

Review



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The heart side of brain neuromodulation

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Neuromodulation refers to invasive, minimally invasive or non-invasive techniques to stimulate discrete cortical or subcortical brain regions with therapeutic purposes in otherwise intractable patients: for example, thousands of advanced Parkinsonian patients, as well as patients with tremor or dystonia, benefited by deep brain stimulation (DBS) procedures (neural targets: basal ganglia nuclei). A new era for DBS is currently opening for patients with drug-resistant depression, obsessive-compulsive disorders, severe epilepsy, migraine and chronic pain (neural targets: basal ganglia and other subcortical nuclei or associative fibres). Vagal nerve stimulation (VNS) has shown clinical benefits in patients with pharmaco-resistant epilepsy and depression. Non-invasive brain stimulation neuromodulatory techniques such as repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS) are also being increasingly investigated for their therapeutic potential in several neurological and psychiatric disorders. In this review, we first address the most common neural targets of each of the mentioned brain stimulation techniques,

and the known mechanisms of their neuromodulatory action on stimulated brain networks. Then, we discuss how DBS, VNS, rTMS and tDCS could impact on the function of brainstem centres controlling vital functions, critically reviewing their acute and long-term effects on brain sympathetic outflow controlling heart function and blood pressure. Finally, as there is clear experimental evidence in animals that brain stimulation can affect autonomic and heart functions, we will try to give a critical perspective on how it may enhance our understanding of the cortical/subcortical mechanisms of autonomic cardiovascular regulation, and also if it might find a place among therapeutic opportunities in patients with otherwise intractable autonomic dysfunctions.

1. Introduction

The last three decades have seen the impressive growth of the brain neuromodulation field, which is a form a targeted, reversible, electrical stimulation of the brain able to induce long-lasting changes of firing neural properties, thereby modifying behaviour. Brain neuromodulation, which usually assists—but does not replace—traditional pharmacological treatments, can be achieved either by invasive (deep brain stimulation, DBS), by minimally invasive (vagal nerve stimulation, VNS) or by non-invasive techniques such as repetitive transcranial magnetic stimulation (rTMS) or transcranial direct current stimulation (tDCS).

As discussed in detail in another article in this theme issue [1], an extensive portion of the autonomic nervous system is located intracranially: briefly, afferent pathways from the thoracolumbar sympathetic system, to which cardiac afferents belong, converge into the nucleus of the solitary tract in the medulla oblongata. This nucleus is an important relay station, because it receives complex reciprocal connections with the other components of the intracranial autonomic network, and is the place where a sympathetic or parasympathetic outflow is coded in response to a variety of afferent stimuli (i.e. emotional, chemical, attentional, motivational, etc.). This is particularly effective in modulating blood pressure and cardiac rate during physical exercise [2], under the top-down, feed-forward, ‘supervision’ of central commands originating at different levels (i.e. cortical and subcortical) of the central nervous system: functional neuroimaging demonstrated the involvement of anterior cingulate cortex, insula and thalamus in this complex function [3–5].

Therefore, although neuromodulatory interventions are generally targeted on discrete cortical (rTMS and tDCS) or subcortical regions (DBS), or afferent fibres (VNS), the resulting behavioural effect may impact on the function of brainstem centres controlling vital functions, such as the cardiovascular ones (table 1). Each target, indeed, is a relay node of a network, whose activity is somewhat altered by the stimulation, and this perturbation may have trans-synaptic or system-level effects including vital nervous centres. This aspect has been relatively underinvestigated, but deserves attention for the potential relevance of side effects of neuromodulatory interventions, for enhancing our understanding of the cortical/subcortical mechanisms of autonomic regulation of cardiovascular function, as well as for the possibility to design new therapeutic strategies in patients with otherwise intractable autonomic dysfunctions.

2. Deep brain stimulation

Invasive neuromodulation through electrodes placed in different subcortical nuclei or structures, or DBS, is an established therapeutic option for selected patients with advanced Parkinson’s disease (PD) [6,7], tremor of different aetiologies [8–10], as well as for other otherwise intractable movement disorders such as dystonia [11,12] and Tourette syndrome [13]. DBS is also an emerging approach to treat pharmacoresistant epilepsy [14], migraine and other chronic pain syndromes, or severe psychiatric disorders such as depression and obsessive-compulsive disorder (see [15] for an exhaustive review).

Table 1. Main characteristics, autonomic effects and potential clinical utility of the different neuromodulatory techniques. OCD, obsessive-compulsive disorder; HR, heart rate; BP, blood pressure; STN, subthalamic nucleus; Th, thalamus; PV/PAG, periventricular-periaqueductal grey matter.

	DBS	VNS	transcutaneous VNS	rTMS	tDCS
invasivity	+++	+++	no	no	no
safety/main side effects	surgical risk: acute and chronic side effects are possible in motor and cognitive domains	minimal surgical risk: dysarthria with stimulation	no	very rare seizure induction; transient headache often reported	slight transient itching on the stimulation site
targets	subcortical grey nuclei or associative fibres, depending on the disease	left vagus nerve at cervical level	periauricular vagus nerve terminals	any cortical area, focally, depending on the goal	any cortical region, depending on the goal
treatments approved by international regulatory agencies	Parkinson; tremors; dystonia; Tourette and OCD (depression; chronic pain)	refractory epilepsy (even in children) and pharmacoresistant depression		drug-resistant depression; chronic neuropathic pain	none yet
treatment duration	chronic	chronic	chronic	one month (with daily sessions), the longest treatment described	one month (with daily sessions), the longest application described
autonomic side effects	modest HR increase (STN, Th); more consistent, intranucleus-dependent, BP changes (PV/PAG)	sympatholytic/vagotonic effects on HR		short-lasting increase of HR and BP during high-frequency rTMS	Possible increase of sympathetic tone along anodal-tDCS stimulation
possible clinical utility in autonomic dysfunctions	STN; Th: regulation of postural hypotension PV/PAG: anti-hypertensive effect	malignant ventricular arrhythmias, especially if associated with ischaemic coronary artery diseases		no persistent autonomic changes described so far	
<i>comment</i>	most of the reported effects are based on relatively small studies, in patients primarily treated for other reasons than dysautonomia, in which HR and BP modifications were not included among the primary aims				

In DBS, extracellular direct currents of variable pulse frequency, intensity and width (20–200 Hz, 1–6 V, 60–120 μ s) are chronically applied through reversible leads indwelled into deep grey nuclei and connected via subcutaneous cables to a controllable internal pulse generator [16]. The mechanisms of action of DBS are multiple and complex, and they are not fully known yet: the basic concept is that electrical stimulation, especially at higher frequencies above 100 Hz, resembles the same inhibitory effect of a destructive neural lesion [17–19]. Neurophysiologically, there is clear evidence of either local or system effects: the former are mainly a consequence of excitation/inhibition of both afferent and efferent axonal fibres, rather than the body cell [20]. System effects [21] imply that DBS modifies the dynamics of the whole network connected with the discrete region being stimulated ([19]; see [15,22] for reviews): possible mechanisms accounting for this effect are synaptic inhibition [18] and the so-called jamming that is a masking of pathological oscillatory signals [23].

Although more than 40 different neural targets have so far been described for DBS treatments of several neurological and psychiatric diseases [21], most of the cardiovascular effects have emerged after implants of the subthalamic nucleus (STN) and internal globus pallidum (GPi) in PD patients, of periventricular–periaqueductal grey matter (PV/PAG) in patients with chronic pain syndromes, and of the hypothalamus (H) for cluster headache. The obvious reason is because (i) the great majority of implanted DBS patients worldwide have advanced PD (STN and GPi) and (ii) these targets are spatially close and/or functionally linked to brainstem vital structures. Moreover, the STN and the PV/PAG are relay stations connecting the limbic system with the motor cortex, and change their firing activity in parallel with exercise-related cardiovascular adaptations [24].

Priori *et al.* [25] showed some of the first evidence that STN DBS in PD patients influences sympathetic and cardiovascular reactivity: while the sympathetic skin response improved, plasma renin increased during DBS-OFF, but arterial blood pressure remained unchanged throughout the upright tilt test duration. Some acute autonomic effects have been observed during the first *reglage* phase of stimulus parameters after the DBS implant (i.e. the attempt to search the most clinically effective contacts and the threshold for side effects due to stimulus spread to neighbouring neural structures): in 88% of implanted STN PD patients, tachycardia arose within seconds after switching ON the STN stimulation, whereas hypertension arose within about 1 min [26]. Heart rate (HR) and mean arterial blood pressure (MAP) significantly increased after high-frequency (i.e. greater than 90 Hz) thalamic and STN—but not after GPi—stimulation in PD patients: changes were modest (HR increased by about 5 ± 3 beat per min; MAP increased by 5 ± 3 mmHg), but consistent across patients and, most importantly, not related to improvement of locomotor signs, suggesting that DBS of STN, thalamus and substantia nigra may activate autonomic central commands [27]. These data fit with the notion that postural hypotension may be improved by STN DBS in the long term, through the increase of peripheral vasoconstriction and baroreflex sensitivity, two factors helping to stabilize blood pressure [28]. However, it should be taken into account that patients with STN DBS (but not those with GPi DBS) usually can decrease the daily dosage of dopaminergic therapy, so that hypotension—a frequent side effect of this therapy—might improve independently by stimulation. In another study, the possibility to enhance sympathetic cardiac regulation was shown by means of HR variability spectral analysis, suggesting even a link between electrode positioning within the STN and HR cumulative effects [29]. However, cardiovascular dysautonomia linked with PD seems to be poorly affected by STN DBS [30], at variance with other autonomic disturbances that may instead improve in the long term after STN DBS (but all are small class IV studies; see [31]).

When the target of DBS is the PV/PAG, a midbrain nucleus with an important role in pain signalling and autonomic control, effects on blood pressure and cardiac function seem more consistent, at least in patients with intractable chronic pain. This target has been proposed as a new treatment option for postural hypotension, following experimental observations that sympathetic effects on blood pressure (i.e. increase or decrease) depend, respectively, on electrode location in the dorsal or ventral regions of the PV/PAG [32,33], and are possibly mediated by suppression or enhancement of the baroreceptor reflex activity [34,35]. Some human studies seem

to confirm this experimental evidence: Green *et al.* [36] showed that ventral PV/PAG DBS induced a mean reduction in systolic blood pressure of 14.2 ± 3.6 mmHg in 7/11 patients, whereas dorsal PV/PAG DBS caused a mean increase of 16.7 ± 5.9 mmHg in 6/11 patients; interestingly, these findings were accompanied by analogous changes in diastolic blood pressure, but not in R-R variability [36]. Hypotensive effects seem to be long-lasting (up to 1 year) and unrelated to pain relief [37,38]. These results were confirmed in successive studies carried out on patients who were hypertensive before the DBS implant [37–39]. Interestingly, the degree of analgesia induced by DBS of the rostral PAG was linearly related to the magnitude of reduction in arterial blood pressure [39].

The hypothalamus is the target of choice for DBS treatment for refractory cluster headache [40]. The involuntary stimulation of its posterior portion led to increase of blood pressure and respiratory rate in a PD patient [41]. Chronic DBS of the posterior H in chronic cluster headache patients is associated with an enhanced sympathoexcitatory drive on the cardiovascular system during the ‘head up tilt testing’, thereby suggesting that DBS at this level can improve cardiovascular autonomic function especially during orthostatic challenge [42].

In conclusion, all available data on cardiovascular effects of DBS are necessarily limited to patients in whom the cardiovascular autonomic dysfunction was not the primary aim for which DBS was carried out. Depending on the target, effects on blood pressure seem more consistent than those on HR, which are subtle and variable [27,39,43]. Although generalization of effects may be difficult because they are not representative of the general population, they provide an important translational step from the bench to the bedside [44].

The long-term effect of DBS on the ample constellation of non-motor symptoms in PD, including autonomic dysfunctions, is an emerging clinical issue [31]. Although autonomic effects of DBS have been recently regarded as a possible and tantalizing therapeutic opportunity [45], large ad hoc longitudinal studies in which autonomic functions are included among primary clinical endpoints are still required to fully translate this opportunity into a solid therapeutic option. Indeed, the expected benefits should overcome both the intrinsic risks and the limited—albeit present—adverse events of the DBS procedure [46].

3. Vagus nerve stimulation

VNS refers to any technique that stimulates the vagus nerve, representing another neuromodulatory opportunity of minimally invasive (or non-invasive) brain stimulation. Moreover, at variance with the other brain stimulation techniques (i.e. DBS, rTMS and tDCS), VNS offers a unique example of how stimulation of autonomic fibres may induce bidirectional effects at central (i.e. modulation of brain activity) and peripheral levels (i.e. cardiovascular effects). Through the anatomical and functional links between the vagus nerve and nucleus tractus solitarius, VNS may target diverse and widespread brain regions. Specifically, in animal experiments, VNS elicited synchronized activity in the orbital cortex [47] and slow waves in the lateral frontal cortex, anterior rhinal sulcus and amygdala [48]. Following this former evidence, VNS became a viable treatment option both in neurology and in psychiatry [49–51]. Nevertheless, disadvantages are related to intraoperative risks, such as lesions of the vagus nerve, or to infection, hoarseness, shortness of breath and the requirement for surgical intervention when the battery runs out [51–53]. Other respiratory complications may include vocal cord movement abnormalities, as well as sleep-related breathing pattern changes, with an associated increase in the number of obstructive apnoeas and hypopnoeas [54].

Therefore, an alternative, non-invasive method, called transcutaneous electrical stimulation of the sensory auricular branch of the vagus nerve, was investigated, and central effects verified by means of functional magnetic resonance imaging (MRI) in healthy volunteers [51]. These newer non-invasive VNS delivery systems do not require surgery, and permit patient-administered stimulation on demand; therefore, they improve the safety and tolerability of VNS, making it more accessible and facilitating further investigations across a wider range of uses [55]. VNS has now obtained approval by the US Food and Drug Administration and EU regulatory agencies for

treatment-resistant partial onset seizure disorder [56], and treatment-resistant depression [57]. In particular, non-invasive VNS has gained popularity for its ease of use, broad spectrum of efficacy and tolerability in extremes of age and mental capacity [58]. Investigational uses of this technique include antinociceptive effects in chronic pain disorders [59], sympatholytic/vagotonic effects in patients with coronary artery disease [60] and in pentobarbital anaesthetized dogs [61].

However, VNS mechanisms of action are still unknown. Concerning epilepsy, early evidence [62] suggested an anticonvulsant action of VNS in dogs, probably due to increased periods of spike-free intervals. This may reflect the mechanism of action of VNS in achieving seizure control: alternating synchronization and desynchronization of electroencephalogram (EEG), with the latter being progressively the dominant feature [63]. In patients with epilepsy, the long-term efficacy of VNS seems to be maintained or improved [64], whereas the frequency of adverse events generally decreases as patients accommodate to stimulation [65]. The therapy is highly cost-effective, resulting in considerable long-term savings even though most patients do not become totally seizure-free [66]. Of note, VNS therapy was demonstrated to be particularly effective in children with drug-resistant epilepsy, reducing seizure frequency without major safety issues [67]. In these cases, VNS increased respiratory frequency and decreased respiratory amplitude with a variable effect on cardiac activity [68].

During clinical trials of VNS in patients with epilepsy, several investigators reported mood improvements in their patients that occurred independently of the reduction in seizure frequency [69]. Of note, reversible changes in HR variability were observed in patients with major depression after VNS [70]. Although some concerns on its effectiveness were raised in the past [71–73], neurochemical data have demonstrated VNS effects on neurotransmitters thought to be important in mood disorders, including serotonin, norepinephrine, GABA and glutamate [69,74]. Long-term benefits of VNS in treatment-resistant depression were also reported [75,76]. VNS seems to be most effective in patients with low to moderate, but not extreme, antidepressant resistance. Two major working hypotheses of VNS in depression were proposed: the ‘monoaminergic’ and the ‘neural plasticity’ hypotheses of depression [77]. Of note, noradrenergic neurons from the locus coeruleus play an important role in the antidepressant-like effect of VNS [78]. Furthermore, transcutaneous VNS modulates the default mode network in major depressive disorder [79].

Other potential therapeutic indications [80] of VNS are chronic pain, migraine, cluster headache, obesity, chronic tinnitus and Alzheimer’s disease [51,80–82]. Of note, VNS may modulate memory formation in humans [83].

Importantly, VNS increased the expression of brain-derived neurotrophic factor and fibroblast growth factor in the hippocampus and cerebral cortex, decreased the abundance of nerve growth factor mRNA in the hippocampus and, similar to the antidepressant drug venlafaxine, increased the norepinephrine concentration in the prefrontal cortex in the rat brain [84]. Transcutaneous VNS also elicited far field potentials from the brainstem [85], as well as inducing production of IL-1 β in the brain and activating the hypothalamic–pituitary–adrenal axis [86]. In healthy subjects, VNS shifts the high-frequency power density of heartbeat dynamics, also inducing a partial cardiorespiratory decoupling [87].

VNS, together with rehabilitative therapy, also enhances functional motor recovery after traumatic brain injury in animals [88]. VNS activates neuronal and astrocytes $\alpha 7nAChR$, and inhibits the apoptosis and oxidant stress responses possibly associated with increased Akt phosphorylation and miR210 expression [89].

VNS has also been linked to cardiac diseases [90–92]. These diseases, in fact, still have a high mortality rate owing to neurohormonal activation and autonomic imbalance with increase in sympathetic activity and withdrawal of vagal activity. VNS could be a viable solution to counteract the sympathetic tone and enhance the vagal tone, with applications for heart failure, atrial fibrillation and coronary heart disease induced by increased sympathetic nerve activity [90,91,93]. The improvement in heart failure and the anti-inflammatory and vasodilatory properties of VNS provide additional antiarrhythmic benefit [94]. VNS, in fact, acts on proinflammatory cytokines, nitric oxide elaboration and myocardial expression of gap junction proteins [95,96].

Of note, conventionally, the left-sided cervical vagus nerve is mostly selected as the site for stimulation because of safety concerns [91,93]. Regarding changes in the ECG morphology, elevated levels of T-wave alternans were found in patients with drug-refractory partial-onset seizures following VNS [97]. Moreover, pure ectopic cycles were observed during sinus arrest caused by VNS [98]. Remarkably, this effect has been suggested to profitably discern between parasytostole and extrasystole events in case pure ectopic cycles are not spontaneously observed [98].

In summary, the acute and long-term efficacy of VNS, especially in treatment of epilepsy and depression, is encouraging, but still under debate. The effectiveness of non-invasive transcutaneous VNS for epilepsy, depression and other conditions has not been investigated beyond small pilot studies [99]. Transcutaneous VNS deserves further study as an antidepressant therapy and for its potential effect on physiological biomarkers associated with depression morbidity and mortality, especially because the exact mode of action of VNS is still not well understood [100–102].

Furthermore, given the complexity of the cardiac autonomic nervous system, including the presence of both afferent and efferent as well as parasympathetic and sympathetic fibres in the vagosympathetic trunk, it is critical to carefully elucidate the mechanisms of VNS and the parameters of stimulation to ensure that VNS achieves the desired therapeutic effect [94,103]. Nevertheless, nowadays, left cervical VNS is an approved therapy for refractory epilepsy and treatment-resistant depression, whereas right cervical VNS has proven promising for treating heart failure, along with reducing malignant ventricular arrhythmias, particularly in the setting of ischaemia, as well as atrial arrhythmias.

4. Repetitive transcranial magnetic stimulation

Repetitive TMS is a 25-year-old non-invasive neuromodulatory technique [104] by which electric currents generated by a rapidly varying magnetic field (up to 2 T) applied on the scalp through a coil can reach the superficial layers of the cortex. At this level, neural elements (mainly interneurons) are activated trans-synaptically [105]. Trains of single pulses may be applied regularly spaced in time or in a patterned way: both types of rTMS produce changes in cortical excitability outlasting the stimulation time. Typically, high-frequency (greater than or equal to 5 Hz) rTMS increases cortical excitability, whereas low-frequency (less than or equal to 1 Hz) rTMS reduces cortical excitability [106]. In the patterned theta burst stimulation (TBS), three pulses at 50 Hz, repeated at 5 Hz (i.e. every 200 ms, or theta frequency) are applied: this produces a longer lasting after-effect [107], with a resulting inhibitory net effect if applied continuously for 40 s (cTBS), or gives rise to enhanced excitability if applied intermittently (iTBS, 2 s of stimulation every 10 s). Sustained changes of cortical excitability can be obtained thanks to a modification of the synaptic efficacy, implying the occurrence of long-term depression or potentiation mechanisms, probably via an NMDA-receptor-dependent mechanism (see [108] for a review). The effects of rTMS take place not only locally, but involve a network-mediated modulation of regional brain activity, either at cortical or even subcortical levels [108]: for example, there is evidence that stimulation at the level of the primary motor cortex (M1) or the dorsolateral prefrontal cortex (DLPFC) induces, respectively, suppression of beta oscillatory activity in the STN [109] and modifies striatal binding at dopaminergic terminals [110] in PD patients.

The impact of TMS-induced electric field on local structures—as well as distributed anatomical and functional networks—has been investigated using various approaches, ranging from initial spherical models of the head roughly calculating the amount and directionality of injected current [111], to those including brain structural information derived from MRI [112,113]. Recent studies have even attempted to model the impact of cortical gyration at the individual level [114], with results suggesting the field strength as being significantly enhanced when the currents run approximately perpendicular to the local gyral orientation [115,116]. This evidence, implying an even more careful selection of coil orientation in order to realistically target given cortical areas, has been recently expanded by studies focusing on the role of tissue anisotropy (using diffusion

tensor (DTI) and diffusion-weighted (DWI) imaging) to determine the probability to target specific white matter tracts [115,117], thus directly perturbing the structural ‘connectome’. Finally, resting-state functional MRI brain networks [118] have also recently been considered, showing how changes in coil orientation and stimulation site location—even within the same anatomical region (e.g. DLPFC)—might lead to the engagement of completely different networks (i.e. default mode versus frontoparietal networks) [119]. Overall, current evidence strongly suggests the need to rely on multimodal imaging efforts in order to reliably assess the impact of TMS, which should be adopted for the modulation of regions related to autonomic functions.

With these neurophysiological and modelling premises, rTMS has gained consensus among neurologists and psychiatrists as a non-invasive neuromodulatory intervention to treat several diseases associated with regional or diffuse dysfunctions of cortical excitability: a recent evidence-based survey [108] indicates that rTMS is definitely effective (level of evidence A) in the treatment of chronic pain syndromes when applied at high frequency on the contralateral M1, and on pharmacoresistant depression when applied at high frequency on the left DLPFC. A level B of evidence (i.e. probable efficacy) has been proposed for the antidepressant effect of low-frequency rTMS of the right DLPFC, high-frequency rTMS of the left DLPFC for the negative symptoms of schizophrenia, and low-frequency rTMS of contralesional motor cortex in the recovery phase from a chronic motor stroke.

As there is experimental evidence in animals that stimulation of the M1 and of the DLPFC (i.e. the cortical targets which reached a level A of evidence for rTMS interventions; figure 1a) may influence cardiovascular autonomic functions [120,121], and that both cortical regions showed associations with sympathetic activity in humans [122,123], similar effects could consequently be expected in subjects who underwent several sessions of rTMS on these cortical targets. Some early studies confirmed this hypothesis: for example, Udupa *et al.* [124] treated daily for two weeks a group of 27 depressed patients by high-frequency rTMS of the left DLPFC, for a total of 18 000 pulses. HR variability measures indicated that rTMS produced significantly greater reduction than serotonergic agents (taken by a second group of 25 patients) in the sympathetic/parasympathetic ratio, suggesting improvement in sympathovagal balance [124]. However, a recent review on the topic failed to demonstrate conclusive evidences that rTMS might impact on autonomic function at a clinically useful degree [125]. This might be due to several, non-mutually exclusive factors: the heterogeneity of stimulation parameters (cortical target, frequency intensity and duration of stimulation), and patients’ characteristics and design of the studies not including a systematic evaluation of cardiovascular variables among their primary or secondary aims.

Although long-lasting autonomic effects of rTMS are substantially lacking, there is evidence that rTMS may alter HR during its application: stimulation of M1 induced a short-lasting increase of HR and blood pressure [126,127]; even in vegetative state patients, high-frequency rTMS can transiently increase HR [128], suggesting that rTMS of M1 may modulate the autonomic outflow in the absence of motor responses (and unspecific arousal). Low-frequency repetitive TMS, particularly after stimulation of the right hemisphere, induced a slight increase in the parasympathetic drive (i.e. significant bradycardia) and no effects on the sympathetic outflow in healthy subjects [129]. However, this was not the case following acute high-frequency rTMS of the left DLPFC [130].

In conclusion, available data do not allow conclusive statements regarding clinically relevant effects of rTMS on autonomic regulation of cardiovascular function. The effects of brain stimulation in healthy subjects on the sympathetic outflow posit the need to design ad hoc studies to confirm the encouraging preliminary results, possibly based on neuroimaging investigations coupled with monitoring of vital parameters.

5. Transcranial direct current stimulation

Different from rTMS, tDCS considers a transcranially delivered constant electrical field aimed at inducing instantaneous (‘online’) and long-lasting (‘offline’) changes in cortical excitability

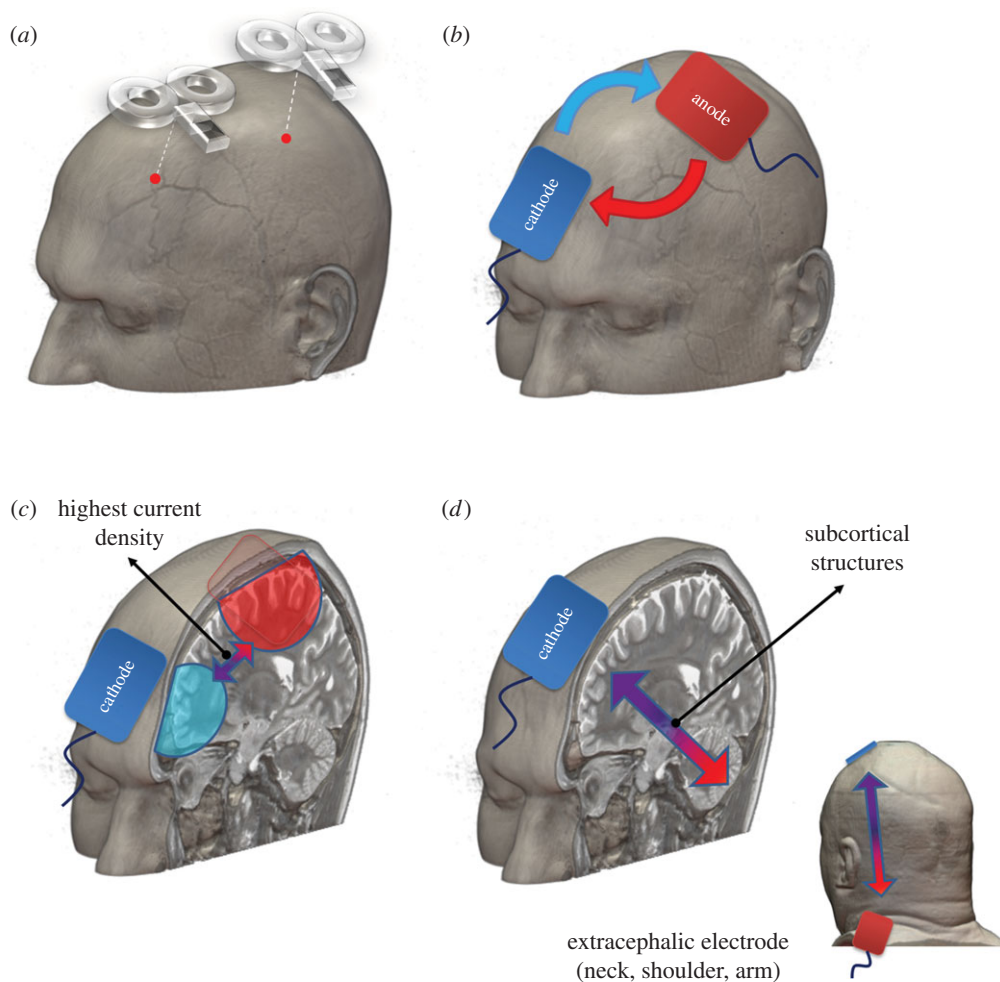


Figure 1. Sites of stimulation of rTMS and tDCS montages, with effects on the brain. (a) The most commonly reported rTMS stimulation sites for targeting cortical regions related to autonomic functions. (b) A bipolar tDCS montage, with anode and cathode electrodes both placed on the scalp, roughly in correspondence of right M1 and left frontopolar cortex. As shown, the result of tDCS is a constant current flow between the two stimulation sites, with current both bridging between the electrodes through the skin, as well as penetrating the scalp (c). tDCS provides a less focal stimulation effect (areas in red and cyan) underneath each electrode, with the highest current density expressed in brain regions in between the two fields. (d) Extracephalic solutions involving one electrode on the scalp and one on ipsi/contralateral arm/shoulder/neck can be adopted in order to facilitate the current flow towards brainstem structures. (Online version in colour.)

levels by means of a cellular membrane polarization process [131,132]. Originally applied through two saline-soaked electrodes placed on the scalp and with intensities in the range 0.5–2 mA, tDCS has demonstrated significant modulation of the physiology of several brain systems. The effects of tDCS spread from the modulation of cortical excitability levels [133] up to high-order cognitive networks [134,135], with initial promising results also for the treatment of neurological and psychiatric conditions [136–138]. The application of a constant field on the scalp generates two electric ‘poles’ with opposite charge, constituted by the two electrodes. During anodal tDCS, the current delivered on the ‘anode’ attracts negative ions in the tissues underneath the electrode: this reduces the resting membrane threshold, thereby facilitating neuronal firing (i.e. it increases cortical excitability). On the contrary, negatively charged electrodes (i.e. cathodal tDCS) affects nearby regions by attracting positive charges, increasing the threshold and making the stimulated

area less prone to be activated in response to exogenous or endogenous stimuli (i.e. reduction of cortical excitability) (figure 1b).

While such a basic mechanism reflects the simplicity of application for tDCS, it also highlights the potential issues related to the estimation of the brain tissues actually being stimulated. Electrical charges leaving each electrode follow diverse routes in their path towards the oppositely charged electrode, passing through biological tissues with different conductivity properties (e.g. skin, muscle, bone, cerebrospinal fluid, grey and white matter, blood vessels). Modelling studies have repeatedly shown how the effect of tDCS is highly dependent on electrode montage, and how an accurate positioning of tDCS electrodes might allow one even to stimulate subcortical structures [139,140]. This made realistic the possibility of targeting both cortical and deep brainstem structures related to autonomic functioning, with interesting scenarios related to the understanding of brain–heart interactions, as well as potential treatment of pathological conditions [141] (figure 1c,d).

There is evidence of autonomic effects of brain stimulation on animals [121,142], with electrical stimulation applied to motor and premotor areas in rat, cat and monkeys eliciting cardioautonomic responses [120], as well as stimulation of different regions of the insular cortex triggering cardiovascular responses consistently [142]. Despite this promising scenario and modelling work suggesting its feasibility in humans, just a handful of studies have investigated the application of tDCS for the modulation of cardiovascular human functions [125], with current literature showing very conflicting results [143,144]. Most of the studies involved the delivery of tDCS using a classic bipolar, cephalic electrode montage (i.e. both anode and cathode are placed on the scalp) targeting M1 and DLPFC, but autonomic function was also tested with tDCS delivered on temporal regions [145]. Whenever documented, positive autonomic effects of tDCS were related to anodal stimulation, with only two studies supporting effects for cathodal tDCS delivered on the DLPFC [146] or on M1, the latter addressing vasomotor reactivity changes [147]. However, only two studies were designed ad hoc to investigate the effect of tDCS on brainstem structures through a unipolar scalp montage linked with an extracephalic (arm/shoulder) electrode positioning: both studies, one targeting M1 [148] and the other one targeting the frontal midline [144], suggest null or mild effects on cardiovascular and respiratory functions, with a progressive shift over time in favour of the sympathetic tone, a finding that however was present during sham (i.e. placebo) tDCS.

Thus, the small number of studies and the heterogeneity of tDCS parameters (e.g. montage, stimulation intensity and duration, monitoring length) do not allow for depicting a definitive scenario for the effect of tDCS on autonomic function. Despite this, several points can be drawn to inform future investigations: first of all, just a few studies attempted to monitor for long-lasting effects of tDCS stimulation, with the vast majority of the investigations focusing on online effects recorded during stimulation or changes happening just a few minutes after the stimulation was turned off. Given that the effect of a classical tDCS session (i.e. 20 min of stimulation) seems to last for almost 1 h, and that extracephalic stimulation has shown a different timing of cortical excitability modulation [148], future investigations should include longer post-tDCS recordings. Indeed, as shown in Santarnecchi *et al.* [148], changes in heart-rate variability and systolic/diastolic pressure seem to correlate with the time course of spontaneous motor cortex excitability during sham tDCS, with a strengthening of such dependence during anodal tDCS of the motor cortex. This suggests the possibility to use tDCS as a tool to uncover the causal link between excitability of specific regions of the cerebral cortex and autonomic functions, if appropriately designed studies are able to monitor their interplay at high temporal resolution.

In conclusion, available studies demonstrated some potential of brain stimulation techniques in modulating cardiovascular function acutely, with most consistent effects in the long term shown for DBS of the PAV/PAG on blood pressure control (table 1). However, the full clinical applicability of these neuromodulatory approaches in patients with otherwise intractable autonomic dysfunctions will remain a ‘therapeutic opportunity’ [44,45] until such time as autonomic variables are considered as primary or secondary aims in large prospective clinical

trials of neuromodulatory therapies, even if performed on patients in which the autonomic dysfunction is not the primary reason for the neuromodulatory intervention.

Data accessibility. There is no additional or supplementary data.

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