim of this review article is to provide a critical review of experimental research that used TENS in healthy humans or in populations of patients mildly cognitively affected. In this category, we included postoperative cognitive dysfunction (POCD), and patients in the early stages of Alzheimer's disease or with mild cognitive impairment (MCI). The reason for the inclusion of these patient populations is twofold: on the one hand, the paucity of TENS studies on healthy participants makes it difficult to draw conclusions on its efficacy for cognitive enhancement, on the other hand, it allows to provide tentative comparative conclusions on the usefulness of this technique for restoring cognitive functions in the acute phases of neurological dysfunction. To this aim, we used the following keyword on PUBMED: "Transcutaneous stimulation AND cognition NOT vagus nerve NOT pain" or "Transcutaneous stimulation AND healthy subjects AND cognition NOT vagus nerve NOT pain". We will first summarize the effects of TENS on memory functions – which have been the focus of most experimental studies – and, subsequently address the effects of TENS on verbal fluency, attention and executive functions.

2. The effect of TENS on memory functions

To the best of our knowledge, only a few studies employed TENS in healthy participants to improve memory functions (see a summary in Table 1). Most of the scientific evidence on this topic comes from clinical studies on patients mildly cognitively affected (Table 1) by conditions such as POCD, early stages of Alzheimer's disease or mild cognitive impairment (MCI).

One of the first studies showing an effect of TENS on memory was conducted on healthy elderly participants undergoing greater occipital nerve stimulation during an associative memory task (Luckey et al., 2020a). Participants with no cognitive impairment and normal memory performance were randomly assigned to active or sham stimulation groups. TENS was applied bilaterally over C2 dermatomes, while participants underwent a Swahili-English word association task. In this task, they had to learn a list of word pairs across three training blocks, with memory recall test sessions administered immediately after each training block and, subsequently, repeated after 7 and 28 days. Although no differences in the learning performance were observed between the two groups on day 1, better memory recall performance was found at days 7 and 28 post-TENS in the active group compared to the sham group, with no change in processing speed. These results showed, for the first time, that memory enhancement in elderly individuals is achievable with a single session of TENS without affecting learning, with effects lasting (at least) 28 days. Interestingly, the authors also observed a significant increase in saliva α-amylase concentrations – a proxy for noradrenaline levels (Box 1) – which persisted for 28 days post-TENS, without any change in cortisol levels (Luckey et al., 2020b). Thus, the authors hypothesized that the mechanism responsible for the observed memory enhancement may involve activation of the locus coeruleus-noradrenergic (LC-NA) pathway (Luckey et al., 2020a), which is known for its role in modulating cognition (Sara, 2009; Wagatsuma et al., 2017). Importantly, no differences in all the possible side effects assessed through a questionnaire (headache, neck pain, scalp pain, tingling, itching, burning sensation, skin redness, sleepiness, trouble concentrating, acute mood changes) were found.

While promising, this study did not assess other cognitive measures, such as attentional ones, which could influence memory performance. Additionally, it remains unclear whether the observed effects were mediated solely by peripheral nerve stimulation or whether direct modulation of parietal lobe activity contributed. Nevertheless, in a similar study by the same research group, Vanneste et al. (2020), with a series of ten elegant experiments, provided further evidence that TENS-induced memory recall enhancement are mostly due to peripheral nerve stimulation, conceivably by LC-NA pathway activation. Indeed, they demonstrated that the memory-enhancing effects of TENS significantly decreased when topical skin anesthetic was applied at the stimulation site, suggesting that the memory enhancing effect was due, in large part, to peripheral nerve stimulation, more than direct parietal lobe neuronal modulation. Moreover, they showed that: 1) memory recall performance at day 7 post-TENS correlated with three different proxy measures of LC-NA activity, namely pupil diameter (Box 1), α-amylase, and event-related potentials (ERPs); 2) the same TENS protocol that enhanced memory recall also increased connectivity strength between the LC and the hippocampus during and after stimulation, and between the LC, the hippocampus and the amygdala only during stimulation, as measured by resting-state functional connectivity MRI; and 3) TENS also modulated the theta and gamma frequency bands in the medial temporal cortex, together with phase-amplitude coupling between theta and gamma oscillations, as measured by EEG. A similar memory enhancing effect was also demonstrated in rats when the stimulation was directly performed with cuff electrodes at the greater occipital nerve following the learning phase of two different memory tasks, the inhibitory avoidance and the object recognition tasks (Vanneste et al., 2020).

The great heterogeneity of TENS protocols contributes to the difficulty of drawing conclusions on the optimal parameters and procedures to obtain memory enhancement. This is further supported by another recent study by Luckey et al. (2022) showing that two different greater occipital nerve TENS protocols – one employing continuous current stimulation and the other adopting alternating current stimulation – resulted in different memory enhancement outcomes in healthy adult participants. Specifically, participants that received continuous current stimulation showed better recall performance only 7 days after the learning phase of a word associative memory task, suggesting that plasticity offline mechanisms might be responsible for the improved memory consolidation, in line with previous studies (Luckey et al., 2020a; Vanneste et al., 2020); on the contrary, participants that received alternating current stimulation showed better performance at day 1, in the immediate recall test, suggesting that continuous and alternating current TENS could affect different memory mechanisms (Luckey et al., 2022). Also, in this study authors assessed some possible side effects of TENS (headache, neck pain, scalp pain, tingling, itching, sleepiness, trouble concentrating and acute mood changes) and found no relevant effects, but greater difficulties in concentrating for the group stimulated with alternating current TENS compared to the sham group.

In a recent series of experiments, the same research group added new evidence on the effects of TENS on memory consolidation and on the possible mechanisms involved (Luckey et al., 2023b). They first replicated previous evidence by Luckey et al. (2022, 2020) and Vanneste et al. (2020), by showing that greater occipital nerve TENS (applied during the learning phase of a word-association memory task) resulted in a memory recall enhancement after 7 days. Furthermore, they demonstrated that the same memory enhancement effect can also be achieved when continuous current TENS is applied post-learning, corroborating the hypothesis that this protocol acted on memory consolidation. Finally, they showed that their TENS protocol also strengthened pro- and retroactive memory and reduced interference. Interestingly, with the support of various neurophysiological measurements performed across eight experiments, they confirmed that TENS effects are mediated by the activation of the LC-NA pathway – as they showed increased levels of saliva α-amylase, larger pupil size, higher gamma power in the medial temporal lobe (but also in the precuneus

Table 1
Experimental studies that explored the effects of TENS on memory functions.

Paper	Subjects	Site of peripheral stimulation	Stimulation protocol	Memory Tasks	Main Effects
Luckey et al., 2020a	30 healthy volunteers (55–70 years old; 8 males and 22 females)	Greater occipital nerve (left and right C2 dermatomes – 35cm^2 saline-soaked surface sponges)	Active ($N = 15$) *vs* sham (N = 15) (between-groups) Constant current of 1.5 mA During 3-study phases (250 s × 3 blocks)	Associative memory task (*Swahili-English word association task*)	= learning performance at day 1 ↑ memory recall at day 7 and 28
Vanneste et al., 2020 (Exp. 4 in the paper)	30 healthy adults (mean age = 20 years; 8 males and 22 females)	Greater occipital nerve (left and right C2 dermatome – 35cm^2 saline-soaked surface sponges)	Active (N = 15) *vs* sham (N = 15) (between-groups) Constant current of 1.5 mA 5 min during the encoding phase, 10 min during consolidation phase	Face-name association memory task	↑ memory for faces and names related to faces
Vanneste et al., 2020 (Exp. 5 in the paper)	20 healthy adults (mean age = 22; 8 males and 12 females)	Greater occipital nerve (left and right C2 dermatome – 35cm^2 saline-soaked surface sponges)	Active (N = 10) *vs* sham ($N = 10$) (between-groups) Constant current of 1.5 mA During 4-study phases (375 s × 4 blocks)	Word association memory task (*Swahili-English word association task*)	↑ memory recall after 7 days
Luckey et al., 2022	85 healthy adults (mean age = 21; 36 males and 49 females)	Greater occipital nerve (left and right C2 dermatome – 35cm^2 saline-soaked surface sponges)	Active [constant (N = 25) or alternated current stimulation (N = 24 at 40 Hz and N = 11 at 1 Hz)] *vs* sham ($N = 25$) (between-groups) 1.5 mA [for participants that receive constant current stimulation] ±1.5 mA [for participants that receive alternated current stimulation] / 1 or 40 Hz with 0° phase difference During 3-study phases (250 s × 3 blocks)	Word associative memory task (*Swahili-English word association task*)	↑ memory recall performance after 7 days from the learning phase [constant current group] ↑ immediate memory recall performance at day 1 [40 Hz alternated current group]
Luckey et al., 2023a	1. 48 healthy subjects (mean age of 20.02) 2. 20 healthy subjects (mean age of 21.11) 3. 24 healthy subjects (mean age of 20.83) 4. 32 healthy subjects (mean age of 21.36) 5. 20 healthy subjects (mean age of 21.18)	Greater occipital nerve (left and right C2 dermatome)	Active *vs* sham (between-groups) Constant current of 1.5 mA 1. 25 min (375 s × 4 blocks) Active during task *vs* Active after task *vs* 2. 750 s (250 s × 3) Active during task 2 3. Active during task 1 4. Active during task 1 5. Active during task 25 min (375 s × 4)	Task 1: Associative memory task (*word association task*) Task 2: Spatial navigation task (*object-location task*) 1. Task 1 2. Task 1 then task 2 3. Task 1 then task 2 4. Task 1 (*Swahili-English)* and Task 1 *(Japanese-English*) 5. Task 1	1. = learning performance at day 1 ↑ memory recall at day 7 (stimulation during and after task) 2. = learning performance at day 1 ↑ memory recall at day 7 (in both tasks – associative + spatial memory) 3. = learning performance at day 1 ↑ memory recall at day 7 (in both tasks – associative memory + spatial memory) 4. = learning performance at day 1 ↑ memory recall at day 7 (in both tasks – associative memory) ↓ interference (between the two tasks) 5. = memory recall (before and after sleep)

(*continued on next page*)

Table 1 (*continued*)

Paper	Subjects	Site of peripheral stimulation	Stimulation protocol	Memory Tasks	Main Effects
Scherder et al. (1998)	18 participants with probable AD (78–92 years old)	Between Th1 and Th5 on the back, each on one side of the spinal column (6 cm^2 carbon rubber electrodes)	Active (N = 9) *vs* sham (*N* = 9) (between-groups) mA to trigger visible (painless) muscular twitches trains of 160 Hz, repetition rate of 2 Hz, pulse width of 100 μ*sec*, 9 pulses *per* train (BURST-TENS) 30 min a day for 5 days a week (6-weeks)	Visual Memory Span Face Recognition Word Fluency Digit Span 8 Word Test	↑ visual short-term memory ↑ non-verbal long-term recognition memory ↑ semantic verbal fluency = verbal short-term memory = verbal long-term memory
Scherder et al. (2000)	20 adults with mild forgetfulness (mean age = 86; 3 males and 17 females)	Between Th1 and Th5 on the back, each on one side of the spinal column (6 cm^2 carbon rubber electrodes)	Active (N = 10) *vs* sham (N = 10) (between-groups) mA to trigger visible (painless) muscular twitches trains of 160 Hz, repetition rate of 2 Hz, pulse width of 100 μsec, 9 pulses *per* train (BURST-TENS) 30 min a day for 5 days a week (6-weeks)	Visual Memory Span California Verbal Learning Test Face and Picture Recognition	↑ visual short-term memory ↑ verbal long-term memory ↑ non-verbal long-term recognition memory ↑ semantic verbal fluency
Scherder and Bouma (1999)	16 patients with a midstage of AD (mean age = 81)	Between Th1 and Th5 on the back, each on one side of the spinal column (6 cm^2 carbon rubber electrodes)	Active (*N* = 8) *vs* sham (N = 8) (between-groups) mA to trigger visible (painless) muscular twitches trains of 160 Hz, repetition rate of 2 Hz, pulse width of 100 μsec, 9 pulses *per* train (BURST-TENS) 30 min a day (6-weeks)	Visual Memory Span Digit Span 8 Word Test Face and Picture Recognition	↑ visual short-term memory = verbal short-term memory = verbal long-term memory = non-verbal long-term recognition memory
Guo et al. (2002)	14 patients with mild or severe AD (mean age = 77 years;)	Jing-Ming acupuncture points (on the internal side of each eye – 0.78 cm^2 ECG electrodes)	Active (*N* = 7) *vs* sham (N = 7) (between-groups) trains of 100 Hz, a repetition rate of 2 Hz, pulse width of 60 μsec 30 min every other day (4-week)	Hasegawa's Dementia Scale (HDS-R) 7-picture short-term memory test (SMT-7)	[Mild AD group]: ↑ personal orientation (HDS-R) ↑ reverse repetition (HDS-R) ↑ recall (HDS-R) ↑ fluency (HDS-R) ↑ visual short-term memory (SMT-7) [Severe AD group]: ↑ place orientation (HDS-R)
Van Dijk et al. (2005)	62 adults with probable AD (mean age = 71; 39 males and 23 females)	Th1, lateral to the spinal column [applied by caregivers]	Active (*N* = 32) *vs* sham (*N* = 30) (between-groups) mA to trigger visible (painless) muscular twitches trains of 160 Hz, repetition rate of 2 Hz, pulse width of 100 μsec, 9 pulses *per* train (BURST-TENS) 30 min a day (6-weeks)	Backward Digit Span Backward Visual Memory Span 8 Words Test Face and Picture Recognition	= verbal short-term memory = non-verbal short-term memory = verbal long-term memory = non-verbal long-term recognition memory
Luijpen et al. (2005)	56 patients with mild cognitive impairment (MCI) (mean age = 87; 14 males and 42 females)	Between Th1 and Th5 on the back, each on one side of the spinal column (6 cm^2 carbon gel electrodes)	Active (N = 30) *vs* sham (*N* = 26) (between-groups) mA to evoke painless muscular contractions trains of 160 Hz, repetition rate of 2 Hz, pulse width of 100 μsec, 9 pulses *per* train (BURST-TENS)	Forward and Backward Digit Span Forward and Backward Visual Memory Span Verbal Learning and Memory test	= verbal short-term memory = non-verbal short-term memory = verbal long-term memory = non-verbal long-term memory

(*continued on next page*)

Table 1 (*continued*)

Paper	Subjects	Site of peripheral stimulation	Stimulation protocol	Memory Tasks	Main Effects
			30 min a day for 5 days a week (6-weeks)	Face and Picture Recognition test	= non-verbal long-term recognition memory
				Word Fluency	= semantic verbal fluency
Wang et al., 2022a	154 patients receiving lumbar spine surgery under general anesthesia (mean age = 66; 87 males and 61 females)	"Baihui" acupoints (GV20, the intersection of the middle line of earline) "Dazhui" acupoints (GV14, in the depression under the spinous process of C7)	Active (N = 103–52 during 3 days and 51 during 7 days) *vs* sham (N = 51 – during 7 days) (between-groups) < 10 mA [adjusted to ensure comfort] Alternated frequency 2/100 Hz 30 min before the surgery and up to 3 or 7 days after the surgery for 30 min once a day	Mini-Mental State Examination (MMSE)	↓ incidence of Post-Operative Cognitive Dysfunction (POCD)
Liu et al., 2021	100 patients undergoing laparoscopic radical resection of colon cancer (mean age = 70; 51 males and 49 females)	"Neiguan" acupoints (PC6, on the palmar side of the forearm) "Hegu" acupoints (LI4, at the back of the hand) "Zusanli" acupoints (ST36, in the anterolateral leg)	Active (N = 50) *vs* sham (N = 50) (between-groups) At the max mA individual tolerance Alternated frequency 2/100 Hz From 30 min before the induction of anesthesia to the end of surgery	Mini-Mental State Examination (MMSE)	↓ cumulative duration of Post-Operative Cognitive Dysfunction (POCD)
Wei et al., 2022	90 patients undergoing video-assisted thoracoscopic surgical (mean age = 72; 46 males and 44 females)	"Neiguan" acupoints (PC6, on the palmar side of the forearm) "Zusanli" acupoints (ST36, in the anterolateral leg)	Active (N = 46) *vs* sham (N = 44) (between-groups) 6–15 mA (based on individual maximum tolerance) Alternated frequency 2/10 Hz (2 Hz for 10 s and 10 Hz for 5 s) alternative dense-disperse frequency 30 min before the induction of anesthesia until the end of the surgery	Mini-Mental State Examination (MMSE) Montreal Cognitive Assessment (MOCA)	↓ incidence of Post-Operative Cognitive Dysfunction (POCD)
Xi et al., 2021	64 patients who received radical resection of gastrointestinal tumors under general anesthesia (mean age = 70; 46 males and 18 females)	"Neiguan" acupoints (PC6, on the palmar side of the forearm) "Yintang" acupoints (GV29, on the forehead of the human body) "Zusanli" acupoints (ST36, 3 in. below the outer knee)	Active (N = 32) *vs* sham (N = 32) (between-groups) < 10 mA Alternated frequency 2/100 Hz 30 min the day before surgery 30 min before the induction of anesthesia until the end of the surgery 30 min from 1st-3rd day post-surgery	Mini-Mental State Examination (MMSE)	[at 3rd day after the operation] ↓ incidence of Post-Operative Cognitive Dysfunction (POCD)

Main effects: = indicates no change; ↑ indicates an improvement; ↓ indicates a decrease.

and the dorsolateral prefrontal cortex), and increased LC-hippocampus connectivity strength. Finally, they also reported evidence of TENS-induced dopaminergic modulation, by showing higher eye-blink rate (see Box 1) after stimulation, increased activity of the ventral tegmental area during stimulation (but not after), and a lower memory recall performance in a group of TENS-stimulated participants under the effect of dopamine antagonists, compared to a stimulated control group (Luckey et al., 2023b).

To summarize, the TENS studies on memory performance tested on healthy volunteers suggest that TENS can be effectively used to enhance memory function. The mnesic mechanisms specifically modulated by the stimulation depend on the chosen parameters. However, some of these studies tested samples of elderly participants, whose cognitive functions, albeit not necessarily mnesic ones, might already be declining. Therefore, it remains to be clarified whether TENS can restore partially affected memory functions, or effectively induce neuro-enhancement. To test the latter hypothesis, future studies should try to enhance memory in healthy, young participants and possibly compare mnesic TENS effects, using the same protocol, between young and elderly volunteers.

We will now summarize the TENS findings on memory function coming from clinical studies.

A series of randomized-double-blind placebo-controlled studies investigated the effect of TENS on memory in elderly participants that met the criteria for the clinical diagnosis of probable AD (elderlies with mild forgetfulness or at the early stages of AD, see Scherder et al., 1998; Scherder and Bouma, 1999; Scherder et al., 2000). Peripheral nerve stimulation was adopted to activate the hippocampus through the

somatosensory system, by increasing the activity of the noradrenergic pathway from the LC – a hypothesis in line with the previously reported data (Luckey et al., 2023a; Luckey et al., 2020a; Vanneste et al., 2020). To this aim, TENS electrodes were placed on the back of participants, between the thoracic vertebrae 1 and 5 (Th1 and Th5), bilaterally each on one side of the spinal column (Scherder et al., 1998). Participants underwent various neuropsychological tests evaluating different aspects of memory, before, at the end of the 6 weeks-long TENS protocol and following a period of 6 weeks without stimulation. The authors used a protocol known as BURST-TENS, consisting of asymmetric biphasic square impulses, which were applied in daily 30 min train bursts. Participants received such stimulation for 6 weeks (5 days a week) and the equivalent sham protocol was adopted in a control group. Compared to pre-active TENS performance, the authors found an improvement in different aspects of memory function, namely visual short-term memory (Visual Memory Span), non-verbal long-term memory (Face Recognition) and semantic memory retrieval (Word Fluency). Conversely, no significant differences, when compared to sham stimulation, were observed in verbal short-term memory (Digit Span) and verbal long-term memory (8 Word Tests). The effects of active TENS were still observed at the follow-up memory assessment, after 6 weeks, while sham stimulated participants showed declined performance in most of the memory tests, suggesting that TENS might have slowed down the AD-induced decrement in memory functions. However, given the small samples included in the study (nine participants per TENS group), the possibility remains that different AD gravity in the two groups might explain the trajectory of cognitive impairment following a period of six weeks.

Indeed, other evidence suggests that the effects of TENS on memory in people with probable AD might be stage-dependent. For instance, only non-verbal short-term memory was positively affected by TENS in a group of patients affected by middle-stage AD, while early-stage AD patients also showed improvements in non-verbal long-term memory, verbal long-term memory and verbal fluency after TENS (Scherder and Bouma, 1999). However, this study also included small patient samples and future longitudinal studies on bigger patient populations are needed to confirm TENS efficacy in reducing AD symptoms.

In line with the stage-dependent hypothesis of TENS effect on memory function of AD patients, Guo et al. (2002) found positive TENS effects on memory functions of mild AD patients, while no effect (other than a short-lasting place orientation performance improvement) was found in severe AD patients. The authors administered TENS (active or sham) daily for 30 min during 4 weeks, with electrodes placed at acupuncture points, on the medial side of each eye. A combination of high and low frequency stimulation was used to activate thick-myelinated Aβ-fibers, thin-myelinated Aδ-fibers and unmyelinated C-fibers (Guo et al., 2002), based on previous studies on animal models (Dudar et al., 1979; Dutar et al., 1985). Memory function was tested before and at the end of the stimulation protocol, using Hasegawa's Demential Scale (HDS-R), which consists of nine items also testing memory functions such as orientation, repetition and recall, and an *ad hoc* created visual short-term memory test. Results from both tests (see details in Table 1) suggest that short-term memory improved following TENS in the mild AD group only. However, the effect was not present at the 6-month follow-up. Moreover, the authors also tested the pupillary reflex of patients following active *vs.* sham TENS. This physiological examination was used to further test the effectiveness of TENS, based on evidence showing that pupillary light response is altered in AD patients compared to healthy elderly individuals (for a review on this topic see Chougule et al., 2019). Guo and colleagues found an improvement in pupillary reflex to light in both mild and severe AD patients following active TENS only. This result is another indirect evidence that the effectiveness of TENS for cognitive improvement might be mediated by the recruitment of the autonomous nervous system, and neuromodulators such as NA and acetylcholine (ACh), produced in the brainstem nuclei that control pupillary reflexes. Finally, the authors claimed the pupillary reflex effect was also found at the 6-month follow-up, although it is unclear in the manuscript which statistical analysis was performed to test this hypothesis. While very promising, the very small sample size in this study limits the generalizability of these results. In fact, despite using the same TENS pattern of stimulation, other studies found no effect on memory in patients with Alzheimer's disease (Van Dijk et al., 2005) or in those with mild cognitive impairment (Luijpen et al., 2005).

A study by Van Dijk et al. (2005) used the BURST-TENS protocol on a larger population of mild and severe Alzheimer's disease patients. The authors tested patients' memory functions using a battery of neuropsychological tasks (see details in Table 1) pre- and post-treatment, as well as at the 6-week follow-up. The intensity of stimulation was set to target Aβ-, Aδ- and C-fibers, with the stimulating electrode placed lateral to the spine on the first thoracic vertebra (Table 1). Results showed that active and sham TENS did not elicit significant changes. However, it should be noted that, compared to previous studies (Guo et al., 2002; Scherder et al., 1998; Scherder and Bouma, 1999; Scherder et al., 2000), van Dijk and colleagues adopted an at-home TENS protocol, where caregivers delivered TENS to patients. Moreover, the stimulation time each day was freely chosen by patients and caregivers, potentially adding variability to the data that was not included as a variable in the analyses. Although the Van Dijk et al. (2005) study included a larger number of patients than previous studies, another relevant difference concerns the inclusion of both mild and severe AD patients in the analyses conducted to test TENS efficacy. Given the cumulating evidence concerning a stage-dependent effect of TENS, this factor could explain the null results. Finally, the sample in this study was characterized by patients with an earlier onset of AD-related symptoms than those in previous studies, which could be a relevant factor impacting TENS efficacy. Early-onset AD is typically associated with more severe symptoms and a more aggressive course of the pathology, again suggesting that the stage and etiology of the pathology can be determinants for the overall effect of TENS on memory functions in AD patients.

Another study showing no evidence of TENS effect on memory comes from MCI patients (Luijpen et al., 2005). The mini-mental state examination (MMSE), a commonly used tool to screen cognitive decline (Hensel et al., 2007), was used in this study to diagnose amnesic MCI in an elderly population with no other signs of cognitive decline or daily living activity impairment. Using an approach similar to the aforementioned studies, Luijpen and colleagues tested the effects of BURST-TENS (located between Th1 and Th5) or sham-stimulation on elderly participants at four time points (6 weeks pre-treatment, 1-day pre-treatment, 6 weeks post-treatment and 6 weeks after the end of treatment), with a battery of neuropsychological tests to specifically evaluate memory. They did not find a significant interaction effect between group and time for any of the memory tests individually, but they found a significant interaction effect between group and time for the global measure of memory. This result was due to a non-significant decrease in MMSE scores of the TENS-stimulated group and a significant increase in the placebo group over the total 18-week experiment period. This result appears to contrast with the TENS stage-dependent efficacy hypothesis (Scherder and Bouma, 1999) and would indicate a detrimental effect of TENS on memory function. However, as the authors themselves pointed out, the early phases of MCI have been associated with region-specific hyperactivation of ACh signaling in the central nervous system, including the hippocampus (Dekosky et al., 2002). This is supposed to be a compensatory mechanism before the renowned loss of cholinergic neurons that manifests in later MCI or when AD occurs (Berry and Harrison, 2023). Since an increase in ACh release is one of the candidate mechanisms by which TENS is supposed to exert its effect through the basal forebrain nucleus, it is possible that TENS could have been detrimental at the early MCI stage, due to an overactivation of the compensatory mechanism in this phase. Finally, these results should be considered with caution, since the detrimental active TENS effect was non-significant, and the improvement found following sham stimulation

could be due to the' brevity and ease of the MMSE. Repeating this test multiple times could result in performance improvement that was not observed in the active TENS group for reasons that might relate to the sample itself and not the stimulation. For instance, it should be noted that the sample was predominantly females (about 80 %), which could have negatively biased the results, as gender can affect the course of the pathology and the effectiveness of treatment (Torromino et al., 2021).

Concerning clinical research investigating TENS effects on memory, it is worth mentioning the studies on the non-homogeneous category of patients that experience the so-called "postoperative cognitive dysfunction" (POCD) (Liu et al., 2021; Wang et al., 2022a; Wei et al., 2022; Xi et al., 2021). It has been shown that the period following different types of surgery can be characterized, in about 25–40 % of patients, by various cognitive impairments, such as reduced memory, attention, perception and abstract thinking ability, as well as changes in mental mood and personality (Amanzio et al., 2018; Le et al., 2014). One hypothesis to explain PODC is that postoperative neuroinflammation may play a key role, particularly at the hippocampal level (Femenía et al., 2018; Kline et al., 2016; Wang et al., 2013).

In a recent study, healthy and cognitively normal elderlies (MMSE score $\geq$ 26) scheduled for lumbar spine surgery were recruited for a randomized double-blind clinical trial testing the effects of TENS on POCD symptoms (Wang et al., 2022b). Participants received (active or sham) TENS at the acupoints 'Baihui' (the intersection of the midline of the top of the head of GV20 and the line connecting the two ear tips) and 'Dazhui' (in the depression under the spinous process of the seventh cervical vertebra of GV14). To test the effect of TENS treatment duration, the authors compared two groups that received either active or sham TENS for the 30 min before surgery and for the following 7 days (30 min *per* day) plus another group that received active TENS only before surgery and for the following three days with the same stimulation timing. Both 3-day and 7-day perioperative TENS interventions were shown to significantly decrease the incidence of POCD compared to sham stimulation, as measured by an MMSE *Z*-score comparing pre- and post-operative scores. This result indicates that TENS was able to prevent surgery-induced cognitive impairment, possibly by diminishing the neuroinflammatory response. Indeed, the authors also showed that serum levels of four different inflammatory factors – interleukin-6 (IL-6), tumor necrosis factor alpha (TNF-α), neuron-specific enolase (NSE) and S100 calcium-binding proteinβ (S100β) – were significantly higher in all groups after surgery compared to before surgery, but lower in the two active TENS groups compared to the sham-stimulated group (Wang et al., 2022a). This effect aligns with evidence from animal models, which have shown a reduction in the inflammatory response in the hippocampus after electroacupuncture (Xie et al., 2021).

Similar results were obtained in elderly individuals who underwent different types of cancer surgery – colon resection (Liu et al., 2021), and gastrointestinal (Xi et al., 2021) or lung cancer surgery (Wei et al., 2022). Patients received active or sham TENS at a combination of three different acupoints (see Table 1) from 30 min before anesthesia induction to the end of surgery. Cognitive functions were assessed with MMSE or the Montreal Cognitive Assessment – MOCA (Nasreddine et al., 2005) – one day before surgery and during the postoperative days (up to seven). Results showed that TENS significantly decreased the cumulative duration of POCD (Liu et al., 2021; Xi et al., 2021) and its overall incidence (Wei et al., 2022). Interestingly, Xi and colleagues (Xi et al., 2021) found TENS to specifically impact the MMSE memory and orientation subscales. The parallel evaluation of the inflammatory factors – high-sensitivity C-reactive protein (hs-CRP), IL-6, NSE, S100β and C-reactive protein (CRP) and the neuropeptide calcitonin gene-related peptide (CGRP) at the serum level – suggested that TENS activated an anti-inflammatory response (Liu et al., 2021; Wei et al., 2022; Xi et al., 2021).

In line with these reports, a recent retrospective study showed a positive effect of TENS – delivered at the median nerve – on a heterogeneous population of hospitalized patients with cognitive impairment, as measured by low MMSE scores (Zhou et al., 2024). TENS effectively increased the MMSE scores, as well as measures of daily living activities, and enhanced P300 latency and amplitude measures, compared to pre-treatment levels. However, in this study, TENS treatment was always accompanied by a conventional therapy tailored to the specific type of patient, which could have, *per se*, produced all the aforementioned outcomes. While the combined TENS and conventional therapy treatments led to enhanced positive effects (whose statistical significance was obtained using methods not specified in the article), a sham TENS condition was not included. The absence of a sham control leaves open the possibility that TENS was not the primary or sole cause of patients' improvement.

Drawing general conclusions from these studies is difficult due to the heterogeneity of samples and the diversity of stimulation sites. However, the consistent finding that TENS reduced patients' inflammatory response following surgery and decreased POCD incidence suggests that it might have improved cognitive functions through different and parallel mechanisms from those in the aforementioned studies (Guo et al., 2002; Luckey et al., 2022; Luckey et al., 2020a; Scherder et al., 1998; Scherder and Bouma, 1999; Scherder et al., 2000; Vanneste et al., 2020). These mechanisms are possibly similar to those already suggested for other neuromodulatory techniques (Guo et al., 2023). However, direct recruitment of neuromodulators in the central nervous system cannot be excluded at present.

Overall, there is a lack of homogeneity across the protocols adopted in these different studies, and the stimulation intensity used for healthy individuals is generally lower compared to that used for patient populations (1.5/2 mA *vs.* 10 mA). Moreover, some studies adjusted the stimulation intensity to a level producing painless but visible muscular twitches instead of using a fixed intensity. Despite important differences across studies exist, there is convincing evidence that memory performance in various domains can be modulated *via* non-invasive transcutaneous stimulation. While the mechanisms through which transcutaneous stimulation might act were not directly explored in the aforementioned studies, some included physiological measures that support the hypothesis that TENS-mediated effects on memory might involve the activation of the LC-NA or the ACh pathways, as well as the release of dopamine. The broadband activation of neuromodulatory pathways might, in turn, act through different parallel and not mutually exclusive mechanisms, such as increasing connectivity strength between the LC and other cortical and subcortical regions (*e.g.*, the hippocampus and amygdala), or modulating the theta and gamma frequency bands and their phase coupling in the temporal lobe. Additionally, TENS has been shown to lower the inflammatory response, which is known to affect hippocampal activity. Thus, both direct and indirect evidence indicates that transcutaneous stimulation might be an effective way to modulate hippocampal activity and its functions in the memory domain.

3. The effects of TENS on attention, executive functions and verbal fluency

Fewer studies have evaluated the effects of TENS on other cognitive functions, such as language and attention (Table 2). To the best of our knowledge, there is no evidence regarding the use of TENS to specifically modulate these functions in healthy humans, but there are a few studies including different types of patients that we chose to report here to give some insight on the potential effects of transcutaneous stimulation also for these functions.

Concerning language, evidence suggests that TENS can exert a positive effect on word fluency in patients at the early – but not mild or severe – stages of Alzheimer's disease (Guo et al., 2002; Scherder et al., 1998; Scherder et al., 2000). As previously mentioned in this review (see Table 1), these results were obtained using a word fluency task (semantic memory retrieval), following applications of TENS to the back (Scherder et al., 1998; Scherder et al., 2000), or in the word fluency subtest of the HDS-R with electrodes applied to the internal side of each

Table 2
Studies that investigated the TENS effects on cognitive functions other than memory.

Paper	Subjects	Site of peripheral stimulation	Stimulation protocol	Tasks	Main Effects
Jonsdottir et al., 2004	22 Children with ADHD (8–14 years old; 21 boys and 1 girl)	Between Th1 and Th5 on the back, each on one side of the spinal column (6 cm^2 carbon rubber electrodes)	Only active group ($N = 22$) (within-group) mA to evoke painless muscular contractions trains of 160 Hz, repetition rate of 2 Hz, pulse width of 100 μsec, 9 pulses *per* train (BURST-TENS) 30 min twice a day for 7 days a week (6-weeks)	Wechsler Intelligence Scale for Children Revised (Arithmetic, Digit Span and Coding subtests) Bourdon-Vos test Stroop Colour test	↑ working memory ↑ visual attention ↑ visuomotor speed ↑ cognitive interference
Guariglia et al., 1998	9 patients with right brain injury (mean age = 65)	Left or right neck muscle, lateral to the spine (0.34 cm^2 electrodes)	Within-group (N = 9) Average of 0.5 mA/mm^2 100 Hz, pulse width of 100 msec From 20 min before testing to the end of the session	Familiar Square Description Free Drawing of Objects Abstract Shape Comparison	[only left-sided stimulation] ↑ mental representations of objects ↑ mental images of space

Main effects: = indicates no change; ↑ indicates an improvement; ↓ indicates a decrease.

eye (Guo et al., 2002). Worth mentioning is a study in which the authors combined peripheral stimulation techniques in post-stroke patients, demonstrating an amelioration of language functions, as well as memory and attention (Rorsman and Johansson, 2006). However, in this study, patients also underwent other rehabilitative programs, which could have influenced language performance, making it difficult to disentangle the specific effects of TENS from conventional therapeutical outcomes on language functions. Future studies should devise *ad hoc* protocols to explore TENS efficacy as a rehabilitative method for language functions.

Based on the previously encouraging results obtained using BURST-TENS protocols on memory functions and verbal fluency, Jonsdottir and colleagues adopted the same stimulation protocol (twice a day for 30 min, every day for 6 weeks), with electrodes placed on the back (between Th1 and Th5), in children with attention deficit hyperactivity disorder (ADHD), to test its effects on cognition, general behavior, and the rest-activity rhythms (Jonsdottir et al., 2004). In this study, the Bourdon-Vos test was used to measure visual attention and visuomotor speed, while the Stroop test – where ADHD children are typically slower than healthy children – was used to measure attention and executive functions (Jonsdottir et al., 2004). Additionally, the Arithmetic, Digit Span and Coding subtests of the Wechsler Intelligence Scale for Children Revised (Wechsler, 1974) were administered. These subtests can be combined into one separate IQ factor called "Third Factor" (F3IQ) (Kaufman, 1975), which evaluates the executive function aspect of working memory. Cognitive performance with these three neuropsychological tests was measured before and at the end of the TENS treatment, as well as 6 weeks after a treatment-free period. Results showed a significant improvement in ADHD children's performance on the F3IQ total score, the Coding subtest, and attention tests after TENS. These improvements persisted at the 6 weeks follow-up, suggesting that TENS can also positively affect executive functions and attention, at least in ADHD children. Future studies should include an ADHD children group exposed to sham TENS, to disentangle the effects of TENS from improvements due to repeated test exposure.

Another experimental study, inspired by previous evidence showing that sensory stimulation attenuated imaginal neglect in right-damaged patients (Geminiani and Bottini, 1992), tested the effects of TENS in neglect patients (Guariglia et al., 1998). Using a within-participants experimental design, the study, reported a significant reduction of neglect symptoms – tested with a letter cancellation task – and imaginal neglect – tested with Familiar Square Description, Free Drawing of Objects and Abstract Shape Comparison – during left-sided TENS, with electrodes placed on the neck. Importantly, right-sided TENS produced unclear results and worsened performance in the Abstract Shape Comparison test for 4 out of 9 participants.

The results of these studies suggest that TENS might be used to improve cognitive functions such as attention and language, but electrode placement should be considered carefully. Future studies involving different patients populations, as well as healthy participants, and comparing active and sham TENS, are needed to further explore the efficacy of this technique for both neurorehabilitation and neuroenhancement of cognitive functions.

4. TENS-mediated modulation of general behavior and mood

Some of the aforementioned studies that investigated cognitive outcomes after TENS also explored other non- purely cognitive domains – such as mood and general behavior, using different neuropsychological tools. In this section, we report these results as examples of possible uses of TENS to improve participants' well-being. This section does not aim to be a comprehensive review of the effects of TENS on general behavior and mood.

The previously reported study from Jonsdottir et al. (2004) also found a significant improvement in the overall behavior of ADHD children following TENS, as assessed through The Revised Conners Parent and Teacher Rating Scales. Specifically, according to parents' scoring, there was a significant improvement in the Anxiety and Impulsive/Hyperactive subscales, while teachers' scoring showed significant improvements in the Learning Problems, Impulsive/Hyperactive, and Conduct Problems II subscales. The reported improvements remained stable 6 weeks after the end of the treatment (Jonsdottir et al., 2004). The subjectivity of parents' and teachers' reports, of course, limits the reliability of these results, which would need to be complemented by objective, quantifiable measures, such as electrophysiological ones. Furthermore, some of the studies by Scherder and colleagues reported a decrease in depressed mood and a beneficial influence on participation in daily-life activities of the elderly individuals with mild forgetfulness or at the early stage of AD, following TENS treatment (Scherder et al., 1998; Scherder et al., 2000). In parallel, Scherder and colleagues did not find a therapeutic effect of TENS on patients' overall affective behavior, as measured by the Behavior Inventory (Scherder et al., 1998).

The aforementioned study by Luijpen et al. (2005), which tested the effect of TENS in MCI patients, instead found a decline in self-efficacy and mood, although this study also showed no cognitive improvement after TENS.

Further research should explore the efficacy of TENS for ameliorating mood and self-efficacy in healthy participants, while controlling, through the comparison of active *vs.* sham TENS, for the possible placebo effect, using a double-blind randomized method.

A recent randomized controlled trial conducted in cancer patients with cancer-related fatigue (CRF) has implemented an innovative and interactive TENS acupoint approach. This approach used a connected somatosensory control equipment to identify and locate target acupoints through a human-computer interaction method, and provide real-time physiological data to adjust the rehabilitation protocol to each patient (Shu et al., 2022). The aim of the study was to compare the effects of this interactive TENS acupoint approach with that of self-administered acupoint massage or sham stimulation. All the procedures were performed at home by patients after proper training. Patients' fatigue levels were assessed using the Revised Piper Fatigue Scale at baseline and after 4 and 8 weeks of treatment. The Piper Fatigue Scale (Portenoy and Itri, 1999) evaluates behavioral, sensory, emotional, and cognitive aspects of fatigue. Results showed a significant decrease in the total fatigue score, including the purely cognitive aspect, compared to both acupoint massage alone and sham stimulation (Shu et al., 2022). Similar to previous researches involving patients, TENS also modulated inflammatory markers, such as CD3+ T cells, CD4+ T cells, CD8+ T cells, CD4+/CD8+ T cells and NK.

5. Conclusions

Research on the use of TENS to modulate cognitive functions, both in healthy volunteers and patients, is still in its early stages. Despite the heterogeneity of protocols and electrode placement, cumulating evidence suggests that TENS can exert positive effects on high-level cognitive functions, particularly, in the domain of memory, which has been more extensively studied. It is important to note that the reported cognitive effects were not accompanied by side effects, which were specifically monitored and documented in some of the reviewed studies through direct observations of researchers or self-report questionnaires by patients (Luckey et al., 2022; Luckey et al., 2020a; Wei et al., 2022; Xi et al., 2021).

At present, multiple possible mechanisms could explain the TENS-induced cognitive improvement. In turn, these mechanisms may depend on several variables, such as electrodes' placement (*e.g.* which peripheral nerve is targeted), the intensity and frequency of stimulation, or its timing. Ultimately, these factors can affect stimulation outcome, as evidenced by the diverse effects found on memory functions following TENS (Luckey et al., 2023b; Luckey et al., 2020a; Luckey et al., 2020a; Vanneste et al., 2020).

The heterogeneity of stimulation protocols and, importantly, the locus of stimulation (specific nerve targeted) is a critical issue that remains to be tackled with future studies, in order to draw clearer conclusions about the mechanisms of TENS. We have reviewed studies that have employed both continuous and alternating stimulation protocols (with different pulse-width) targeting different nerves – *i.e.* the greater occipital nerve, facial nerves, the median nerve, as well as thoracic nerves. This heterogeneity severely affects the possibility to generalize conclusions on TENS cognitive effects. Despite these inconsistencies in the stimulation settings, there is coherence in the literature regarding TENS-induced activation of specific neurotransmitter systems – quantified through systemic proxies – and, consequently, the neural circuits affected. These measures represent promising candidates for quantifying TENS-mediated cognitive effects and for explaining the underlying mechanisms. However, further research is needed to replicate these studies, on larger participant samples to validate these results.

From a broader perspective, since TENS involves the stimulation of the peripheral nervous system, its modulation of memory functions likely depends on mechanisms of heterosynaptic plasticity (Faress et al., 2024; Frey and Morris, 1997; Mikaitis et al., 2018). Accordingly, it is renowned that the molecular and cellular mechanisms underlying memory involve changes in synaptic efficiency and neural network architecture, the timing and strength of which can be regulated by several factors (Torromino, 2024).

In this sense, there are some candidate mechanisms plausibly involved in the memory enhancing effects found in healthy volunteers, as well as in patients with memory deficits.

A possible way through which TENS in particular and PNS more generally could affect cognition, and memory specifically, is by inducing the release of neuromodulators, such as monoamines and hormones into systemic circulation (Clark et al., 1999) or in the brain itself (Hassert et al., 2004; Miyashita and Williams, 2004). Accordingly, cognitive functions like memory formation and attention are known to be affected by modulatory neurotransmitters or arousal (Cahill et al., 1994; Nielson and Jensen, 1994; Sara et al., 1999; Yerkes and Dodson, 1908), as well as by the type, timing and level of subcortical and thalamic activation (Groenewegen and Berendse, 1994; Torromino et al., 2022; Vetere et al., 2021; Xu and Südhof, 2013).

On this vein, the LC-NA pathway and the ACh septo-hippocampal pathway, whose role in cognition, and memory in particular, is well known (Cahill et al., 1994; Froeliger et al., 2009; Hasselmo, 2006; Nielson and Jensen, 1994; Sara, 2009; Sara et al., 1999), are among the best candidates. Some reviewed studies reported that TENS induced changes in physiological parameters that are associated with these pathways, such as α-amylase levels and pupil dilation and reflex (Guo et al., 2002; Luckey et al., 2022; Luckey et al., 2020a; Vanneste et al., 2020). The involvement of Ach is further supported by evidence showing that sensory stimulation significantly increased ACh release in the hippocampus of rats through the septo-hippocampal pathway (Dudar et al., 1979; Dutar et al., 1985).

Intriguingly, tactile stimulation has also been shown to elicit hippocampal responses. These include triggering the hippocampus activation through the thalamus and the somatosensory cortex (S1) (Pereira et al., 2007), increasing S1-hippocampus rhythm phase synchronization (Grion et al., 2016), stimulating memory-related plasticity in the hippocampus and improving related memory performance, and finally augmenting the survival and differentiation of hippocampal cells in adulthood (de los Angeles et al., 2016).

TENS-mediated activation of brain regions such as the hippocampus is thought to occur indirectly through the activation of afferent nerves, such as thick-myelinated Aβ-fibers, thin-myelinated Aδ-fibers and unmyelinated C-fibers (Coffey and Mahon, 1982; Dudar et al., 1979; Dutar et al., 1985). Along this neuroanatomical pathway, the NTS has been proposed to play a pivotal role in linking TENS-induced somatosensory activation to the LC and other neuromodulatory systems, including the dopaminergic one (see Luckey et al., 2023a), due to its aforementioned ascending projections to key subcortical and cortical regions (Mohr et al., 2011; Yap et al., 2020). Due to the variable peripheral positioning of the TENS electrodes, it is hard at present to provide tentative links between the stimulated nerves and the activation of one or more of these neuromodulatory pathways. Moreover, cognitive functions emerge from the concurrent and fine-tuned activation of all these systems. For instance, all the neuromodulatory systems activated by TENS exert strong signaling within the hippocampus (Gasbarri et al., 1997; Meneses and Perez-Garcia, 2007; Nicoll, 1985; Schwarz and Luo, 2015).

In addition to these pathways, one of the primary targets of the spinal somatosensory ascending pathway is the contralateral thalamus, an important hub in the brain that might be involved in the TENS-mediated memory enhancement effects (Wang et al., 2022b). Subcortically located and divided into several sensorimotor and associative nuclei, the thalamus spreads various connections to other cortical and subcortical regions (Behrens et al., 2003; Hwang et al., 2017), which are more directly implicated in cognition, making it a "cognitively flexible" brain

region (Hwang et al., 2017). Accordingly, the thalamic volume, activity and the associated thalamo-cortical connectivity have been associated with cognitive and sensorimotor performances in humans and animal models (Philp et al., 2014; Torromino et al., 2022). While the thalamus could be central to explaining TENS cognitive effects, studies directly investigating the TENS-induced thalamic activation in humans or animal models are still lacking.

Studies in the field of pain have also shown that specific frequencies of stimulation, both with electric acupuncture and TENS (Wang et al., 1992), can induce the release of different opioid neuropeptides – such as met-enkephalin and dynorphin-A –, at the spino-subcortical level, exerting an analgesic effect (Han, 2003). We cannot exclude an indirect analgesic-mediated effect of these neuromodulators on the cognitive improvement exerted by TENS in POCD patients, in which there have been documented hippocampal dysfunctions due to inflammatory response (Femenía et al., 2018; Kline et al., 2016; Wang et al., 2013). However, this is unlikely to be the main mechanism explaining TENS-induced cognitive effects in healthy people, for whom neither pain modulation nor hippocampal dysfunction can be expected. Nonetheless, the potential link between pain modulation, opioid neuropeptide pathways, and TENS cognitive effects remains to be elucidated.

At the whole brain system level, the engagement of neuromodulators and neuropeptides can translate into several brain activity changes. These changes have been partially characterized in the studies reviewed here or in parallel research that used TENS for different purposes. For instance, as previously reported in this manuscript, TENS can increase connectivity strength between the LC, hippocampus and amygdala, modulate theta and gamma frequency bands in the medial temporal cortex, and the phase-amplitude coupling between theta and gamma oscillations (Luckey et al., 2023b; Vanneste et al., 2020). Additional evidence coming from studies on the efficacy of TENS beyond cognition, has shown a link between TENS and brain entrainment (Al-Zamil et al., 2024; Niederhauser et al., 2008; Saricaoglu et al., 2023). For instance, Saricaoglu et al. (2023) recorded EEG data during the application of TENS in a 22-year-old patient with sensory loss in the dominant hand, before and after a rehabilitation protocol that included also TENS. They found that, after rehabilitation, TENS-EEG showed increased parietal and occipital alpha, as well as frontal and parietal beta activities. Activity in the primary somatosensory cortex of healthy participants, as measured through multi-channel near-infrared spectroscopy (NIRS) – a method for non-invasively monitoring relative concentrations of oxygenated, deoxygenated and total hemoglobin in the cortex – was found to be enhanced, contralaterally, by electrical stimulation of the distal anterior forearm, over the median nerve (Niederhauser et al., 2008).

Interestingly, Asamoah et al. (2019) pointed out that even some effects of transcranial direct current stimulation (tDCS), a non-invasive method for directly modulating brain activity (Ficarella, 2024), may actually be mediated by the stimulation of peripheral nerves in the skin. According to their computational model, the electric field generated by a typical epicranial stimulation protocol is not sufficient to induce significant neural entrainment in the brain, paradoxically leaving the mechanism through which tDCS exerts its effects unexplained (Asamoah et al., 2019). The authors hypothesized that peripheral stimulation mediates, at least to some extent, the cerebral effects of tDCS. Furthermore, they provide support to this hypothesis by demonstrating that transcutaneous peripheral stimulation of the skin in rats produces brain entrainment similar to direct transcranial stimulation and showing that topical inhibition of the skin significantly reduces the brain entrainment induced by current stimulation (Asamoah et al., 2019). Replicating this effect in healthy humans would help validate their hypothesis.

Finally, it is interesting to note that many of the neurotransmitter signaling pathways and neural circuits recruited by TENS are pivotal not only for cognition but also for mood stability, as described in the previous paragraph, which suggests the presence of a correlation between these phenomena. Indeed, epidemiological studies have extensively documented the comorbidity of mood disorders and cognitive impairment, highlighting overlapping dysfunctional mechanisms in both these conditions, such as changes in neurotrophic factors and neuropeptides signaling, cerebrovascular diseases, glucocorticoid neurotoxicity, white and grey matter anomalies (Zacková et al., 2021). However, establishing a causal relationship between mood and behavioral improvement and the cognitive enhancement is methodologically challenging due to inherent constraints. Thus, this remains an interesting issue to be disentangled by future research.

From the evidence present in the literature and summarized here, we conclude that the employment of TENS for the modulation of brain activity and cognition is a promising field. Future research should be carried out, through carefully planned placebo-controlled studies and neurobiological investigations of the mechanisms in animal and computational models. Specifically, thanks to a combination of the most recent techniques available in animal model research, it will be possible to specifically target different groups of nerves with different stimulation protocols and compare the induced effects at behavioral and cognitive levels, as well as at the level of neural circuits and neurotransmitter systems, even employing a functional approach. Hopefully, in the near future, this will create a consensus concerning the neurophysiological mechanisms behind the cognitive effects of TENS and provide the foundation for standardizing stimulation protocols in healthy humans and patients.

5.1. Final remarks

From a purely theorical-speculative perspective, the hypothesis that TENS can be used to enhance cognition is in line with the perspective of Embodied Cognition (Barsalou, 2008; Caramazza et al., 2014; Foglia and Wilson, 2013; Gallese, 2005; Gallese and Lakoff, 2005). Within this perspective, the body is a central agent in regulating cognitive functions, as information coming from peripheral sensory systems determines the quality and quantity of brain activity and cortical entrainment and, consequently, affects the relative behavioral output, be it an action or a thought (Torromino, 2024). Therefore, the assumption that «high-level cognitive functions can be grounded in our bodily interactions with the world» (Gallese and Cuccio, 2018) also implies that non-invasive PNS might efficiently modulate cognition.

The potential of TENS as a neuromodulatory technique is particularly relevant in the context of neuroenhancement. Sometimes referred to as cosmetic neurology or self-enhancement (Chatterjee, 2004; Hamilton et al., 2011), neuroenhancement encompasses all interventions and techniques aiming at the enhancement of human cognitive abilities beyond what is considered physiologically normal (Antal et al., 2022). The desire to improve, or simply alter, cognition is rooted in our daily routines, in habits such as consuming caffeinated beverages or taking drugs to manage mood, sleep or energy levels. While it is crucial to consider the ethical implications of using non-invasive modulatory techniques for neuroenhancement – as explored in previous research (Antal et al., 2022; Chatterjee, 2004; Hamilton et al., 2011) – developing efficient and safe protocols for non-invasively influencing brain activity has garnered enormous attention. The potential to enhance cognitive abilities has already been envisaged with non-invasive brain stimulation techniques, such as transcranial magnetic and electrical stimulation (*e.g.* Antal et al., 2022). This potential may now include the use of peripheral stimulation techniques, such as TENS and non-invasive vagal nerve stimulation (Ficarella, 2024).

Nonetheless, whether through the direct, using non-invasive brain stimulation techniques, or indirect modulation of brain activity, through PNS – but also other non-invasive peripheral stimulation techniques such as vagal nerve stimulation (see McGinley and Lee, 2022) –, we can attain neuroenhancement and create cognitively "super humans" is a scientific, as well as ethical, question that remains unanswered. Notably, some evidence suggests that the improvement of one cognitive function might be obtained at the expenses of others (Hamilton et al., 2011).

Whether, and how, TENS can contribute to the field of neurorehabilitation and enhancement remains to be seen in future years.

Funding

This work was supported by the University Research Funding Program (FRA) 2022 of the University of Naples Federico II granted to G.T.

Box 1. The neuroanatomical hubs and neuromodulatory systems activated by TENS.

Some of the experimental evidence reviewed here have shown the activation of the noradrenergic, cholinergic, dopaminergic and serotoninergic pathways induced by TENS through the evaluation of non-invasive proxies. These four main neuromodulators are released upon the activation of key neuroanatomical hubs located in the midbrain and the hindbrain (Fig. 1).

The **noradrenergic system** originates in the locus coeruleus (LC) and it is anatomically connected with the majority of the cortical and subcortical brain regions (Avery and Krichmar, 2017; Briand et al., 2007). Among them, parietal and sensory cortices as well as the hippocampus are particularly relevant in the context of TENS-mediated effects on cognition. The LC receives inputs from both the brainstem (including the NTS) and the cortex, and has long been renowned for its function in the regulation of arousal, through the fine-tuning of its tonic activation (Berridge and Waterhouse, 2003). However, phasic activation of the LC has been associated with learning and memory processes and novel or salient input detection (reviewed in Avery and Krichmar, 2017). Overall, experimental studies suggest that the fine-tuning of tonic and phasic LC-NE activity is at the base of an inverted-U-shaped relationship between signal detection and task performance in rodents and humans (Avery and Krichmar, 2017). Several experimental studies have used pupillometry as a proxy measure of the LC-NE activation, based on the evidence that LC activation anticipates pupil diameter fluctuations (Joshi et al., 2016), although it is not a specific measure of LC activity (Megemont et al., 2022). Another indirect measure of LC activity is the salivary level of the α-amylase, which co-varies with circulating levels of noradrenaline (van Stegeren et al., 2007), and is modulated by pharmacologically induced sympathetic activation (Petrakova et al., 2017).

The **cholinergic system** originates in the basal forebrain and is bidirectionally connected with cortical and limbic regions of the forebrain (Avery and Krichmar, 2017). The level of acetylcholine (ACh) released by the basal forebrain has been associated with attention and memory encoding, consolidation and retrieval (Avery and Krichmar, 2017). ACh levels in the brain are low and change rapidly, as Ach is quickly metabolized by the enzyme acetylcholinesterase (Chang et al., 2006; Soreq and Seidman, 2001). Moreover, ACh modulates neuronal function *via* both tonic and phasic release. Most available methods for ACh detection primarily assess tonic levels (*i.e.*, slow methods) and are not suitable for detecting phasic events, such as TENS-induced ACh modulations (Mineur and Picciotto, 2023).

The **dopaminergic system** originates in the mesencephalic nuclei of the ventral tegmental area (VTA) and the substantia nigra pars compacta (SNc), which receive inputs from subcortical areas, such as the lateral habenula and the pedunculopontine tegmental nucleus (Avery and Krichmar, 2017; Briand et al., 2007). The VTA and the SNc are renowned for their respective connection with cortico-limbic (prefrontal cortex, hippocampus, thalamus, and amygdala) and striatal regions, subserving to numerous cognitive and behavioral functions, including saliency, novelty detection, reward evaluation, working memory (Berridge and Robinson, 1998; Durstewitz and Seamans, 2008; Schultz, 1997). Since Parkinson's Disease (PD) involves a progressive loss of dopaminergic neurons in the SNc, a significant body of research has focused on the identification of non-invasive methods to estimate dopaminergic levels in the brain (for a review, see De Bartolo et al., 2024). Among them, eye-blink rate is commonly used as proxy of dopamine signaling (Karson, 1983; Zhang et al., 2015), based on the fact that dopamine agonists and antagonists significantly increase and decrease it in animals, and that patients with dopaminergic dysfunction, such as parkinsonian and schizophrenic, show altered eye-blink rates compared to controls (Karson, 1983).

The **serotoninergic system** originates in the raphe nuclei of the brainstem, projects to several cortical regions, the striatum and the amygdala and receives inputs from the cortex (Avery and Krichmar, 2017). This pathway contributes to a broad range of functions, such as impulsivity, anxiety state regulation and reward and punishment evaluation (Avery and Krichmar, 2017). Alteration of serotonin brain levels are associated with abnormal psychotic functions and are typically established by analyzing the serotonin metabolite 5-hydroxy indole acetic acid (5-HIAA) in the cerebrospinal fluid, which is also considered a potential biomarker for the neurological and psychiatric disorders (Jayamohananan et al., 2019). However, collecting cerebrospinal fluid involves an invasive procedure, not applicable, in most cases, with healthy participants. Since melatonin is synthesized from serotonin and it is excreted as sulphatoxymelatonin in the urine, some authors have suggested the use of urinary sample for serotoninergic brain level estimation (Batllori et al., 2017). Future studies should test serotoninergic-mediated TENS effects on cognition through sulphatoxymelatonin urinary levels.

It should be noted that cognitive functions rely on more than one neuromodulatory system and that these pathways are reciprocally connected (Briand et al., 2007). Therefore, while finding non-invasive proxy for the activation of such neuromodulatory brain pathways, especially to quantify TENS efficacy, is pertinent, a one-to-one match between the activation of such neuromodulatory pathways and cognitive functions does not exist. For instance, all these pathways project to the hippocampus (Avery and Krichmar, 2017), a target region of interest for the effects of TENS on memory functions. Nonetheless, taking into consideration how these pathways are interconnected when evaluating TENS effects on cognition is central and should be better explored in future research.

CRediT authorship contribution statement

Giulia Fiorentini: Writing – review & editing, Writing – original draft, Methodology. **Eva Massé:** Writing – review & editing, Methodology. **Stefania C. Ficarella:** Writing – review & editing, Methodology. **Giulia Torromino:** Writing – review & editing, Writing – original draft, Supervision, Project administration, Methodology, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors of this manuscript have no potential conflict of interest to disclose.

Data availability

No data was used for the research described in the article.

References

Al-Zamil, M., Kulikova, N.G., Minenko, I.A., Shurygina, I.P., Petrova, M.M., Mansur, N., Kuliev, R.R., Blinova, V.V., Khripunova, O.V., Shnayder, N.A., 2024. Comparative analysis of high-frequency and low-frequency transcutaneous electrical stimulation of the right median nerve in the regression of clinical and neurophysiological manifestations of generalized anxiety disorder. J. Clin. Med. 13. https://doi.org/10.3390/jcm13113026.

Amanzio, M., Palermo, S., Zucca, M., Rosato, R., Rubino, E., Leotta, D., Bartoli, M., Rainero, I., 2018. Neuropsychological correlates of instrumental activities of daily living in neurocognitive disorders: a possible role for executive dysfunction and mood changes. Int. Psychogeriatr. 30, 1871–1881. https://doi.org/10.1017/S1041610218000455.

Antal, A., Luber, B., Brem, A.K., Bikson, M., Brunoni, A.R., Cohen Kadosh, R., Dubljević, V., Fecteau, S., Ferreri, F., Flöel, A., Hallett, M., Hamilton, R.H.,

Herrmann, C.S., Lavidor, M., Loo, C., Lustenberger, C., Machado, S., Miniussi, C., Moliadze, V., Nitsche, M.A., Rossi, S., Rossini, P.M., Santarnecchi, E., Seeck, M., Thut, G., Turi, Z., Ugawa, Y., Venkatasubramanian, G., Wenderoth, N., Wexler, A., Ziemann, U., Paulus, W., 2022. Non-invasive brain stimulation and neuroenhancement. Clin. Neurophysiol. Pract. 7, 146–165. https://doi.org/10.1016/j.cnp.2022.05.002.

Asamoah, B., Khatoun, A., Laughlin, M.M., 2019. tACS motor system effects can be caused by transcutaneous stimulation of peripheral nerves. Nat. Commun. 10. https://doi.org/10.1038/s41467-018-08183-w.

Avery, M.C., Krichmar, J.L., 2017. Neuromodulatory systems and their interactions: a review of models, theories, and experiments. Front. Neural Circuits 11, 1–18. https://doi.org/10.3389/fncir.2017.00108.

Barsalou, L.W., 2008. Grounded cognition. Annu. Rev. Psychol. 59, 617–645. https://doi.org/10.1146/annurev.psych.59.103006.093639.

Batllori, M., Molero-Luis, M., Arrabal, L., de las Heras, J., Fernandez-Ramos, J.-A., Gutiérrez-Solana, L.G., Ibáñez-Micó, S., Domingo, R., Campistol, J., Ormazabal, A., Sedel, F., Opladen, T., Zouvelou, B., Pons, R., Garcia-Cazorla, A., Lopez-Laso, E., Artuch, R., 2017. Urinary sulphatoxymelatonin as a biomarker of serotonin status in biogenic amine-deficient patients. Sci. Rep. 7, 14675. https://doi.org/10.1038/s41598-017-15063-8.

Behrens, T.E.J., Johansen-Berg, H., Woolrich, M.W., Smith, S.M., Wheeler-Kingshott, C. A.M., Boulby, P.A., Barker, G.J., Sillery, E.L., Sheehan, K., Ciccarelli, O., Thompson, A.J., Brady, J.M., Matthews, P.M., 2003. Non-invasive mapping of connections between human thalamus and cortex using diffusion imaging. Nat. Neurosci. 6, 750–757. https://doi.org/10.1038/nn1075.

Berridge, K.C., Robinson, T.E., 1998. What is the role of dopamine in reward: hedonic impact, reward learning, or incentive salience? Brain Res. Rev. 28, 309–369. https://doi.org/10.1016/S0165-0173(98)00019-8.

Berridge, C.W., Waterhouse, B.D., 2003. The locus coeruleus-noradrenergic system: modulation of behavioral state and state-dependent cognitive processes. Brain Res. Rev. 42, 33–84. https://doi.org/10.1016/S0165-0173(03)00143-7.

Berry, A.S., Harrison, T.M., 2023. New perspectives on the basal forebrain cholinergic system in Alzheimer's disease. Neurosci. Biobehav. Rev. 150, 105192. https://doi.org/10.1016/j.neubiorev.2023.105192.

Bowles, S., Hickman, J., Peng, X., Williamson, W.R., Huang, R., Washington, K., Donegan, D., Welle, C.G., 2022. Vagus nerve stimulation drives selective circuit modulation through cholinergic reinforcement. Neuron 110, 2867–2885 e7. https://doi.org/10.1016/j.neuron.2022.06.017.

Briand, L.A., Gritton, H., Howe, W.M., Young, D.A., Sarter, M., 2007. Modulators in concert for cognition: modulator interactions in the prefrontal cortex. Prog. Neurobiol. 83, 69–91. https://doi.org/10.1016/j.pneurobio.2007.06.007.

Buzsáki, G., Tingley, D., 2023. Cognition from the body-brain partnership: exaptation of memory. Annu. Rev. Neurosci. 46, 191–210. https://doi.org/10.1146/annurev-neuro-101222-110632.

Cahill, L., Prins, B., Weber, M., McGaugh, J.L., 1994. β-Adrenergic activation and memory for emotional events. Nature 371, 702–704. https://doi.org/10.1038/371702a0.

Caramazza, A., Anzellotti, S., Strnad, L., Lingnau, A., 2014. Embodied cognition and mirror neurons: a critical assessment. Annu. Rev. Neurosci. 37, 1–15. https://doi.org/10.1146/annurev-neuro-071013-013950.

Chakravarthy, K., Nava, A., Christo, P.J., Williams, K., 2016. Review of recent advances in peripheral nerve stimulation (PNS). Curr. Pain Headache Rep. 20. https://doi.org/10.1007/s11916-016-0590-8.

Chang, Q., Savage, L.M., Gold, P.E., 2006. Microdialysis measures of functional increases in ACh release in the hippocampus with and without inclusion of acetylcholinesterase inhibitors in the perfusate. J. Neurochem. 97, 697–706. https://doi.org/10.1111/j.1471-4159.2006.03765.x.

Chatterjee, A., 2004. Cosmetic neurology. Neurology 63, 968–974. https://doi.org/10.1212/01.WNL.0000138438.88589.7C.

Chougule, P.S., Najjar, R.P., Finkelstein, M.T., Kandiah, N., Milea, D., 2019. Light-induced pupillary responses in Alzheimer's disease. Front. Neurol. 10, 1–12. https://doi.org/10.3389/fneur.2019.00360.

Clark, K.B., Naritoku, D.K., Smith, D.C., Browning, R.A., Jensen, R.A., 1999. Enhanced recognition memory following vagus nerve stimulation in human subjects. Nat. Neurosci. 2, 94–98. https://doi.org/10.1038/4600.

Coffey, G.H., Mahon, M.V., 1982. Pain: theories and a new approach to treatment. J. Natl. Med. Assoc. 74, 147–153.

De Bartolo, M.I., Belvisi, D., Mancinelli, R., Costanzo, M., Caturano, C., Leodori, G., Berardelli, A., Fabbrini, G., Vivacqua, G., 2024. A systematic review of salivary biomarkers in Parkinson's disease. Neural Regen. Res. 19, 2613–2625. https://doi.org/10.4103/NRR.NRR-D-23-01677.

de los Angeles, G.A.M., del Carmen, R.O.M., Wendy, P.M., Socorro, R.M., 2016. Tactile stimulation effects on hippocampal neurogenesis and spatial learning and memory in prenatally stressed rats. Brain Res. Bull. 124, 1–11. https://doi.org/10.1016/j.brainresbull.2016.03.003.

Deer, T.R., Naidu, R., Strand, N., Sparks, D., Abd-Elsayed, A., Kalia, H., Hah, J.M., Mehta, P., Sayed, D., Gulati, A., 2020. A review of the bioelectronic implications of stimulation of the peripheral nervous system for chronic pain conditions. Bioelectron. Med. 6. https://doi.org/10.1186/s42234-020-00045-5.

Dekosky, S.T., Ikonomovic, M.D., Styren, S.D., Beckett, L., Wisniewski, S., Bennett, D.A., Cochran, E.J., Kordower, J.H., Mufson, E.J., 2002. Upregulation of choline acetyltransferase activity in hippocampus and frontal cortex of elderly subjects with mild cognitive impairment. Ann. Neurol. 51, 145–155. https://doi.org/10.1002/ana.10069.

Dudar, J.D., Whishaw, I.Q., Szerb, J.C., 1979. Release of acetylcholine from the hippocampus of freely moving rats during sensory stimulation and running. Neuropharmacology 18, 673–678. https://doi.org/10.1016/0028-3908(79)90034-0.

Durstewitz, D., Seamans, J.K., 2008. The dual-state theory of prefrontal cortex dopamine function with relevance to catechol-O-methyltransferase genotypes and schizophrenia. Biol. Psychiatry 64, 739–749. https://doi.org/10.1016/j.biopsych.2008.05.015.

Dutar, P., Lamour, Y., Jobert, A., 1985. Activation of identified septo-hippocampal neurons by noxious peripheral stimulation. Brain Res. 328, 15–21. https://doi.org/10.1016/0006-8993(85)91317-4.

Faress, I., Khalil, V., Hou, W.-H., Moreno, A., Andersen, N., Fonseca, R., Piriz, J., Capogna, M., Nabavi, S., 2024. Non-Hebbian plasticity transforms transient experiences into lasting memories. Elife 12, 1–21. https://doi.org/10.7554/eLife.91421.

Femenía, T., Giménez-Cassina, A., Codeluppi, S., Fernández-Zafra, T., Katsu-Jiménez, Y., Terrando, N., Eriksson, L.I., Gómez-Galán, M., 2018. Disrupted neuroglial metabolic coupling after peripheral surgery. J. Neurosci. 38, 452–464. https://doi.org/10.1523/JNEUROSCI.1797-17.2017.

Ficarella, S.C., 2024. Non-invasive modulation of brain activity during human-machine interactions. In: Santoianni, F., Giannini, G., Ciasullo, A. (Eds.), Mind, Body, and Digital Brains. Springer Nature Switzerland, pp. 157–171. https://doi.org/10.1007/978-3-031-58363-6_11.

Foglia, L., Wilson, R.A., 2013. Embodied cognition. WIREs Cognit. Sci. 4, 319–325. https://doi.org/10.1002/wcs.1226.

Francis, J., Dingley, J., 2015. Electroanaesthesia - from torpedo fish to TENS. Anaesthesia 70, 93–103. https://doi.org/10.1111/anae.12887.

Frey, U., Morris, R.G.M., 1997. Synaptic tagging and long-term potentiation. Nature 385, 533–536. https://doi.org/10.1038/385533a0.

Froeliger, B., Gilbert, D.G., McClernon, F.J., 2009. Effects of nicotine on novelty detection and memory recognition performance: double-blind, placebo-controlled studies of smokers and nonsmokers. Psychopharmacology 205, 625–633. https://doi.org/10.1007/s00213-009-1571-y.

Gallese, V., 2005. Embodied simulation: from neurons to phenomenal experience. Phenomenol. Cogn. Sci. 4, 23–48. https://doi.org/10.1007/s11097-005-4737-z.

Gallese, V., Cuccio, V., 2018. The neural exploitation hypothesis and its implications for an embodied approach to language and cognition: insights from the study of action verbs processing and motor disorders in Parkinson's disease. Cortex 100, 215–225. https://doi.org/10.1016/j.cortex.2018.01.010.

Gallese, V., Lakoff, G., 2005. The Brain's concepts: the role of the sensory-motor system in conceptual knowledge. Cogn. Neuropsychol. 22, 455–479. https://doi.org/10.1080/02643290442000310.

Gasbarri, A., Sulli, A., Packard, M.G., 1997. The dopaminergic mesencephalic projections to the hippocampal formation in the rat. Prog. Neuro-Psychopharmacol. Biol. Psychiatry 21, 1–22. https://doi.org/10.1016/S0278-5846(96)00157-1.

Geminiani, G., Bottini, G., 1992. Mental representation and temporary recovery from unilateral neglect after vestibular stimulation. J. Neurol. Neurosurg. Psychiatry 55, 332–333. https://doi.org/10.1136/jnnp.55.4.332-a.

Goroszeniuk, T., Pang, D., 2014. Peripheral neuromodulation: a review. Curr. Pain Headache Rep. 18. https://doi.org/10.1007/s11916-014-0412-9.

Grion, N., Akrami, A., Zuo, Y., Stella, F., Diamond, M.E., 2016. Coherence between rat sensorimotor system and Hippocampus is enhanced during tactile discrimination. PLoS Biol. 14, 1–26. https://doi.org/10.1371/journal.pbio.1002384.

Groenewegen, H.J., Berendse, H.W., 1994. The specificity of the 'nonspecific' midline and intralaminar thalamic nuclei. Trends Neurosci. 17, 52–57. https://doi.org/10.1016/0166-2236(94)90074-4.

Guariglia, C., Lippolis, G., Pizzamiglio, L., 1998. Somatosensory stimulation improves imagery disorders in neglect. Cortex 34, 233–242. https://doi.org/10.1016/s0010-9452(08)70750-0.

Guo, Y., Shi, X., Uchiyama, H., Hasegawa, A., Nakagawa, Y., Tanaka, M., Fukumoto, I., 2002. A study on the rehabilitation of cognitive function and short-term memory in patients with Alzheimer's disease using transcutaneous electrical nerve stimulation. Front. Med. Biol. Eng. 11, 237–247. https://doi.org/10.1163/156855701321138905.

Guo, B., Zhang, M., Hao, W., Wang, Y., Zhang, T., Liu, C., 2023. Neuroinflammation mechanisms of neuromodulation therapies for anxiety and depression. Transl. Psychiatry 13, 5. https://doi.org/10.1038/s41398-022-02297-y.

Hamilton, R., Messing, S., Chatterjee, A., 2011. Rethinking the thinking cap: ethics of neural enhancement using noninvasive brain stimulation. Neurology 76, 187–193. https://doi.org/10.1212/WNL.0b013e318205d50d.

Han, J.S., 2003. Acupuncture: neuropeptide release produced by electrical stimulation of different frequencies. Trends Neurosci. 26, 17–22. https://doi.org/10.1016/S0166-2236(02)00006-1.

Hasselmo, M.E., 2006. The role of acetylcholine in learning and memory. Curr. Opin. Neurobiol. 16, 710–715. https://doi.org/10.1016/j.conb.2006.09.002.

Hassert, D.L., Miyashita, T., Williams, C.L., 2004. The effects of peripheral vagal nerve stimulation at a memory-modulating intensity on norepinephrine output in the basolateral amygdala. Behav. Neurosci. 118, 79–88. https://doi.org/10.1037/0735-7044.118.1.79.

Helm, S., Shirsat, N., Calodney, A., Abd-Elsayed, A., Kloth, D., Soin, A., Shah, S., Trescot, A., 2021. Peripheral nerve stimulation for chronic pain: a systematic review of effectiveness and safety. Pain Ther. 10, 985–1002. https://doi.org/10.1007/s40122-021-00306-4.

Hensel, A., Angermeyer, M.C., Riedel-Heller, S.G., 2007. Measuring cognitive change in older adults: reliable change indices for the Mini-mental state examination. J. Neurol. Neurosurg. Psychiatry 78, 1298–1303. https://doi.org/10.1136/jnnp.2006.109074.

Hwang, K., Bertolero, M.A., Liu, W.B., D'Esposito, M., 2017. The human thalamus is an integrative hub for functional brain networks. J. Neurosci. 37, 5594–5607. https://doi.org/10.1523/JNEUROSCI.0067-17.2017.
Ianì, F., 2019. Embodied Memories: Reviewing the Role of the Body in Memory Processes 1747–1766.
Ianì, F., 2022. Il corpo nella psicologia cognitiva. Psicoter. Psicoanal. 157–172. https://doi.org/10.3280/psp2022-001012.
Jayamohananan, H., Manoj Kumar, M.K., T P, A., 2019. 5-HIAA as a potential biological marker for neurological and psychiatric disorders. Adv. Pharm. Bull. 9, 374–381. https://doi.org/10.15171/apb.2019.044.
Johnson, M., 2007. Transcutaneous electrical nerve stimulation: mechanisms, clinical application and evidence. Rev. Pain 1, 7–11. https://doi.org/10.1177/204946370700100103.
Jonsdottir, S., Bouma, A., Sergeant, J.A., Scherder, E.J.A., 2004. Effects of transcutaneous electrical nerve stimulation (TENS) on cognition, behavior, and the rest-activity rhythm in children with attention deficit hyperactivity disorder, Combined Type. Neurorehabil. Neural Repair 18, 212–221. https://doi.org/10.1177/1545968304270759.
Joshi, S., Li, Y., Kalwani, R.M., Gold, J.I., 2016. Relationships between pupil diameter and neuronal activity in the locus coeruleus, colliculi, and cingulate cortex. Neuron 89, 221–234. https://doi.org/10.1016/j.neuron.2015.11.028.
Karson, C.N., 1983. Spontaneous eye-blink rates and dopaminergic systems. Brain 106, 643–653. https://doi.org/10.1093/brain/106.3.643.
Kaufman, A.S., 1975. Factor analysis of the WISC-R at 11 age levels between 61/2 and 161/2 years. J. Consult. Clin. Psychol. 43, 135–147. https://doi.org/10.1037/h0076502.
Kline, R., Wong, E., Haile, M., Didehvar, S., 2016. Peri-operative inflammatory cytokines in plasma of the elderly correlate in prospective study with postoperative changes in cognitive test scores. Int. J. Anesthesiol. Res. 176, 313–321. https://doi.org/10.19070/2332-2780-1600065.
Le, Y., Liu, S., Peng, M., Tan, C., Liao, Q., Duan, K., Ouyang, W., Tong, J., 2014. Aging differentially affects the loss of neuronal dendritic spine, Neuroinflammation and memory impairment at rats after surgery. PLoS One 9, e106837. https://doi.org/10.1371/journal.pone.0106837.
Lin, I., Wiles, L., Waller, R., Goucke, R., Nagree, Y., Gibberd, M., Straker, L., Maher, C.G., O'Sullivan, P.P.B., 2020. What does best practice care for musculoskeletal pain look like? Eleven consistent recommendations from high-quality clinical practice guidelines: systematic review. Br. J. Sports Med. 54, 79–86. https://doi.org/10.1136/bjsports-2018-099878.
Liu, T., Yin, C., Li, Y., Gao, F., Yu, L., Wang, Z., Wang, Q., 2021. Effects of transcutaneous electrical acupoint stimulation on postoperative cognitive decline in elderly patients: a pilot study. Clin. Interv. Aging 16, 757–765. https://doi.org/10.2147/CIA.S309082.
Luckey, A.M., McLeod, S.L., Robertson, I.H., To, W.T., Vanneste, S., 2020a. Greater occipital nerve stimulation boosts associative memory in older individuals: a randomized trial. Neurorehabil. Neural Repair 34, 1020–1029. https://doi.org/10.1177/1545968320943573.
Luckey, A.M., McLeod, S.L., Robertson, I.H., To, W.T., Vanneste, S., 2020b. Greater occipital nerve stimulation boosts associative memory in older individuals: a randomized trial. Neurorehabil. Neural Repair 34, 1020–1029. https://doi.org/10.1177/1545968320943573.
Luckey, A.M., McLeod, S.L., Mohan, A., Vanneste, S., 2022. Potential role for peripheral nerve stimulation on learning and long-term memory: a comparison of alternating and direct current stimulations. Brain Stimul. 15, 536–545. https://doi.org/10.1016/j.brs.2022.03.001.
Luckey, A.M., Adcock, K., Vanneste, S., 2023a. Peripheral nerve stimulation: a neuromodulation-based approach. Neurosci. Biobehav. Rev. 149, 105180. https://doi.org/10.1016/j.neubiorev.2023.105180.
Luckey, A.M., McLeod, L.S., Huang, Y., Mohan, A., Vanneste, S., 2023b. Making memories last using the peripheral effect of direct current stimulation. Elife 12, 1–36. https://doi.org/10.7554/eLife.75586.
Luijpen, M.W., Swaab, D.F., Sergeant, J.A., Van Dijk, K.R.A., Scherder, E.J.A., 2005. Effects of transcutaneous electrical nerve stimulation (TENS) on memory in elderly with mild cognitive impairment. Behav. Brain Res. 158, 349–357. https://doi.org/10.1016/j.bbr.2004.09.017.
McGinley, M.J., Lee, S.T., 2022. Why study mechanisms of brain stimulation therapies? To modulate the right neurons, in the right way, at the right time. Neuron 110, 2709–2712. https://doi.org/10.1016/j.neuron.2022.08.004.
Megemont, M., McBurney-Lin, J., Yang, H., 2022. Pupil diameter is not an accurate realtime readout of locus coeruleus activity. Elife 11, 1–17. https://doi.org/10.7554/ELIFE.70510.
Melzack, R., Wall, P.D., 1965. Pain mechanisms: a new theory. Science (80) 150, 971–979.
Meneses, A., Perez-Garcia, G., 2007. 5-HT1A receptors and memory. Neurosci. Biobehav. Rev. 31, 705–727. https://doi.org/10.1016/j.neubiorev.2007.02.001.
Mikaitis, M., Pineda García, G., Knight, J.C., Furber, S.B., 2018. Neuromodulated synaptic plasticity on the SpiNNaker neuromorphic system. Front. Neurosci. 12, 1–13. https://doi.org/10.3389/fnins.2018.00105.
Mineur, Y.S., Picciotto, M.R., 2023. How can I measure brain acetylcholine levels in vivo? Advantages and caveats of commonly used approaches. J. Neurochem. 167, 3–15. https://doi.org/10.1111/jnc.15943.
Miyashita, T., Williams, C.L., 2004. Peripheral arousal-related hormones modulate norepinephrine release in the hippocampus via influences on brainstem nuclei. Behav. Brain Res. 153, 87–95. https://doi.org/10.1016/j.bbr.2003.11.005.
Mohr, P., Rodriguez, M., Slavíčková, A., Hanka, J., 2011. The application of Vagus nerve stimulation and deep brain stimulation in depression. Neuropsychobiology 64, 170–181. https://doi.org/10.1159/000325225.
Nasreddine, Z.S., Phillips, N.A., Bédirian, V., Charbonneau, S., Whitehead, V., Collin, I., Cummings, J.L., Chertkow, H., 2005. The Montreal cognitive assessment, MoCA: a brief screening tool for mild cognitive impairment. J. Am. Geriatr. Soc. 53, 695–699. https://doi.org/10.1111/j.1532-5415.2005.53221.x.
Nicoll, R.A., 1985. The septo-hippocampal projection: a model cholinergic pathway. Trends Neurosci. 8, 533–536. https://doi.org/10.1016/0166-2236(85)90190-0.
Niederhauser, B.D., Rosenbaum, B.P., Gore, J.C., Jarquin-Valdivia, A.A., 2008. A functional near-infrared spectroscopy study to detect activation of somatosensory cortex by peripheral nerve stimulation. Neurocrit. Care. 9, 31–36. https://doi.org/10.1007/s12028-007-9022-2.
Nielson, K.A., Jensen, R.A., 1994. Beta-adrenergic receptor antagonist antihypertensive medications impair arousal-induced modulation of working memory in elderly humans. Behav. Neural Biol. 62, 190–200. https://doi.org/10.1016/S0163-1047(05)80017-2.
Ong Sio, L.C., Hom, B., Garg, S., Abd-Elsayed, A., 2023. Mechanism of action of peripheral nerve stimulation for chronic pain: a narrative review. Int. J. Mol. Sci. 24, 4540. https://doi.org/10.3390/ijms24054540.
Ottestad, E., Orlovich, D.S., 2020. History of peripheral nerve stimulation - update for the 21st century. Pain Med. (United States) 21, S3–S5. https://doi.org/10.1093/PM/PNAA165.
Pereira, A., Ribeiro, S., Wiest, M., Moore, L.C., Pantoja, J., Lin, S.C., Nicolelis, M.A.L., 2007. Processing of tactile information by the hippocampus. Proc. Natl. Acad. Sci. USA 104, 18286–18291. https://doi.org/10.1073/pnas.0708611104.
Petrakova, L., Boy, K., Mittmann, L., Möller, L., Engler, H., Schedlowski, M., 2017. Salivary alpha-amylase and noradrenaline responses to corticotropin-releasing hormone administration in humans. Biol. Psychol. 127, 34–39. https://doi.org/10.1016/j.biopsycho.2017.04.016.
Philp, D.J., Korgaonkar, M.S., Grieve, S.M., 2014. Thalamic volume and thalamo-cortical white matter tracts correlate with motor and verbal memory performance. Neuroimage 91, 77–83. https://doi.org/10.1016/j.neuroimage.2013.12.057.
Portenoy, R.K., Itri, L.M., 1999. Cancer-related fatigue: guidelines for evaluation and management. Oncologist 4, 1–10. https://doi.org/10.1634/theoncologist.4-1-1.
Rorsman, I., Johansson, B., 2006. Can electroacupuncture or transcutaneous nerve stimulation influence cognitive and emotional outcome after smoke? J. Rehabil. Med. 38, 13–19. https://doi.org/10.1080/16501970510040362.
Sara, S.J., 2009. The locus coeruleus and noradrenergic modulation of cognition. Nat. Rev. Neurosci. 10, 211–223. https://doi.org/10.1038/nrn2573.
Sara, S.J., Roullet, P., Przybyslawski, J., 1999. Consolidation of memory for odor–reward association: β-adrenergic receptor involvement in the late phase. Learn. Mem. 6, 88–96. https://doi.org/10.1101/lm.6.2.88.
Saricaoglu, M., Hanoglu, L., Guntekin, B., Ozkara, C., 2023. The effects of cognitive, physical, and somatosensory rehabilitation after right temporo-parietal tumor resection on cognitive, motor, somatosensory, and electrophysiological parameters: a case report. Physiother. Theory Pract. 39, 2241–2250. https://doi.org/10.1080/09593985.2022.2064787.
Scherder, E.J., Bouma, A., 1999. Effects of transcutaneous electrical nerve stimulation on memory and behavior in Alzheimer's disease may be stage-dependent. Biol. Psychiatry 45, 743–749. https://doi.org/10.1016/S0006-3223(98)00072-9.
Scherder, E., Bouma, A., Steen, L., 1995. Effects of simultaneously applied short-term transcutaneous electrical nerve stimulation and tactile stimulation on memory and affective behaviour of patients with probable alzheimer's disease. Behav. Neurol. 8, 3–13. https://doi.org/10.1155/1995/825651.
Scherder, E., Bouma, A., Steen, L., 1998. Effects of peripheral tactile nerve stimulation on affective behavior of patients with probable Alzheimer's disease. Am. J. Alzheimers Dis. 13, 61–69. https://doi.org/10.1177/153331759801300203.
Scherder, E.J.A., Van Someren, E.J.W., Bouma, A.V.D., Berg, M., 2000. Effects of transcutaneous electrical nerve stimulation (TENS) on cognition and behaviour in aging. Behav. Brain Res. 111, 223–225. https://doi.org/10.1016/S0166-4328(00)00170-4.
Schultz, W., 1997. Dopamine neurons and their role in reward mechanisms. Curr. Opin. Neurobiol. 7, 191–197. https://doi.org/10.1016/S0959-4388(97)80007-4.
Schwarz, L.A., Luo, L., 2015. Organization of the locus coeruleus-norepinephrine system. Curr. Biol. 25, R1051–R1056. https://doi.org/10.1016/j.cub.2015.09.039.
Shu, J., Ren, W., Chen, S., Li, L., Zhu, H., Jin, A., 2022. Effect of somatosensory interaction transcutaneous electrical Acupoint stimulation on Cancer-related fatigue and immunity: a randomized controlled trial. Am. J. Clin. Oncol. Cancer Clin. Trials 45, 316–324. https://doi.org/10.1097/COC.0000000000000922.
Soreq, H., Seidman, S., 2001. Acetylcholinesterase — new roles for an old actor. Nat. Rev. Neurosci. 2, 294–302. https://doi.org/10.1038/35067589.
Strand, N.H., D'Souza, R., Wie, C., Covington, S., Maita, M., Freeman, J., Maloney, J., 2021. Mechanism of action of peripheral nerve stimulation. Curr. Pain Headache Rep. 25, 47. https://doi.org/10.1016/B978-0-323-83007-2.00003-5.
Teoli, D., An, J., 2023. Transcutaneous electrical nerve stimulation. NIH. Natl. Libr. Med. 193–205. https://doi.org/10.1201/b13562-17.
Torromino, G., 2024. In: Santoianni, F., Giannini, G., Ciasullo, A. (Eds.), Mind, Body, and Digital Brains. Integrated Science, 20. Springer, Cham. https://doi.org/10.1007/978-3-031-58363-6_12.
Torromino, G., Maggi, A., De Leonibus, E., 2021. Estrogen-dependent hippocampal wiring as a risk factor for age-related dementia in women. Prog. Neurobiol. 197, 101895. https://doi.org/10.1016/j.pneurobio.2020.101895.
Torromino, G., Loffredo, V., Cavezza, D., Sonsini, G., Esposito, F., Crevenna, A.H., Gioffrè, M., De Risi, M., Treves, A., Griguoli, M., De Leonibus, E., 2022. Thalamo-

hippocampal pathway regulates incidental memory capacity in mice. Nat. Commun. 13, 1–14. https://doi.org/10.1038/s41467-022-31781-8.
Van Dijk, K.R.A., Scheltens, P., Luijpen, M.W., Sergeant, J.A., Scherder, E.J.A., 2005. Peripheral electrical stimulation in alzheimer's disease: a randomized controlled trial on cognition and behavior. Dement. Geriatr. Cogn. Disord. 19, 361–368. https://doi.org/10.1159/000084706.
van Stegeren, A.H., Wolf, O.T., Everaerd, W., Scheltens, P., Barkhof, F., Rombouts, S.A.R. B., 2007. Endogenous cortisol level interacts with noradrenergic activation in the human amygdala. Neurobiol. Learn. Mem. 87, 57–66. https://doi.org/10.1016/j.nlm.2006.05.008.
Vanneste, S., Mohan, A., Yoo, H. Bin, Huang, Y., Luckey, A.M., Lauren McLeod, S., Tabet, M.N., Souza, R.R., McIntyre, C.K., Chapman, S., Robertson, I.H., To, W.T., 2020. The peripheral effect of direct current stimulation on brain circuits involving memory. Sci. Adv. 6, 1–19. https://doi.org/10.1126/SCIADV.AAX9538.
Varela, F.J., Thompson, E., Rosch, E., 1991. The Embodied Mind: Cognitive Science and Human Experience. The MIT Press.
Vetere, G., Xia, F., Ramsaran, A.I., Tran, L.M., Josselyn, S.A., Frankland, P.W., 2021. An inhibitory hippocampal–thalamic pathway modulates remote memory retrieval. Nat. Neurosci. 24, 685–693. https://doi.org/10.1038/s41593-021-00819-3.
Wagatsuma, A., Okuyama, T., Sun, C., Smith, L.M., Abe, K., Tonegawa, S., 2017. Locus coeruleus input to hippocampal CA3 drives single-trial learning of a novel context. Proc. Natl. Acad. Sci. USA 115, E310–E316. https://doi.org/10.1073/pnas.1714082115.
Wang, J.Q., Mao, L., Han, J.-S., 1992. Comparison of the Antinociceptive effects induced by Electroacupuncture and transcutaneous electrical nerve stimulation in the rat. Int. J. Neurosci. 65, 117–129. https://doi.org/10.3109/00207459209003283.
Wang, Y., He, H., Li, D., Zhu, W., Duan, K., Le, Y., Liao, Y., Ou, Y., 2013. The role of the TLR4 signaling pathway in cognitive deficits following surgery in aged rats. Mol. Med. Rep. 7, 1137–1142. https://doi.org/10.3892/mmr.2013.1322.
Wang, L.-H., Ding, W.-Q., Sun, Y.-G., 2022a. Spinal ascending pathways for somatosensory information processing. Trends Neurosci. 45, 594–607. https://doi.org/10.1016/j.tins.2022.05.005.
Wang, L.F., Liang, W.D., Wang, B.Y., Guo, M.L., Zhou, J.S., Chen, L., Zhong, M.L., Ye, J. M., 2022b. Transcutaneous electrical acupoint stimulation for reducing cognitive dysfunction in lumbar spine surgery: a randomized, controlled trail. Front. Aging Neurosci. 14, 1–10. https://doi.org/10.3389/fnagi.2022.1034998.
Wechsler, D., 1974. Manual for the Wechsler Intelligence Scale for Children-Revised. The Psychological Corporation, San Antonio.
Wei, H., Huang, J. Sheng, Zhao, F., Xie, Z. Qiang, Xia, Z. Yang, Gan, J. Hui, 2022. Transcutaneous electrical Acupoint stimulation improves postoperative cognitive function in senior patients undergoing video-assisted Thoracoscopic surgery: a randomized controlled trial. Chin. J. Integr. Med. 28, 730–735. https://doi.org/10.1007/s11655-022-3516-1.
Xi, L., Fang, F., Yuan, H., Wang, D., 2021. Transcutaneous electrical acupoint stimulation for postoperative cognitive dysfunction in geriatric patients with gastrointestinal tumor: a randomized controlled trial. Trials 22, 1–10. https://doi.org/10.1186/s13063-021-05534-9.
Xie, L., Liu, Y., Zhang, N., Li, C., Sandhu, A.F., Williams, G., Shen, Y., Li, H., Wu, Q., Yu, S., 2021. Electroacupuncture improves M2 microglia polarization and glia anti-inflammation of Hippocampus in Alzheimer's disease. Front. Neurosci. 15, 1–12. https://doi.org/10.3389/fnins.2021.689629.
Xu, W., Südhof, T.C., 2013. A neural circuit for memory specificity and generalization. Science (80) 339, 1290–1296.
Yap, J.Y.Y., Keatch, C., Lambert, E., Woods, W., Stoddart, P.R., Kameneva, T., 2020. Critical review of transcutaneous Vagus nerve stimulation: challenges for translation to clinical practice. Front. Neurosci. 14. https://doi.org/10.3389/fnins.2020.00284.
Yerkes, R.M., Dodson, J.D., 1908. The relation of strength of stimulus to rapidity of habit-formation. J. Comp. Neurol. Psychol. 18, 459–482. https://doi.org/10.1002/cne.920180503.
Zacková, M.L., Jáni, M.M., Brázdil, M., Nikolova, Y.S., Marečková, K., 2021. Cognitive impairment and depression: Meta-analysis of structural magnetic resonance imaging studies. NeuroImage Clin. 32. https://doi.org/10.1016/j.nicl.2021.102830.
Zhang, T., Mou, D., Wang, C., Tan, F., Jiang, Y., Lijun, Z., Li, H., 2015. Dopamine and executive function: increased spontaneous eye blink rates correlate with better set-shifting and inhibition, but poorer updating. Int. J. Psychophysiol. 96, 155–161. https://doi.org/10.1016/j.ijpsycho.2015.04.010.
Zhou, Y., Yang, H., You, M., Feng, Z., Dong, X., 2024. Cognition-enhancement effect of median nerve electrical stimulation in patients with cognitive impairment: a retrospective cohort study. World Neurosurg. 184, e537–e545. https://doi.org/10.1016/j.wneu.2024.01.165.