

Supplementary information

The brain–heart axis: effects of cardiovascular disease on the CNS and opportunities for central neuromodulation

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Supplemental table 1. Published and ongoing clinical trials evaluating the changes in (cardiac) autonomic tone with central neuromodulatory therapies

Study	n	Patients	Sham group	Target	Follow-up	Stimulation parameters	Results (summary)
Spinal Cord Stimulation							
Tse <i>et al</i>, 2015¹	17	HFrEF (LVEF 20%-35%, NYHA III, ICD in situ, on OMT)	No	Bilateral high thoracic epidural space (T1–T3)	6 mo	Two (8 electrode) leads Stimulation ON: 24 hrs/day Current: 90% to 110% of paresthesia threshold (range 1–15 mA); Frequency: 50 Hz Pulse width: 200 µs	Safe, feasible; Significant improvement in NYHA class, peak maximum oxygen consumption, LVEF, and LVESV
Zipes <i>et al.</i>, 2016²	66	HFrEF (LVEF ≤35%, NYHA III, QRS duration <120 ms, LVEDD ≥55 mm).	Yes	High thoracic epidural space (T2-4), Single lead	6 mo	Single (8 electrode) lead. Stimulation ON: 12 hrs/day Current: 90% of paresthesia threshold. Frequency: 50 Hz Pulse width: 200 µs	No meaningful change in clinical outcomes for heart failure patients
Goudman <i>et al.</i> 2019³	22	Failed back surgery syndrome		Low thoracic epidural space (T8-10)	Single session	Median charge/r pulse: 0.105 (0.06–0.7) µC Median charge/sec: 550 (49.5–750) µC Median duty cycle: 30 (25–30) %	↑ vagal tone; ↓ LF:HF ratio
NCT0253 0203	T	Patients undergoing an OFF-pump CABG procedure	Yes	-	5 days	-	N/A
NCT0517 8056	R	Non-progressive C3-T1 AIS A-C Spinal Cord Injury	Yes	-	16 wks.	-	Pending; Secondary outcomes include change in BRS and HRV
NCT0517 1205	R	Parkinson's disease	No	-	24 mo	-	Pending; Secondary outcomes include HRV
Deep Brain Stimulation							
Pereira <i>et al.</i>, 2010⁴	1	Refractory hypertension	No	Left PAG (& ventropostero-medial thalamus)	12 mo	Quadripolar electrode	↓ BP, ↓ HRV
Green <i>et al.</i>, 2010⁵	5	Intractable pain syndromes	No	PAG: different electrode locations	Single session	Frequency: 10-50 Hz Pulse width: 120 µs	Increased BP with ↑ LF and ↑ LF:HF ratio in some sites, Decreased BP with

						Amplitude: 3-4.5 V	↓ LF and ↓ LF:HF ratio in other sites, no effect on HF power
Erola et al., 2006⁶	14	Parkinson's disease	No	Bilateral subthalamic nuclei	12 mo	-	No change in 24-hour HRV
Azevedo et al., 2010⁷	20	Parkinson's disease	Yes	Bilateral subthalamic nuclei	Single session	-	No significant effect on autonomic function.
Chen et al., 2011⁸	16	Parkinson's disease	No	Bilateral subthalamic nuclei	9 - 32 mo	Frequency: 130 Hz Pulse width: 60 μ s Amplitude: 0.5 V (up to max 4 V)	↑ LF in patients who had significantly reduced Parkinson's symptoms
Sumi et al., 2012⁹	28	Parkinson's disease	Yes	Bilateral subthalamic nuclei	Single session	-	↑ vagally mediated baroreflex function
Trachani et al., 2012¹⁰	12	Parkinson's disease	Yes	Bilateral subthalamic nuclei	6 mo	Frequency: 130 - 145 Hz Pulse width: 60 - 90 μ s Amplitude: 2 - 4 V	No effect on cardiac autonomic function
NCT0501 1773	Recruiting	Patients already implanted with depth electrodes	No	Substantia nigra, Pedunculo-pontine nucleus, Hypothalamus, PAG, or Hippocampus	4 nights	-	Pending; Secondary outcome measures include HRV
NCT0638 7914	Recruiting	Refractory post stroke pain	Yes	PAG and sensory thalamus	1 mo	Frequency: up to 80 Hz Pulse width: 5000 μ s Amplitude: 6 mA	Pending; Secondary outcome measures include HRV
Transcranial Direct Current Stimulation							
Rodriguez et al., 2022¹¹	13	Resistant hypertension	Yes	Primary motor cortex, M1 region	10 days	-	↓ central SBP, ↓ LF, ↑ HF
Gomez-Alvaro et al., 2024¹²	13	Fibromyalgia	Yes	Dorsolateral prefrontal cortex	3 wks.	Sham vs. 1 mA vs. 2 mA	↑ sympathetic tone: ↑ LF, ↑ LF:HF ratio, ↓ HF
Pinto et al., 2023¹³	20	COVID-19 patients	Yes	Bilateral prefrontal cortex	Single session	Current: 2 mA Duration: 30 min	↑ vagal tone: ↑ HF, ↓ LF
Sesa-Ashton et al., 2022¹⁴	22	Healthy controls		Left (n=10) or right (n=22) dorsolateral prefrontal cortex	Single session	Frequency: 0.8 Hz Sinusoidal current: +2 to -2 mA Duration: 100 cycles	↑ sympathetic tone: ↑ MSNA and ↑ BP
Brunoni et al., 2013¹⁵	46	Major depressive disorder	Yes	Left dorsolateral prefrontal cortex	6 wks.	Current: 2 mA	No effect on HRV

Brunoni et al., 2013¹⁶	20	Healthy controls	Yes	Left and right dorsolateral prefrontal cortex	Single session	Current: 1.5 mA Duration: 34 min	With emotional stressors, vagal activity increased during left, but not right, dorsolateral prefrontal cortex stimulation
Clancy et al., 2014¹⁷	14	Healthy controls	Yes	Primary motor cortex, M1 region	Single session	Current: 1mA Duration: 15 min	↑ LF:HF ratio
Hamner et al., 2015¹⁸	15	Healthy controls	Yes	Primary motor cortex, M1 region	Single session	Current: 2 mA Duration: 40 min	In the setting of acute pain: no effect on cardiovascular autonomic tone
Montenegro et al., 2011¹⁹	20	Healthy controls	Yes	Left temporal lobe	Single session	Current: 2 mA Duration: 20 min	↑ vagal and ↓ sympathetic modulation of HR in athletes, but not in healthy controls
Okano et al., 2015²⁰	10	Healthy controls	Yes	Left temporal and insular cortex	Single session	Current: 2 mA Duration: 20 minutes	Delayed parasympathetic withdrawal during exercise
Heinz et al. 2020²¹	12	Hemiparetic post-stroke patients	Yes	Left temporal cortex	Single session	Current: 2 mA Duration: 20 min Frequency: 2/day for 5 days	No immediate effects on HRV with exercise
Chang et al. 2020²²	60	Schizophrenia	Yes	Dorsolateral prefrontal cortex	3 mo	Current: 2 mA Duration: 20 min	No effect on HRV
RBR-10w787j6	R	HFrEF patients (LVEF ≤40%, NYHA II-III, on OMT)	Yes	Left temporal region	4 wks.	Current: 2 mA Duration: 20 min	Pending; Secondary outcome measures include change in HRV with exercise
NCT0610 9727	R	Healthy controls	Yes	Cerebellum	1 yr	Current: 2 mA Duration: 20 min	Pending; Secondary outcome measures include HRV
NCT0337 1225	RC	Fibromyalgia	Yes	Left primary motor cortex	6 wks.	Duration: 20 min	Pending; Secondary outcome measures include change in HRV with exercise
NCT0239 8344	30	Hemiparesis stemming from a stroke	Yes	Left temporal cortex	1 yr	Current: 2 mA Duration: 20 min	Pending; Outcome measures include HRV
NCT0418 9354	-	Anxi-depressive disorder	Yes	-	90 days	Current: 2 mA Duration: 20 min	Pending; Secondary outcome measures include HRV
NCT0645 5527	100	Mild to moderate depression	Yes	Dorsolateral prefrontal cortex	4 wks.	Current: 2.0 mA Duration: 30 min	Pending; Outcome measures include HRV
NCT0583 0851	R	Chronic low back pain	Yes	-	6 mo	Current: 2.0 mA Duration: 30 min	Pending; Secondary outcome measures include change in HRV with exercise
NCT0407 7632	?	Chronic low back pain	Yes	Primary motor cortex	Single session	Current: 2mA Duration: 20 min	Pending; Secondary outcome measures include HRV

Transcranial magnetic stimulation

Clarke et al., 2006²³	33	Migraine patients	No	Pain area	1 day	Pulse width: 70 μ s Peak voltage: 187 V Duration: 2 pulses	↓ LF:HF ratio
Gulli et al., 2013²⁴	12	Healthy controls	No	Orbitofrontal cortex	Single session	Frequency: 0.7 Hz Duration: 2x 8 min	Slight ↑ vagal tone. No effects on sympathetic tone. Significant bradycardia after stimulation of the right hemisphere.
Cabrerizo et al., 2014²⁵	10	Healthy controls	No	Primary motor cortex	Single session	Frequency: 10 Hz Stimulation ON/OFF: 1 sec / 59 sec Stimulation trains: 5	↑ LF:HF ratio in 60% of all cases
McCarthy et al., 2024²⁶	12	Healthy controls	No	Right dorsolateral prefrontal cortex and right motor cortex	Single session	Intensity: 80 - 120% motor threshold	↓ sympathetic tone: ↓ MSNA
Casanova et al., 2014²⁷	18	Autism spectrum disorder	No	Dorsolateral prefrontal cortex	18 wks.	Frequency: 0.5 Hz Sessions: 18 Pulses/session: 160	↑ vagal tone: ↑ HF, ↓ LF, ↓ LF:HF ratio
Fang et al., 2025²⁸	1	Major depressive disorder	No	Right dorsolateral prefrontal cortex	-	Frequency: 1 Hz Intensity: 100% motor threshold Duration: 30 min Pulses/session: 1800	Severe bradycardia
Remue et al., 2015²⁹	19	Healthy controls	Yes	Left and right dorsolateral prefrontal cortex	Single session	Frequency: 20 Hz Intensity: 110% motor threshold Stimulation ON/OFF: 1.9 sec / 12.1 sec Pulses / session: 1560	Left-sided stimulation: ↓ stress responses and ↑ vagal tone during stress
Udupa et al., 2007³⁰	27	Major depressive disorder	No	Primary motor cortex	2 wks.	Frequency: 15 Hz Intensity: 100% motor threshold Stimulation ON/OFF: 10 sec / 60 sec Stimulation trains: 10	↓ LF: HF
Yoshida et al., 2001³¹	16	Healthy controls	Yes	Central electrode, vertex of the scalp	5 days	Frequency: 0.2 Hz Intensity: 90% motor threshold Stimulation trains: 70 Duration: 350 sec	↑ sympathetic tone: Transient ↑ LF

NCT0645 1809	S	Major depressive disorder	No	Left dorsolateral prefrontal cortex	-	Frequency: 10 Hz Intensity: 110% motor threshold Duration: 20 min: 30 sessions	Suspended
NCT0513 9862	NR	Major depressive disorder	No	Left dorsolateral prefrontal cortex	10 wks.	-	Pending; Secondary outcome measures include HRV
NCT0674 8274	R	Healthy controls	Yes	Dorsolateral prefrontal cortex	Single session	Frequency: 10 Hz Duration: 19 min	Pending; Secondary outcome measures include HRV
NCT0448 6222	T	Elderly with major depressive disorder	Yes	Dorsolateral prefrontal cortex	19 days	Frequency: 10 Hz Intensity: 120% motor threshold Duration: 150 min	Terminated
NCT0696 8026	R	Recurrent Pregnancy Loss and Anxiety	No	Right dorsolateral prefrontal cortex	Single session	Frequency: 1 Hz Intensity: 100-150% motor threshold Duration: 600 min Stimulation trains: 6	Pending; Outcome measures include HRV
NCT0516 1819	R	Somatic symptom disorder	Yes	Left dorsolateral prefrontal cortex	3 wks.	Frequency: 10 Hz Intensity: 120% motor threshold Stimulation trains: 40	Pending; Secondary outcome measures include HRV
NCT0668 9345	R	Chronic pain	Yes	Left dorsolateral prefrontal cortex	5 days	Frequency: 5 Hz Intensity: 110% motor threshold Duration: 3 min	Pending; Secondary outcome measures include HRV
NCT0559 3237	R	Chronic neuropathic pain	Yes	Motor cortex	6 mo	Frequency: 10 Hz Stimulation ON/OFF: 10 sec/ 50 sec stimulation trains:30 Pulses/session: 3000	Pending; Secondary outcome measures include HRV

Ongoing or incomplete studies are highlighted dark grey. S = suspended, R = recruiting, RC = recruiting completed (results pending), T = terminated, ? = not reported, NR = ongoing but not yet recruiting
BRS: Baroreflex sensitivity; CABG: Coronary artery bypass graft surgery; HF: High frequency power; HFrEF: Heart failure with reduced ejection fraction; HR: Heart rate; HRV: Heart rate variability; ICD: Implantable cardioverter-defibrillator; LF: Low frequency power; LVEF: Left ventricular ejection fraction; LVEDD: Left ventricular end diastolic diameter; LVESV: Left ventricular end systolic volume; MSNA: Muscle sympathetic nerve activity; NYHA: New York heart association classification; OMT: optimal medical therapy.

Supplemental table 2. Published clinical studies of evaluating cardiac autonomic function with peripheral neuromodulatory therapies

Study	n	Patients	Sham / Control	Target	Follow-up	Stimulation parameters	Results
Vagal nerve stimulation Activation of vagal efferent and afferent fibers, modulation of parasympathetic outflow							
NECTAR-HF, 2015³²	96	HFrEF patients (LVEF $\leq$ 35%, LVEDD $\geq$ 55 mm, NYHA II or III, on OMT)	Yes	Right cervical vagus	6 months	Frequency: 20 Hz Stimulation ON/OFF: 10 sec/ 50 sec Pulse width: 300 μ s	No effect on primary and secondary endpoints of cardiac remodeling or functional capacity. Quality-of-life measures improved
INOVATE-HF, 2016³³	707	HFrEF patients (LVEF $\leq$ 40%, an LV end diastolic dimension 50 - 80 mm, NYHA III, on OMT)	Yes	Right cervical vagus	16 months	Closed loop, titrated to goal current of 3.5 to 5.5 mA	Neutral; stopped for futility. $\uparrow$ Quality-of-life measures
ANTHEM-HF, 2014³⁴	60	HFrEF (LVEF $\leq$ 40%, left ventricular end-diastolic diameter 50 - 80 mm, on OMT)	No	Left (n = 31) or right (n = 29) cervical vagus.	6 months	Frequency: 10 Hz Target output: 1.5–3.0 mA Titrated to pulse width of 250 μ s Stimulation ON/OFF: 14 sec / 66 sec (1,080 cycles/d).	$\uparrow$ cardiac function (incl. LVEF, LVESV, LVESD) and HRV
ANTHEM-HFpEF, 2023³⁵	52	HFpEF or HFmrEF (NYHA II-III, LVEF $\geq$ 40%, on OMT)	No	Right cervical vagus	12 months	Titrated over 10 weeks Frequency: 5 Hz Maximum amplitude: 2.4 $\pm$ 0.5 mA Pulse width: 250 μ s	$\downarrow$ heart failure symptoms, $\uparrow$ exercise tolerance, $\uparrow$ Quality-of-life measures. $\downarrow$ incidence of ventricular arrhythmias
Zhu <i>et al.</i>, 2020³⁶	14	Epilepsy	No	Left cervical vagus	3 weeks	Current: 0.5 - 1.5 mA Frequency: 30 Hz Pulse width: 250 μ s Stimulation ON/OFF: 30 sec/300 sec	$\uparrow$ thalamic-hippocampal functional connectivity
Berger <i>et al.</i>, 2024³⁷	23	Drug resistant epilepsy	No	-	>6 months	Individualized	$\downarrow$ locus coeruleus activity

Henry <i>et al.</i> , 1999 ³⁸	11	Epilepsy	Yes (low stimulation)	Left cervical vagus	3 months	Individualized	↑ thalamic synaptic activities
Clancy <i>et al.</i> 2014 ³⁹	48	Healthy control	Yes	Transcutaneous auricular vagal nerve stimulation	Single session	Frequency: 30Hz Pulse width: 200 µs Amplitude: 10-50mA Duration: 15 min	↑ vagal tone: ↑ HF, ↓ LF, ↓ LF:HF ratio
Antonino <i>et al.</i> 2017 ⁴⁰	13	Healthy males	Yes	Transcutaneous auricular vagal nerve stimulation	Single session	Frequency: 230Hz Pulse width: 200 µs Amplitude: 10-50mA Duration: 15 min	↓ HR, ↓ LF:HF ratio, ↑ cardiac baroreflex sensitivity (spontaneous)
Sclocco <i>et al.</i> , 2020 ⁴¹	16	Healthy control	Yes	Left transcutaneous auricular vagal nerve stimulation	Single session	Frequency: 25Hz Pulse width: 450 µs Duration: 1 sec	Activation of autonomic nuclei, including NTS, locus coeruleus, and medial and dorsal raphe nuclei
Gentile <i>et al.</i> , 2025 ⁴²	16	HFrEF and HFmrEF patients	Yes	Left or right transcutaneous auricular vagal nerve stimulation	Single session	Frequency: 30Hz Pulse width: 200 µs Amplitude: 1mA below discomfort threshold Duration: 10 minutes	No effect on HR or BP. Right, but not left-sided tVNS ↑ vagal baroreflex, no effects on HRV parameters
Baroreflex activation therapy Activation of baroreceptors, increasing central parasympathetic outflow and decreasing central sympathetic outflow							
BeAT-HF, 2020 ⁴³	264	HFrEF (NYHA II-III, LVEF ≤35%, on OMT)	Yes	Unilateral carotid sinus	6 months	Amplitude titrated; Average settings: Frequency: 40 Hz Amplitude 8.7-mA Pulse width: 125 µs	↓NT-proBNP, ↑6MWD
Rheos Pivotal, 2011 ⁴⁴	265	Resistant hypertension	No	Bilateral carotid sinus	12 months	Implanted bilateral electrodes	↓BP; safety concerns noted
Groenland <i>et al.</i> , 2022 ⁴⁵	13	Resistant hypertension	No	Left or right internal carotid artery	3 months	MobiusHD implant	↑activity during Valsalva in central sympathetic regions assessed by BOLD fMRI. No changes in brain areas

							involved in the baroreflex
Renal denervation							
Ablation of renal sympathetic efferent and afferent fibers							
SYMPPLICITY HTN-3, 2014⁴⁶	535	Resistant hypertension	Yes	Renal sympathetic nerves	6 months	RF ablation catheter	Neutral vs sham
SPYRAL HTN-ON MED, 2022⁴⁷	80	Uncontrolled hypertension	Yes	Main & branch renal arteries	36 months	Multielectrode RF	↓SBP vs sham
RADIANCE-HTN TRIO, 2021⁴⁸	136	Resistant hypertension	Yes	Main renal arteries	2 months	Ultrasound catheter	↓SBP vs sham
RADIANCE II, 2023⁴⁹	224	Resistant hypertension	Yes	Main renal arteries	2 months	Ultrasound catheter	↓SBP vs sham

6MWD: 6-minute walking distance; BP: Blood pressure; HF: High frequency power; HFmrEF: Heart failure with mildly reduced ejection fraction; HFrEF: Heart failure with reduced ejection fraction; HRV: Heart rate variability; LF: Low frequency power; LVEF: Left ventricular ejection fraction; LVEDD: Left ventricular end diastolic diameter; LVESV: Left ventricular end systolic volume; LVESD: left ventricular end systolic diameter; NYHA: New York heart association classification; OMT: optimal medical therapy; SBP: Systolic blood pressure

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