Review

Neurobiological effects of deep brain stimulation: A systematic review of molecular brain imaging studies

Aleksi Kokkonen [a,b,1,*], Emma A. Honkanen [a,b,1], Daniel T. Corp [c,d], Juho Joutsa [a,b,d,*]

[a] Turku Brain and Mind Center, Clinical Neurosciences, University of Turku, Turku, Finland
[b] Turku PET Center, Neurocenter, Turku University Hospital, Turku, Finland
[c] Cognitive Neuroscience Unit, School of Psychology, Deakin University, Geelong, Australia
[d] Center for Brain Circuit Therapeutics, Brigham and Women's Hospital, Boston, MA, United States of America

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ABSTRACT

Deep brain stimulation (DBS) is an established treatment for several brain disorders, including Parkinson's disease, essential tremor, dystonia and epilepsy, and an emerging therapeutic tool in many other neurological and psychiatric disorders. The therapeutic efficacy of DBS is dependent on the stimulation target, but its mechanisms of action are still relatively poorly understood. Investigating these mechanisms is challenging, partly because the stimulation devices and electrodes have limited the use of functional MRI in these patients. Molecular brain imaging techniques, such as positron emission tomography (PET) and single photon emission tomography (SPET), offer a unique opportunity to characterize the whole brain effects of DBS. Here, we investigated the direct effects of DBS by systematically reviewing studies performing an 'on' vs 'off' contrast during PET or SPET imaging. We identified 62 studies (56 PET and 6 SPET studies; 531 subjects). Approximately half of the studies focused on cerebral blood flow or glucose metabolism in patients Parkinson's disease undergoing subthalamic DBS (25 studies, $n = 289$), therefore Activation Likelihood Estimation analysis was performed on these studies. Across disorders and stimulation targets, DBS was associated with a robust local increase in ligand uptake at the stimulation site and target-specific remote network effects. Subthalamic nucleus stimulation in Parkinson's disease showed a specific pattern of changes in the motor circuit, including increased ligand uptake in the basal ganglia, and decreased ligand uptake in the primary motor cortex, supplementary motor area and cerebellum. However, there was only a handful of studies investigating other brain disorder and stimulation site combinations (1–3 studies each), or specific neurotransmitter systems, preventing definitive conclusions of the detailed molecular effects of the stimulation in these cases.

1. Introduction

Deep brain stimulation (DBS) is a neuromodulation technique where electrodes with multiple stimulation contacts are stereotactically implanted into specific targets in the brain. In contrast to irreversible surgical lesions, DBS is based on high frequency electrical stimuli to the target structure from the implanted electrodes causing reversible effects to the brain. (Aum and Tierney, 2018) Currently, DBS is widely used to treat neurological and psychiatric syndromes, such as Parkinson's disease, essential tremor, dystonia, epilepsy and obsessive-compulsive disorder (Lee et al., 2019; Lozano et al., 2019). DBS has also shown some efficacy in various other diseases, including depression, chronic pain and dementias (Frizon et al., 2020; Hardenacke et al., 2013; Holtzheimer et al., 2017).

Many of the currently used DBS targets have been derived from earlier neurosurgical lesion targets (Baron et al., 1996; Benabid et al., 1991; Benazzouz et al., 1993; Bergman et al., 1990; Lozano et al., 1995; Siegfried and Lippitz, 1994). Initially, due to the clinical effects mimicking surgical lesions, DBS was considered to cause a virtual lesion (Dostrovsky and Lozano, 2002). However, later studies have also shown that DBS is associated with increased regional neuronal firing rates (Hashimoto et al., 2003), increased cerebral blood flow (Hershey et al., 2003) and increased glucose metabolism (Volonté et al., 2012). The current hypotheses of the mechanisms of action include direct activation and inhibition of neural activity, and disruption of information flow and synaptic filtering (Lozano et al., 2019).

Neuroimaging of patients with DBS is challenging. Until recently, the use of MRI in patients with DBS has been limited because of safety concerns as strong magnetic fields can cause DBS device heating and tissue damage, interfere with DBS function or cause malfunction of

the device (Boutet et al., 2020). Currently, many of the devices are cleared for specific MRI protocols, such as GE-EPI (gradient-echo echo-planar imaging), which has been shown to have low SAR (specific absorption rates) and minimal electrode heating at both 1.5 and 3T (Carmichael et al., 2007) and body transmit at 1.5T (Kahan et al., 2014). Studies using MRI have demonstrated network effects of DBS, and suggested that, for example, functional connectivity and patient specific pathway activation models could be valuable in predicting treatment response (Gunalan et al., 2017; Kahan et al., 2014; Saenger et al., 2017; Younce et al., 2021). However, there are still limitations with the scanners and imaging sequences, issues that interfere with the MRI signal quality and the time window of functional MRI may not be optimal for investigating all effects of DBS (Saleh et al., 2016).

Molecular imaging techniques, including positron emission tomography (PET) and single photon emission tomography (SPET) have been safely been applied in patients with DBS for more than two decades (Ceballos-Baumann et al., 1999; Fukuda et al., 2001). Available ligands can be used to measure e.g., changes in brain regional blood flow, tissue metabolism and neurotransmitter function, proving a unique opportunity to comprehensively study the neurobiological effects of DBS in the living human brain. However, PET and SPET have their own limitations compared to functional MRI, such as poor temporal resolution, use of ionizing radiation, more limited availability, and relatively high costs.

A number of PET and SPET studies have investigated the neurobiological effects of DBS. However, the findings are heterogeneous and the results may be confounded by the effects of surgery, disease progression, and interventions during scanning. Thus, the aim of this study was to perform a systematic literature review on PET and SPET outcomes regarding the studies of DBS 'on' vs 'off' scanning at rest across all target sites and brain diseases

2. Methods

2.1. Literature search

A systematic search was conducted using PubMed from database inception until August 5th, 2021. The Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement was followed (Moher et al. 2016). We searched for original articles of human studies investigating the acute effects of DBS using PET or SPET imaging. To focus on the direct acute effects of DBS, only studies directly comparing the imaging results in DBS 'on' and 'off' while patients were at rest were included in the final sample.

Article selection process is described in Fig. 1. The search syntaxes were formed combining '(DBS OR deep brain stimulation)' with '(pet OR positron emission tomography)' or '(spect OR spet OR single photon)'. The original search returned 502 publications. All titles and abstracts of these publications were reviewed by the investigators. The inclusion criteria were brain PET/SPET imaging performed in patients with DBS, an original research article written in English, and at least three patients included in the study. Altogether 160 articles were selected for full review of the paper. After reading the full paper articles were excluded if 1) the PET or SPET imaging was not conducted in both DBS 'on' and 'off' condition, 2) did not include imaging results while patients were at rest to exclude task-related effects on imaging, 3) did not report DBS 'on' vs 'off' contrast or 4) was a re-analysis/duplicate of published data already included in our review. Two studies (Hilker et al., 2004, 2008) including partially same subjects were included in the review as different imaging analysis methods were applied (Voxel-wise and region of interest (ROI)). This resulted in 60 original research articles. In addition, two articles not captured by our search were identified from the references of the included articles.

Altogether, 62 original articles matched the inclusion criteria and were included in this review. Study design, demographic information (clinical condition, sample size, treatment duration), DBS target, imaging parameters (tracer, analysis method) and significant imaging outcomes were collected from the articles.

2.2. ALE meta-analysis

To investigate the network-level effects of DBS we conducted an Activation Likelihood Estimation (ALE) meta-analysis of studies measuring whole brain regional blood flow or metabolism in Parkinson's disease with subthalamic nucleus (STN) DBS (15 studies, $n = 149$). Other brain disorder and stimulation site combinations did not have sufficient number of studies for ALE meta-analysis ($n \leq 3$ each). All studies that conducted whole brain analyses and reported coordinates in Montreal Neurological Institute (MNI) or Talairach space were included in the analyses. Talairach coordinates were converted to MNI, as described earlier (Lancaster et al., 2007). The coordinates are based on the statistical thresholds used in each article.

The ALE meta-analysis was conducted using GingerALE (v3.2; http://www.brainmap.org/ale/) (Eickhoff et al., 2009). As per the most recent recommendations (Eickhoff et al., 2012, 2016), each analysis was performed with cluster-forming thresholds of $p < 0.001$ (uncorrected), 1000 permutations, and a cluster-level inference threshold correcting for multiple comparisons with family-wise error rate (FWE) at $p < 0.05$. Separate analyses were run for coordinates of increased and decreased ligand uptake, combining both imaging techniques (PET and SPET) in the same analyses. To ensure that the results were not dependent on the imaging type (blood flow vs. glucose metabolism), the analyses were repeated separately for studies measuring brain regional blood flow (9 studies, $n = 105$) and metabolism (6 studies, $n = 44$) and compared between these two imaging types. The statistical threshold was set to $p < 0.001$ (uncorrected) and minimum cluster size of 200 mm^3 (Eres et al., 2018; Laird et al., 2005).

3. Results

A summary of the 62 studies included in the qualitative review is shown in Table 1. The vast majority of included studies investigated Parkinson's disease (38 studies, 61% of all studies). Of these 38 studies, the most common stimulation target was the STN (29 studies), followed by globus pallidus interna/externa (GPi/GPe) (3 studies), ventral intermediate nucleus of thalamus (VIM) (3 studies), and pedunculopontine nucleus (PPN) (3 studies).

The next commonly studied disorder / stimulation site combinations were dystonia with GPi-DBS (3 studies in primary dystonia, 2 studies in secondary dystonia), and essential tremor with VIM-DBS (3 studies), which are both established and widely used in clinical practice. The ventral capsule/ventral striatum (VC/VS) DBS in Obsessive-Compulsive Disorder (OCD) was also investigated by three individual studies. In all other disorder / stimulation site combinations, there was only a single study investigating either regional cerebral blood flow, glucose metabolism or a neurotransmitter function (dopamine/opioid/serotonin).

The details of individual studies and main findings are listed in Table 2 . There was considerable variation study design, patient populations, analysis methods, and sample sizes between studies. In general, the sample sizes were modest [sample size mean 8.6 (SD 5.4), median 7.5 (range 3–31)]. Most of the studies investigated patients with bilaterally implanted electrodes.

Given that the vast majority of studies (57 studies, 92% of all studies) investigated either regional cerebral blood flow (rCBF) or glucose metabolism, we review these studies according to the disease (first neurological, then psychiatric) and stimulation site. The remaining five studies investigating specific neurotransmitter systems will then be reviewed in a subsequent section.
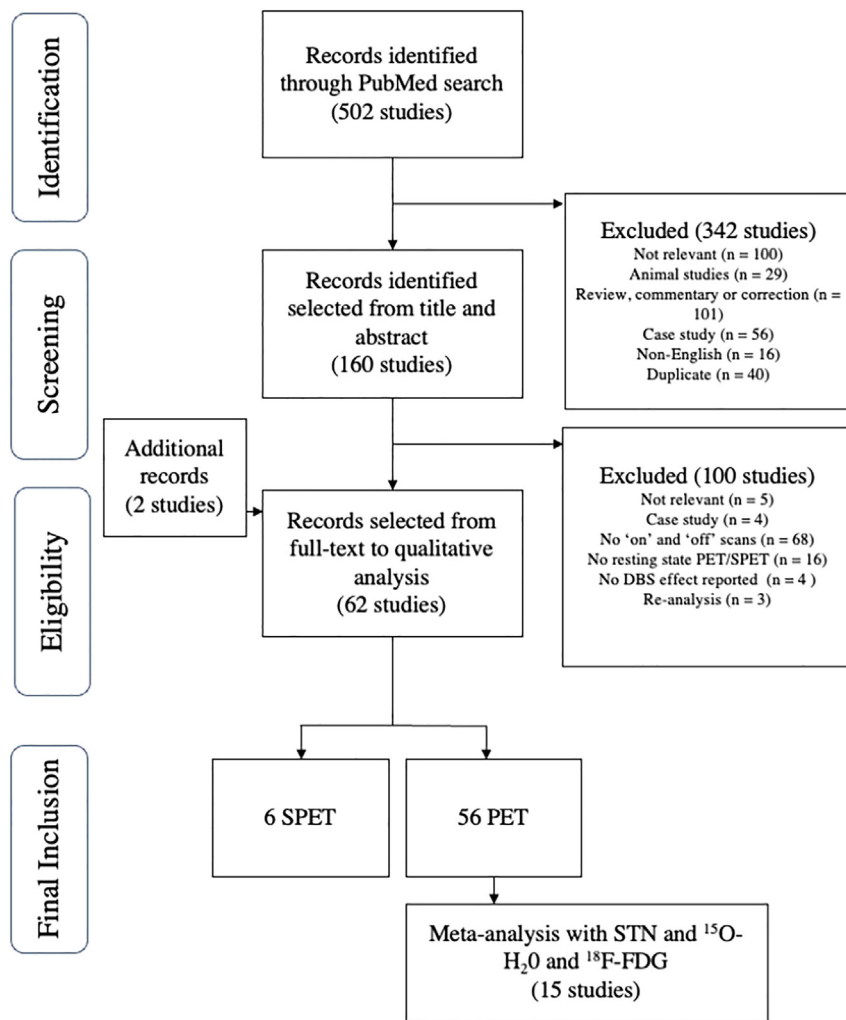
3.1. Diseases

3.1.1. Parkinson's disease (PD)

The mean (SD, range) number of subjects in PD studies was 9.7 (6.3, 3–31) and the DBS treatment duration at the time of study ranged from approximately 1 month to 2.5 years (Table 2). The 'on/off' time before scans were typically tens of minutes in studies investigating rCBF and >12 h in studies investigating glucose metabolism. Most of the studies used a counterbalanced design to control for the order of the scans between patients.

3.1.1.1. Subthalamic nucleus. Of the 29 studies investigating the effects of STN-DBS in PD, 24 used ^{15}O-H$_2$O or ^{18}F-FDG to measure rCBF or glucose metabolism, respectively (Table 1). Approximately half of the studies reported increase of blood flow or metabolism at the stimulation site (12 studies) and there were no reports of decreased ligand uptake at the stimulation site. The remote effects included both increased and decreased ligand uptake, most commonly in the basal ganglia, sensorimotor cortical regions and cerebellum (Table 2). However, there was considerable variation in the exact brain locations with DBS-induced response in remote brain regions across individual studies (Fig. 2).

STN-DBS studies in PD investigating rCBF or glucose metabolism was the only disease / stimulation site combination with sufficient number of studies for an ALE meta-analysis (15 studies, $n = 149$). In this analysis, there was a significant increase of ligand uptake proximal to the stimulation site (subthalamic area, globus pallidus, and thalamus) (Fig. 3A, Table 3). In addition, there was a significant decrease of ligand uptake

in the primary motor cortex, supplementary motor area (SMA) and cerebellum (Fig. 3B, Table 3). There was no significant difference in ALE results between studies investigating regional blood flow and metabolism (**Figure S1**). Thus, STN-DBS seems to produce both consistent increases ligand uptake in brain, locally at the stimulation site and connected basal ganglia nuclei, while the remote effects of STN-DBS within the motor network appear to decrease the ligand uptake.

3.1.1.2. Globus pallidus. Only three small studies ($n = 5$–7 each) investigated effects of GPi-DBS in PD (Table 2). One of the studies also had some subjects with GPe electrodes in addition to GPi electrodes but the effects of these two stimulation sites were tested separately (Payoux et al., 2009).

In contrast to the findings with STN-DBS, GPi-DBS was not associated with changes in blood flow or metabolism at the stimulation site. This could be explained by the lower number of studies and subjects investigating GPi-DBS, or reflect different neuronal populations activated between these two regions. Interestingly, STN-DBS also induced changes in GPi, but the none of the GPi-DBS studies showed any changes in STN, which may reflect effects on different basal ganglia circuits depending on the stimulation site (Jakobs et al., 2019). Similarly, the clinical effects of STN and GPi-DBS also differ, as dopaminergic medication can usually be substantially reduced with STN-DBS (Ramirez-Zamora and Ostrem, 2018). In the remote regions, increase in regional blood flow was seen in the putamen (Payoux et al., 2009). GPi stimulation also increased glucose metabolism in the premotor cortex (PMC) (Fukuda et al., 2001) but decreased rCBF in the sensorimotor cortex,

Table 1
Clinical conditions, DBS targets and tracers.

Condition	DBS target	Tracer				
		rCBF		*rCMRglc*	*dopamine*	*other*
		^{15}O-H$_2$O	other	^{18}F-FDG		
Parkinson's Disease (38)	STN	14 *	^{99m}Tc-ECD	12 *	2x [^{11}C]raclopride ^{18}F-FDOPA ^ [^{11}C]DTBZ	5-HT$_{1B}$R
	GPi/GPe	2		1		
	VIM	1	^{99m}Tc-ECD	1		
	PPN[1]	2		1		
Primary dystonia (3)	GPi	2	^{99m}Tc-ECD			
Secondary dystonia (2)	GPi[2]	1	^{99m}Tc-ECD			
Essential tremor (4)	VIM	3				
	Thalamus			1		
Huntington's Disease	GPe	1				
Cluster headache	Hypothalamus	1				
Neuropathic pain	PAG	1 #				[^{11}C]DPN #
Tourette's syndrome	GPi and CM/Voi		^{99m}Tc-HMPAO			
Levy-Body Dementia	NBM			1		
Alzheimer's Disease	VC/VS			1		
Obsessive-Compulsive Disorder (7)	STN			1		
	VC/VS		^{15}O ^{15}O-CO$_2$	1		
	BST			1		
	NAc				[^{123}I]IBZM	
	Anterior limb of capsula interna			1		
Depression (2)	SCG			1		
	SGC or VAC/NAc	1				

[1]Includes a study with PPN+cZi; [2]Voa in one subject; ^ includes ^{18}F-FDG-tracer; * includes two same studies with both tracers; # same study; rCBF = regional cerebral blood flow; rCMRglc = regional cerebral metabolic rate for glucose; ^{15}O-H$_2$O = Oxygen-15 labelled water; ^{18}F-FDG = Fluorodeoxyglucose; 18F-FDOPA = Fluorodopa; 99mTc-ECD = Technetium-99 m ethyl cysteinate dimer; 99mTc-HMPAO = Technetium-99 m hexamethylpropyleneamine oxime; [11C]DPN = Diprenorphine; [^{11}C]DTBZ = Dihydrotetrabenazine; 5-HT$_{1B}$R = 5-hydroxytryptamine receptor 1B (serotonin); ^{15}O-CO2 = Oxygen-15 labeled carbon dioxid; [^{123}I]IBZM = [^{123}I]iodobenzamide.
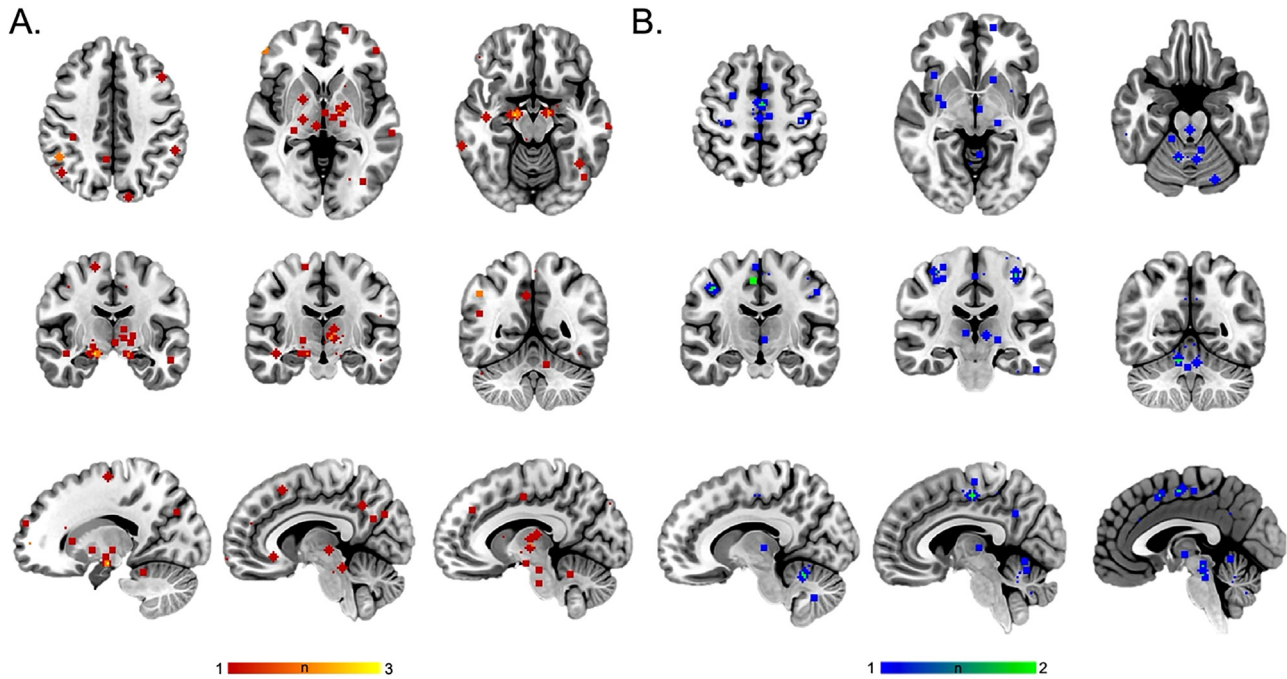
Fig. 2. Peak locations of stimulation induced changes in Parkinson's disease with STN-DBS. Peak coordinates of increased (A) and decreased (B) regional blood flow and glucose metabolism extracted from individual studies investigating STN-DBS in Parkinson's disease. The number of overlapping peaks is illustrated with red-yellow and blue-green color scales, respectively. Each peak coordinate location is indicated with 4 mm radius sphere created around the peak coordinates.

Table 2
Details of the individual studies investigating the direct effects of DBS.

authors	N	DBS parameters				imaging parameters			Effects		
		target	treatment duration	ON time	OFF time	method	tracer	imaging analysis	local	subcortical	other
Parkinson's Disease _rCBF and CMRglc_											
Ceballos-Bauman et al. (1999)	9	STN	≥ 4 months	10 min	10 min	PET	^{15}O-H$_2$O	Voxel-wise	↔	↑ ipsilateral ventral thalamus, ipsilateral GPi	↑ ipsilateral parietal and parieto-occipital cortex, contralateral DLPFC ↓ ipsilateral primary motor cortex, ACC
Sestini et al. (2002)	10	STN	4.8 (1.4) months	treatment duration	6 h	SPET	^{99m}Tc ECD	Voxel-wise	↔	↔	↑ R pre-SMA, bilateral medial frontal gyrus, DLPFC, anterior gingulate gyrus
Hershey et al. (2003)	9	STN	5.7 (2.1) months	≥ 30 min	≥ 30 min	PET	^{15}O-H$_2$O	Voxel-wise	↑ L STN	↑ L SN, L red nucleus, L thalamus (lateral posterior nucleus) ↓ R cerebellum anterior lobe, L claustrum	↓ medial frontal gyrus, R superior parietal cortex, L precentral gyrus, L medial frontal gyrus, L superior frontal gyrus, L superior frontal gyrus, L superior frontal gyrus, R middle frontal gyrus, R middle/superior frontal gyrus, R superior temporal gyrus, R middle temporal gyrus
Haslinger et al. (2005)	6	STN	15.9 (8.3) months	n.a	n.a	PET	^{15}O-H$_2$O	Voxel-wise	↑	↔	↓ bilateral precentral gurys/primary motor cortex, mesial frontal gyrus/caudal parts of mesial premotor cortex (SMA)
Herzog et al. (2006)	11	STN	n.a	20 min*	20 min	PET	^{15}O-H$_2$O	Voxel-wise + ROI	↑	↓ cerebellum	↓ bilateral SMC, SMA
Campbell et al. (2008)	24	STN	8.7 (5.9) months	≥ 42 min*	≥ 42 min	PET	^{15}O-H$_2$O	ROI	n.a	n.a	↔
Herzog et al. (2008)	9	STN	22.2 (13.4) months	20 min*	20 min	PET	^{15}O-H$_2$O	Voxel-wise + ROI	↑	↓ cerebellum	↓ bilateral sensorimotor cortex, SMA
Karimi et al. (2008)	31	STN	12 (11.5) months	≥42 min*	≥ 42 min	PET	^{15}O-H$_2$O	Voxel-wise + VOI	↔	↑ bilateral thalami, R midbrain	↓ R PMC
Geday et al. (2009)	9	STN	12 (8.3) months	4 h*	4 h	PET	^{15}O-H$_2$O	Voxel-wise	↑	↑ L putamen ↓ R cerebellum, L thalamus,	↓ L SMA, L motor cortex
Bradberry et al. (2012)	11	STN	24 (12) months	20 min	20 min	PET	^{15}O-H$_2$O	Voxel-wise	↑	↑ posterolateral cerebellum (crus II), amygdala, hippocampus, globus pallidus, ventrolateral thalamus ↓ putamen, posterolateral cerebellum (Lobule VI), cerebellar vermis,	↑ superior parietal lobule, inferior frontal gurys ↓ SMA, precentral gyrus, postcentral gyrus
Sidtis et al. (2012)	7	STN	25.6 (21.2) months	one week*	30 min	PET	^{15}O-H$_2$O	Voxel-wise	↔		↑ global CBF
Hill et al. (2013)	30	D-STN/V-STN (unilat.)	22.4 (20.8) months	≥ 42min*	≥ 42min	PET	^{15}O-H$_2$O	ROI	↑	↑ GPi, thalamus	↔ PMC, SMA

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Table 2 (*continued*)

Study	N	Target	Duration			Modality	Tracer	Analysis	Dir	Subcortical findings	Cortical findings
										↔ cerebellum	
Park et al. (2015)	10	STN	32.8 months	treatment duration	≥ 60min	PET	¹⁵O-H₂O	Voxel-wise + ICA	↔	Voxelwise: ↑ R globus pallidus, R precuneus, bilateral cerebellum ↓ L thalamus, L midbrain, R precentral gyrus	Voxelwise: ↓ bilateral SMA, R superior frontal gyrus
Hilker et al. (2004)	8	STN	6(2) months	> 12 h*	> 12 h	PET	¹⁸F-FDG	Voxel-wise	↑	↑ R posterior cerebellum, bilateral lower ventrolateral thalami, R lentiform nucleus	↑ R frontal lobe (correspondin to DLPFC and OFC), R parietal inferior lobule, R middle temporal gyrus, R posterior cingulate, L anterior cingulate
										↓ L rostral anterior cerebellum	
Hilker et al. (2008)	12	STN	3.8(1.8) months	> 12 h*	> 12 h	PET	¹⁸F-FDG	VOI	↑	↑ GP	
Asanuma et al. (2006)	9	STN	n.a	≥ 12 h*	≥ 12 h	PET	¹⁸F-FDG	Voxel-wise + network analysis	↑	↑ L ventrolateral thalamus	↑ R medial posterior parietal cortex (precuneus)
										↓ bilateral cerebellar vermis, R putamen, L Gpi	↓ L prefrontal cortex, bilateral SMC, bilateral precentral gyrus
Trost et al. (2006)	6	STN (unilat.)	6 months	≥ 24 h*	> 24hours	PET	¹⁸F-FDG	Voxel-wise + network analysis	↔	↓ ipsilateral cerebellar vermis, midbrain, rostral pons	↑ ipsilateral prefrontal cortex, ipsilateral parietal cortex ↓ ipsilateral SMA, ipsilateral precentral gyrus
Huang et al. (2007)	9	STN	n.a	n.a	n.a	PET	¹⁸F-FDG	PDCP+PDRP			↔ PDCP ↓ PDRP
Nagaoka et al. (2007)	8	STN	1 month	hours	overnight	PET	¹⁸F-FDG	Voxel-wise	↔	↑ R anterior cerebellar lobe	↑ R middle frontal gyrus (premotor area)
Arai et al. (2008)	8 FDG 4 DOPA	STN (unilat.)	13 (9.6) months	≥ 12 h	≥ 12 h	PET	¹⁸F-FDG and ¹⁸F-DOPA	FDG: Voxel-wise DOPA: ROI	FDG: ↔ DOPA: n.a	FDG:↑ ipsilateral nuclei of the thalamus ↓ contralateral Gpi DOPA: ↔ caudate nucleus, putamen	FDG: ↔ DOPA: n.a
Hirano Set al. (2008)	8	STN	n.a	n.a	n.a	PET	¹⁸F-FDG ja ¹⁵O-H₂O	PDRP			↓ PDRP
Wang et al. (2010)	5	STN	6 months	≥ 24 h*	≥ 24 h	PET	¹⁸F-FDG	Voxel-wise	↔	↑ L midbrain, L pons.	↓ supramarginal gyrus (parietal cortex), precuneus (parietal cortex)
										↓ R GPi, bilateral thalamus, cerebellum (posterior lobe)	
Garraux et al. (2011)	8	STN	24 (range 12–48) months	n.a	n.a	PET	¹⁸F-FDG	Voxel-wise +VOI	↑	↑ thalamus, caudate nucleus, L GP, R PPN, L cerebellum	↑ widespread
Volonté et al. (2012)	14	STN	6 months	one day*	>8 h	PET	¹⁸F-FDG	Voxel-wise +ROI	↑	↑ ventrolateral thalamus	↓ rostral cerebellum
Ko et al. (2013)	14 (10) FDG	STN	n.a	n.a	≥ 1 h	PET	¹⁸F-FDG and ¹⁵O-H₂O	NMRP			↓ NMRP
Fukuda et al. (2001) (AnnNeurol)	6	GPi (3 unilat., 3 bilat.)	n.a	> 12 h*	12 h	PET	¹⁵O-H₂O	Voxel-wise	↔	↔	↔
Payoux et al. (2009)	5	GPi/GPe (unilat.)	26–35 months	≥ 8 min*	≥ 8minutes	PET	¹⁵O-H₂O	Voxel-wise	↔	GPi: ↑ ipsilateral putamen	GPi: ↓ ipsilateral primary SMC and PMC, posterior and anterior supplementary motor area, ACC
										GPe: ↓ ipsilateral cerebellum ↑ cerebellum	GPe: ↓ ipsilateral PMC
Fukuda et al. (2001) (Brain)	7	GPi (unilat.)	n.a	≥ 12 h*	≥ 12 h	PET	¹⁸F-FDG	Voxel-wise	↔		↑ L PMC
Wielepp et al. (2001)	4	VIM (unilat.)	mean 12 months	14 days	120min	SPET	⁹⁹ᵐTc ECD	Voxel-wise	↔	↔	↔
Fukuda et al. (2004)	8	VIM (unilat.)	12–24 months	≥ 10min	≥ 10min	PET	¹⁵O-H₂O	Voxel-wise	↑	↑ ipsilateral brainstem	↑ ipsilateral middle occipital cortex

Table 2 (*continued*)

Mure et al. (2011)	9	VIM (7 unilat., 2 bilat.)	n.a	treatment duration or from previous day	3 h	PET	^{18}F-FDG	Network analysis	N/A	↓ contralateral cerebellum ↑ anterior cerebellum, dentate nucleus, caudate nucleus	↓ ipsilateral SMC, SMA ↑ primary motor cortex
Ballanger et al. (2009)	3	PPN (unilat.)	15.3 (9.9) months	30 min*	30 min	PET	^{15}O-H$_2$O	Voxel-wise	↑	↑ cerebellum, thalamus, ipsilateral ventral midbrain	↑ SMC (post-hoc analysis) ↑ contralateral DLPFC, caudal ACC, OFC, superior and middle temporal gurys, ipsilateral occipital cortex
Khan et al. (2012)	4	PPN and cZi	23.8 (22.3) months	n.a	overnight	PET	^{15}O-H$_2$O	Voxel-wise	↔	↑ midbrain, thalamus, globus pallidus, putamen, cerebellum	↓ sensorimotor cortical areas
Stefani et al. (2010)	6	PPN	≥ 12 months	≥12 h	≥ 12 h	PET	^{18}F-FDG	Voxel-wise	↔	↑ L ventral striatum	↑ bilateral frontal inferior gyrus, DLPFC, OFC, anterior cingulate, superior frontal gyrus, parietal inferior lobula, supramarginal gyrus, L subgyral, R insula, R superior temporal gyrus
										↓ L cerebellar anterior lobe, R cerebellar posterior lobe	
Dopamine											
Hilker et al. (2003)	6	STN	5.7 (1.9) months	≥ 12 h	≥ 12 h	PET	[^{11}C] Raclopride	VOI	↔	n.a	n.a
Strafella et al. (2003)	6	STN	3–6 months	overnight	overnight	PET	^{11}C] Raclopride	ROI	↔	n.a	n.a
Smith et al. (2019)	3	STN	n.a	n.a	1 hour in 2 subjects and 12 h in one	PET	[^{11}C]DTBZ	VOI	n.a	↓ caudate, putamen	n.a
Serotonin											
Jørgensen et al. (2021)	13	STN	30 (21.6) months	n.a	switched off during scan	PET	5-HT$_{1B}$R	VOI			↑ BPND temporal, limbic and occipital cortex
Primary dystonia rCBF											
Detante et al. (2004)	6	GPi (unilat.)	12.8 (11.7) months	3.4 h (range 0.25–6.5 h)*	3.4 h (range 0.25–6.5 h)	PET	^{15}O-H$_2$O	Voxel-wise	↑ ipsilat.	↑ ipsilateral thalamus, contralateral cerebellar hemisphere and caudate nucleus	↑ ipsilateral medial frontal gyrus, cingulate cortex, contralateral DLPFC, inferior frontal gurys, temporal cortex, bilateral parietal cortex ↓ ipsilateral primary motor cortex ↓ bilateral anterior cingulate
Yianni et al. (2005)	5	GPi	13.2 (5.8) months	n.a	n.a	SPET	^{99m}Tc-HMPAO	ROI	↔	↓ bilateral cerebellum, pons, midbrain, L lentiform nucleus, L thalamus	
Greuel et al. (2020)	6	GPi	21.8 (13.2) months	n.a	12h	PET	^{15}O-H$_2$O	Voxel-wise	↔	↔	↔
Secondary dystonia rCBF											
Katsakiori et al. (2009)	6	Gpi (1 Voa, 1 unilat. GPi)	19.75 (SD 11.4) months	n.a	n.a	SPET	^{99m}Tc-ECD	Voxel-wise	↔	↔	↓ primary motor cortex, supplementary motor cortex, anterior cingulate gyrus, DLPFC and frontopolar area

Table 2 (*continued*)

| Study	N	Target	Duration	ON	OFF	Modality	Tracer	Analysis			
Thobois et al. (2008)	5	GPi	n.a	≥ 3 h*	≥ 3 h	PET	^{15}O-H$_2$O	Voxel-wise	↔	↑ cerebellum	↑ R occipital cortex, L superior parietal cortex ↓ L primary motor cortex, bilateral ACC, SMA
Essential tremor *rCBF*											
Ceballos-Baumann et al., 2001	6	VIM (unilat.)	n.a	5 min	5 min	PET	^{15}O-H$_2$O	Voxel-wise	↔	↔	↑ ipsilateral primary motor cortex ↓ contralateral retroinsular area (depth of superior temporal gyrus)
Perlmutter et al., 2002	10	VIM (unilat.)	15 (13) months	2 min	n.a	PET	^{15}O-H$_2$O	Voxel-wise + ROI	Voxel-wise: ↔ ROI: ↑	Voxel-wise: ↔ ROI: n.a	Voxel-wise: ↑ ipsilateral SMA ROI: n.a
Haslinger et al. (2003)	9	VIM (unilat.)	9.7 (7.2) months	n.a	n.a	PET	^{15}O-H$_2$O	Voxel-wise	↑	↔	↑ ipsilateral SMC
CMRglc											
Reich et al. (2016)	10	thalamic (bilat.)	23–27 months (SD 7)	treatment duration	72h	PET	^{18}F-FDG	Voxel-wise	↑	↑ cerebellum (nodule)	↔
Huntington's disease *rCBF*											
Ligot et al. (2011)	5	GPe	12–19 months	7 days	7 days	PET	^{15}O-H$_2$O	Voxel-wise	↔	↔	↔
Cluster headache *rCBF*											
May et al. (2006)	10	hypothalamus (unilat.)	1–22 months	60s	60s	PET	^{15}O-H$_2$O	Voxel-wise	↑	↑ ipsilateral thalamus, ipsilateral trigeminal nulceus and ganglion ↓ contralateral anterior insula	↑ precuneus, temporal gyrus, ACC, primary somatosensory cortex ↓ middle temporal gurys, posterior cingulate gyrus, bilateral temporal inferior gyrus, superior frontal gyrus
Neuropathic pain *rCBF*											
Sims-Williams et al. (2017)	5	PAG	36 (26) months	60 min (^{15}O-H$_2$O) and 90 min ([^{11}C]DPN)	60 min (^{15}O-H$_2$O) and 90 min ([^{11}C]DPN)	PET	^{15}O-H$_2$O and [^{11}C]DPN	Voxel-wise	^{15}O-H$_2$O: ↔ [^{11}C]DPN: ↓	^{15}O-H$_2$O: ↔ [^{11}C]DPN: ↔	^{15}O-H$_2$O: ↔ [^{11}C]DPN: ↔
Tourette syndrome *rCBF*											
Haense et al. (2016)	5	GPi + CM/Voi	n.a	3 months	3 months	SPET	^{99m}Tc-ECD	Voxel-wise + VOI	↔	Voxel-wise: GPi: ↑ bilateral precuneus GPi: ↓ putamen, R caudate, R talamus, cerebellum, L cuneus CM/Voi: ↓ cerebellum VOI: Gpi: ↓ putamen, CM/Voi: ↓ cerebellum	Voxel-wise: GPi: ↑ R frontal cortex, bilateral middle and R anterior cingulate GPi: ↓ L temporal lobe; CM/Voi: ↑ L superior frontal cortex, L SMA and middle frontal cortex, L pre- and postcentral cortex, L inferior parietal and postcentral cortex CM/Voi: ↓ L middle occipital cortex, R middle and superior temporal cortex, R fusiform gyrus VOI: GM/Voi: ↓ L middle occipital cortex

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Table 2 (*continued*)

											GM/Voi: ↑ L superior frontal cortex
Lewy-body dementia											
CMRglc											
Maltête et al. (2020)	5	NBM	> 4 months	3 months	3 months	PET	18F-FDG	Voxel-wise	↔	↔	↑ superior lingual gyrus
Alzheimer's disease											
CMRglc											
Scharre et al. (2018)	3	VC/VS	17–19 months	treatment duration	Scan prior to any stimulation after implantation	PET	18F-FDG	Visual analysis	↔	↔	↑ orbitofrontal, ventromedial prefrontal and dorsolateral prefrontal cortical regions (2/3 patients)
Obsessive-compulsive disorder											
rCBF											
Rauch et al. (2006)	6	VC/VS	n.a	10 min	10 min	PET	15O-CO2	ROI	n.a	↑ R putamen, L GP, R thalamus	↑ OFC, R subgenual ACC
Dougherty et al. (2016)	6	VC/VS	60 (11) months	1 min	> 2 h or 10 min	PET	15Oxygen	ROI	↔	dorsal contact on: ↑ thalamus, striatum, globus pallidus	ventral contact on: ↑ dorsal ACC. ↔ OFC or vmPFC
CMRglc											
Abelson et al. (2005)	3	anterior limb of capsula interna	3–6 weeks	3 or 6 weeks*	Scan after implation before any stimulation and 3 or 6 weeks	PET	18F-FDG	Visual analysis	↔	↔	↓ OFC (2/3 subjects) ↔ (1/3 subject)
Le Jeune et al. (2010)	10	STN	> 3 months	3 months	3 months	PET	18F-FDG	Voxel-wise	↔	↔	↓ L cingulate gyrus, L frontal lobe (medial gyrus)
Suetens et al. (2014)	9	BST	n.a	median 68d (28–123d)	median 24d (7–99d)	PET	18F-FDG	Voxel-wise	↔	↔	↓ ACC, medial frontal gyrus, R temporal gyrus
Balderman et al. (2019)	3	VC/VS	6–12 months	treatment duration	24–48h	PET	18F-FDG	Visual analysis + VOI	Visual: ↑VS (patient 1) VOI: ↑	Visual: ↑ caudate nucleus (patient 1) ↑ thalamus (patient 2)	Visual: ↑ frontal, parietal and occipital lobes (patient 1) ↑ orbitofrontal and temporal cortex (patient 3) ↓ frontal and parietal cortex (patient 2)
Dopamine											
Figee et al. (2014)	15	NAc	> 12 months	2 scans: >12 months and 1 h	8 days	SPET	([123I]IBZM)	ROI	↓	↓ putamen ↔ caudatus	n.a
Depression											
rCBF											
Conen et al. (2018)	7	SGC or VAC/NAc	> 3 months	3 months	2 h	PET	15O-H2O	Voxel-wise	↔	↔	↓ dorsal ACC (VAC stimulation)
CMRglc											
Martín-Blanco et al. (2015)	7	SCG	9 months	treatment duration	48h	PET	18F-FDG	Voxel-wise	↑ R cingulate gyrus	↑ R putamen	↑ R medial frontal gyrus

*counterbalanced between subjects; # includes 8 same subjects as Hilker et al., 2004; n.a = not available; ROI = region of interest; VOI = volume of interest; ICA = independent component analysis; DLPFC = dorsolateral prefrontal cortex; STN = subthalamic nucleus; GPi/GPe = globus pallidus interna/externa; Voa = ventralis oralis anterior; DLPFC = dorsolateral prefrontal cortex; SMC = sensorimotor cortex; SMA = supplementary motor area; ACC = anterior cingulate cortex; SCG = subcallosal cingulate gyrus; SGC = subgenual cingulate gyrus; VAC = ventral anterior capsule; NAc = nucleus accumbens; BST = bed nucleus of stria terminalis; OFC = orbitofrontal cortex; NBM = nucleus basalis of meynert; CM/Voi = centromedian-parafascicular/ventralis oralis internus nuclei of the thalamus; VC/VS = ventral capsule/ventral striatum; PAG = periaqueductal gray; VIM = ventral intermediate nucleus of thalamus; PMC = premotor cortex; SN = substantia nigra; PPN = pedunculopontine nucleus; cZi = caudal zona incerta; PDCP = Parkinson's disease cognitive pattern; PDRP = Parkinson's disease related pattern; NMRP = normal movement related activation pattern.
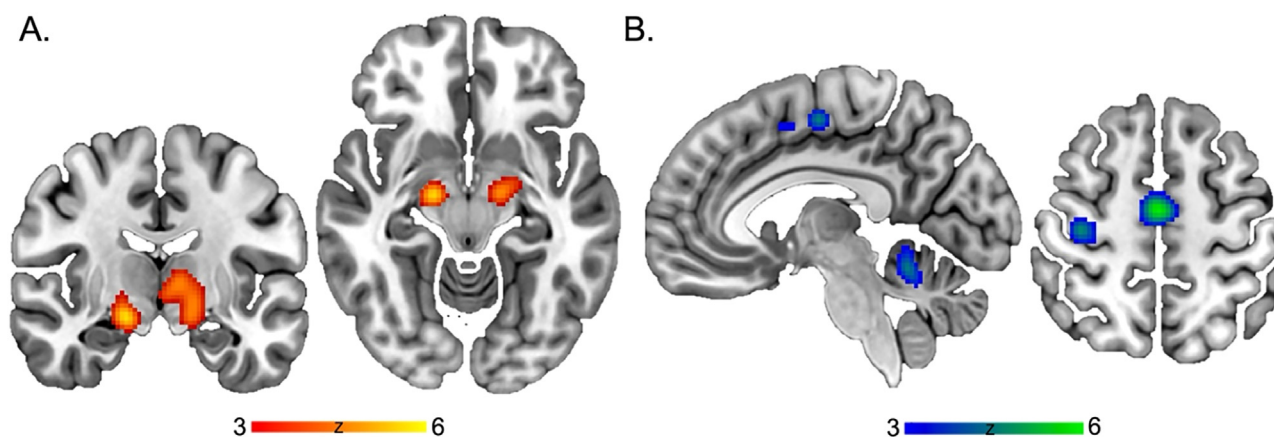
Fig. 3. ALE meta-analysis of stimulation-induced changes with STN-DBS in Parkinson's disease. STN-DBS stimulation resulted in significantly increased ligand uptake (blood flow and glucose metabolism) in subthalamic area, globus pallidus and thalamus (A), and decreased ligand uptake in the primary motor cortex, supplementary motor area, and cerebellum (B). Cluster threshold $P_{FWE} < 0.05$.

Table 3

Significant clusters in the ALE meta-analysis.

Cluster #	Brain area	Cluster size (mm³)	Studies included in contrast	Studies contributed to the cluster	Center Coordinate (x,y,z)	p	Z
Increase 1	Subthalamic area, globus pallidus, thalamus (left)	5408	11	11	(−14,−11,−1)	<0.0001	5.36
Increase 2	Subthalamic area, globus pallidus, thalamus (right)	1608	11	5	(17,−12,−10)	<0.0001	5.47
Decrease 1	Supplementary motor area	3256	10	8	(1,−10,53)	<0.0001	6.03
Decrease 2	Cerebellum	3136	10	7	(2,−56,−15)	<0.0001	4.88
Decrease 3	Primary motor cortex (right)	2056	10	6	(37,−18,52)	<0.0001	4.67

PMC and SMA (Payoux et al., 2009). In the cerebellum, GPi stimulation increased glucose metabolism (2001) and GPe stimulation decreased rCBF (Payoux et al., 2009). One of the studies did not identify any stimulation-related changes in rCBF (Fukuda et al., 2001).

3.1.1.3. Ventral intermediate nucleus of thalamus. There were three studies investigating the ventral intermediate nucleus of thalamus (VIM) DBS (Table 2). Unilateral VIM stimulation induced changes in rCBF ipsilaterally in the cerebrum and contralaterally in the cerebellum. Specifically, stimulation increased perfusion at the stimulation site, ipsilateral brainstem area and occipital cortex, and decreased perfusion in the cerebellum, primary sensorimotor cortex and SMA (Fukuda et al., 2004). In addition, VIM stimulation revealed a covariance pattern with increased metabolic activity in the cerebellum, dentate nucleus and in primary motor cortex (Mure et al., 2011). The smallest study found no stimulation-induced changes in rCBF (Wielepp et al., 2001).

3.1.1.4. Pedunculopontine nucleus. The pedunculopontine nucleus (PPN) was the stimulation target in three studies (Table 2). One of the studies reported an increased rCBF at the stimulation site (Ballanger et al., 2009) whereas the two other studies found no local changes. PPN-DBS increased rCBF and/or glucose metabolism in the thalamus, striatum, globus pallidus, ventral striatum, and numerous cortical areas. In addition, there was an increased rCBF and decreased glucose metabolism in the cerebellum, and decreased ligand uptake in rCBF was seen in sensorimotor cortical regions.

3.1.2. Dystonia
3.1.2.1. Globus pallidus interna. **Primary dystonia.** There were three studies investigating the effects of GPi-DBS to rCBF in primary dystonia (Table 2). Only one of these three studies showed local increase in ligand uptake at the stimulation site (Detante et al., 2004), and there was no overlap between studies in remote regions showing changes in

rCBF following stimulation (Table 2). One of the studies did not find any stimulation related changes in rCBF (Greuel et al., 2020).

Secondary dystonia. Two studies investigated the effects of GPi-DBS to rCBF in secondary dystonia (one in tardive dystonia (Thobois et al., 2008) and second in a group of heterogeneous etiologies including drug-induced, postanoxic, cerebral palsy and postencephalitic dystonia (Katsakiori et al., 2009)) (Table 2). Neither of the studies found changes at the stimulation site but both studies reported decreased rCBF in motor cortical regions (M1, SMA) and the cingulate cortex.

There were no obvious differences in the imaging results between primary and secondary dystonia, but the number or studies and patients included in these studies are too small for definitive conclusions. In summary, GPi-DBS in dystonia seems to cause rCBF decrease in cortical regions involved in motor control but no reproducible local effects at the stimulation site. There are no published studies investigating brain glucose metabolism or neurotransmitter systems in dystonia.

3.1.3. Essential tremor (ET)
3.1.3.1. Thalamus. All four essential tremor studies targeted the thalamus (Table 2). Three studies (75%) showed increased rCBF or glucose metabolism locally. VIM stimulation increased rCBF ipsilaterally in some of the motor cortical regions (M1, SMA, premotor cortex) in most of the studies, and cerebellum in one study. Overall, DBS targeting thalamus in ET increased ligand uptake locally at the stimulation site and in the motor network.

3.1.4. Other neurological diseases
There was only a single study in each of the other neurological diseases (Huntington's disease, cluster headache, neuropathic pain, Tourette syndrome, Lewy-body dementia and Alzheimer's disease) (Table 1).

In Huntington's disease ($n = 5$), GPe-DBS was not associated with any changes in rCBF (Ligot et al., 2011).

In cluster headache ($n = 10$), hypothalamic stimulation resulted rCBF increases in the hypothalamus, thalamus, trigeminal nucleus and several cortical areas. RCBF decreases were observed in anterior insula and in frontal, temporal and cingulate gyruses (May et al., 2006).

In neuropathic pain ($n = 5$), no changes in rCBF was associated with periaqueductal gray (PAG) stimulation but decreased [^{11}C]DPN uptake was seen locally (discussed later in paragraph 3.2.) (Sims-Williams et al., 2017).

In Tourette syndrome ($n = 5$), combined GPi and centromedian-parafascicular/ventralis oralis internus nuclei of the thalamus (CM/Voi) DBS stimulation showed no changes in ligand uptake at the stimulation site but a widespread rCBF changes were seen in several brain regions. Decreases were observed in thalamus, basal ganglia and cerebellum while increases unilaterally in frontal cortex and bilaterally in precuneus and anterior cingulum (Haense et al., 2016).

In Lewy-body dementia ($n = 5$), 3-month nucleus basalis of Meynert stimulation increased glucose metabolism in the superior lingual gyrus (Maltête et al., 2021).

In Alzheimer's disease ($n = 3$) no changes in ligand uptake at the stimulation site (VC/VS) was seen in visual analysis but changes in glucose metabolism was detected in the orbitofrontal, ventromedial prefrontal and dorsolateral prefrontal cortical regions in two of the three patients (Scharre et al., 2018).

3.1.5. Obsessive-compulsive disorder (OCD)

OCD was the second most studied brain disorder after PD (7 studies, 11% of all studies). Two of the studies investigated rCBF, four glucose metabolism and one dopamine function (discussed below in paragraph 3.2.). The stimulation sites in rCBF and glucose metabolism studies were VC/VS, STN, BST (bed nucleus of the stria terminalis), NAc (nucleus accumbens) and anterior limb of the capsula interna (Table 1).

Across these studies, there was a relatively consistent set of brain regions modulated by the stimulation, including the anterior cingulate cortex (4 studies) and ventromedial prefrontal cortex (3 studies), indicating that the different stimulation sites may be modulating a common network, as suggested by indirect connectivity analyses of DBS volumes of activation (Baldermann et al., 2021; Li et al., 2021). However, most of these studies did not show any significant changes in tracer uptakes locally at the stimulation site.

3.1.6. Depression

Two studies investigated the effects of DBS in depression (Table 2). The first study investigated glucose metabolism with subcallosal cingulate (SCG) stimulation and reported increased local and remote (the right putamen and medial frontal gyrus) increase in ligand uptake (Martín-Blanco et al., 2015). The more recent study investigated effects of subgenual cingulate gyrus (SGC) and ventral anterior capsule or nucleus accumbens (VAC/NAc) stimulation on rCBF. VAC stimulation decreased rCBF in the dorsal ACC, but there were no changes in rCBF with SGC stimulation (Conen et al., 2018).

3.2. Neurotransmitter systems

There was only a small number of published studies investigating specific neurotransmitter systems across all disorders and stimulation sites (7 studies, $n = 52$, Table 2). In PD STN-DBS efficacy correlates with response to levodopa and STN BDS treatment usually leads to substantially reduced need for dopaminergic medications (Vingerhoets et al., 2002). Therefore, STN-DBS was initially hypothesized to mediate its therapeutic efficacy via increasing striatal dopamine neurotransmission. However, this hypothesis was rejected after two studies provided contradicting evidence by showing no changes in striatal postsynaptic D2/D3 receptor binding, which is used as an indirect measure of changes in synaptic dopamine levels, following STN-DBS (Hilker et al., 2003; Strafella et al., 2003). STN-DBS also does not change the dopamine synthesis capacity (Arai et al., 2008), but may decrease

vesicular monoamine transporter (VMAT2) levels (Smith et al., 2019). However, the latter study also included patients scanned pre and post operation, making it possible that the observed change in VMAT2 levels is caused by chronic DBS treatment rather than directly by the STN stimulation.

In contrast to the findings with PD showing practically no effects to the dopamine system, NAc stimulation in OCD ($n = 15$) resulted in decreased D2/3 receptor binding in NAc and putamen, indicating increased dopamine release in these regions (Figee et al., 2014). In the only study investigating the serotonin system, STN-DBS increased 5-HT$_{1B}$ receptor binding in the temporal, limbic and occipital regions, suggesting that DBS reduces synaptic serotonin levels in PD (Jørgensen et al., 2021). PAG stimulation in patients with neuropathic pain was associated with reduction of postsynaptic opioid receptor binding at the stimulation site, suggesting increased synaptic opioid levels during active stimulation (Sims-Williams et al., 2017).

4. Discussion

The present study is the first to collate all molecular imaging studies investigating the direct effects of DBS across diseases and stimulation sites. There are several important findings: 1) the local effects of DBS were mainly increases in ligand uptake with no studies showing decreased rCBF or glucose metabolism at the stimulation site; 2) the effects of DBS nearly always extended to remote brain regions beyond the stimulation site; and 3) the effects of DBS are target-specific, which seem similar across clinical conditions. However, data about the effects of DBS on neurotransmitter systems is still limited. These findings provide important insight into the neurobiological mechanisms of DBS that can benefit future development of therapeutic use of DBS.

4.1. Local effects of the stimulation

Across all disorders and stimulation targets, one third (21/62, 34%) of the studies found a local effect of DBS. The stimulation effect in all these 21 studies was increased activity at the stimulated region with no studies showing reduced activity. Approximately half of the studies investigating VIM-DBS or STN-DBS showed increased local activity, which was confirmed by the ALE meta-analysis. However, 9/10 GPi-DBS studies did not show any local effects across investigated diseases (PD, dystonias). These findings suggest that the local effects of DBS may differ based on the target nucleus and findings cannot be generalized across all stimulation sites.

Increase in neuronal activity has been shown to lead to increased rCBF and glucose metabolism, offering a possibility to use rCBF and metabolism as proxy to measure changes in neuronal activity (Mann et al., 2021). Our findings mainly show an increased rCBF and metabolic activity at the stimulation site, which is in line with induced axonal spiking at the stimulation site observed in neurophysiological recordings. DBS is considered to act on depolarizing axons and causing the action potentials travel both ways toward somas and synapses. In addition to efferent axons, the volume of tissue activated involves inhibitory and excitatory afferent fibers to dendrites and cell bodies, which may explain the heterogeneity seen in the results of the studies. (Jakobs et al., 2019). Although none of the reviewed studies directly compared physiological VTAs in other studies with local activation cluster sizes, the clusters tended to be larger compared to VTAs, suggesting that the metabolic effects of the stimulation spread locally beyond the direct electrical activation (Ceballos-Baumann et al., 2001; Fukuda et al., 2004; Reich et al., 2016). However, it should be noted that molecular imaging results are affected by partial volume effects and spatial smoothing, which both can increase the observed cluster sizes.

4.2. Effects extending beyond the stimulation site

Almost all included studies found some remote effects, demonstrating that the effects of DBS are not restricted to the stimulation site but extend to connected brain regions. The best available evidence comes from PD and STN-DBS studies focused on cerebral blood flow or glucose metabolism (25 studies, $n = 289$) where stimulation increased ligand uptake in the stimulation target, basal ganglia and thalamus, and reduced ligand uptake in the motor cortical regions and cerebellum. These findings are in line with the current views that the clinical efficacy of DBS in PD is mediated via functional changes in the motor network rather than merely disrupting the information flow at the stimulation site. However, although a consistent remote effect pattern was identified in the ALE meta-analysis, there also was variability in brain regions reported in individual studies. We were unable to identify specific methodological issues driving these differences, and the observed remote effects are likely to depend on multiple factors, such as disease severity, timing of investigation, choice of the ligand, and image acquisition, preprocessing and statistical approach. Direct comparisons between different stimulation sites within a disease are required to investigate if all of these targets activate a common network, suggested by recent work applying indirect connectomic approach (Zhang et al., 2021). It also should be noted that increases/decreases in rCBF or glucose metabolism in remote brain regions may not directly translate to increases/decreases in neuronal activity in the corresponding circuit. For example, decreased activity and metabolism of a GABAergic output nucleus may result into remote excitation in the connected regions (Jakobs et al., 2019). Thus, the effects of DBS on neuronal activity cannot be solely dissolved by molecular imaging.

4.3. Are the neurobiological effects disease specific?

There are no published studies directly comparing the effect of DBS between different clinical conditions. However, the local effects of the stimulation seem to be similar across disorders. Thalamic stimulation in both PD and ET is associated with increased local perfusion and glucose metabolism, but there was no local changes in 90% of the studies with GPi stimulation in both PD and dystonias. The remote effects of the stimulation were highly heterogeneous across individual studies, preventing definitive conclusions regarding similarity of these effects between disorders. It should also be noted that there is variation between diseases in imaging confounders. Patients with ET have action tremor, which doesn't affect imaging, but PD patients have rest tremor, which is likely to be present during imaging. Some of the studies used movement tracking methods during scanning to exclude patients with excessive movement during the scan, but motion can still have effect on image quality. Furthermore, PD and ET are usually associated with immediate symptom relief after initiating DBS (Zhou et al., 2019), which can contribute to the imaging findings. However, this is not the case with dystonia, where the clinical effects of DBS are often delayed (Crowell and Shah, 2016; Honkanen et al., 2021). Further studies directly comparing different clinical conditions are needed to fully evaluate the effects of the underlying neurobiology and clinical response to the neurobiological effects observed in molecular imaging studies.

4.4. Methodological considerations

4.4.1. Study design

Although we restricted our inclusion to studies investigating the direct effects of DBS on resting brain activity, there was still a lot of variation between included studies in the sample sizes, study design and imaging protocols. Mean (SD, median [range]) of subjects per study was 8.6 (5.4, 7.5, [3–31]). Duration of the stimulation 'off/on' before scanning DBS on varied from minutes to months/years (treatment time) and PET/SPET imaging protocol depend on the selected tracer. Some of the included studies used a counterbalanced design to mitigate scanning order effects. All these factors may have influenced the imaging outcomes, increasing heterogeneity of the findings.

4.4.2. Deep brain stimulation (DBS)

Most of the studies did not adjust the stimulation settings during the study and used the individual settings used in the clinical treatment of these patients. Stimulation settings varied between and within studies (amplitude 1.2–10.5 V, pulse width 60–450µs and frequency 25–210 Hz). Studies focusing on OCD seemed to use a slightly higher amplitudes (range 1.8–10.5 V) than studies focusing on other diseases (PD 1.2–4.7 V, ET 1.8–4.6 V, dystonia 2.5–4.6 V). In all studied diseases the frequency of DBS varied mainly between 125 and 185 Hz with no obvious differences between clinical conditions. Pulse width was between 60 and 270 µs in PD, OCD and ET studies, while in secondary dystonia (Katsakiori et al., 2009) higher pulse durations up to 450µs were used. Effects of pulse width, amplitude and frequency have largely been ignored in PET and SPET studies, and the low numbers of clinically heterogeneous subjects included in individual studies usually do not allow meaningful comparisons between different stimulation parameters.

4.4.3. PET/SPET imaging

The spatial resolution is substantially different in PET and SPET imaging, as PET scanners can reach 2–3 mm spatial resolution and SPET 6–8 mm (Khalil et al., 2011; Moses, 2011). The resolution is dependent on the used tracer and scanner. Studies in this review used a range of different scanners, including for example, Siemens/CTI ECAT EX-ACT HR 47 tomograph (Hershey et al., 2003), GE advanced tomograph (Trost et al., 2006) and dual head camera (ECAM variable, Siemens) (Haense et al., 2016) that all have substantially different performance. The development in scanner technology and image analysis techniques over time is likely to be reflected in increasing sensitivity to detect significant changes in brain function.

Most of the tracers used in the studies included in this review measured regional cerebral blood flow or glucose metabolism. By far, the two most common PET tracers were ^{15}O-H$_2$O (29 studies) and ^{18}F-FDG (23 studies). Other PET tracers, that were used in one or two studies were ^{18}F-FDOPA, 5-HT$_{1B}$R and carbon based tracers [^{11}C]raclopride, [^{11}C]DTBZ, and [^{11}C]DPN. The most common SPET tracer was rCBF tracer ^{99m}Tc-ECD (used in 4/6 of the SPET studies) and the two other SPET tracers were ^{99m}Tc-HMPAO and [^{123}I]IBZM. The availability of these tracers vary between centers, which is likely to contribute to the selection of the tracer in individual studies.

5. Conclusions

Our findings demonstrate that the local effects of DBS are generally excitatory and when stimulation effect is seen, it always extends beyond the stimulation site to other brain regions. These findings have important implications for therapeutic use of DBS, highlighting that DBS cannot be considered purely as a lesion, disrupting the information flow at the stimulation site.

Data and code availability statement

The data and code are available from the corresponding author upon reasonable request.

Declaration of Competing Interest

The authors declare no relevant conflicts of interest.

Credit authorship contribution statement

Aleksi Kokkonen: Investigation, Methodology, Data curation, Writing – original draft, Writing – review & editing. **Emma A. Honkanen:**

Investigation, Data curation, Writing – original draft, Writing – review & editing, Visualization. **Daniel T. Corp:** Formal analysis, Writing – review & editing. **Juho Joutsa:** Conceptualization, Methodology, Validation, Writing – original draft, Writing – review & editing, Supervision, Project administration.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.neuroimage.2022.119473.

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