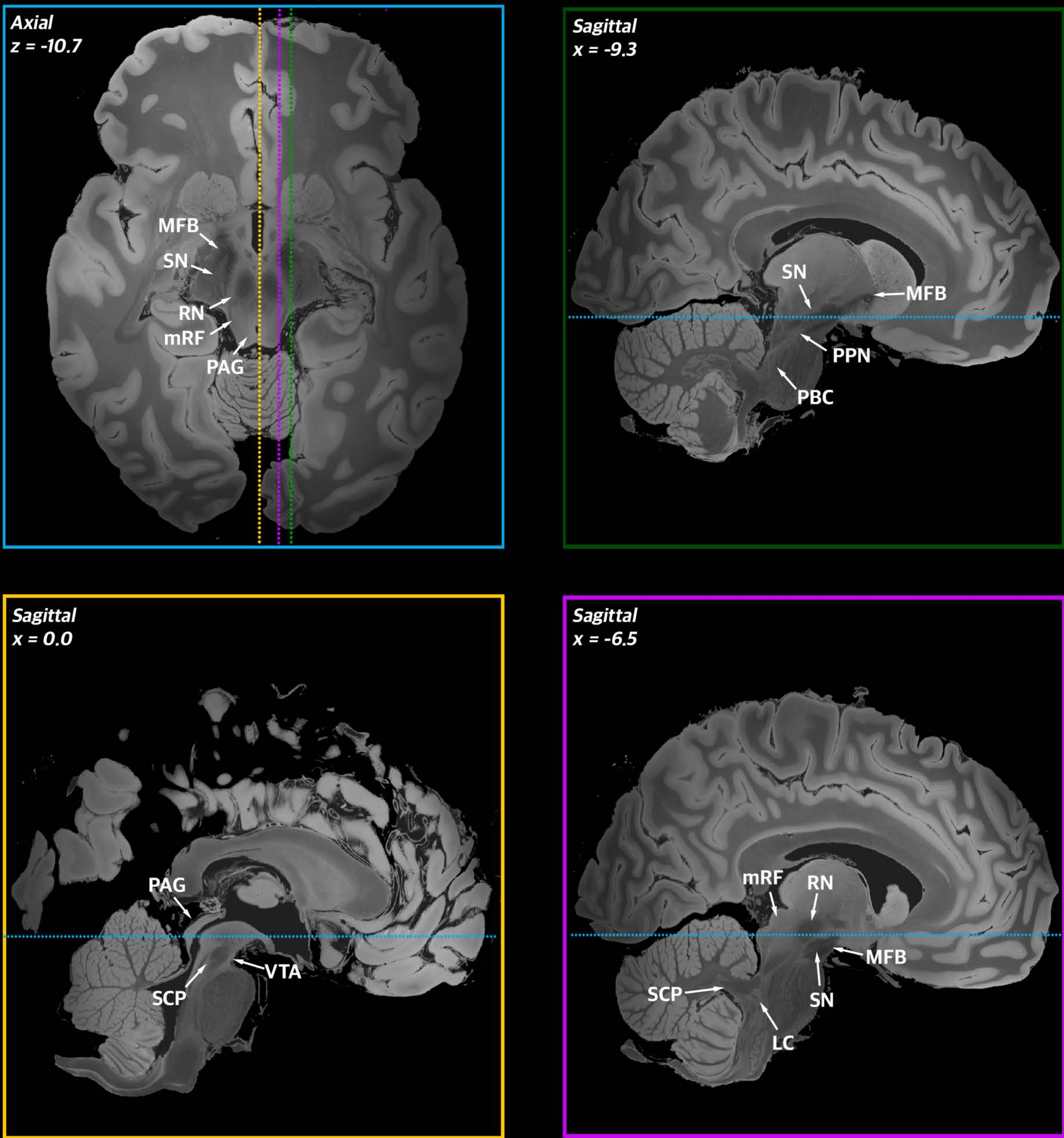
Supplementary Figure 1. Uncoloured brainstem regions and nuclei targeted by DBS. Brainstem regions and nuclei that have been targeted by DBS are shown on a high resolution brain template(7 Tesla, 100 micron resolution brain in MNI152 (nonlin asym) space). Brainstem targets (taken from the Harvard Ascending Arousal Network atlas or constructed from Human Connectome Project imaging data (http://www.humanconnectomeproject.org/) are labelled in two planes (axial - top left panel; sagittal - top right and bottom panels). Dotted lines denote the anatomical level displayed in panels bordered by the corresponding colour (e.g. the blue dotted line denotes the level of the axial slice displayed in the top left panel). Abbreviations. **DBS** = deep brain stimulation; **LC** = locus coeruleus; **MFB** = medial forebrain bundle; **mRF** = mesencephalic reticular formation; **PAG** = periaqueductal gray; **PBC** = parabrachial complex; **PPN** = pedunculopontine nucleus; **RN** = red nucleus; **SCP** = superior cerebellar peduncles; **SN** = substantia nigra; **VTA** = ventral tegmental area.



Axial
z = -10.7
MFB
SN
RN
mRF
PAG
Sagittal
x = -9.3
SN
MFB
PPN
PBC
Sagittal
x = 0.0
PAG
VTA
SCP
Sagittal
x = -6.5
mRF
RN
MFB
SCP
SN
LC

Table 1 - Clinical outcomes of Brainstem DBS. Table cataloguing the sustained/long-term clinical outcomes of stimulation of brainstem targets, as reported by brainstem DBS studies.

Study	n	Etiology	Indication for DBS	Targets	Stimulation parameters	Follow-up time	Reported outcome
SUBSTANTIA NIGRA (SN)							
Weiss et al. 2013	12	PD	Axial motor impairment	STN, STN & SN	SNr: 125 Hz, 60 µs, 0.7-3.0 V STN: 125 Hz, 60-180 µs, 1.4-4.6 V	3 weeks	No significant differences in axial motor impairment, gait or quality of life between baseline, STN stimulation, and combined STN/SNr stimulation
Ulla et al. 2011	5	PD	Parkinsonism	STN (retrospective localization to SN)	130 Hz, 60 µs, 2-4 V	6 month	Chronic SN stimulation not performed
Wille et al. 2011	5	PME	Seizure	Bilateral STN/SN pars reticulata (n=1), bilateral STN/SN pars reticulata & bilateral VIM (n=4)	100-110 Hz, 60-120 µs, 1.8-4 V (at 12 months)	12-42 months	Sustained partial or complete myoclonus reduction (30-100% reduction) in all patients; best clinical effects seen with STN/SN-DBS
	1	PME	Seizure	Bilateral STN/SN pars reticulata		42 months	Sustained partial myoclonus reduction
	4	PME	Seizure	Bilateral STN/SN pars reticulata & bilateral VIM		12-32 months	Sustained complete myoclonus suppression in 1 patient; sustained partial myoclonus reduction in 3 patients
Blomstedt et al. 2009	1	PD	PD	R STN/SN (intra-operatively), bilateral STN	120 Hz, 60 µs, 2V	5 years	SN only stimulated intra-operatively
Vesper et al. 2007	1	Myoclonic epilepsy	Seizure	Bilateral STN/SN	130-160 Hz, 90 µs, 2.3-3.0 V	12 months	Seizure intensity/frequency reduced by 50%; generalized tonic-clonic seizure frequency decreased from 1-2/month to 0/month; patient no longer confined to wheelchair
Broggi et al. 2006	1	Epilepsy (post-traumatic drug resistant partial motor seizures)	Seizure	Posteromedial SN	N/A	15 months	60% reduction of seizures
Ulla et al. 2006	1	PD	Motor	Bilateral STN/SN	SN: 130 Hz, 60 µs, 2.2 V STN: 130 Hz, 60 µs, 2.5 V	3 months	Bilateral STN-DBS: 46% UPDRS-III improvement and eventual dysarthria; bilateral SN-DBS (most ventral contacts): 12% UPDRS-III improvement and acute mood changes
Kulisevsky et al. 2002	3	PD	Motor	Bilateral STN/SN pars reticulata	130 Hz, 60 µs, 2-3 V	1 week	Stimulation-induced mania in all patients occurred with stimulation through the most ventral contacts (positioned in SN); resolved when stimulation switched to more dorsal contacts 9-12 days post-surgery; improvement in UPDRS-III score (mean 51%), fluctuation score (70%), and dyskinesia score (mean 50%) noted at 1 week post-surgery
Bejjani et al. 1999	1	PD	Motor	Bilateral SN pars compacta and pars reticulata (STN was intended target) - only L side stimulated SN at most ventral contacts	130 Hz, 60 µs, 2.4 V (L SN contact)	1 month	SN only stimulated acutely; mood and PET results reported
RED NUCLEUS (RN)							
Lefranc et al. 2014	1	Cerebellar tremor	Tremor	L RN	20/60/130 Hz, 2-7 mA	Not internalized	Disappearance of postural tremor during insertion and immediately following stimulation onset; no improvement in postural/intentional tremor with subsequent stimulation
Bejjani et al. 2002	4	PD	Tremor	White matter between the RN and SN	130 Hz, 60 µs, 1-2 V	1 month	N/A
Feinstein et al. 1989	1	Cerebral palsy	Spasticity	L LC & L dentate nucleus & R RN	60 Hz, 120µs, 0.2 mA	N/A	N/A

VENTRAL TEGMENTAL AREA (VTA)/POSTERIOR HYPOTHALAMUS (pHypo)							
Akram et al. 2017	7	Headache	CH	Unilateral VTA, Bilateral VTA	N/A	33 months	6 patients were responders
Akram et al. 2016	21	Headache	CH	Unilateral VTA	185 Hz, 60 µs	18 months	60% overall improvement in median headache frequency; decreased headache impact test score
Leone et al. 2013	19	Headache	CH	Unilateral pHypo, Bilateral pHypo	180 Hz, 60 µs, <7 V	6-11 years	12 patients almost (<1 attack every 3 months) or completely pain-free at last follow-up; several pain-free patients no longer had active stimulation
	8	Headache	CH	L pHypo	180 Hz, 60 µs, 2.6-4.5 V or stimulation off at last follow-up (n=4)	6-11 years	5 patients almost or completely pain-free; 2 had relief with recurrence in periods; 1 had no benefit
	6	Headache	CH	R pHypo	180 Hz, 60 µs, 2-4.6 V or stimulation off at last follow-up (n=1)	8-10 years	2 patients almost or completely pain-free; 2 had partial benefits with some tolerance/recurrence; 2 had regular recurrent attacks
	4	Headache	CH	Bilateral pHypo	R: 180 Hz, 60 µs, 1-1.6 V, L: 180 Hz, 60 µs, 3.5 V or stimulation off at last follow-up (n=2)	6-11 years	1 patient had reduced attack frequency/intensity; 1 pain-free with recurrence in periods; 2 developed tolerance and had sporadic attacks
	1	Headache	CH	N/A			
Fontaine et al. 2010a	10	Headache	CH	Unilateral retro-hypothalamic region	186-195 Hz, 60 µs	1 year	5 patients considered responders (>50% in weekly attack frequency), 3 patients had some improvement, 2 patients worsened
	5	Headache	CH	L retro-hypothalamic region	186-195 Hz, 60 µs, 1.5-2.5 V	1 year	3 patients had >75% reduction in attack frequency, 1 had 25-50% reduction, 1 worsened
	5	Headache	CH	R retro-hypothalamic region	187-194 Hz, 60 µs, 2-2.8 V	1 year	1 patient had >75% reduction in attack frequency, 1 had 50-75% reduction, 2 had <25% reduction, 1 worsened
Fontaine et al. 2010b	11	Headache	CH	Unilateral pHypo	185 Hz, 60 µs, 1.0-2.8 V	1-11 years	No significant difference in weekly CH attack frequency between stimulation-ON and OFF periods while randomized; weekly attack frequency decreased by 48.4% during open-label period
Walcott et al. 2009	1	Headache	CH	R pHypo	185 Hz, 60 µs, 1.5 V	27 months	Resolution of facial pain and recurrence when stimulation turned off in blinded fashion
Bartsch et al. 2008	6	Headache	CH	L pHypo	130-180 Hz, 3.5-5.5 V	9-24 months	30-90% reduction in pain intensity; 3 patients experienced profound decrease in attack frequency (~1 attack per month) and >70% pain reduction during recurring attacks, 1 patient had no attacks for 6 months but subsequently had recurrent attacks (4-6 per day), 2 still experienced 60-70 attacks per month with <30% pain reduction
Franzini et al. 2008a	17	Pain & headache	Various	pHyp	Various settings	4-62 months	All MS trigeminal neuralgia patients improved; no patients with neuropathic/atypical facial pain had reduced pain
	N/A	Headache	CH	Unilateral pHyp	50 Hz, 90 µs, 0.6-3.3 V	12-62 months	Reported on in **Franzini et al. 2007**
	3	Pain	Neuropathic pain and atypical facial pain	pHyp	180 Hz, mean: 1.3 V	4 months	No reduction in pain
	5	Pain	MS trigeminal neuralgia	pHyp	N/A	1-3 years	2 patients pain-free; 3 patients had reduced pain but still required analgesic medication
Pinsker et al. 2008	2	Headache	CH	Uniateral hypo	180-185 Hz, 60 µs, 2.5-5.5 V	3-12 months	Insufficient pain reduction
		Headache	CH	L pHypo	180 Hz, 60 µs, 5.5 V	12 months	Insufficient pain reduction
		Headache	CH	L pHypo	185 Hz, 60 µs, 2.5V	3 months	Insufficient pain reduction
Franzini et al. 2008b	2 (2 others with ZI-DBS)	Epilepsy	Various	Bilateral VTA	180 Hz, 90 µs, 1.5-3.5 V	5-9 years	75-80% seizure reduction

		Epilepsy	Post-anoxia	Bilateral VTA	180 Hz, 90 µs, 1.5 V	5 years	75% seizure reduction rate
		Epilepsy	Idiopathic	Bilateral VTA	185 Hz, 90 µs, 3.5 V	9 years	80% seizure reduction rate
Franzini et al. 2007	22	Various	Various	pHypo	180 Hz, 60 µs, 0.6–3.3 V	1-52 months	Good pain relief for headache; poor pain relief for atypical facial pain; reduced seizures and improved behaviour in autism patient
	16	Headache	CH	Bilateral pHypo (n=2); unilateral pHypo (n=14)	180 Hz, 60 µs, 0.6–3.3 V	1-52 months	All patients achieved pain relief (71% of days were pain-free); duration of attacks significantly reduced
	1	Headache	SUNCT	Unilateral pHypo	180 Hz, 60 µs, 0.9-1.8 V	15 months	Pain reduction with sporadic attacks
	3	Pain	Atypical facial pain	Unilateral pHypo	180 Hz, 60 µs, 0.9-1.8 V	6-10 months	No pain reduction
	2	Disruptive behaviour	Autism	pHypo	180 Hz, 60 µs, 1 V	15-18 months	Improvement of disruptive behaviour and reduction in seizure rate
Starr et al. 2007	4	Headache	CH	Unilateral pHypo	185-Hz, 60 µs, 1-3 V	12-15 months	2 patients had >50% reduction in pain, 1 had <50% reduction in pain, 1 had transient complete suppression of headache but not persistent improvement
Vetrugno et al, 2007	3	Headache, sleep apnea	CH	Unilateral pHypo	NA	4 months	Abolition of nocturnal CH attacks; improved sleep efficiency
Cortelli et al, 2007	8	Headache	CH	Unilateral pHypo	130-180 Hz, 60-90 µs, 1.3-2.8 V	N/A	6 patients pain-free state without drugs; the remaining 2 patients required low dose verapamil prophylaxis
Owen et al, 2007a	1	Headache	CH	Unilateral pHypo	180 Hz, 90 µs	8 months	No CH attacks following implantation
Leone et al, 2006b	16	Headache	CH	Unilateral pHypo	180 Hz, 60 µs	N/A	Acute response to stimulation reported
Leone et al, 2006a	16	Headache	CH	pHypo	180 Hz, 60 µs, <7 V	1-52 months	10 patients pain-free
	2	Headache	CH	Bilateral pHypo	L: 180 Hz, 60 µs, 2.4-3.2 V R: 180 Hz, 60 µs, 2.8-3 V	L: 25-52 months R: 21-41 months	Pain-free (n=1), sporadic attacks (n=1)
	14	Headache	CH	Unilateral pHypo	180 Hz, 60 µs, 0.6-3.3 V	1-47 months	Pain-free (n=9), sporadic attacks (n=2), 1 attack every 2 days (n=1), 1 attack per day (n=2)
Schoenen et al, 2005	4 (2 others not implanted/died of intra-operative complications)	Headache	CH	Unilateral pHypo	185 Hz, 60-90 µs, 2-4.5 V	12-17 months	Excellent pain relief in 3 patients; unsatisfactory relief in 1 patient
	3	Headache	CH	L pHypo	185 Hz, 90 µs, 2-4.5 V	17 months	1 patient unstable for 7 months, then pain-free for 5 months with recent relapse at last follow-up; 1 patient had relief for 8 months and was pain-free for 5 months before last follow-up; 1 patient had relief for 8 months followed by relapse, then relief again for 4 months before last follow-up
	1	Headache	CH	R pHypo	185 Hz, 60 µs, 3.3 V	12 months	Pain-free for 9 months followed by relapse; pain-free again fore 3 months before last follow-up
Leone et al, 2005	1	Headache	SUNCT	L pHypo	180 Hz, 60 µs, 0.9-1.8 V	15 months	Pain reduction after 1 month of stimulation; tolerance to stimulation occurred but increasing amplitude reduced pain
Leone et al, 2004	1	Headache	CH	Bilateral pHypo	Unspecified	3 years	Long-lasting pain relief without the need for pharmaceutical prophylaxis and without major side effects.
Franzini et al. 2003	5	Headache	CH	Bilateral, unilateral pHypo	180 Hz, 60 µs, 0.7-3 V	2-18 months	All patients benefited from complete pain control within 4 months of starting DBS
	1	Headache	CH	Bilateral pHypo	Unspecified	R: 22 months L: 12 months	R: complete pain control after 1 month; L: immediate pain control
	3	Headache	CH	L pHypo	Unspecified	2-18 months	Complete pain control after 2 months (n=2); complete pain control after 48 hours (n=1)

	1	Headache	CH	R pHypo	Unspecified	7 months	Complete pain control after 4 months
Leone et al. 2001	1	Headache	CH	L pHypo	180 Hz, 60 µs, 3 V	13 months	Pain free under continuous stimulation; pain recurred within 48 hours of stimulation cessation
MEDIAL FOREBRAIN BUNDLE (MFB)							
Coenen et al. 2019a	24	Uniplar depression, bipolar depression	TRD	Bilateral slMFB	130 Hz, 60 µs, 3 mA	N/A	Clinical outcomes reported in **Schlaepfer et al. 2013 & Coenen et al. 2019**; L fronto-polar/orbitofrontal volume found to differentiate responders from non-responders on pre-op MRI
Coenen et al. 2019b	16	Unipolar depression (n=15), bipolar depression (n=1)	TRD	Bilateral slMFB	131 Hz, 60 µs, 3 mA	12 months	50% of patients considered remitters (MADRS<10); significant overall MADRS, HAMD, QoL improvement compared to baseline; no difference in cognitive domains compared to baseline
Fenoy et al. 2018	6	Unipolar depression	TRD	Bilateral slMFB	130 Hz, 60 µs, 3-4 V	12 months (n=5); 1 week (n=1, drop-out)	4 patients considered remitters (HAM-D<7) and responders (≥50% MADRS reduction) at 12 months, 1 considered non-responder, 1 dropped out; improvements from baseline observed at short-term (1 week; MADRS: 15-77%, CGI: 0-66%, HAM-A: -50-65%) and long-term (12 months; MADRS: 21-100%, CGI: 0-80%, HAM-A: 33-94%, HAM-D: 16-100%) follow-up
Blomstedt et al. 2017	1	Unipolar depression, anorexia nervosa	TRD	Bilateral MFB (bilateral electrodes implanted in bed nucleus of stria terminalis 24 months later)	130 Hz, 120 µs, ~3 V bipolar (initially) and 4.3V monopolar (after electrode revision)	24 months	37% MADRS reduction, 32% HAM-D reduction, 29% HAM-A reduction, 83% GAF improvement, 6% BMI reduction
Bewernick et al. 2017	8	Depression	TRD	Bilateral slMFB	N/A	12 months (primary outcome); up to 4 years (secondary outcomes)	6 patients considered responders (≥50% MADRS reduction), 50% considered remitters (MADRS<10) at 12 months post-op; improvements on MADRS, HAM-D, BDI, HAM-A, SF-36, and GAF maintained through long-term follow-up
Conen et al. 2017	2	OCD	Compulsive behaviour	Bilateral slMFB	130 Hz, 60 µs, 2.5-3.6 mA	12 months	Immediate and long-term improvement in compulsive behaviour; 35% YBOCS reduction in 1 patient, 50% YBOCS reduction in 1 patient at 12 months
Fenoy et al. 2016	4	Unipolar depression	TRD	Bilateral slMFB	130 Hz, 60 µs, 3-4 V	12 months	**See Fenoy et al. 2018**
Schlaepfer et al. 2013	7	Unipolar depression, bipolar depression	TRD	Bilateral slMFB	130 Hz, 60 µs, 2.3-4.9 mA	12 weeks	6 patients considered responders (≥50% MADRS improvement) after 2 days of stimulation; 4 had sustained improvement after 12 weeks
MESENCEPHALIC RETICULAR FORMATION (mRF)							
Yamamoto et al. 2013; Yamamoto et al. 2010; Yamamoto & Katayama. 2005; Yamamoto et al. 2005; Yamamoto et al. 2002; Katayama et al. 1991; Tsubokawa et al. 1990	2 (19 other patients received centromedian parafascicular thalamic DBS)	TBI, Vascular brain injury, Anoxic injury	Persistent vegetative state	mRF (cuneiform nucleus)	25 Hz	10+ years	8 of 21 patients treated with either mRF-DBS (n=2) or thalamic DBS (n=19) demonstrated improved levels of consciousness/arousal within 4-12 months of DBS onset (becoming able to speak or communicate non-verbally); all patients remained incapable of self-care
PERIAQUEDUCTAL GRAY/PERIVENTRICULAR GRAY (PAG/PVG)							
Hollingworth et al. 2017	3	Trigeminal anaethetica dolorsa, phantom limb pain, CPSP	Neuropathic pain	R PVG/PAG/CMPf (single electrode, n=2), R	10 Hz, 60-110 µs, 3.5-4.5 V	3 years	Improvement in pain severity and quality of life in all 3 patients

				PVG/PAG/CMPf (single electrode) & NAcc (n=1)			
	1	Trigeminal anaethetica dolorsa	Neuropathic pain	R PVG/PAG/CMPf	10 Hz, 60 µs, 4.5 V	3 years	89% VAS improvement
	1	Phantom limb pain	Neuropathic pain	R PVG/PAG/CMPf	10 Hz, 90 µs, 4 V	3 years	40% VAS improvement
	1	CPSP	Neuropathic pain	R PVG/PAG/CMPf & R NAc	10 Hz, 110 µs, 3.5 V	3 years	67% VAS improvement with PVG/PAG/CMPf-DBS; NAcc-DBS unhelpful and not used
Sim-Williams et al. 2017	5	Anaesthesia dolorosa, phantom limb pain	Neuropathic pain	Unilateral PAG & CMPf (n=4), unilateral PAG & VPL (n=1)	N/A	N/A	>50% improvement in pain and significant improvement in mood in all patients; acute PET imaging results reported
Gray et al. 2014	18	Phantom limb pain, CPSP, cephalalgia	Neuropathic pain	PVG/PAG	5–50 Hz, 60–450 ms, 0.3–5.8 V	6–73 months	Stimulation significantly associated with improvement of pain reduction (MPQ), quality of life (SF-36), level of disability, anxiety/depression (HADS), and deterioration of working memory
Boccard et al. 2013	21	Phantom limb pain, brachial plexus, CPSP, spine, cephalgia	Neuropathic pain	PVG	5-50 Hz, 200-450 µs, 0.5-5 V, Mean: 22.8 Hz, 193.8 µs, 2.3 V	2-4 years	Stimulation associated with long-term (>1 year) pain relief (MPQ/VAS), quality of life (SF-36, EQ-5D), and general heath state; DBS efficacy varied based on etiology
Pereira et al. 2013a	4	Various	Neuropathic pain	PVG	15-50 Hz, 120-300 µs, 1.5-3 V	1 week	28-100% VAS improvement; 250-300% NPS improvement
		Oral pain	Neuropathic pain		50 Hz, 120 µs, 2.9 V		28% VAS improvement
		Stroke	Neuropathic pain		50 Hz, 250 µs, 2.8 V		100% VAS improvement
		Phantom limb pain	Neuropathic pain		50 Hz, 300 µs, 3 V		60% VAS improvement; 250% NPS improvement
		Failed Back Surgery	Neuropathic pain		15 Hz, 210 µs, 1.5 V		70% VAS improvement; 300% NPS
Pereira et al. 2013 b	5	Stroke, oral facial pain, head trauma, cerebral arteriovenous malformation, phantom limb	Neuropathic pain	Unilateral PVG/PAG	10-80 Hz, 120-450 µs, 2-3 V	1 week	4 of 5 patients received beneficial pain relief during externalized trial stimulation
Papuc et al. 2013	1	Ischemic stroke and tremor	Neuropathic pain	PVG/PAG & VPL	5-100 Hz, 210 µs, 1.5-2.5 V	N/A	Some pain reduction with PVG/PAG-DBS alone; further relief and significant tremor reduction with combined PVG/PAG and VPL-DBS
Mallory et al. 2012	1	CPSP	Neuropathic pain	NAcc & sensory thalamus & PVG	130 Hz, 90-300 µs, 3-3.5 V	11 months	No pain relief with thalamic DBS; combined NAcc and PVG-DBS associated with pain reduction without adverse effects
Green et al. 2012	6	Glossopharyngeal neuralgia, brachial plexus injury, phantom limb pain, CPSP, brachial plexus injury	Neuropathic pain	PAG & VPL (n=5), PAG (n=1)	20-50 Hz, 90-450 µs, 0.5-7 V	9-81 months	No clinical outcome data reported
Hyam et al. 2012a	10	Hemibody pain, trigeminal neuralgia, facial pain, arm pain, phantom limb pain, occipital neuralgia	Pain	Unilateral PAG	5-40 Hz, 120-450 µs, 0.5-7.3 V	N/A	Acute lung function testing performed
Patel et al. 2011	1	CPSP	Neuropathic pain	PVG/PAG	10 Hz, 210 µs, 5.4 V	33 months	Refractory hypertension was controlled chronically with PVG stimulation
Carter et al. 2011	1	Phantom limb pain	Neuropathic pain	Unilateral PVG/PAG	40 Hz, 450 µs, 3.1 V	N/A	No clinical outcome data reported
Green et al. 2010	5	Phantom limb pain, oral/facial pain, CPSP, other etiologies	Neuropathic pain	Unilateral PVG/PAG	10-50 Hz, 20 µs, 3-4.5 V	N/A	No clinical outcome data reported
Pereira et al. 2010a	16	Amputation, cortical stroke, subcortical stroke, brainstem stroke, scalp schwannoma resection, thalamic stroke, brachial plexus avulsion,	Neuropathic pain	Rostral PAG	5-50 Hz, 60-450 µs, 1-5.8 V	N/A	No clinical outcome data reported

		malignancy, scalp trauma, spinal cord injury					
Pereira et al. 2010b	1	Facial pain	Neuropathic pain	PAG & VPM	50 Hz,120 µs, 2.9 V	1 year	PAG (not VPM) stimulation associated with long-term decrease in mean systolic and diastolic blood pressure (131/85 mmHg ON vs. 144/196 mmHG OFF) and partial pain reduction
Pickering et al. 2009	1	CPSP	Neuropathic pain	PVG	5 Hz, 240 µs, 2 V	4 months	40% pain reduction (NPS) that gradually lessened over time
Owen et al. 2008	4	Lower leg stump pain, brachial plexus injury, other etiologies causing hemibody pain	Neuropathic pain	Unilateral PVG	N/A	1 week	2 patients experienced complete pain relief, 1 had partial relief (MPQ)
Owen et al. 2007b	1	Lower leg stump pain	Neuropathic pain	PVG/PAG	N/A	N/A	Excellent pain reduction when using the deepest contact
Spooner et al. 2007	1	CPSP	Neuropathic pain	Unilateral PVG & bilateral cingulate gyrus	PVG: 20 Hz (low), 130 Hz (high); cingulate gyrus: 130 Hz	4 months	PVG and cingulate-DBS associated with pain reduction, mood improvement in mood, and reduced lidocaine use
Green et al. 2007	1	Oral pain	Neuropathic pain	PAG & VPM	30 Hz, 2 V	N/A	PVG stimulation reduce arterial blood pressure and pain. VPM stimulation had no effect on blood pressure, but improved pain relief
Kringelbach et al. 2007	1	phantom limb pain	Neuropathic pain	PVG/PAG	7 Hz, 300 µs, 1.5 V	N/A	74% pain reduction (MPQ) and corresponding changes in mid-anterior orbitofrontal and subgenual cingulate cortices (magnetoencephalography); pain returned immediately if stimulation interrupted
Pereira et al. 2007	2	Various	Neuropathic pain	PVG & VPL	N/A	1 year	34-43% VAS reduction; 5-65% MPQ reduction
		L hemibody pain	Neuropathic pain	R PVG and R VPL		1 year	43% VAS reduction; 65% MPQ reduction
		R arm pain	Neuropathic pain	L PVG & L VPL		1 year	34% VAS reduction; 5% MPQ reduction
Owen et al. 2007a	47	Post stroke pain, phantom limb pain, brachial plexus, anaesthesia dolorosa, spinal cord injury, other	Neuropathic pain	PVG, PVG & somatosensory thalamus	PVG: 120-450 Hz, 5-30 µs, 0.8-4.5 V Somatosensory thalamus: 60-400Hz, 10-50 µs, 0.7–4.4V	1-76 months	Of 27 with PVG-DBS or combined PVG and VPL/VPM-DBS not lost to follow-up, 13 had good-to-excellent pain relief (≥50% VAS improvement), 13 had moderate relief (20-50% VAS improvement), 1 had poor relief (<20% VAS improvement); PVG-DBS alone reduced VAS scores by 59% while combined PVG and VPL/VPM-DBS reduced VAS scores by 36%
Green et al. 2006b	16	phantom limb pain, thalamic hemorrhage, cortical infarction, post-traumatic head pain, pontine hemorrhage, occipital neuralgia, Post surgical supraorbital pain, brachial plexus injury	Neuropathic pain	Unilateral PAG (n=10), unilateral PAG & VPL (n=4), bilateral PAG (n=2)	5-80 Hz, 120-450µs, 0.5-5 V	1 week (VAS) 1 year (MPQ)	Ventral electrodes associated with greater pain reduction (VAS) compared to dorsal electrodes; acute blood pressure changes reported
Green et al. 2006a	11	Thalamic hemorrhage, thalamic infarct, brachial plexus injury, anesthesia dolorosa, postsurgical supraorbital pain, pontine hemorrhage, post-traumatic head pain	Neuropathic pain	Unilateral PVG (n=8), unilateral PVG & VPL (n=3)	50 Hz, 120µs, <3 V	1 year	4 patients had good-to-excellent pain relief (≥50% VAS improvement), 5 had moderate relief (20-50% VAS improvement), 2 had poor relief (<20% VAS improvement); PVG-DBS alone reduced VAS scores by 53% while combined PVG and VPL/VPM-DBS reduced VAS scores by 26%
Owen et al. 2006	12	CPSP	Neuropathic pain	PVG, PVG & VPL	N/A	27 months	Significant reduction in pain overall (48.8% VAS; 38% MCQ); 2 patients had good-to-excellent pain relief (≥50% VAS improvement), 7 had moderate relief (20-50% VAS improvement), 3 had poor relief (<20% VAS improvement)
Rasche et al. 2006	55	Various	Neuropathic pain (n=54), nociceptive pain (n=2)	PVG & VPL	N/A	0.5-8 years	21 patients had good-to-excellent pain relief (≥50% VAS improvement), 5 had moderate relief (25-50% VAS improvement), 29 had poor relief (<25% VAS improvement)

	13	Failed back surgery syndrome	Neuropathic pain	PVG & VPL		0.5-8 years	75-100 pain reduction in 4 patients, 50-75% reduction in 5 patients, 25-50% reduction in 1 patient, no benefit in 3 patients
	6	Complex regional pain syndrome	Neuropathic pain	PVG & VPL		2-8 years	75-100% pain reduction in 2 patients, 50-75% reduction in 2 patients, no benefit in 2 patients
	6	Dysesthesia dolorosa	Neuropathic pain	PVG & VPM		0.5-5 years	75-100% pain reduction in 2 patients, 50-75% reduction in 1 patient, 25-50% benefit in 1 patient, no benefit in 2 patients
	4	phantom limb pain	Neuropathic pain	PVG & VPL		0.5-6.5 years	75-100% pain reduction in 1 patient, 25-50% reduction in 1 patient, no benefit in 2 patients
	12	Spinal cord injury	Neuropathic pain	PVG & VPL		0.5-4 years	75-100% pain reduction in 1 patient, 25-50% reduction in 1 patient, 0-25% reduction in 3 patients, no benefit in 7 patients
	11	CPSP	Neuropathic pain	PVG & VPL		1-2.5 years	50-75% pain reduction in 1 patient, 25-50% reduction in 1 patient, no benefit in 9 patients
	1	Postherpetic neuralgia	Neuropathic pain	PVG & VPL		5.5 years	50-75% pain reduction
	2	Coccygodynia, polyarthritis	Nociceptive pain	PVG & VPL		1 year	50-75% pain reduction in 1 patient, no benefit in 1 patient
Hamani et al. 2006	8	CPSP (n=3), atypical face pain (n=2), phantom limb pain (n=1), syringomyelia (n=1)	Neuropathic pain	Ipsilateral PVG/PAG & VC	VC: 100 Hz, 90 ls, 2.1 V PVG: 100 Hz, 300 ls, 4.1 V	1 year	5 patients had initial benefit with PVG/PAG and VC-DBS and were internalized; only 1 (with syringomyelia) had good long-term benefit
Green et al. 2005	15	Various	Neuropathic pain	Unilateral PVG/PAG (n=11), unilateral PVG/PAG & VPL (n=4)	10 Hz, 120 ms, 4 V	N/A	Acute blood pressure changes reported
Bittar et al. 2005	3	phantom limb pain	Neuropathic pain	PVG & VPL (n=2), PVG (n=1)	N/A	8-20 months	55-70% pain reduction (MPQ)
Nandi & Aziz et al. 2004	11	NA	Neuropathic pain	PVG & VPL	5-35 Hz	3-36 months	Highest pain reduction seen with low frequency stimulation of PVG (5-35Hz), VPL stimulation alone was not to provide pain relief.
Nandi et al. et al. 2003	8	Various	Neuropathic pain	PVG & VPL	5-100 Hz		Moderate pain relief (20-50% VAS improvement) in 7 patients; 32-46% VAS score reduction overall
	1	Multiple Screlosis	Neuropathic pain	PVG & VPL		30 months	46% pain reduction (VAS)
	1	Trigeminal neuralgia	Neuropathic pain	PVG & VPL		N/A	N/A (not internalized)
	5	CPSP	Neuropathic pain	PVG & VPL		3-12 months	32-44% pain reduction (VAS)
	1	Chiari malformation	Neuropathic pain	PVG & VPL		3 months	32% pain reduction (VAS)
Nandi et al. 2002a	3 (1 other patient received VPL-DBS)	Various	Neuropathic pain	PVG & VPL (n=2), PVG (n=1)	25 Hz, 120 µs, 2.8 V	6 months	Moderate pain relief in 1 patient
	2	Hemibody pain	Neuropathic pain	PVG & VPL	25 Hz, 120 µs, 2.8 V	6 months	40% pain reduction (VAS) in 1 patient, no long-term benefit in 1 patient
	1	Face and leg pain	Neuropathic pain	PVG	N/A	N/A	No benefit
Nandi et al. 2002b	2	Trigeminal neuralgia, subarachnoid hemorrhage	Neuropathic pain	VPL/PVG	5-25 Hz	1 week	Both patients experienced pain relief (better relief with low frequency stimulation)
Phillips & Bhakta et al. 2000	1	CPSP, post-stroke paresis	Neuropathic pain & paresis	PVG	80 Hz, 200 ms, 2 V	5 months	Reduced arm/leg pain and improved voluntary movement
Rezai et al. 1999	3	Traumatic spinal cord injury	Neuropathic pain	PVG & thalamus, thalamus	25 - 50 Hz, 75-100 µs, 2 V	N/A	No clinical outcome data reported
Kumar et al. 1997	52	Failed back syndrome, peripheral neuropathy or radiculopathy, thalamic pain, trigeminal	Neuropathic pain	PVG, PVG & thalamus	25-50 Hz, 0.1-0.5 ms, 1-5 V	6-170 months	PVG-DBS reduced pain by at least 50% (VAS) in 46 patients

		neuropathy, traumatic spinal cord lesions, causalgic pain, phantom limb pain, carcinoma pain					
Vilela Filho et al. 1996	11	CPSP	Neuropathic pain	PVG & thalamus, PVG & ML	N/A	N/A	No clinical outcomes reported
Tasker & Vilela Filho et al. 1995	25	Peripheral pain	Neuropathic pain	PVG	N/A	N/A	No effect on pain
Young et al. 1993	9	Low-back pain, post-fracture thoracic back pain, post-traumatic neck & L arm pain, low back & bilateral leg pain, cervical nerve root injury, CPSP, thalamic pain syndrome, bilateral leg paresthesias & spasms, back & R leg pain	Neuropathic pain	R PVG (n=2), L PVG (n=1), R PVG & VPL (n=4), L PVG & VPL (n=2)	25-120 Hz, 0.1-0.5 µs	N/A	Acute pain levels and endogenous opioid levels reported (cerebrospinal fluid analysis)
Young et al. 1992	6	Intractable chronic pain	Pain Relief	Unilateral PBC (n=2), unilateral PBC & PVG/PAG (n=4)	50-60 Hz, 100 µs, 3-6 V	0.5-2 years	Good-to-excellent pain relief in 3 patients
		Spinal cord injury	Pain relief	R PVG & R PBC		2 years	Excellent pain relief
		Multiple myeloma	Pain relief	L PVG & L PBC		8 months	Good pain relief
		Post-herpetic neuralgia	Pain relief	R PVG & R PBC		Electrode not internalized	No pain relief
		Thalamic (central post-stroke) pain	Pain relief	L PAG & L PBC		3 months	No pain relief
Kumar et al. 1990	41	Failed back syndrome, multiple arachnoid cysts, peripheral nerve trauma, sciatic neuropathy, cancer pain, cauda equina syndrome, phantom limb pain	Pain	Unilateral PVG	25-50 Hz, 0.1-0.5 µs, 1-5 V	0.5-10 years	Amputation, CPSP, scalp schwannoma resection, thalamic stroke, brachial plexus avulsion, malignancy, scalp trauma, spinal cord injury
Young & Chambi et al. 1987	45	Various	Neuropathic pain	PAG/PVG	N/A	1 year	All patients experienced immediate pain reduction; at 1 year follow-up, 29 had good pain benefit, 4 had partial benefit due to DBS tolerance, 12 had no benefit due to tolerance
Hosobuchi et al. 1987	7	Head and neck malignancy	Chronic intractable pain	PAG	30 Hz, 0.5 ms, 0.5-1.5 mA	N/A	Pain outcomes not reported
Levy et al. 1987	94	Various	Neuropathic pain, nociceptive pain	PAG/PVG & VPL, PAG/PVG	10±5 Hz, 20-100 Hz, 1-5 V	2-14 years	Initial pain relief and hardware internalization in 47 patients; long-term relief in <40% of these internalized patients
	3	CPSP	Neuropathic pain	PAG/PVG			No benefit
	13	Peripheral neuropathies	Neuropathic pain	PAG/PVG			Initial pain relief/electrode internalization in 5 patients
	7	Facial anesthesia dolorosa	Neuropathic pain	PAG/PVG			Initial pain relief/electrode internalization in 2 patients
	7	Paraplegic pain	Neuropathic pain	PAG/PVG & VPL, PAG/PVG			Initial pain relief/electrode internalization in 2 patients
	2	Postcordoctomy dysesthesia	Neuropathic pain	PAG/PVG & VPL			Initial pain relief/electrode internalization in 1 patient
	2	Phantom limb pain	Neuropathic pain	PAG/PVG & VPL			No benefit
	4	Thoracic neuralgias	Neuropathic pain	PAG/PVG			Initial pain relief/electrode internalization in 3 patients
	4	Miscellaneous neuropathic pain	Neuropathic pain	PAG/PVG & VPL, PAG/PVG			Initial pain relief/electrode internalization in 4 patients
	47	Low back and skeletal pain	Nociceptive pain	PAG/PVG & VPL, PAG/PVG			Initial pain relief/electrode internalization in 28 patients

	5	Cancer pain	Nociceptive pain	PAG/PVG & VPL, PAG/PVG			Initial pain relief/electrode internalization in 2 patients
Hosobuchi et al. 1986	65	Herniated lumbar disc, cancer, peripheral neuropathy, cauda equina syndrome, nonmalignant abdominal pain, nonmalignant perineal pain, nonmalignant perineal pain, osteoporosis of spine, atypical facial pain	Neuropathic pain	Bilateral PAG & thalamus (n=36), bilateral PAG (n=29)	20-30 Hz, 2-4 V	2-14 years	50 patients considered 'successes' (not requiring narcotics for analgesia); 15 considered failures
Young & Brechner et al. 1986	17	Malignancy	Neuropathic pain	R PVG (n=1), bilateral PVG (n=10), L PVG & L VPL (n=3), R PVG & R VPL (n=3)	N/A	1-21 months	13 patients achieved virtually total short-term pain relief (no longer requiring narcotic analgesics) and 2 achieved partial short-term relief; 10 patients experienced long-term relief
Young et al. 1985	42 (6 other patients with somatosensory thalamus-DBS)	Various	Neuropathic pain	PVG/PAG, PVG/PAG & thalamus, PVG/PAG & internal capsule, thalamus	N/A	2-60 months	15 patients had excellent pain relief, 16 had partial pain relief, 11 had poor pain relief
	16	Failed Back Syndrome	Neuropathic pain	PVG/PAG	N/A		9 patients had excellent pain relief, 5 had partial pain relief, 2 had poor pain relief
	7	Cancer	Neuropathic pain	PVG/PAG & somatosensory thalamus	N/A		3 patients had excellent pain relief, 3 had partial pain relief, 1 had poor pain relief
	4	Post-operative pain	Neuropathic pain	PVG/PAG	N/A		1 patient had excellent pain relief, 1 had partial pain relief, 2 had poor pain relief
	4	Anesthesia dolorosa	Neuropathic pain	PVG/PAG	N/A		2 patients had partial pain relief, 2 had poor pain relief
	4	Brachial plexus avulsion	Neuropathic pain	PVG/PAG & somatosensory thalamus	N/A		2 patients had partial pain relief, 2 had poor pain relief
	4	Post-traumatic pain	Neuropathic pain	PVG/PAG & internal capsule	N/A		2 patients had excellent pain relief, 1 had partial pain relief, 1 had poor pain relief
	2	Post-herpetic neuralgia	Neuropathic pain	PVG/PAG	N/A		Partial pain relief
	1	Glossodynia	Neuropathic pain	PVG/PAG & somatosensory thalamus	N/A		Poor Pain relief
Tsubokawa et al. 1985	24	Phantom limb pain, stump pain, myelopathy, postherpetic neuralgia	Neuropathic pain	PAG & somatosensory thalamus	N/A	N/A	Pain relief with PAG-DBS in 3 patients
Roizen et al. 1985	33	N/A	Neuropathic pain	PAG	N/A	N/A	PAG-DBS 1 hour before surgery decreased anaesthetic requirements
Meyerson et al. 1985	6	N/A	Neuropathic pain	PVG	N/A	N/A	Concentration of substance-P-like immunoreactivity increased in lumbar CSF following stimulation (cerebrospinal fluid analysis)
Tsubokawa et al. 1984	1 (13 other patients with VPL DBS)	Rectal cancer (all patients had pain due to malignancy)	Pain	PAG	N/A	2 months	Somatic pain relief in 10 patients
Dionne et al. 1984	12	N/A	Neuropathic pain	PVG	N/A	Intra-operative	Increased levels of beta-endorphin not directly associated with pain relief
Hosobuchi et al. 1983	11	Back surgery, retroperitoneal schwannoma, injury	neuropathic pain	L PVG & somatosensory thalamus	NA	12-36 months	All patients had some pain relief (in 2 pain components); 4 patients experienced moderate headache, PVG-DBS became less effective after 12-18 months in 2 patients
Boivie & Meyerson et al. 1982	5	Pelvic malignancy	Pain	Unilateral PAG	30 Hz, 0.2 msec, 0.2-0.4 mA	N/A	Pain relief in 3 patients
Richardson et al. 1982	9	CPSP, deafferentation pain, chest wall pain, failed back syndromes	Pain	PVG/PAG	N/A	N/A	Significant pain relief in 4 patients
Dieckmann and	46	Brachial plexus avulsion, phantom limb	Neuropathic pain	PVG, VPM/VPL	30-60 Hz	up to 4.5 years	Long-term improvement in pain in 32 patients

Witzmann et al. 1982		pain, anaesthesia dolorosa, thalamic pain, post-herpetic neuralgia, postcordotomy dysesthesia					
Plotkin et al. 1982	48	Carcinoma lung, cervical spondylosis, sciatic nerve entrapment, non-united fracture femur, paraparesis, quadriparesis, diffuse disc disease, stump pain, osteoporosis, failed low back syndrome	Chronic intractable pain	PVG	N/A	4-18 months	38 patients became pain-free or experienced substantial pain relief
Hosobuschi et al. 1979	6	Postcordotomy dysesthesia, thalamic syndrome, lumbosacroarachnoiditis, carcinoma of rectum, carcinoma of colon	Pain	PAG, posterior limb of the internal capsule	N/A	N/A	PAG stimulation associated with significant increase in intraventricular beta-endorphin
Akil et al. 1978	8	N/A	Pain	PVG	N/A	N/A	Increase of enkepahlin-like activity upon stimulation
Richardson & Akil et al.1977a	4	Various	Neuropathic pain	PAG	25-75 Hz, 3.5-5 V	N/A	Good-to-excellent pain relief in 3 patients
		Amputation procedure	Neuropathic pain	Anterior PAG	25-75 Hz, 0-5 V	N/A	Good-to-excellent pain relief
		Carcinoma of breast	Neuropathic pain	Posterior PAG	50-75 Hz, 3.5V	N/A	Good-to-very good pain relief
		Carcinoma of L ureter and kidney	Neuropathic pain	Posterior PAG	75 Hz, <2 V	N/A	Small degree of pain relief
		Post-stroke tremor	Neuropathic pain	Rostral PAG	75 Hz, 4-5 V	N/A	Very good pain relief
Richardson & Akil et al.1977b	8	Various	Neuropathic pain	Bilateral PVG (n=4), unilateral PVG (n=4)	10-25 Hz, 0.6-1 V	N/A	6 patients experienced good-to-excellent pain relief
	4	Lumbar disc disease, malignancy, brachial plexus injury	Neuropathic pain	Bilateral PVG	10-25 Hz, 0.2 ms, 1V	N/A	Good to excellent pain relief
	4	Vertebral disc disease	Neuropathic pain	Unilateral PVG	N/A	N/A	2 with poor pain relief, 2 with good pain relief
Hosobuschi et al. 1977	6	Carcinoma of larynx, carcinoma of rectum, carcinoma of colon, diabetic neuropathy, sacral cordoma, anaesthesia dolorosa	Neuropathic pain	L PVG, bilateral PVG		5-18 months	Complete pain reduction in 5 patients
PEDUNCULOPONTINE NUCLEUS (PPN)							
Goetz et al. 2019	11	PD	Axial disability	Bilateral PPN & STN (n=7), bilateral PPN(n=4)	10-30 Hz, 0.8-3.8 V	2 years	Significant composite gait score improvement (UPDRS-derived) versus baseline (OFF-med); 58% freezing of gait duration reduction at 12 months, 57% reduction at 24 months (OFF-med)
	7	PD	Axial disability	Bilateral PPN & STN	R: 25 Hz, 1.4-3.8 V L: 25 Hz, 1.2-3.3 V		4 good responders, 1 mild responder, 2 bad responders
	4	PD	Axial disability	Bilateral PPN	R: 25 Hz, 0.8-2 V L: 25Hz, 0.81-1.5 V		2 good responders, 1 excluded due to protocol noncompliance, 1 excluded due to severe backward fall
Strumpf et al. 2016	6	PD	Axial disability	Bilateral STN & PPN (n=3), bilateral PPN (n=2), R PPN (n=1)	8-20 Hz (LFS)/60 Hz (HFS) 60 µs, 1-2.5 V	3-13 months	In 5 patients, greater difference in visual signal required to discern a difference under low frequency conditions versus high frequency or no stimulation conditions
Mestre et al. 2016	9	PD	Axial disability	Unilateral PPN	5-130 Hz; 60-120 µs; 1.9 V (range from 0.7-3.8 V)	4 years	At 2 years, patient-reported freezing (UPDRS part II, off-time) was significantly better when compared with baseline with 62.5% of responders; at 4 years, there was no significant change in gait-related items of UPDRS part II

Yousif et al. 2016	4	PD	Axial disability	Bilateral STN & PPN	20-30Hz, 0.6-1.8V	N/A	Lowered vestibular perceptual thresholds with PPN-ON versus PPN-OFF
Nosko et al. 2015	11	PD	Axial disability	Bilateral STN & PPN, Bilateral PPN	N/A	1 year	Compared with 60–80 Hz, 10–25 Hz PPNa stimulation led to decreased akinesia, gait difficulties, daytime sleepiness in 7 patients
Ricciardi et al. 2015	1	PD (& Pisa Syndrome)	Axial disability	Unilateral PPN	30 Hz, 60 µs, 2 V (bipolar stimulation)	4 years	Gradual worsening of full UPDRS-III and subscores 27-30 over time despite PPN-DBS; general cognitive worsening (especially short-term memory, semantic verbal fluency, object naming) observed after PPN-DBS switched OFF and reversed over 2 months following switching stimulation back ON
Welter et al. 2015	6	PD	Axial disability	Bilateral PPN	Unspecified	4-6 months	Significant decrease in freezing episodes in 4 patients, reduced falls in 3 patients, and significantly improved quality of life with PPN-DBS
Mazzone et al. 2014	10	PD	Axial disability	R PPTg (n=9), L PPTg (n=1)	40 Hz, 60 µs, 2.5-3.0 V	1 year	47% UPDRS-III items 27-30 improvement (med-ON); lower does of L-dopa required; improved gait initiation, cadence, stride length, left pelvic tilt range of motion, and backward shift of centre of pressure on gait analysis
Mazzone et al. 2013	26	PD (22) PSP (4)	Axial disability	Bilateral PPTg (n=6) L PPTg (n=1) R PPTg (n=20)	25 Hz (n=6)/40 Hz (n=20), 60 µs, 4.3-6.9 V (PSP)/2.1-4.5 V (PD)	1 month	59% UPDRS-III improvement with PPTg-DBS versus DBS-OFF (OFF-med); 44% items 27-30 improvement (OFF-med); 41% Hoehn % Yahr improvement
Shih et al. 2013		Pisa Syndrome	Axial disability	L PPN	130Hz, 90µs, 1.5V	14 months	Improvement in axial lean with a reduction in falls
Schrader et al. 2013	1	PD	Axial disability	Bilateral GPi & PPN	PPN: 25 Hz, 60 µs, 2.5 V GPI: 130 Hz, 210 µs, 3 V	4 weeks	Combined GPi and PPN-DBS markedly improved freezing of gait, gait ignition, and unsteadiness; GPi-DBS or PPN-DBS alone had a mild effect
Hazrati et al. 2012	2	PSP	Axial disability	Unilateral PPN		3 months 6 months	Minor UPDRS-III improvement versus DBS-OFF, mild PSPRS improvement in 1 patient
		PSP	Axial disability	R PPN	20 Hz, 60 µs, 3.0 V	3 months	11% UPDRS-III and 6% PSPRS improvement versus DBS-OFF
		PSP	Axial disability	L PPN	20 Hz, 60 µs, 1.8 V	6 months	5% UPDRS-III improvement, no PSPRS improvement versus DBS-OFF
Jenkinson et al. 2012	2	PD	Axial disability	Bilateral PPN	20 Hz, 60-90 µs, 2.5 V	N/A	25-30% UPDRS-III items 27-30 improvement; decreased fall frequency; acute eye movements recorded
Khan et al. 2012b	4	PD	Axial disability	Bilateral PPN/caudal ZI	PPN: 25-60 Hz, 60 µs, 1.9-3 V ZI: 60 Hz, 60 µs, 3-3.5 V	24 months (3-44)	PPN-DBS: 19% total UPDRS-III improvement (off-med); 33% items 27-30 improvement (off-med); zona incerta-DBS: 47% total UPDRS-III improvement (off-med); 41% items 27-30 improvement (off-med); combined PPN/zona incerta-DBS: 47% total UPDRS-III improvement (off-med); 50% items 27-30 improvement (off-med)
Khan et al. 2012a	5	PD	Axial disability	Bilateral PPN Bilateral caudal ZI	Unspecified	12-60 months (mean of 27 mths)	Bilateral PPN-DBS: 18% motor UPDRS improvement; bilateral ZI-DBS: 31% motor UPDRS improvement; combined unilateral PPN & bilateral ZI-DBS stimulation: 35% motor UPDRS improvement; combined bilateral PPN & ZI-DBS: 42% motor UPDRS improvement
Mazzone et al. 2012	14	PD	Axial disability	Unilateral PPN	25 Hz, 60 µs, less than 2.5-3.0 V	1 month for UPDRS, 7-10 days for jaw analysis	59% mean improvement in UPDRS motor scores from pre-op baseline (OFF-med); 47% mean improvement on items 27-30 and 54% mean improvement on items 18-19 (OFF-med)
Insola et al. 2012	10	PD	Axial disability	Unilateral PPN	N/A	N/A	N/A
Peppe et al. 2012	5	PD	Axial disability	Bilateral STN & PPTg	STN: 185 Hz, 90µs, 2.1-2.9V PPN: 25 Hz, 60 µs, 1.8-2.2 V	3 months, 1 year	At 3 months: 27% UPDRS-III improvement with combined PPTg/STN-DBS versus STN-DBS alone at 3 months; 41% PDSS mean global score increase with STN-ON, 35% increase with PPTg-ON, and 57% increase with PPTg-cycle

							At 1 year: 26% UPDRS-III improvement with combined PPTg/STN-DBS or STN-DBS alone
Thevathasan et al. 2012	7	PD	Axial disability	Bilateral PPN	36-42 Hz, 60 µs, 2.2–4.3 V	2-29 months	Bilateral PPN-DBS: reduced turn task duration by 58%, unilateral PPN-DBS by 36%; bilateral stimulation associated with greater cadence percent improvement
Aviles-Olmos et al. 2011	1	PD	Axial disability	R PPN	30 Hz, 60 µs, 3 V	6 months	No objective change on UPDRS III subscores 28 and 30; improved freezing and walking velocity as per gait analysis
Caliandro et al. 2011	3	PD	Axial disability	R PPN (n =2), L PPN (n =1)	25 Hz, 60 µs, 1.5-2.0 V	Unspecified	Increased tibialis anterior activation during steady state of gait; extent of increased activation correlated with lower UPDRS-III; no significant improvement in UPDRS-III
Ceravolo et al. 2011	6	PD	Axial disability	Bilateral PPN & STN	25 Hz	12 months	Significantly improved delayed recall/executive functions; mean UPDRS improvement of 21% (variable outcomes)
Franzini et al. 2011	1	PD	Axial disability	R PPN	25 Hz, 60 µs, 2 V	6 months	48% UPDDRS-III improvement; improved hand dexterity
Khan et al. 2011	7	PD	Axial disability	Bilateral PPN & caudal zona incerta	PPN: 60 Hz, 60 µs, 2.4 V	12 months	Off medication, PPN stimulation improved the motor UPDRS by 18.8% (mean = 43.1+14., p=0.01). PPN stimulation improved the motor UPDRS axial subscore by 26.3%. On medication, PPN stimulation improved UPDRS by 17.9% (mean = 24.9±11.6, p = 0.03). Combined PPN/ZI stimulation: UPDRS axial subscore improved by 50 and 49% (off and on meds).
Thevathasan et al. 2011a	8	PD	Axial disability	Bilateral mid-lower PPN	30 or 35 Hz, 60µs, 2.5–4.3V	6-34 months	PPN-DBS restored 'StartReact'; UPDRS-III items 27-30 improvement noted in 5 patients, GFQ improvement in 6, FOGQ improvement in 5, FallsQ in 3
Thevathasan et al. 2011b	5	PD	Axial disability	Bilateral mid-lower PPN	35 Hz, 60 µs, mean 3.5 V	2 years	47% mean GFQ improvement (significant improvement from baseline at 6 months and 2 years); improved FOGQ in all patients; improvement in OFF-med UPDRS-III items 27-30 in all patients
Wilcox et al. 2011	1	PPFG	Axial disability	Bilateral PPN	35 Hz, 60 µs, 2.8-3.8 V	14 months	64% GFQ and 50% FOGQ improvement; notable increase in stride length, cadence, walking velocity; reduced time spent in double-limb support; improvement in mediolateral but not anteroposterior standing balance; subacute PET imaging findings reported
Arnulf et al. 2010	2	PD	Axial disability	Bilateral PPN	PPN: 15-25 Hz, 60 or 90 µs, 1.2-3.8 V	1 year	Moderate to major improvement of all gait measures
Stefani et al. 2010c	6	PD	Axial disability	Bilateral STN & PPN	PPN: 25 Hz, 60 µs, 1.5-2.0 V	Unspecified	PPN-DBS improved delayed recall, executive function, phonemic fluency in all patients; 2 patients who underwent sleep architecture testing showed increased sleep efficiency (from <80% to >90%), mildly reduced Stage 1, increased Stage 2 and REM, and decreased awakenings
Costa et al. 2010	5	PD	Axial disability	Bilateral STN & PPN	PPN: 25 Hz, 60 µs, 1.8-2.2 V	≥3 months	29% UPDRS-III improvement; acute effect of DBS on *n-back* task and reaction time reported
Ferraye et al. 2010a	6	PD	Axial disability	Bilateral STN & PPN	PPN: 15-25 Hz, 60 or 90 µs, 1.2-3.8 V	1 year	Open-label improvement in duration of freezing episodes (med-OFF) and freezing-related falls but not gait or postural stability; no significant change from DBS-OFF observed in double-blind evaluation
Ostrem et al. 2010	1	PPFG	Axial disability	Bilateral PPN	25 Hz, 60 µs, 4.9/4.4 V (L/R)	Preop: 3 month 6 month 12 month	UPDRS-III total unchanged from baseline; mild improvement of timed gait measures; worsening of UPDRS daily living subscore
Peppe et al. 2010	5	PD	Axial disability	Bilateral STN & PPTg	PPN: 25 Hz, 60 µs, 1.5-2.0 V	≥1 year	Combined STN and PPTg-DBS associated with significant differences in mean gait velocity in OFF-med but not ON-med condition
Schweder et al. 2010	1	PD	Axial disability	Bilateral PPN	Unspecified	12 months	PPN-DBB associated with 42% GFQ improvement and 14% FOGQ improvement;

							PPN-DBS reduced cortical and brainstem connectivity and normalized (increased) cerebellar connectivity (probabilistic tractography)
Stefani et al. 2010b	1	PD	Axial disability	Bilateral STN & PPN	PPN: 20 Hz (initially ON only during sleep; later ON continuously with STN DBS)	~1-2 years	Bedtime PPN-DBS': increased verbal fluency and working memory; restored rapid-eye movement sleep phases; increased 'well-being'; continuous PPN-DBS: severe dopamine dysregulation syndrome (pathological gambling, compulsive shopping, hypersexuality, drug craving) developed after several weeks of continuous stimulation - relieved by switching off PPN-DBS
Stefani et al. 2010a	6	PD	Axial disability	Bilateral STN & PPN	PPN: 25 Hz, 60 µs, 1.4-2.4 V	≥1 year	Increased verbal fluency and working memory; state of 'well-being' with occasional euphoria; restoration of REM sleep phases; increased rCBF in various prefrontal cortical areas and left ventral striatum, amongst other metabolic changes (PET imaging)
Thevathasan et al. 2010	11	PD	Axial disability	Bilateral PPN (n=8), bilateral PPN & zona incerta (n=3)	30 Hz, 60 µs, 2.0-3.7 V	2-38 months	Chronic stimulation improved fall frequency; fall score improvement correlated with improvement in reaction time (assessed acutely following PPN stimulation)
Moro et al. 2010	6	PD	Axial disability	Unilateral PPN	5-130 Hz; 60-120 µs; 1.9 V (range from 0.7-3.8 V)	3 and 12 months	Significant open-label improvement in overall ON-DBS UPDRS score at 3 and 12 months versus baseline (tendency for decline in motor improvement between 3 and 12 months); no significant difference between ON and OFF UPDRS-II/UPDRS-III scores during double-blind assessment
Ballanger et al. 2009	3	PD	Axial Disability	Unilateral PPN	50-90 Hz, 60-120 µs, 1.4-2.6 V	4-22 months	Variable improvement in total clinical and axial outcomes; acute PET imaging findings reported
	2	PD	Axial Disability	L PPN	70-90 Hz, 70-120 µs, 1.4-2.6 V	22 months	UPDRS-III total worsened by 7.5-34.2%. Items 28-30 improved by 16.7-53.8%
	1	PD	Axial Disability	R PPN	50 Hz, 60 µs, 1.4 V	4 months	UPDRS-III total worsened by 14.3%. Items 28-30 was unchanged
Ferraye et al. 2009	2	PD	Axial Disability	Bilateral PPN	N/A	N/A	No clinical results reported
Lim et al. 2009	5	PD, PSP	Axial disability	Unilateral PPN	5-70 Hz, 1-2.8 V	4-12 months	1-22% increase in REM sleep
	3	PD	Axial disability	unilateral PPN	70 Hz, 1-2.3 V	4 months	REM% increased by 2-14%
	2	PSP	Axial disability	unilateral PPN	5-30 Hz, 2-2.8 V	7 months	REM% increased by 1-7%
Zanini et al. 2009	5	PD	Axial disability	Bilateral STN & PPN	PPN: 25 Hz, 60 µs, 1.5-2.2 V	6-12 months	Stimulation of STN, PPN, or both targets showed a trend towards reduction of grammatical errors.
Romigi et al. 2008	1	PD	Axial disability	Bilateral STN & PPN	PPN: 25 Hz, 2 V, 60 µs	1 year	PPN-DBS improved sleep efficiency and increased REM up to 12.9%
Strafella et al. 2008	1	PD	Axial disability	L PPN	70 Hz, 90 µs, 2.2 V	3 months	19% UPDRS-III improvement with PPN-DBS versus stimulation-OFF; increased rCBF to thalamus, putamen, cerebellum, and insular cortex (PET imaging)
Plaha et al. 2007	11 (only 2 patients received PPN stimulation)	PD	Parkinsonism	Bilateral PPN	N/A	N/A	N/A
Stefani et al. 2007	6	PD	Axial disability	Bilateral STN & PPN	PPN: 25 Hz, 60 µs, 1.5-2.0 V	3 months	66% UPDRS-III improvement with combined STN and PPN-DBS (most effective configuration)
Plaha & Gill et al. 2005	2	PD	Axial disability	Bilateral PPN	20-25 Hz, 90 µs, 2.5-4.0 V	16-42 days	Improvement in total clinical outcomes and axial domains; 50-55% total UPDRS-III improvement; 40-67% items 27-30 improvement
Mazzone et al. 2005	2	PD	Axial disability	Bilateral PPN	10 or 80 Hz, 60 µs, 2 V	Acute only	No clinical results reported

LOCUS COERULEUS (LC)							
Feinstein et al. 1989	3	Cerebral Palsy and Epilepsy		LC			
		Cerebral palsy	Spasticity	L LC & L dentate nucleus & R RN	60 Hz, 120 µs, 0.2 mA	N/A (long term)	Increased ease of feeding/decreased choking on food; reduced REM and non-REM sleep; patient more quiet/relaxed
		Epilepsy	Seizure	LC (side unknown)	50 Hz, 100 µs, 0.9mA	7 months	50% decrease in required medication dosage at 3 weeks; decreased seizure frequency (from 3-22 seizures/mo to 0-7 per month) at 7 months
		Epilepsy	Seizure	R LC	0.2-0.4 mA	6 weeks	Lengthening of pre-seizure aura to ~10-30 mins (permitting time to self-inject diazepam). Generally shorter-lasting seizures
PARABRACHIAL COMPLEX (PBC)							
Young et al. 1992	6	Intractable chronic pain	Pain Relief	Unilateral PBC (n=2), unilateral PBC & PVG/PAG (n=4)	50-60 Hz, 100 µs, 3-6 V	0.5-2 years	Good-to-excellent pain relief in 3 patients
		Spinal cord injury	Pain relief	R PVG & R PBC		2 years	Excellent pain relief
		Post-herpetic neuralgia	Pain relief	R PBC		3 months	Excellent pain relief
		Multiple myeloma	Pain relief	L PVG & L PBC		8 months	Good pain relief
		Post-herpetic neuralgia	Pain relief	R PBC		6 months	No pain relief
		Post-herpetic neuralgia	Pain relief	R PVG & R PBC		Electrode not internalized	No pain relief
		Thalamic (central post-stroke) pain	Pain relief	L PAG & L PBC		3 months	No pain relief
Katayama et al. 1985	2	Opioid-resistant chronic pain due to lung cancer	Pain relief	Unilateral PBC & sensory thalamus	10-30 Hz	2 months	Intermittent PBC stimulation provided sufficient pain reduction to not require analgesics; thalamic stimulation alone did not confer satisfactory pain relief
SUPERIOR CEREBELLAR PEDUNCLE (SCP)							
Horisawa et al. 2019	1	Fixed Dystonia	Increased muscle tone and pain	SCP, dentate nucleus	200 Hz, 150 µs, 8 V	6 months	Ipsilateral body relaxation and pain reduction; improved trunk opisthotonus and neck dystonia; improved ADLs
Harat et al. 2009	13	Cerebral Palsy	Increased muscle tone	SCP	N/A	2 years	Reduced muscle tone in 11 patients; speech improvement in 7 patients; mood improvement and decreased pain in all patients; decreased frequency/intensity of seizures in patients with epilepsy
Galanda & Hovath et al. 1997	32	Cerebral palsy (n=31), stroke (n=1)	Spasticity and dyskinesias	SCP	200 Hz, 1-0.2 mA, 1-6 V (3-8 times/day for 15-20 mins)	N/A	Decreased hypertonus/spasticity (stopping stimulation resulted in recurrence of spasticity); decreased involuntary movements (gradually, after ~1 month of stimulation)

Abbreviations. **ADL** = activities of daily living; **BDI** = Beck's depression inventory; **BP** = blood pressure; **CGI** = Clinical global impressions; **CH** = cluster headache; **CPSP** = central post-stroke pain; **CRPS** = complex regional pain syndrome; **CSF** = cerebrospinal fluid; **DBS** = deep brain stimulation; **ESS** = Epworth sleepiness scale; **EQ-5D** = European quality of life - 5D; **FallsQ** = falls questionnaire; **fMRI** = functional magnetic resonance imaging; **FOGQ** = freezing of gait questionnaire; **GAF** = global assessment of function; **GPi** = globus pallidus internus; **HAMA** = Hamilton Anxiety rating scale; **HAMD** = Hamilton depression rating scale; **Hz** = hertz; **L** = left; **LC** = locus coeruleus; **MADRS** = Montgomery-Asberg Depression Rating scale; **MFB** = medial forebrain bundle; **ML** = medial lemniscus; **mmHg** = millimeters of mercury; **MPQ** = Mcgill pain questionnaire; **mRF** = mesencephalic reticular formation; **MS** = multiple sclerosis; **N/A** = not applicable; **NAcc** = nucleus accumbens; **NPS** = neuropathic pain scale; **OCD** = obsessive compulsive disorder; **PAG** = periaqueductal gray; **PBC** = parabrachial complex; **PD** = Parkinson's disease; **PPFG** = primary progressive freezing of gait; **PDSS** = Parkinson's disease sleep scale; **PET** = positron emission tomography; **PME** = progressive myoclonic epilepsy; **PPN** = pedunculopontine nucleus; **PSP** = progressive supranuclear palsy; **PSPRS** = progressive supranuclear palsy rating scale; **PVG** = periventricular gray; **QoL** = quality of life; **R** = right; **REM** = rapid eye movement sleep; **RN** = red nucleus; **SC** = superior colliculus; **SCP** = superior cerebellar peduncles; **SF-36** = 36 item short form survey; sl**MFB** = superolateral branch of medial forebrain bundle **SN** = substantia nigra; **SNr** = substantia nigra pars reticulata; **STN** = subthalamic nucleus; **SUNCT** = short lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing; **TBI** = traumatic brain injury; **TRD** = treatment resistant depression; **UPDRS** = unified Parkinson's disease rating scale; **V** = volts; **VAS** = visual analogue scale; **VPL** = ventral posterolateral nucleus; **VPM** = ventral posteromedial nucleus; **VTA** = ventral tegmental area; **YBOCS** = Yale-Brown Obsessive Compulsive Disorder; **Zi** = zona incerta.

Table 2 - Acute effects of Brainstem DBS. Table cataloguing the acute effects associated with stimulation of brainstem targets, as reported by brainstem DBS studies.

Study	n	Reported substrate	Stimulation parameters	Reported acute effects of stimulation
SUBSTANTIA NIGRA (SN)				
Ulla et al. 2011	5	Bilateral SN/STN	130 Hz, 60 µs, 2-4 V	Sustained elevated mood (>1 hour) after less than 5 minutes of stimulation at SN-located contacts; increased rCBF in dorsal anterior cingulate, right primary motor, medial prefrontal cortex, right pallidum and decreased rCBF in left temporal cortex and bilateral occipital cortex in manic versus euthymic condition (PET imaging)
Blomstedt et al. 2008	1	R SN pars reticulata (most ventral contact prior to 2 mm retraction of lead)	120 Hz, 60 µs, 2V	Decreased rigidity; sorrowful affect/crying, depressed mood ('everything is so dark', depressed mood confirmed by patient), transient suicidal ideation beginning within a few seconds of stimulation and ending within 10 seconds of stimulation cessation
Vesper et al. 2007	1	Bilateral SN pars reticulata (ventral contacts)/STN (dorsal contacts)	130 Hz, 90 µs, started at 2.3 V increased to 3 V	Dysesthesias in hands (subsided after a few minutes)
Ulla et al. 2006	1	Bilateral SN (STN was intended target)	130 Hz, 60 µs, 2.2 V, at ventral-most contacts	Manic symptoms (mood exaltation, inflated self-esteem/overestimation of self-capacities leading to frequent falls, logorrhea associated with flight of ideas, distractibility, psychomotor agitation, subsequent emotional lability) reversibly elicited after 45 minutes of stimulation
Kulisevsky et al. 2002	3	Bilateral SN pars reticulata (STN was intended target)	130 Hz, 60 µs, 2 V	Manic symptoms elicited (elation, inflated self- esteem, overactivity, logorrhea with flight of ideas, sexual indiscretion, and insomnia) within 48 hr of stimulation onset
Bejjani et al. 1999	1	Bilateral SN pars compacta and pars reticulata (STN was intended target) - only L side stimulated SN at most ventral contacts	L SN: 130 Hz, 60 µs, 2.4 V at ventral-most contact	Depressed mood, negative affect (crying, agitation), illusion of bodily motion elicited within 5 seconds of stimulation onset and disappeared ~1 minute after stimulation cessation (replaced by mild hypomanic state for next 5 minutes); increased rCBF in right parietal lobe, left orbitofrontal cortex, left globus pallidus, left amygdala, and left anterior thalamus in L SN-DBS ON vs OFF state (PET imaging)
RED NUCLEUS (RN)				
Lefranc et al. 2014	1	L RN	20/60/130 Hz, 2-7 mA	Increased intentional tremor intensity, confusion, dysautonomic symptoms (tachycardia, flushing, polypnoea) with higher amplitude stimulation; paresthesias (with lower/middle RN stimulation), oculomotor dysfunction (with upper/lower RN stimulation) at lower frequencies only
Bejjani et al. 2002	4	L (n=1) and bilateral (n=3 - only one side stimulated at a time) white matter between red nucleus and anterodorsal substantia nigra (in vicinity of oculomotor nerve)	130 Hz, 60 µs, 1-3 V	Contralateral upper limb tremor & dystonic pressure, ipsilateral diplopia (impaired abduction and vertical eye movements), enophthalmos; immediately reversible with stimulation cessation
Feinstein* et al. 1989	1	R RN	150 Hz, 200 µs, 0.3-0.6 mA	Inadequate spasticity control in left upper extremity (both arms loosened initially but tightened again after 10 minutes of stimulation); strabismus at higher amplitude
VENTRAL TEGMENTAL AREA (VTA)/POSTERIOR HYPOTHALAMUS (pHypo)				
Akram et al, 2017	7	Bilateral VTA	N/A	Transient dizziness, intermittent diplopia, nausea
Akram et al, 2016	21	Bilateral VTA	185 Hz, 60 µs	Diplopia, vertigo, oscillopsia, ophthalmoplegia
Leone et al, 2013	19	Bilateral pHypo	180 Hz, 60 µs, 7 V	Short lasting vertigo and transient double vision
Maniyar et al, 2012	1	L pHypo	185 Hz, 60 µs, 2 V	Repeated paroxysms of sneezing
Seijo et al, 2011	5	Bilateral pHypo	130 Hz, 60-12 µs, 2-3.5 V	Persistent myosis, euphoria, dizziness, blurring vision, concentration difficulties, cervical dystonia, generalized headache, increased appetite
Fontaine et al, 2010	11	Bilateral pHypo	185 Hz, 60 µs, 3 V	Transient hemiparesis and loss of consciousness, micturition syncopes
Lyons et al, 2009	1	L pHypo	160 Hz, 90 µs, 1-4 V	Significant erectile dysfunction, jaw pulling and leg jerking

Bartsch et al, 2008	6	L pHypo	13-35 Hz, 60 µs, 1-3.5V	Arterial hypertension, diplopia, vertigo, feelings of panic
Kuhn et al, 2008	1	Bilateral pHypo	130 Hz, 90 µs, 1-5 V	Pleasant sense of inner pacification
Broggi et al, 2007	20	Bilateral pHypo	180 Hz, 60 µs, 1-3 V	Asymptotic orthostatic hypotension triggered by electrical stimulation
Leone et al, 2006	16	Bilateral pHypo	180 Hz, 60 µs, 4-5 V	Acute stimulation begun/ramped up upon CH attack onset caused side-effects (sweating, dizziness, diplopia, other visual disturbances) in 28/136 CH attacks, ≥50% pain reduction in 25/136 attacks, and complete pain relief in 17/136 attacks
Schoenen et al, 2005	4	Unilateral pHypo	185 Hz, 60-90 µs, 2-4.5 V	Diplopia and dizziness occurred in all patients at above 1.5 V
Franzini et al, 2003	5	Bilateral pHypo	180 Hz, 60 µs, 1-7 V	Conjugated ocular deviation in all patients with stimulation of >4 V
MEDIAL FOREBRAIN BUNDLE (MFB)				
Schlaepfer et al. 2013	7	Bilateral slMFB	2.3-4.9 mA	Blurred vision, strabismus, dizziness, increased sweating reported at higher stimulation amplitudes
Fenoy et al. 2018; Fenoy et al. 2016	6	Bilateral slMFB	8-10 V; >8.5 V	Transient/reversible diplopia reported in all patients during stimulation of certain contacts/during larger parameter changes
Blomstedt et al. 2017	1	Bilateral slMFB	>3 V (prior to electrode revision)	Blurred vision
Bewernick et al. 2017	8	Bilateral slMFB	N/A	Strabismus/oculomotor changes (n=8) & blurred vision (n=5) reported at higher voltages, especially at lowest contact, Other effects reported were dizziness (n=4), intraocular pressure (n=2), sweating (n=2) blood pressure decrease (n=1 patient), dyskinesia (n=1), and sensation of 'internal unrest' (n=1).
Coenen et al. 2017	2	Bilateral slMFB	3.5-3.6 mA	Tachycardia, oculomotor changes at the deepest contact
Coenen et al. 2019	16	Bilateral slMFB	>3 mA	Oculomotor symptoms, transient hypomania (n=6), restlessness (n=1), dyskinesia (n=1)
MESENCEPHALIC RETICULAR FORMATION (mRF)				
Tsubokawa et al. 1990; Katayama et al. 1991; Yamamoto et al. 2002; Yamamoto et al. 2005; Yamamoto & Katayama, 2005; Yamamoto et al. 2010; Yamamoto et al. 2013	2	Unilateral mRF	25-50 Hz, variable voltage	Immediate strong arousal responses (eye opening, pupil dilation, mouth opening/meaningless vocalization, slight movement of extremities, minor increase in systemic blood pressure)
PERIAQUEDUCTAL GRAY/PERIVENTRICULAR GRAY (PAG/PVG)				
Hollingworth et al. 2017	3	PVG/PAG	10 Hz, 60-110 µs, 3.5-4.5 V	Cold sensation (n=1), warm sensation and reduced cold pain (n=1), reduced allodynia (n=1)
Sim-Williams et al. 2017	5	Unilateral rostral dorsal/lateral PAG	N/A	ON-DBS and OFF-DBS PET imaging scans performed 4.5 hours apart showed increased opioid peptide binding in caudal dorsal PAG with analgesic PAG-DBS but no blood flow changes; systemic naloxone administration did not affect analgesic effect of DBS
Gray et al. 2014	N/A	Bilateral superior PVG	10-50 Hz, 120 µs, 5 V	Warm feeling or paresthesia in the area of pain/pain suppression
Pereira et al. 2013b	5	Unilateral PVG/PAG	10-80 Hz, 120-450 µs, 2-3 V	Rostral PVG/PAG stimulation produced warmth sensation/analgesia in the legs, caudal stimulation in arms and then face; stimulation altered somatosensory evoked potential in corresponding areas
Papuc et al. 2013	1	Bilateral PVG/PAG	50 Hz	Alleviation of thalamic hand tremor; paresthesia in the contralateral limb
Boccard et al. 2013	85	Bilateral posterior PVG	22.8 ± 11.4 Hz, 193.8 ± 104.5 µs, 2.3 ± 1.1 V	Occasional sensation of warmth, pain relief in contralateral painful body areas
Green et al. 2012	6	PAG & VPL (n=5), PAG (n=1)	20-50 Hz, 90-450 µs, 0.5-7 V	PAG stimulation associated with higher maximum cystometric capacity
Hyam et al. 2012a	10	Unilateral PAG	5-40 Hz, 120-450 µs, 0.5-7.3 V	Stimulation associated with increased peak expiratory flow rate (13±5%); no change in forced vital capacity

Mallory et al. 2012	1	R PVG/PAG	130 Hz, 300 µs, 3.5 V	Eye deviation; pain relief
Carter et al. 2011	1	Unilateral PVG/PAG	40 Hz, 450 µs, 3.1 V	Stimulation associated with transient increase then persistent decrease in mean brachial blood pressure (7%), increased brachial artery flow (106%), decreased total peripheral resistance (15%), increased stroke volume (13%), and cardiac output (12%)
Patel et al. 2011	1	Unilateral PVG/PAG	10 Hz, 210 µs, 5.4 V	Gradual decrease in blood pressure starting immediately after stimulation onset
Green et al. 2010	5	Unilateral PVG/PAG	10-50 Hz, 20 µs, 3-4.5 V	Altered systolic/diastolic blood pressure and heart rate variability
Pereira et al. 2010	16	Rostral PAG	5-50 Hz, 60-450 µs, 1-5.8 V	Ventral but not dorsal PAG stimulation altered heart rate variability (decreasing LF/HF power ratio); LF/HF ratio changes correlated with subjective reporting of analgesic efficacy (VAS)
Pickering et al. 2009	1	R PVG/PAG	5 Hz, 240 µs, 2 V	Pain reduction and improvement in allodynia; degree of somatotopy evident: proximal electrodes affected lower limbs, distal electrodes affected face/upper limbs
Owen et al. 2007a	47	Bilateral VPL, PVG	5-30 Hz, 120-450 µs, 2-4V	Pain relief; sensation of warmth; eye bobbing (at intensity double that required for sensory effects)
Pereira et al. 2007	3	Bilateral VPL, PVG	50 Hz, 50 µs, 2.9 V	Reduced pain
Green et al. 2006b	16	Unilateral (n=14) and Bilateral (n=2) PAG	5-80 Hz, 120-450µs, 0.5-5 V	Decreased (n=7; mean reduction: 13+/-6 mmHg), or increased (n=4; mean increase: 12+/-6 mmHg) systolic blood pressure
Hamani et al. 2006	21	Bilateral VPL, PVG	25-120 Hz, 60-250 µs, <10 V	'Pleasant sensation of warmth' with 25-50 Hz PVG stimulation (n=2); anxiety with >100 Hz PVG stimulation (n=1); medial eye deviation (n=1)
Owen et al. 2006	15	Bilateral proximal part of PVG/PAG	N/A	Paresthesias and sensation of warmth in contralateral area of pain; 'eye bobbing' induced at intensity of stimulation at least twice that required for sensory effects
Rasche et al. 2006	56	Bilateral VPL, PVG, medial lemniscus	40-70 Hz	Feeling of warmth, floating, and dizziness (50 Hz, 210 us); below AC-PC line, diplopia, gaze deviation, or gaze paralysis; blood pressure and heart rate elevation and anxiety (at higher intensities); pain (at higher, suprathreshold intensities)
		Bilateral medial lemniscus	40-70 Hz	Paresthesias in the contralateral body with more posterior stimulation
Green et al. 2005 (PMID:16237319)	15	Unilateral PVG/PAG (n=11), unilateral PVG/PAG and VPL thalamus (n=4)	10Hz, 120 µs, 4 V	Ventral PVG/PAG stimulation (n=7) reduced arterial blood pressure (mean systolic decrease: 14±4 mmHg) while dorsal stimulation (n=6) increased arterial blood pressure (mean systolic increase: 17±6); thalamic stimulation produced no blood pressure changes
Nandi & Aziz, 2004	24	Bilateral VPL, PVG (combined or separate)	5-35 Hz	Sensation of warmth in area of pain (n=17); pain relief (n=17)
Nandi et al. 2003	8	Bilateral PVG	5-35 Hz	Sensation of warmth in area of pain; satisfactory pain relief (n=6)
Nandi et al. 2002b	2	L (contralateral to pain) VPL & PVG	9.6 V	Fit induced during post-op titration
Phillips & Bhakta, 2000	1	L PVG	80 Hz, 200 µs, 2 V	Improvement in voluntary movement in paretic arm/leg; pain relief during rest
Rezai et al. 1999	3	PVG	25 - 50 Hz, 75-100 µs, 2 V	Generalized, diffuse warm sensation with corresponding activation of cingulate cortex (fMRI)
Filho et al. 1996	11	PVG, VC, medial lemniscus	N/A	VC and medial lemniscus stimulation induced unpleasant paresthesias (n=6); PVG stimulation alone induced pleasant (n=5) paresthesias
Young et al. 1993	9	Unilateral PVG (n=3), unilateral PVG & VPL (n=6)	25-120 Hz, 0.1-0.5 µs	Both PVG and VPL-DBS reduced pain (VAS) acutely; PVG-DBS but not VPL-DBS associated with acute increases in CSF beta-endorphin and methionine-enkephalin levels (cerebrospinal fluid analysis)
Kumar et al. 1990	38	Unilateral PVG	25-50 Hz, 0.1-0.5 µs, 1-5 V	Contralateral warmth/cold sensations, pleasure/sense of relaxation; pain reduction reported after 10 minutes of intra-operative stimulation in some cases
		Edinger-Westphal nuclei/oculomotor nerve nuclei	25-50 Hz, 0.1-0.5 µs, 1-5 V	Blurred vision, (at higher amplitudes) oscillopsia, nystagmus, upward gaze palsy
		Medial lemniscus	25-50 Hz, 0.1-0.5 µs, 1-5 V	Contralateral face paresthesias
Levy et al. 1987	1	PAG/PVG	N/A	Patient immediately fell asleep upon stimulation initiation
Hosobuchi et al. 1987	5	Dorsal PAG	N/A	Immediate pain relief (n=7), nausea (n=5), fright/"funny feeling" (n=1), cold sensation in face/oropharynx (n=2), contralateral piloerection (n=1)

Kumar et al. 1987	2	PAG	Best stimulation parameters are 25-50Hz, 0.1-0.5 µs,1-5V	Blurred vision
	15	PAG	Best stimulation parameters are 25-50Hz,0.1-0.5 µs,1-5V	Migraine-like symptoms
Young et al. 1985	2	PAG	N/A	Eye movement disorder
Richardson et al. 1982	9	PVG/PAG	N/A	Vertigo (n=1), tingling (n=2), warmth (n=3), increased pulse and blood pressure (n=1)
Richardson & et al. Akil 1977a	4	PAG	25-75 Hz, 3.5-5 V	Mild dizziness (n=3), nausea (n=1), contralateral arm paresthesias (n=1), chest tightness (n=1), nystagmus/conjugate deviation (n=1)
Richardson & Akil et al.1977b	8	PVG	10-25 Hz, 0.6-1 V	Paresthesias, heat/cold sensation, blurred vision, nystagmus, dizziness, mouth dryness
PEDUNCULOPONTINE NUCLEUS (PPN)				
Mazzone et al. 2013	N/A	PPTg	N/A	Contralateral hemibody paresthesias elicited by stimulation onset or amplitude increase - disappeared spontaneously over time
Jenkinson et al. 2012	2	Bilateral PPN region (possibly affecting SCP and uncinate fasciculus of the cerebellum)	5-20 Hz, 60 µs, 2.5 V	Transient 'shimmering' visual percept and small amplitude horizontal eye movement (eye movement frequency matched stimulation frequency) in 1 patient
Mazzone et al. 2012	N/A	Unilateral PPTg	25 Hz, 60 µs, <2.5-3 V	Contralateral hemibody paresthesias elicited by stimulation onset, disappeared spontaneously within a few minutes
Aviles-Olmos et al. 2011	1	R most caudal contact	N/A	Involuntary urinary voiding
Khan et al. 2011	N/A	Bilateral medial longitudinal fasciculus (lowest contact)	N/A	Upward gaze palsy at higher voltages
	N/A	Bilateral laterally placed medial lemniscus	N/A	Paresthesia at higher voltages
Franzini et al. 2011	1	L PPN	25 Hz, 60 µs, 2 V	Improvement of hand dexterity
Wilcox et al. 2011	1	Bilateral PPN	35 Hz, 60 µs, 2.8-3.8 V	ON-DBS and OFF-DBS PET imaging scans performed 4 days apart showed normalization of hypoactive cerebellar and brainstem regions with PPN stimulation
Moro et al. 2010	6	Unilateral PPN (with suspected medial lemniscus, oculomotor system, spinothalamic tract involvement)	2-185 Hz, 60 µs	Contralateral paresthesias in 6 patients; oscillopsia in 5 patients; contralateral warm sensation in 3 patients
Stefani et al. 2010	1	Unilateral PPTg	20 Hz	State of well-being occasionally perturbed by euphoria
Thevathasan et al. 2010a	8	Unilateral PPN (n=8), unilateral PPN & zona incerta (n=3)	20-35 Hz, 60 µs, 2.0-3.7 V	PPN-DBS improved reaction time, gait, and balance
Ferraye et al. 2010a	N/A	Bilateral PPN	25-130 Hz	Contralateral hemibody paresthesias (and pleasant heat sensation in 1 patient) at 130 Hz; ipsilateral oscillopsia and bilateral limb myoclonus at higher amplitudes of 25 Hz
Arnulf et al. 2010	2	Bilateral PPN	Low frequency: 10-25 Hz; high frequency: 80 Hz	Increased alertness with low frequency stimulation; non-rapid eye movement sleep induced by high frequency stimulation
Costa et al. 2010	5	Bilateral PPN, STN	PPN: 25 Hz, 60 µs, 2 V	PPN-DBS improved average response times on *n-back* task versus OFF-stimulation condition; *d*isturbing paresthesia commonly reported with PPN stimulation onset that always disappeared in <3 min at low voltage/frequency settings
Thevathasan et al. 2010	11	Bilateral PPN and zona incerta (ZI)	20-35 Hz	Improvement in items 27-30 of motor UPDRS but residual UPDRS did not change with therapeutic stimulation
Ferraye et al. 2009	2	Bilateral PPN, oculomotor nerve	5-25 Hz	Trembling' vision; no clinically observable abnormal eye movement but frequency-locked, voltage-dependent vertical/oblique movements of ipsilateral eye detected with oculomotor recording
Ballanger et al. 2009	3	Unilateral PPN	50-90 Hz, 60-120 µs, 1.4-2.6 V	Increased glucose metabolism in bilateral thalamus, cerebellum, and ipsilateral ventral midbrain within 30 minutes of turning PPN stimulation ON; cortical metabolism changes also observed
Ostrem et al. 2009	1	Bilateral PPN	<5 V	Visual effect (shimmer)
Plaha et al. 2008	2	Bilateral PPN	Maximal stimulation at 5-80 Hz, 90 µs	Pins and needles in arms with and without diplopia
Stefani et al. 2007	N/A	Bilateral PPN	N/A	Paresthesias that disappeared in <3 minutes (unless high frequency or high volume was delivered)

Mazzone et al. 2005	2	Bilateral PPN	10 or 80 Hz, 60 µs, 2 V	Improved finger tapping at 10 Hz; modest worsening of finger tapping at 80Hz; feeling of 'well-being' at all settings
Plaha & Gill, 2005	2	Bilateral PPN, medial longitudinal fasciculus, medial lemniscus	"High frequency", 90 µs, 2.5-4 V	Upper gaze palsy with stimulation of the lowermost contact adjacent to medial longitudinal fasciculus; paresthesias with stimulation of upper three contacts near to laterally placed medial lemniscus
LOCUS COERULEUS (LC)				
Feinstein et al. 1989	1	L LC	60 Hz, 120 µs, 0.2 mA	Increased motility of fingers, arms and legs and greater ROM in shoulders and wrists
SUPERIOR CEREBELLAR PEDUNCLE (SCP)				
Horisawa et al. 2019	1	Bilateral SCP, Dentate nucleus	8-10 V	Ipsilateral relaxation at lower voltages; forced laughter, nystagmus, ipsilateral eye deviation at >8.5 V
Galanda & Hovath et al. 1997	32	SCP	200 Hz, 1-0.2 mA, 1-6 V	Muscle tone/spasticity reduction over 15-20 minutes following stimulation onset; intense feeling of pleasure (diminishing over time); reversible side-effects (pronounced posture, dyskinesias, feeling of fear) at higher amplitudes

Abbreviations. r**CBF** = regional cerebral blood flow; **CH** = cluster headache; **DBS** = deep brain stimulation; **Hz** = hertz; **L** = left; **LC** = locus coeruleus; **MFB** = medial forebrain bundle; **ML** = medial lemniscus; **mmHg** = millimeters of mercury; **mRF** = mesencephalic reticular formation; **N/A** = not applicable; **PAG** = periaqueductal gray; **PBC** = parabrachial complex; **PD** = Parkinson's disease; **PET** = positron emission tomography; **PPN** = pedunculopontine nucleus; **PSP** = progressive supranuclear palsy; **PVG** = periventricular gray; **R** = right; **RN** = red nucleus; **SC** = superior colliculus; **SCP** = superior cerebellar peduncles; **SN** = substantia nigra; **SNr** = substantia nigra pars reticulata; **STN** = subthalamic nucleus; **V** = volts; **VAS** = visual analogue scale; **VPL** = ventral posterolateral nucleus; **VPM** = ventral posteromedial nucleus; **VTA** = ventral tegmental area; **Zi** = zona incerta.

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