npj | parkinson's disease

Review article

Published in partnership with the Parkinson's Foundation

https://doi.org/10.1038/s41531-024-00774-3

Multimodal neuroimaging to characterize symptom-specific networks in movement disorders

Elizabeth G. Ellis[1,2] ✉, Garance M. Meyer[3], Valtteri Kaasinen[4,5], Daniel T. Corp[1,2], Nicola Pavese[6,7], Martin M. Reich[8] & Juho Joutsa[1,4,5] ✉

Movement disorders, such as Parkinson's disease, essential tremor, and dystonia, are characterized by their predominant motor symptoms, yet diseases causing abnormal movement also encompass several other symptoms, including non-motor symptoms. Here we review recent advances from studies of brain lesions, neuroimaging, and neuromodulation that provide converging evidence on symptom-specific brain networks in movement disorders. Although movement disorders have traditionally been conceptualized as disorders of the basal ganglia, cumulative data from brain lesions causing parkinsonism, tremor and dystonia have now demonstrated that this view is incomplete. Several recent studies have shown that lesions causing a given movement disorder occur in heterogeneous brain locations, but disrupt common brain networks, which appear to be specific to each motor phenotype. In addition, findings from structural and functional neuroimaging in movement disorders have demonstrated that brain abnormalities extend far beyond the brain networks associated with the motor symptoms. In fact, neuroimaging findings in each movement disorder are strongly influenced by the constellation of patients' symptoms that also seem to map to specific networks rather than individual anatomical structures or single neurotransmitters. Finally, observations from deep brain stimulation have demonstrated that clinical changes, including both symptom improvement and side effects, are dependent on the modulation of large-scale networks instead of purely local effects of the neuromodulation. Combined, this multimodal evidence suggests that symptoms in movement disorders arise from distinct brain networks, encouraging multimodal imaging studies to better characterize the underlying symptom-specific mechanisms and individually tailor treatment approaches.

Movement disorders are neurological disorders characterized by abnormal body movement. Common examples of abnormal movement phenomenology include parkinsonism, tremor, and dystonia. Etiologies of movement disorders are typically heterogeneous, including both idiopathic (e.g. Parkinson's disease [PD], essential tremor, idiopathic cervical dystonia) or secondary (e.g. caused by brain lesions) disorders[1–3]. Historically, most of these disorders were conceptualized as disorders of the basal ganglia, but accumulating evidence across decades of animal and human studies, and studies of brain lesions, has demonstrated that these abnormal movements can develop without damage to the basal ganglia[4,5]. Moreover, brain abnormalities in idiopathic cases often extend beyond the basal ganglia and a single patient can present with several phenotypically different movement disorders simultaneously[6,7]. Numerous methods have been applied to clarify our understanding of the neural bases of these disorders. Here, we provide

[1]Turku Brain and Mind Center, University of Turku, Turku, Finland. [2]Cognitive Neuroscience Unit, School of Psychology, Deakin University, Geelong, VIC, Australia. [3]Center for Brain Circuit Therapeutics, Department of Neurology, Brigham & Women's Hospital, Harvard Medical School, Boston, MA, USA. [4]Clinical Neurosciences, University of Turku, Turku, Finland. [5]Neurocenter, Turku University Hospital, Turku, Finland. [6]Institute of Clinical Medicine, Department of Nuclear Medicine & PET, Aarhus University, Aarhus, Denmark. [7]Translational and Clinical Research Institute, Newcastle University, Upon Tyn, UK. [8]Department of Neurology, University Hospital of Würzburg, Josef-Schneider-Straße 11, 97080 Würzburg, Germany.
✉e-mail: elizabeth.ellis@utu.fi; jtjout@utu.fi

an overview of recent evidence from different neuroimaging approaches, including studies of causal brain lesions, structural and molecular neuroimaging, and imaging with deep brain stimulation (DBS), which provide evidence of symptom-specific network dysfunctions. Given the large number of movement disorders and available neuroimaging tools, this review provides an overview of evidence from selected neuroimaging techniques. For more detailed information in individual disorders and methods, we refer the reader to more focused reviews on these topics (for e.g. for a systematic review of arterial spin labeling MRI in PD see Joshi et al.[8]; for a meta-analysis of presynaptic striatal dopaminergic function in atypical parkinsonism see Kaasinen et al.[9]; for a systematic review of structural MRI in dystonia see MacIver et al.[10]).

Localization based on causal brain lesions

One of the limitations of most case-control neuroimaging studies is that the findings are correlative in nature, and establishing causal relationships between brain changes and clinical symptoms is often challenging[11]. Causal brain lesions have been the cornerstone of the localization of neurological symptoms throughout the history of neurology, yet have gained renewed interest in recent times[12]. The main advantage in studying brain lesions is that they can provide causal inference between the damaged brain area and the resulting clinical symptoms[11]. For example, lesions causing parkinsonism and hemichorea have confirmed the role of damage of the nigrostriatal tract and subthalamic nucleus (STN) in these symptoms, respectively[4,13].

However, lesions causing identical symptoms can occur in heterogenous locations and clearly outside the anatomical brain structures that are thought to be key in driving symptoms, leaving the localization unclear (Fig. 1A). For example, only approximately 30% of lesions causing movement disorders seem to hit the presumed anatomical structures, demonstrating that although these classic lesion locations can be sufficient, they are not necessary to cause the relevant symptom[3]. These observations align with more recent views of neurological symptoms emerging from disruption of brain networks, rather than individual anatomical structures. Under this view, damage within a brain network can result in dysfunction of connected network, leading to corresponding functional deficits[14].

Recent brain lesion studies have adopted this idea by moving beyond the traditional approach of analyzing lesion location only, to study the connections disrupted by lesions (Fig. 1B)[12,15]. This approach has become possible via development of modern neuroimaging techniques investigating brain connectivity, including resting state functional connectivity MRI and diffusion tensor imaging, that have been used to build normative connectomes (or "wiring diagrams") of the human brain[14]. These connectomes complement available anatomical brain templates by providing a template of intrinsic brain connections[14]. Techniques such as lesion network mapping and lesion disconnectome mapping combine anatomical lesion locations with these connectomes, providing information about the networks disrupted by each lesion, and allowing mapping symptoms to brain networks[16,17]. These techniques leverage the concept of diaschisis, which states that structural lesions can result in changes in the brain regions

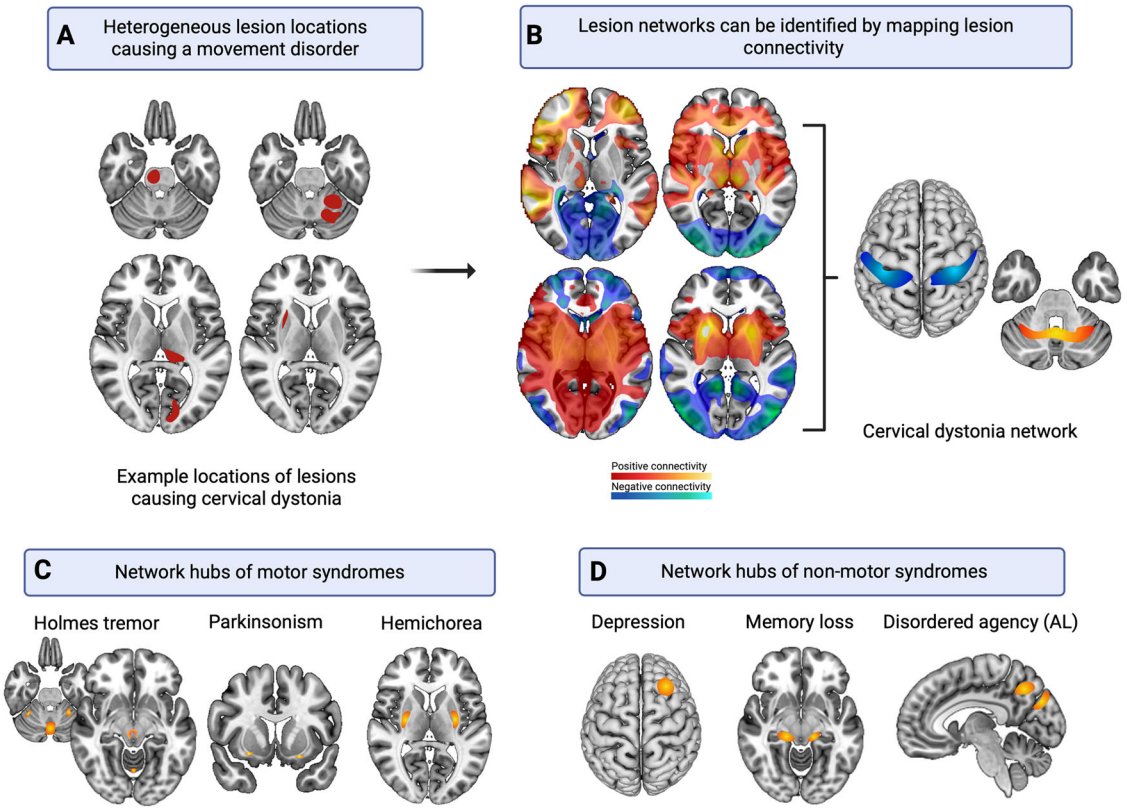

Fig. 1 | Insights from lesion network mapping. Lesions causing cervical dystonia are found in heterogeneous locations (example lesion locations shown in red, (**A**)) but are connected to a common network characterized by connectivity to the cerebellum and somatosensory cortex (**B**). Similarly, heterogeneous lesion locations causing other movement disorders (**C**) and non-motor symptoms (**D**) map to common networks, characterized by connectivity to distinct brain regions (here referred to as 'network hubs'). Lesions causing Holmes tremor mapped to six regions (Table 1) of which the red nucleus, vermis and lateral cerebellum hubs are depicted here; parkinsonism localized to the claustrum; hemichorea-hemiballismus to the posterolateral putamen. Lesions causing depression mapped to the dorsolateral prefrontal cortex; loss of memory to the presubiculum and retrosplenial cortex; disordered agency to the precuneus. Note: Lesions and lesion networks have here been recreated with BioRender.com, functional connectivity profiles are shown with arbitrary units for illustrative purposes only, with warm colors representing positive functional connectivity from lesion locations and cool colors representing negative functional connectivity from lesion locations in (**B**)–(**D**). Original publications with exhaustive lesion location information: Cervical dystonia[5]; Holmes tremor[20]; Parkinsonism[4]; Hemichorea[13]; Depression[24]; Memory loss[25]; Disordered agency[150]. AL alien limb syndrome.

Table. 1 | Lesion Network Mapping Studies of Movement Disorders

Disorder	Lesion locations	Hubs of lesion network	Publication
Parkinsonism	SMA; SNr; basal ganglia; pontomesencephalic; midbrain tegmentum; sublentiform nucleus; precentral gyrus; medial frontal lobe; cerebral peduncle; temporal lobe; mesencephalic; midbrain; medial temporal lobe; insula; thalamus; brainstem	Claustrum	Joutsa et al.[4]
Hemichorea-hemiballismus	Cortex; STN; basal ganglia; midbrain; subcortical white matter	Posterolateral putamen	Laganiere et al.[13]
Holmes tremor	Midbrain; cerebellum; basal ganglia; pons; medulla; occipital lobe	Red nucleus, GPi, VOP, pulvinar nucleus, vermis and lateral cerebellum, flocculonodular and ponto-medullary	Joutsa et al.[20]
Cervical dystonia	Cerebellum; brainstem; basal ganglia; thalamus; occipital lobe	Sensorimotor cortex and cerebellum	Corp et al.[5]
Tics	Basal ganglia; temporal lobe; parietal lobe; insula; corpus callosum; thalamus; internal capsule; midbrain; pons; medulla oblongata	Anterior striatum	Ganos et al.[22]
	Basal ganglia, frontal lobe, temporal lobe, parietal lobe, thalamus, internal capsule, cerebellum, brainstem	Basal ganglia, cingulate gyrus, precuneus	Zouki et al.[23]
Freezing of gait	Brainstem; basal ganglia; cortex; subcortical white matter	Dorsal medial cerebellum	Fasano et al.[21]
Alien limb	Medial frontal cortices; corpus callosum; parietal lobes; thalamus	Precuneus	Darby et al.[150]
Akinetic mutism	Anterior cingulate cortex; basal ganglia; thalamus; brainstem	Anterior cingulate cortex	Darby et al.[150]

Original publications provide exhaustive lesion location information.
GPi globus pallidus interna, *SMA* supplementary motor area, *SNr* substantia nigra, *STN* subthalamic nucleus, *VOP* ventral oralis posterior (thalamus).

connected to the lesion location, demonstrated both in animal lesion experiments and molecular brain imaging in humans with focal brain lesions[18,19].

To date, lesion network mapping has been used to localize the brain networks causally linked with several movement disorders, including parkinsonism[4], cervical dystonia[5], hemichorea-hemiballism[13], Holmes' tremor[20], freezing of gait[21], and tics (Fig. 1C; Table 1)[22,23]. Each of these studies have demonstrated that although the causal lesions can occur in heterogeneous locations, they localize to common networks, which are specific to each symptom. For example, lesions causing hemichorea-hemiballismus are connected to the posterior putamen[13], lesions causing cervical dystonia to the cerebellum and primary somatosensory cortex[5], and lesions causing parkinsonism to the claustrum[4], aligning with neuroimaging and postmortem neuropathological findings in corresponding idiopathic disorders.

The lesion network mapping approach has also been used in non-motor symptoms that are common in movement disorders, such as depression[24] or loss of memory[25]. Similar to movement disorders, lesions in heterogeneous locations causing these symptoms were connected to common brain regions: lesions causing depression to the dorsolateral prefrontal cortex and lesions causing loss of memory to the presubiculum and retrosplenial cortex (Fig. 1D). Combined, these findings support the view that symptoms arise from disruption of distinct brain networks. In neurodegenerative movement disorders, such as PD, neuropathological changes progress and extend spatially[26,27]. The disease progression is reflected in the evolution of symptoms that could be explained via involvement of additional functional networks.

Brain imaging in movement disorders

Structural brain imaging. Structural brain imaging is mainly used in clinical practice to identify or exclude secondary etiologies in individual patients[28]. However, there are certain instances where structural markers can be used to support the diagnosis of idiopathic movement disorders. For example, midbrain atrophy in progressive supranuclear palsy[29,30] or striatal and cerebellar atrophy in multiple system atrophy, but the sensitivity and specificity of these markers is relatively low, especially in the early phases of the diseases[31]. At the group-level, structural brain imaging has provided valuable insight into the neuroanatomy of many movement disorders, including the assessment of brain volume, morphometry, and white matter integrity (Fig. 2A)[32]. These studies have confirmed the involvement of the basal ganglia (e.g., in PD, essential tremor, and dystonia[33–36]), yet this is often reported alongside a multitude of other structural changes, creating a heterogeneous literature base[35,37–40].

In essential tremor, a recent meta-analysis[36] demonstrated that for every study reporting atrophy in the cerebellum for patients compared to controls (the most consistent finding in essential tremor literature[1,39]), there was also another study reporting no structural changes in this brain region[39]. Diffusion imaging is seemingly more consistent in its implication of microstructural cerebellar abnormalities, commonly within the cerebellar peduncles[39]. The heterogeneity of structural imaging findings is even more apparent in PD, where there may be no gray matter abnormalities that would be implicated more often than expected by chance[38]. Although structural changes within the cerebello-thalamo-cortical circuitry are often reported in dystonia,[10] there seems to be only minimal overlap in the precise locations reported, and most studies also report abnormalities beyond this circuitry[37].

Overall, these inconsistencies across movement disorders can be in part attributed to variability in neuroimaging methodology and clinical heterogeneity of the patient populations[39,41], leaving localization ambiguous, and not yet clinically useful at the individual patient level.

Molecular brain imaging. Molecular neuroimaging techniques allow for looking beyond spatial locations and structural abnormalities into changes in brain activity and neurotransmitter function (Fig. 2B). Dopaminergic function in PD, imaged with positron emission tomography (PET) or single photon emission computed tomography (SPECT), is by far the most studied neurotransmitter system in movement disorders. Loss of nigrostriatal presynaptic dopamine function is the hallmark finding in PD and associated with overall motor symptom severity[42]. However, the relationship between dopamine function and symptom severity is not uniform across all symptoms of PD. For instance, while rigidity and bradykinesia demonstrate a moderate correlation with the extent of striatal dopaminergic depletion[43], parkinsonian rest tremor appears to be associated with both dopaminergic and non-dopaminergic function in the striatum and cerebello-thalamo-cortical circuitry[44,45].

In addition to the motor symptoms, the dopamine system also is involved in non-motor symptoms, including apathy and impulse control disorders. These symptoms are linked with abnormalities in the mesolimbic and -cortical pathways[46]. Dopaminergic abnormalities in PD evolve with disease progression, including a continuous decline in presynaptic dopamine signaling in the nigrostriatal tract, spread of the dopaminergic deficit to the other dopaminergic pathways, and temporal variations in dopamine

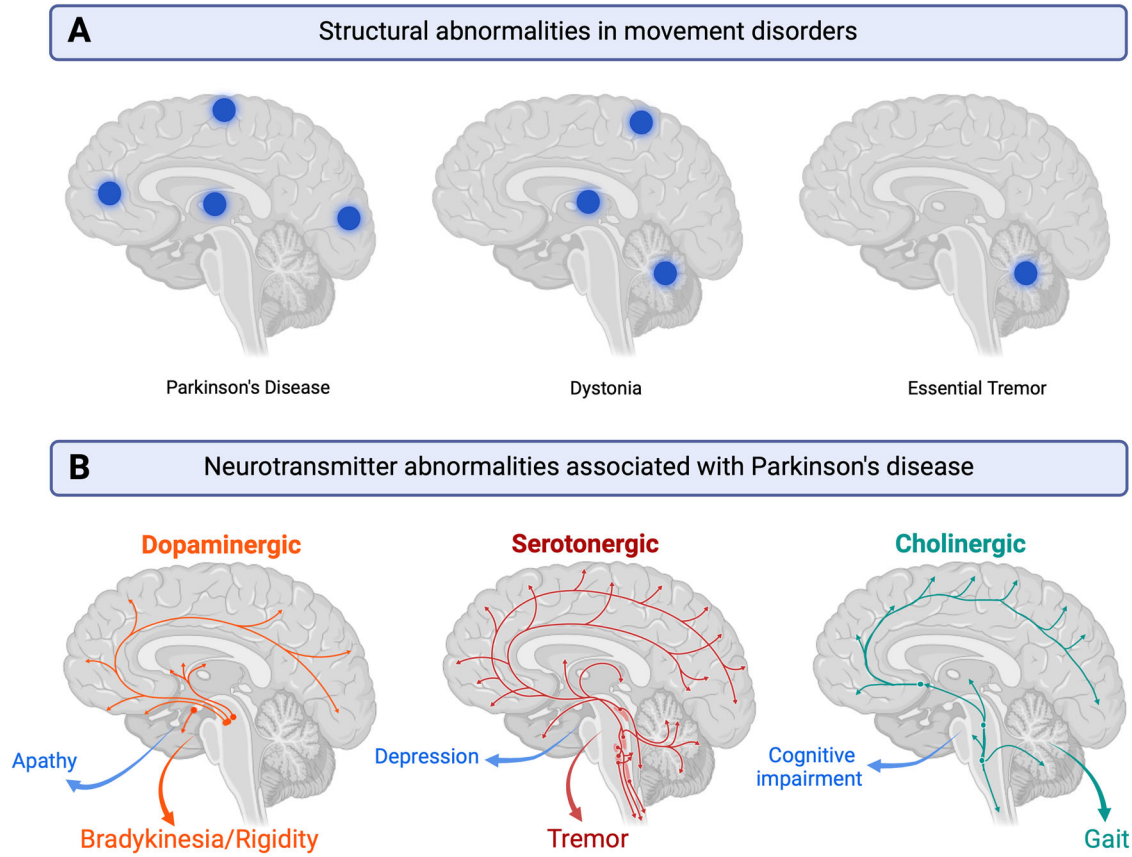

Fig. 2 | Insights from structural and molecular neuroimaging. Meta-analyses and systematic reviews of neuroimaging studies have highlighted that structural abnormalities (**A**) are commonly implicated within the basal ganglia, and motor, frontal and occipital cortex in Parkinson's disease[141,151]; within thalamic, cerebellar, and cortical motor regions in dystonia[36,37]; and within the cerebellum and cerebellar peduncles in essential tremor[39]. Molecular imaging (**B**) implicates multiple neurotransmitters associated with symptoms of Parkinson's disease, including an association between the dopaminergic (modeled in orange) system and bradykinesia/rigidity[43] and apathy[46], the serotonergic (red) system with tremor and several non-motor symptoms[52,54], and the cholinergic (green) system with cognition and gait[57]. Neurotransmitter systems are here modeled for visualization purposes only.

receptor availability, that are reflected in clinical symptom profiles at different disease stages[47]. For example, hallucinations are considered to be linked to the dopamine system but usually only appear at later disease stages, whereas depression can precede even the onset of motor symptoms.

The temporal evolution of neurotransmitter function is, however, not limited to the dopaminergic system, also affecting other neurotransmitter systems in PD[48–50]. Several PET and SPECT studies have now shown progressive serotonergic dysfunction in PD patients, involving the basal ganglia, brainstem, and cortical regions[48,51,52]. While these changes are more severe in patients with longer disease duration, early changes within the serotonergic raphe complex have also been reported in de novo PD and appear to correlate with severity and consistency of rest tremor[51,52], and non-motor symptoms, including fatigue[53], excessive daytime sleepiness[54,55], and depression[56]. The spatial distribution of the serotonergic dysfunction differs between these symptoms, suggesting that they could be caused by dysfunction of different serotonergic networks[53–55]. Similarly, the involvement of the cholinergic system in PD has been linked to REM sleep behavioral disorder (RBD), cognitive impairment, and gait problems[57]. While RBD often appears before the onset of motor symptoms, cognitive impairment and gait problems are generally late symptoms of the disease, appearing with the spatially spreading neurodegeneration in the cholinergic system[58]. Taken together, these studies suggest that symptoms associated with the same neurotransmitter system can be localized to different brain networks.

Examining the broader interplay between subcortical and cortical metabolism offers another perspective of symptom-specific brain networks. Utilizing fluorodeoxyglucose (FDG) PET, spatial covariance analysis has been used to identify distinct metabolic patterns for specific PD types[59]. The PD-related pattern (PDRP) is associated with bradykinesia and rigidity, and is characterized by increased pallido-thalamic and pontine metabolism alongside relative decreases in metabolism of the premotor cortex, supplementary motor area (SMA), and parietal cortical regions[60]. In contrast, the PD-tremor related pattern (PDTP) is characterized by increased metabolic activity in the cerebellum and dorsal pons, the primary motor cortex, and partially in the caudate nucleus and putamen[61]. The PD-related cognitive pattern shows metabolic abnormality in pre-SMA, prefrontal cortex, precuneus, parietal association areas and cerebellar vermis and dentate nuclei[62]. FDG-PET patterns have also been identified for atypical parkinsonisms including progressive supranuclear palsy[63], multiple system atrophy[63], and corticobasal syndrome[64,65]. These patterns distinguish parkinsonism patients from controls and have been independently validated in all but corticobasal syndrome[66,67]. Symptom-specific networks, as evidenced through neurotransmitter studies and distinct PD-related metabolic patterns, emphasize the multifaceted nature of these conditions, supporting a multifaceted approach to characterize the underlying mechanisms of symptoms.

Insights from neuromodulation

Deep brain stimulation: stimulation site. Neuromodulation techniques, particularly DBS, are increasingly used to treat movement disorders. DBS is highly efficacious in controlling the cardinal motor symptoms of PD, dystonia, and essential tremor[68–70]. However, some of the other symptoms of PD, such as freezing of gait, and most non-motor

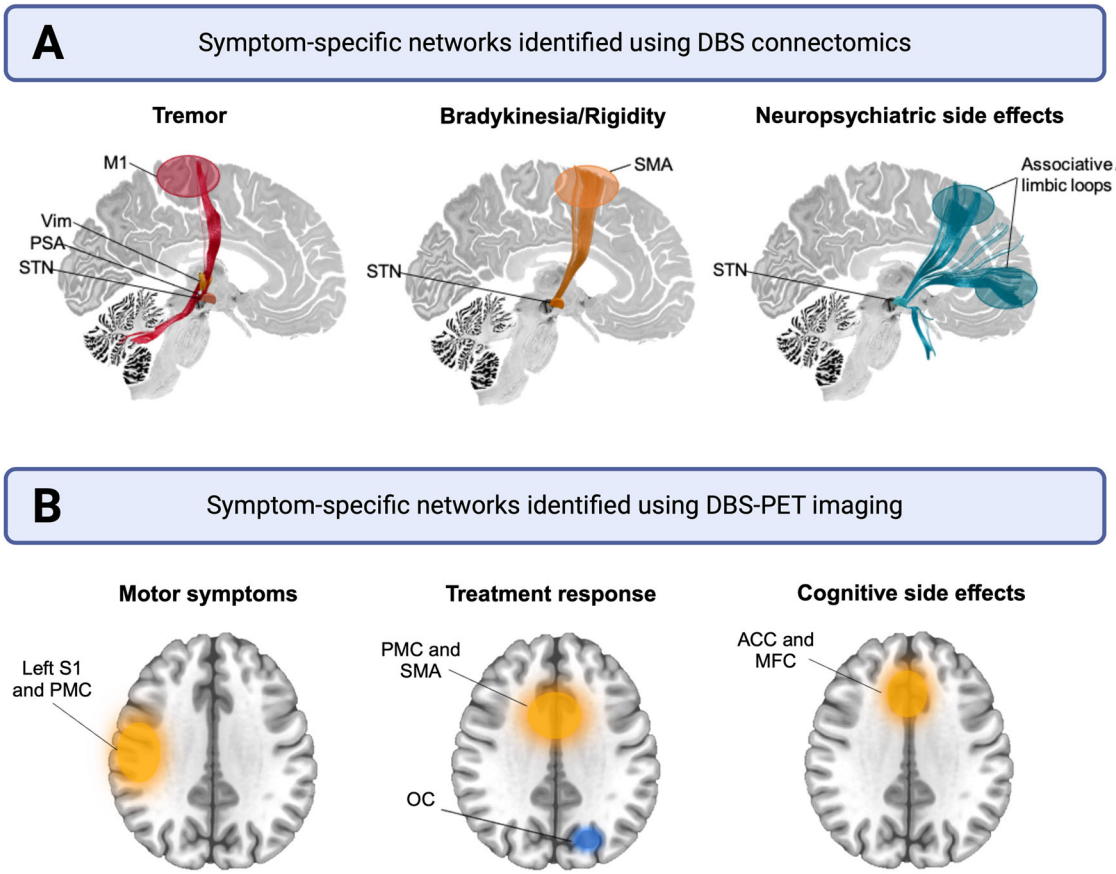

Fig. 3 | Insights from neuromodulation. Symptom-specific networks in Parkinson's disease derived by associating connectome-based structural and functional connectivity profiles from stimulation sites (STN-DBS) to clinical outcomes (**A**)[78,87,101,102]. Tracts and structures were obtained from the DBS tractography atlas (Middleborough et al.[152]) and visualized on the BigBrain ultrahigh resolution template[153]. Symptom specific networks in cervical dystonia with GPi-DBS, identified using [^{18}F]FDG PET imaging (**B**)[137]. Warm colors represent increased metabolism and cool colors represent decreased metabolism. STN subthalamic nucleus, M1 primary motor cortex, Vim ventral intermedial nucleus of the thalamus, PSA posterior subthalamic area, SMA Supplementary motor area, NP Neuropsychiatric, brady bradykinesia, rigid rigidity, S1 primary somatosensory cortex, PMC pre-motor cortex, OC occipital cortex, ACC anterior cingulate cortex, MFC Middle frontal cortex.

symptoms, have variable responses to STN or GPi DBS, and off-target stimulation has been shown to cause side effects[71,72]. Studies using the volume of tissue activated (VTA)[73] or the magnitude of the stimulation-induced electric field[74] have shown that the motor benefit of DBS critically depends on the exact location of the stimulated tissue. Moreover, aggregation of stimulation fields of large cohorts of patients with DBS combined with clinical outcome data have been used to determine the optimal stimulation sites. These "sweetspots" include, for example, the dorsolateral border of the STN in PD[74] and the posterior ventromedial globus pallidus internus in dystonia[75]. Potential side-effects induced by stimulation are considered to be associated with the unintentional current spread to the nearby neural structures. For example, the induction of phosphenes may be caused by current spread to the optic tracts, which lie ventral to the GPi[76]. However, other side-effects, such as cognitive decline or delayed-onset ataxia, may not localize to a single anatomical location[77,78].

Deep brain stimulation: networks. Beyond purely local effects, it has become clear that DBS acts by modulating large-scale brain networks[79,80]. Substantial effort has been made to identify the specific networks responsible for mediating the therapeutic (or adverse) effects of the stimulation. Assuming that dysfunction of these networks underlies the symptoms at baseline, this can be a powerful approach to identify and/or further validate symptom-specific networks (Fig. 3A). Once the stimulation site is located (which can be done by modeling the VTA or electric fields[81,82]), the brain regions that are structurally or functionally connected to this site can be identified indirectly using normative connectomes[83].

Early studies investigating the structural connectivity profiles of stimulation sites highlighted the key role of the motor cortico-basal ganglia-thalamocortical loop for improvement of the cardinal symptoms of PD with STN-DBS[84,85], which was also recently observed in the functional connectivity profiles of GPi-DBS[86]. Structural connectivity of the stimulation site with specific nodes within the motor network has been shown to be associated with improvement of specific motor symptoms, specifically the SMA with bradykinesia and rigidity, and the M1 with tremor improvement[87]. Although the effects of STN-DBS for freezing of gait on the group-level are variable, gait improvement was shown to be associated with structural connectivity within the motor and associative cortico-basal ganglia-thalamocortical loops, and downstream to the brainstem, including the substantia nigra and pedunculopontine nucleus[72].

Further support for symptom-specific, rather than disease-specific, networks for DBS comes from tremor. The dentato-rubro-thalamic tract has been identified as the likely anatomical target for tremor improvement across disorders (PD[88,89] and essential tremor[90–95]) and targets (ventral intermedial nucleus of the thalamus [VIM] and subthalamic/posterior subthalamic area)[96,97]. However, targeting partially different networks could be optimal to treat specific types of tremor[98]. For example, when compared to essential tremor, improvement of dystonic tremor after VIM-DBS was associated with the additional modulation of pallidothalamic structural

connections, suggesting that both the cerebello-thalamocortical and basal ganglia-thalamocortical network play a role in the pathophysiology of dystonic tremor[98]. In addition, improvement of dystonia following GPi-DBS has been associated with functional connectivity to the cerebellum and somatomotor cortex, aligning with the networks identified from causal lesions[5,75,99,100]. Finally, neuropsychiatric side-effects of STN-DBS, such as worsened depression[101] or impulsivity[102], as well as cognitive decline[78] in PD have been related to stimulation of the associative and limbic cortico-basal ganglia-thalamocortical loops, again aligning with findings from lesion studies[78,101,102]. Of note, a recent study emphasized the potential direct clinical relevance of these findings. This study showed that VTAs causing cognitive decline in PD were more strongly functionally connected to a brain network encompassing the anterior cingulate, caudate, hippocampus, and cognitive portions of the cerebellum[78]. Then, a 'heat map' of brain areas most connected to this circuit could be leveraged for DBS reprogramming in a single patient, which resulted in improved cognition[78].

Measures of DBS-induced changes in the brain: fMRI. The use of fMRI allows for direct characterization of DBS effects on large scale brain networks, but this has been historically limited by safety concerns and technical challenges, including the potential heating of the DBS electrodes, implanted pulse generator dysfunction, and susceptibility artifacts caused by the DBS hardware[103]. Formal approval for fMRI with active DBS for Medtronic systems in 2015, and other efforts regarding safety testing[104–109], have alleviated many of these concerns, promoting this line of research in recent years[110].

In PD, STN-DBS has been shown to modify activity[106–108,111–119] and connectivity[107,120–128] in the cortico-basal ganglia-thalamocortical motor loop and cerebellum. Interestingly, some studies have reported that these changes corresponded to a normalization of the abnormal connectivity patterns towards a healthy state[120,124,127]. However, the direction of the effects across studies has not been consistent and, for example, both increases[114,116,119] and decreases[111,116,118] in the activation of the M1 have been reported. GPi-DBS in PD seems to have comparable network effects in the motor system, but the effects outside the motor network were less widespread than with STN-DBS, which is also known to be associated with more non-motor clinical effects[121,128,129].

Several studies have sought to determine which of these widespread changes contribute to clinical outcomes, and have identified correlations between changes in activity or connectivity in motor networks and motor improvement[110,121,129]. In the largest study to date (N = 67), a specific pattern of DBS-induced activation of the ipsilateral thalamus and deactivation of ipsilateral M1 and contralateral cerebellum could discriminate (and predict) clinically optimal vs. suboptimal contacts in PD[111]. Still, only a few studies could link specific DBS-induced changes to individual symptoms. Gibson et al.[114]. showed that bradykinesia and rigidity improvement correlated with DBS-induced M1 activation, while tremor improvement correlated with thalamic, brainstem, and cerebellar activation. Moreover, a case study of acute depressive affect induced by STN-DBS demonstrated changes in activity of prefrontal regions[119], consistent with the idea that neuropsychiatric side effects might relate to the undesired recruitment of non-motor networks[114,130].

Few studies have investigated the fMRI correlates of DBS for movement disorders other than PD. DBS of the VIM or caudal zona incerta for the treatment of tremor was associated with changes in activity and connectivity in the sensorimotor cortex, cerebellum, and thalamus[109,131,132]. Clinical tremor improvement has been shown to correlate with the changes in activity and connectivity in the cerebellum[132]. In addition, GPi-DBS for dystonia was shown to induce deactivation of the sensorimotor cortex, which was correlated with clinical improvement, as well as changes in functional connectivity between the sensorimotor cortex and the basal ganglia[110]. A second study in dystonia demonstrated a restoration of global connectivity patterns in the motor network towards a healthy state after GPi-DBS[133]. Combined, studies in PD and other movement disorders provide compelling evidence of the network-level effects of DBS and their role in clinical outcomes.

Measurements of DBS-induced changes in the brain: molecular brain imaging. PET and SPECT imaging can also demonstrate brain-wide effects of DBS, allowing for investigating metabolic and neurotransmitter-level changes induced by stimulation. As the clinical effects of STN-DBS are similar to, and correlate with, the effects of levodopa in PD, early studies investigated if the mechanisms of action of STN-DBS was mediated by increasing striatal dopamine levels[134]. However, these studies failed to show any difference between stimulation on and off in the striatal binding of the postsynaptic dopamine receptor ligand [^{11}C]raclopride, which is sensitive for competition with endogenous dopamine in the striatum[134]. Investigating cerebral blood flow and metabolism has demonstrated that STN-DBS is associated with increased activity at the stimulation site, and decreased activity in the primary motor cortex, supplementary motor area and cerebellum[134]. These findings corroborate the results from connectomic and fMRI studies, again demonstrating network-level effects of DBS rather than an increase in striatal dopamine function or purely local lesion-like effects.

The few molecular imaging studies in essential tremor have demonstrated that VIM-DBS increases both local and remote activity within the motor network[134]. Of note, one study showed activation of the motor cortex during effective stimulation of the VIM (130 to 160 Hz), which was not present during ineffective tremor reduction with 50 Hz stimulation[135]. Effects on tremor control could be disentangled from delayed side-effects affecting gait, where a remote activity of the mid cerebellum could be detected[136]. Similarly, there are only a handful of studies investigating the molecular-level effects of DBS in the context of dystonia. Although the changes in regional blood flow have remained inconclusive[134], a recent study with the largest sample to date investigating the effects of GPi-DBS (stimulation on vs. off) in cervical dystonia, demonstrated that stimulation is associated with both local and remote changes in regional brain glucose metabolism[137]. Motor improvement was associated with the remote effects in the sensorimotor cortical regions, not with the local metabolic response at the stimulation site (Fig. 3B)[137]. Similarly, stimulation-induced side-effects, including decline in executive function and emergence of parkinsonism, were associated with remote activations in the prefrontal cortex and putamen, respectively[137].

Integration of findings from different modalities: towards multimodal studies

Movement disorders are multisystem disorders, involving multiple neurotransmitter systems, tissue types, and brain networks, with interplay between these mechanisms appearing to drive symptom generation and alleviation. It is therefore logical that the neural bases of these disorders and their symptoms will not be fully accounted for by a single imaging modality, but via integration of evidence across modalities.

Aggregation of one modality of neuroimaging findings by meta-analysis is common in movement disorder literature (e.g.,[138–140].). Analysis of one modality enables clear interpretation of results, identifying, for example, the most consistently atrophied regions in a given disorder. However, meta-analyses across multiple imaging modalities (e.g.,[36,141].) offer insight into the differences and commonalities across imaging techniques, and may provide evidence in support of the use of a particular modality in a disorder or disease stage. For instance, in PD, Albrecht et al.[141] meta-analyzed results from [^{18}F]FDG PET (glucose metabolism), T1-weighted and diffusion MRI. While there was overlap in results across modalities, the findings provided support for the higher sensitivity of PET over MRI[141]. In cervical dystonia, results of structural and functional studies converge upon several common regions including cortical sensorimotor and basal ganglia areas, and the cerebellum[36]. However, it is still true that each modality provides us with unique findings which may not be seen with other modalities (e.g. subtle functional changes preceding structural change)[36]. Therefore, it may not be as simple as identifying the brain area that represents convergence across structural, functional, and treatment evidence. Instead, a deeper integration of multiple modalities may be required to identify both convergent and uniquely sensitive changes across the disease course.

Newer techniques, such as 'coordinate network mapping'[142], are also aimed at reconciling previously published neuroimaging findings - not by

identifying the most commonly affected structures as in traditional meta-analysis, but by combining imaging findings with the connectome data to map the brain networks implicated by these neuroimaging studies. Following this network mapping logic, it may be that "inconsistent findings" in movement disorder literature are not replicating due to a focus on *discrete anatomical location*. Instead, similar to lesion-induced cases, idiopathic movement disorders and symptoms may better localize to *brain networks*[142]. For instance, in essential tremor, Younger et al.[35] demonstrated that despite heterogeneity in previously reported locations of abnormality from structural and molecular studies, 100% of these locations were *functionally connected* to a brain network centered upon the cerebellum[35]. Further, these network mapping methods can be used to localize symptom-specific networks. For example, in PD dementia Weil et al.[143] identified a brain network common to over 90% of previously reported imaging abnormalities, focused upon the right hippocampus[143]. This coordinate mapping technique is similar to 'lesion network mapping' discussed above, examining the functional connections of lesions causing movement disorders, yet an advantage of this approach is that it can be applied to multimodal neuroimaging data in *idiopathic* disorders. Currently available findings suggest that these techniques converge on the same brain networks in movement disorders, but this is an area of ongoing investigation[4,11,12,15].

Taking a different approach, multimodal imaging studies offer the unique ability to simultaneously explore the links between molecular alterations, structure, and function in neurological disorders. Sintini et al.[144] applied T1-weighted MRI, diffusion MRI, and flortaucipir PET (estimating the density and distribution of aggregated tau neurofibrillary tangles) to reveal an association between Tau uptake and neurodegeneration in progressive supranuclear palsy patients. Similarly, our understanding of the noradrenergic system in PD has been furthered by a recent hybrid MRI-PET study[145], revealing a potential uncoupling of noradrenergic alterations at structural and molecular levels. Such studies can test hypotheses proposed by single modality investigations, and unravel the complex interactions between different components. However, multimodal studies are commonly less feasible to conduct over single modality studies or meta-analysis.

The possibility to present multi layered models encompassing complex interactions between molecular, structural, and functional relationships in brain disorders has been advanced by recent efforts to map neurotransmitter systems to the brains' structural and functional organization[146]. This work provides the scaffolding for continued efforts to eventually achieve whole-brain, cortical and subcortical atlases linking levels of neuroimaging evidence and disease related data.

Levels of evidence to establish symptom-specific networks

Multiple levels of evidence are required to establish symptom-specific networks (examples provided in Fig. 4). Numerous techniques can be used to

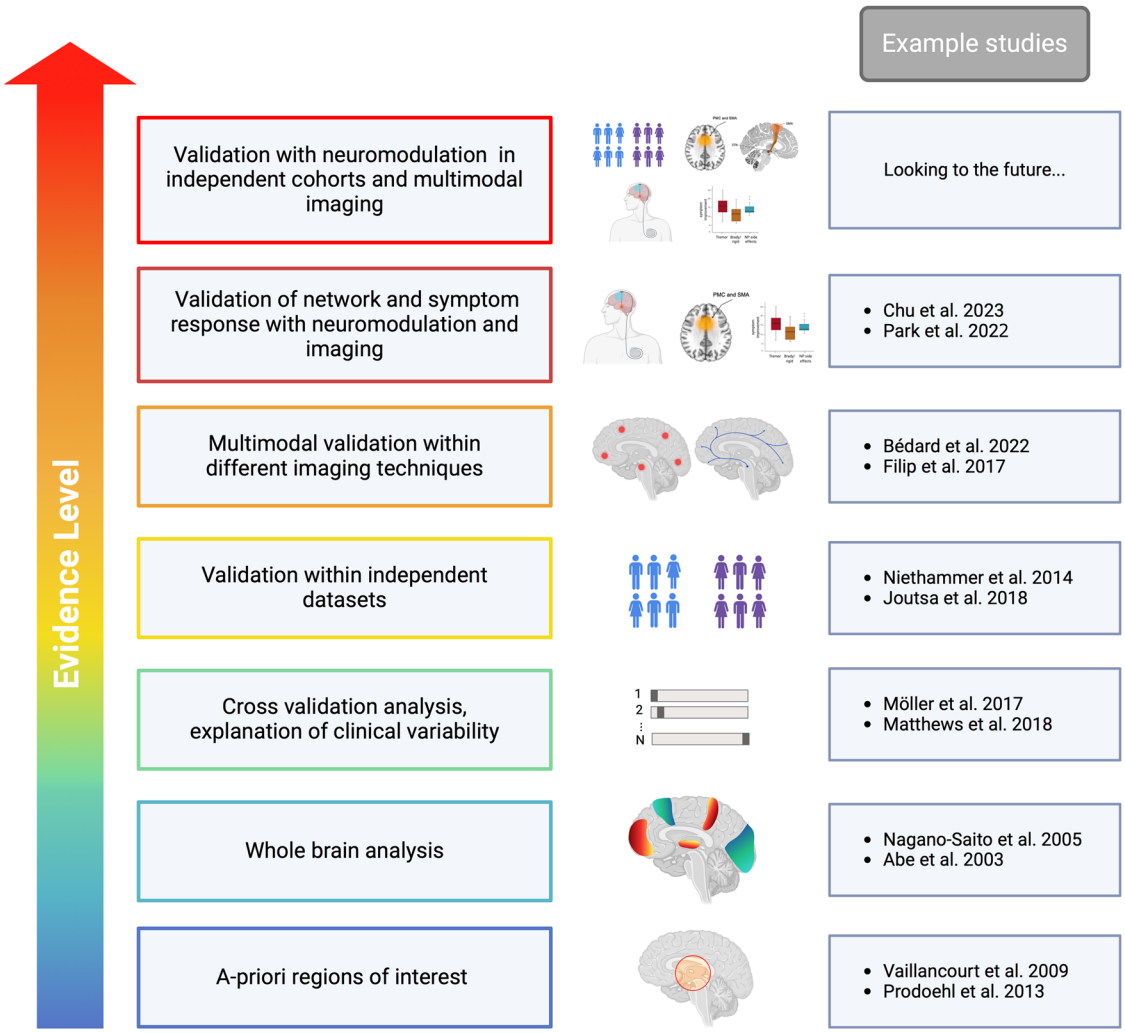

Fig. 4 | Non-exhaustive levels of evidence towards symptom-specific networks. Evidence from group-level neuroimaging studies is built upon by validation in independent datasets, and perturbation of suspected symptom networks with neuromodulation. Evidence gathered across these levels can establish symptom-specific networks in movement disorders. Prior research studies provided as examples of each level of evidence: Vaillancourt et al.[154]; Prodoehl et al.[155]; Nagano-Saito et al.[156]; Abe et al.[157]; Möller et al.[158]; Matthews et al.[159]; Niethammer et al.[64]; Joutsa et al.[4]; Bédard et al.[160]; Filip et al.[161]; Chu et al.[120]; Park et al.[162].

test these hypotheses in human studies, including, but not limited to: computational models[147]; lesion network mapping[16], disconnectome mapping[17]; meta-analytic mapping (for e.g., meta-analytic connectivity modeling[148]); DBS site mapping[149]; structural and functional neuroimaging, and perturbation experiments with brain stimulation combined with functional imaging. Overall, in the identification of a network, a-priori region of interest and whole-brain neuroimaging studies provide a basis of the regions involved in the symptom of interest. Results from these studies may point toward a network related to symptoms and can be strengthened through validation in independent cohorts, with cross-validation methods, assessed longitudinally, in multi-site studies, and critically tested in multi-modal imaging studies. These efforts may also be furthered by 'Big Data' projects such as 'OpenNeuro' (https://openneuro.org), for example by providing access to validation cohorts. Building upon group-level results wherein a symptom-specific network has been proposed, brain stimulation can then be used to modulate the network to test whether it moderates symptoms. Paired with neuroimaging, these studies could confirm the engagement of the target network. At present, these networks are tested with a single imaging modality, and neuromodulation in isolation, however, in future these experiments can be combined with multimodal imaging (e.g. simultaneous PET-fMRI), preferably with validation in independent data-sets to comprehensively characterise the symptom-specific networks and their mechanisms.

Conclusion

Recent evidence supports the notion that symptoms of movement disorders arise from disruption of specific brain networks. While basal ganglia circuitry is commonly implicated, abnormal movements can also arise without damage specifically to the basal ganglia. The complexity of patients' symptom profiles is reflected in the complexity of the neural systems and neurotransmitters involved, rather than tied to a singular abnormality. Equally, the effects of neuromodulation are not only local at the target site, but act by modulating networks connected to the stimulated tissue at the treatment target location. Taken together, this evidence encourages the use of multimodal neuroimaging to comprehensively characterize these symptom specific brain networks. This fine-grained approach can advance and refine our future discovery of effective therapeutic targets.

Received: 2 February 2024; Accepted: 5 August 2024;
Published online: 14 August 2024

References

1. Louis, E. D. & Faust, P. L. Essential tremor pathology: neurodegeneration and reorganization of neuronal connections. *Nat. Rev. Neurol.* **16**, 69–83 (2020).
2. Fahn, S. Classification of movement disorders. *Mov. Disord.* **26**, 947–957 (2011).
3. Pandey, S. et al. Gaps, controversies, and proposed roadmap for research in poststroke. *Mov. Disord. Mov. Disord.* **37**, 1996–2007 (2022).
4. Joutsa, J., Horn, A., Hsu, J. & Fox, M. D. Localizing parkinsonism based on focal brain lesions. *Brain* **141**, 2445–2456 (2018).
5. Corp, D. T. et al. Network localization of cervical dystonia based on causal brain lesions. *Brain* **142**, 1660–1674 (2019).
6. Poewe, W. H., Lees, A. J. & Stern, G. M. Dystonia in parkinson's disease: Clinical and pharmacological features. *Ann. Neurol.* **23**, 73–78 (1988).
7. Aerts, M. B., Jankovic, J., van de Warrenburg, B. P. & Bloem, B. R. Phenomenology, classification, and diagnostic approach to patients with movement disorders. In *Movement Disorders in Neurologic and Systemic Disease* 1 (Cambridge University Press, 2014).
8. Joshi, D., Prasad, S., Saini, J. & Ingalhalikar, M. Role of arterial spin labeling (ASL) images in Parkinson's disease (PD): a systematic review. *Acad. Radio.* **30**, 1695–1708 (2023).
9. Kaasinen, V., Kankare, T., Joutsa, J. & Vahlberg, T. Presynaptic striatal dopaminergic function in atypical parkinsonism: A metaanalysis of imaging studies. *J. Nucl. Med.* **60**, 1757–1763 (2019).
10. MacIver, C. L., Tax, C. M. W., Jones, D. K. & Peall, K. J. Structural magnetic resonance imaging in dystonia: A systematic review of methodological approaches and findings. *Eur. J. Neurol.* **29**, 3418–3448 (2022).
11. Siddiqi, S. H., Kording, K. P., Parvizi, J. & Fox, M. D. Causal mapping of human brain function. *Nat. Rev. Neurosci.* **23**, 361–375 (2022).
12. Joutsa, J., Lipsman, N., Horn, A., Cosgrove, G. R. & Fox, M. D. The return of the lesion for localization and therapy. *Brain* **146**, 3146–3155 (2023).
13. Laganiere, S., Boes, A. D. & Fox, M. D. Network localization of hemichorea-hemiballismus. *Neurology* **86**, 2187–2195 (2016).
14. Fox, M. D. Mapping symptoms to brain networks with the human connectome. *N. Engl. J. Med.* **379**, 2237–2245 (2018).
15. Joutsa, J., Corp, D. T. & Fox, M. D. Lesion network mapping for symptom localization: Recent developments and future directions. *Curr. Opin. Neurol.* **35**, 453–459 (2022).
16. Boes, A. D. et al. Network localization of neurological symptoms from focal brain lesions. *Brain* **138**, 3061–3075 (2015).
17. Foulon, C. et al. Advanced lesion symptom mapping analyses and implementation as BCBtoolkit. *Gigascience* **7**, 1–17 (2018).
18. Carrera, E. & Tononi, G. Diaschisis: Past, present, future. *Brain* **137**, 2408–2422 (2014).
19. von Monakow, C. *Die Lokalisation Im Grosshirn Und Der Abbau Der Funktion Durch Kortikale Herde*. (JF Bergmann, 1914).
20. Joutsa, J., Shih, L. C. & Fox, M. D. Mapping holmes tremor circuit using the human brain connectome. *Ann. Neurol.* **86**, 812–820 (2019).
21. Fasano, A., Laganiere, S. E., Lam, S. & Fox, M. D. Lesions causing freezing of gait localize to a cerebellar functional network. *Ann. Neurol.* **81**, 129–141 (2017).
22. Ganos, C. et al. A neural network for tics: insights from causal brain lesions and deep brain stimulation. *Brain* **145**, 4385–4397 (2022).
23. Zouki, J. et al. Mapping a network for tics in Tourette syndrome using causal lesions and structural alterations. *Brain Commun*. 5, 1–36 (2023).
24. Padmanabhan, J. L. et al. A human depression circuit derived from focal brain lesions. *Biol. Psychiatry* **86**, 749–758 (2019).
25. Ferguson, M. A. et al. A human memory circuit derived from brain lesions causing amnesia. *Nat. Commun.* **10**, 1–9 (2019).
26. Park, C. H. et al. Simulating the progression of brain structural alterations in Parkinson's disease. *NPJ Parkinsons Dis.* **8**, 1–8 (2022).
27. Halliday, G. M. & McCann, H. The progression of pathology in Parkinson's disease. *Ann. N. Y Acad. Sci.* **1184**, 188–195 (2010).
28. Mascalchi, M., Vella, A. & Ceravolo, R. Movement disorders: Role of imaging in diagnosis. *J. Magn. Reson. Imaging* **35**, 239–256 (2012).
29. Hoglinger, G. U. et al. Clinical diagnosis of progressive supranuclear palsy: the movement disorder society criteria. *Mov. Disord.* **32**, 853–864 (2017).
30. Whitwell, J. L. et al. Radiological biomarkers for diagnosis in PSP: Where are we and where do we need to be? *Mov. Disord.* **32**, 955–971 (2017).
31. Wenning, G. K. et al. The movement disorder society criteria for the diagnosis of multiple system atrophy. *Mov. Disord.* 37, 1131–1148. https://doi.org/10.1002/mds.29005 (2022).
32. Nahab, F. B. & Hattori, N. *Neuroimaging of Movement Disorders*. *Neuroimaging of Movement Disorders* (Humana Press, Totowa, NJ, 2013). https://doi.org/10.1007/978-1-62703-471-5.
33. Xu, X. et al. Grey matter abnormalities in Parkinson's disease: a voxel-wise meta-analysis. *Eur. J. Neurol.* **27**, 653–659 (2020).
34. Cerasa, A. et al. Neuroanatomical correlates of dystonic tremor: A cross-sectional study. *Parkinsonism Relat. Disord.* **20**, 314–317 (2014).
35. Younger, E. et al. Mapping essential tremor to a common brain network using functional connectivity analysis. *Neurology*. https://doi.org/10.1212/wnl.0000000000207701 (2023).

36. Huang, X., Zhang, M., Li, B., Shang, H. & Yang, J. Structural and functional brain abnormalities in idiopathic cervical dystonia: A multimodal meta-analysis. *Parkinsonism Relat. Disord.* **103**, 153–165 (2022).
37. Corp, D. T., Morrison-Ham, J., Jinnah, H. A. & Joutsa, J. The functional anatomy of dystonia: Recent developments. *Int Rev. Neurobiol.* **169**, 105–136 (2023).
38. Ellis, E. G. et al. Large-scale activation likelihood estimation meta-analysis of parkinsonian disorders. *Brain Commun.* **5**, 1–12 (2023).
39. Holtbernd, F. & Shah, N. J. Imaging the pathophysiology of essential tremor—a systematic review. *Front Neurol.* **12**, 1–17 (2021).
40. Pietracupa, S., Bologna, M., Tommasin, S., Berardelli, A. & Pantano, P. The contribution of neuroimaging to the understanding of essential tremor pathophysiology: a systematic review. *Cerebellum* **21**, 1029–1051 (2022).
41. Botvinik-Nezer, R. et al. Variability in the analysis of a single neuroimaging dataset by many teams. *Nature* **582**, 84–88 (2020).
42. Kaasinen, V. & Vahlberg, T. Striatal dopamine in Parkinson disease: A meta-analysis of imaging studies. *Ann. Neurol.* **82**, 873–882 (2017).
43. Francois, J. G., Vingerhoets, Schulzer, M., Calne, D. B. & Snow, B. J. Which clinical sign of Parkinson's disease best reflects the nigrostriatal lesion? *Ann. Neurol.* **41**, 58–64 (1997).
44. Helmich, R. C., Janssen, M. J. R., Oyen, W. J. G., Bloem, B. R. & Toni, I. Pallidal dysfunction drives a cerebellothalamic circuit into Parkinson tremor. *Ann. Neurol.* **69**, 269–281 (2011).
45. Dirkx, M. F. et al. Dopamine controls Parkinson's tremor by inhibiting the cerebellar thalamus. *Brain* **140**, 721–734 (2017).
46. Qamar, M. A. et al. Presynaptic dopaminergic terminal imaging & non-motor symptoms assessment of Parkinson's disease: Evidence for dopaminergic basis? *Parkinsons Dis.* **3**, 1–19 (2017).
47. Kaasinen, V., Vahlberg, T., Stoessl, A. J., Strafella, A. P. & Antonini, A. Dopamine receptors in parkinson's disease: a meta-analysis of imaging studies. *Mov. Disord.* **36**, 1781–1791 (2021).
48. Politis, M. et al. Staging of serotonergic dysfunction in Parkinson's disease: An in vivo 11C-DASB PET study. *Neurobiol. Dis.* **40**, 216–221 (2010).
49. Bohnen, N. I. et al. Progression of regional cortical cholinergic denervation in Parkinson's disease. *Brain Commun.* **4**, 1–12 (2022).
50. Schumacher, J. *et al*. Structural and molecular cholinergic imaging markers of cognitive decline in Parkinson's disease. *Brain*. **146**, 4964–4973 (2023).
51. Qamhawi, Z. et al. Clinical correlates of raphe serotonergic dysfunction in early Parkinson's disease. *Brain* **138**, 2964–2973 (2015).
52. Pasquini, J., Ceravolo, R., Brooks, D. J., Bonuccelli, U. & Pavese, N. Progressive loss of raphe nuclei serotonin transporter in early Parkinson's disease: A longitudinal 123I-FP-CIT SPECT study. *Parkinsonism Relat. Disord.* **77**, 170–175 (2020).
53. Pavese, N., Metta, V., Bose, S. K., Chaudhuri, K. R. & Brooks, D. J. Fatigue in Parkinson's disease is linked to striatal and limbic serotonergic dysfunction. *Brain* **133**, 3434–3443 (2010).
54. Pavese, N. Imaging the aetiology of sleep disorders in dementia and Parkinson's disease. *Curr. Neurol. Neurosci. Rep.* **14**, 501 (2014).
55. Wilson, H., Giordano, B., Turkheimer, F. E., Chaudhuri, K. R. & Politis, M. Serotonergic dysregulation is linked to sleep problems in Parkinson's disease. *Neuroimage Clin.* **18**, 630–637 (2018).
56. Politis, M. et al. Depressive symptoms in PD correlate with higher 5-HTT binding in raphe and limbic structures. *Neurology* **75**, 1920–1927 (2010).
57. Pasquini, J., Brooks, D. J. & Pavese, N. The cholinergic brain in Parkinson's disease. *Mov. Disord. Clin. Pr.* **8**, 1012–1026 (2021).
58. Gersel Stokholm, M. et al. Cholinergic denervation in patients with idiopathic rapid eye movement sleep behaviour disorder. *Eur. J. Neurol.* **27**, 644–652 (2020).
59. Rus, T. et al. Stereotyped relationship between motor and cognitive metabolic networks in Parkinson's disease. *Mov. Disord.* **37**, 2247–2256 (2022).
60. Poston, K. L. & Eidelberg, D. Functional brain networks and abnormal connectivity in the movement disorders. *Neuroimage* **62**, 2261–2270 (2012).
61. Mure, H. et al. Parkinson's disease tremor-related metabolic network: Characterization, progression, and treatment effects. *Neuroimage* **54**, 1244–1253 (2011).
62. Huang, C. et al. Metabolic brain networks associated with cognitive function in Parkinson's disease. *Neuroimage* **34**, 714–723 (2007).
63. Eckert, T. et al. Abnormal metabolic networks in atypical parkinsonism. *Mov. Disord.* **23**, 727–733 (2008).
64. Niethammer, M. et al. A disease-specific metabolic brain network associated with corticobasal degeneration. *Brain* **137**, 3036–3046 (2014).
65. Pardini, M. et al. FDG-PET patterns associated with underlying pathology in corticobasal syndrome. *Neurology* **92**, E1121–E1135 (2019).
66. Teune, L. K. et al. Validation of parkinsonian disease-related metabolic brain patterns. *Mov. Disord.* **28**, 547–551 (2013).
67. Ma, Y., Tang, C., Spetsieris, P. G., Dhawan, V. & Eidelberg, D. Abnormal metabolic network activity in Parkinson's disease: Test-retest reproducibility. *J. Cereb. Blood Flow. Metab.* **27**, 597–605 (2007).
68. Della Flora, E., Perera, C. L., Cameron, A. L. & Maddern, G. J. Deep brain stimulation for essential tremor: A systematic review. *Mov. Disord.* **25**, 1550–1559 (2010).
69. Fan, H., Zheng, Z., Yin, Z., Zhang, J. & Lu, G. Deep brain stimulation treating dystonia: a systematic review of targets, body distributions and etiology classifications. *Front Hum. Neurosci.* **15**, 1–11 (2021).
70. Okun, M. S. Deep-Brain Stimulation for Parkinson' s Disease. *N. Engl. J. Med.* 367, 1529–1538 (2012) https://doi.org/10.1056/NEJMct1208070.
71. Kurtis, M. M., Rajah, T., Delgado, L. F. & Dafsari, H. S. The effect of deep brain stimulation on the non-motor symptoms of Parkinson's disease: A critical review of the current evidence. *NPJ Parkinsons Dis.* **3**, 1–12 (2017).
72. Strelow, J. N. et al. Structural connectivity of subthalamic nucleus stimulation for improving freezing of gait. *J. Parkinsons Dis.* **12**, 1251–1267 (2022).
73. Reich, M. M. et al. Probabilistic mapping of the antidystonic effect of pallidal neurostimulation: A multicentre imaging study. *Brain* **142**, 1386–1398 (2019).
74. Dembek, T. A. et al. Probabilistic sweet spots predict motor outcome for deep brain stimulation in Parkinson disease. *Ann. Neurol.* **86**, 527–538 (2019).
75. Horn, A. et al. Optimal deep brain stimulation sites and networks for cervical vs. generalized dystonia. *Proc. Natl Acad. Sci.* **119**, 1–11 (2022).
76. Koeglsperger, T., Palleis, C., Hell, F., Mehrkens, J. H. & Bötzel, K. Deep brain stimulation programming for movement disorders: Current concepts and evidence-based strategies. *Front Neurol.* **10**, 1–20 (2019).
77. Lange, F. et al. Distinct phenotypes of stimulation-induced dysarthria represent different cortical networks in STN-DBS. *Parkinsonism Relat. Disord.* **109**, 105347 (2023).
78. Reich, M. M. et al. A brain network for deep brain stimulation induced cognitive decline in Parkinson's disease. *Brain* **145**, 1410–1421 (2022).
79. Deniau, J. M., Degos, B. & Bosch, C. Deep brain stimulation mechanisms: Beyond the concept of local functional inhibition. *Eur. J. Neurosci.* **32**, 1080–1091 (2010).
80. Henderson, J. M. 'Connectomic surgery': Diffusion tensor imaging (DTI) tractography as a targeting modality for surgical modulation of neural networks. *Front Integr. Neurosci.* **6**, 1–6 (2012).
81. Duffley, G., Anderson, D. N., Vorwerk, J., Dorval, A. D. & Butson, C. R. Evaluation of methodologies for computing the deep brain stimulation volume of tissue activated. *J Neural Eng* **16**, (2019).

82. Neudorfer, C. et al. Lead-DBS v3.0: Mapping deep brain stimulation effects to local anatomy and global networks. *Neuroimage* **268**, 119862 (2023).
83. Horn, A. & Fox, M. D. Opportunities of connectomic neuromodulation. *Neuroimage* **221**, 117180 (2020).
84. Accolla, E. A. et al. Brain networks modulated by subthalamic nucleus deep brain stimulation. *Brain* **139**, 2503–2515 (2016).
85. Vanegas-Arroyave, N. et al. Tractography patterns of subthalamic nucleus deep brain stimulation. *Brain* **139**, 1200–1210 (2016).
86. Sobesky, L. K. et al. Effective subthalamic and pallidal deep brain stimulation - are we modulating the same network? *medRxiv* 2021.02.02.21250817 (2021).
87. Akram, H. et al. Subthalamic deep brain stimulation sweet spots and hyperdirect cortical connectivity in Parkinson's disease. *Neuroimage* **158**, 332–345 (2017).
88. Prent, N. et al. Distance to white matter tracts is associated with deep brain stimulation motor outcome in Parkinson's disease. *J. Neurosurg.* **133**, 433–442 (2020).
89. Sweet, J. A. et al. Fiber tractography of the axonal pathways linking the basal ganglia and cerebellum in Parkinson disease: Implications for targeting in deep brain stimulation: Clinical article. *J. Neurosurg.* **120**, 988–996 (2014).
90. Akram, H. et al. Connectivity derived thalamic segmentation in deep brain stimulation for tremor. *Neuroimage Clin.* **18**, 130–142 (2018).
91. Calabrese, E. et al. Postmortem diffusion MRI of the human brainstem and thalamus for deep brain stimulator electrode localization. *Hum. Brain Mapp.* **36**, 3167–3178 (2015).
92. Fenoy, A. J. & Schiess, M. C. Comparison of tractography-assisted to atlas-based targeting for deep brain stimulation in essential tremor. *Mov. Disord.* **33**, 1895–1901 (2018).
93. Middlebrooks, E. H. et al. Directed stimulation of the dentato-rubro-thalamic tract for deep brain stimulation in essential tremor: a blinded clinical trial. *Neuroradiol. J.* **35**, 203–212 (2022).
94. Petry-Schmelzer, J. N. et al. Selecting the most effective dbs contact in essential tremor patients based on individual tractography. *Brain Sci.* **10**, 1–7 (2020).
95. Pouratian, N. et al. Multi-institutional evaluation of deep brain stimulation targeting using probabilistic connectivity-based thalamic segmentation: Clinical article. *J. Neurosurg.* **115**, 995–1004 (2011).
96. Coenen, V. A. et al. The dentato-rubro-thalamic tract as the potential common deep brain stimulation target for tremor of various origin: an observational case series. *Acta Neurochir. (Wien.)* **162**, 1053–1066 (2020).
97. Dembek, T. A. et al. PSA and VIM DBS efficiency in essential tremor depends on distance to the dentatorubrothalamic tract. *Neuroimage Clin.* **26**, 102235 (2020).
98. Tsuboi, T. et al. Comparative connectivity correlates of dystonic and essential tremor deep brain stimulation. *Brain* **144**, 1774–1786 (2021).
99. Okromelidze, L. et al. Functional and structural connectivity patterns associated with clinical outcomes in deep brain stimulation of the globus pallidus internus for generalized dystonia. *Am. J. Neuroradiol.* **41**, 508–514 (2020).
100. Al-Fatly, B. et al. Neuroimaging-based analysis of DBS outcomes in pediatric dystonia: Insights from the GEPESTIM registry. *Neuroimage Clin.* **39**, 103449 (2023).
101. Irmen, F. et al. Left prefrontal connectivity links subthalamic stimulation with depressive symptoms. *Ann. Neurol.* **87**, 962–975 (2020).
102. Mosley, P. E. et al. The structural connectivity of subthalamic deep brain stimulation correlates with impulsivity in Parkinson's disease. *Brain* **143**, 2235–2254 (2020).
103. Boutet, A. et al. Improving safety of MRI in patients with deep brain stimulation devices. *Radiology* **296**, 250–262 (2020).
104. Boutet, A. et al. 3-Tesla MRI of deep brain stimulation patients: safety assessment of coils and pulse sequences. *J. Neurosurg.* **132**, 586–594 (2020).
105. Boutet, A. et al. Functional MRI safety and artifacts during deep brain stimulation: Experience in 102 patients. *Radiology* **293**, 174–183 (2019).
106. Jech, R. et al. Functional magnetic renonance imaging during deep brain stimulation: A pilot study in four patients with parkinson's disease. *Mov. Disord.* **16**, 1126–1132 (2001).
107. Kahan, J. et al. Therapeutic subthalamic nucleus deep brain stimulation reverses cortico-thalamic coupling during voluntary movements in Parkinson's disease. *PLoS One* **7**, e50270 (2012).
108. Phillips, M. D. et al. Parkinson disease: Pattern of functional MR imaging activation during deep brain stimulation of subthalamic nucleus - Initial experience. *Radiology* **239**, 209–216 (2006).
109. Rezai, A. R. et al. Thalamic stimulation and functional magnetic resonance imaging: Localization of cortical and subcortical activation with implanted electrodes: Technical note. *J. Neurosurg.* **90**, 583–590 (1999).
110. Loh, A. et al. Probing responses to deep brain stimulation with functional magnetic resonance imaging. *Brain Stimul.* **15**, 683–694 (2022).
111. Boutet, A. et al. Predicting optimal deep brain stimulation parameters for Parkinson's disease using functional MRI and machine learning. *Nat. Commun.* **12**, 1–13 (2021).
112. Dimarzio, M. et al. Use of functional MRI to assess effects of deep brain stimulation frequency changes on brain activation in Parkinson disease. *Neurosurgery* **88**, 356–365 (2021).
113. DiMarzio, M. et al. Use of functional magnetic resonance imaging to assess how motor phenotypes of Parkinson's disease respond to deep brain stimulation. *Neuromodulation* **23**, 515–524 (2020).
114. Gibson, W. S. et al. Symptom-specific differential motor network modulation by deep brain stimulation in Parkinson's disease. *J. Neurosurg.* **135**, 1771–1779 (2021).
115. Hancu, I. et al. On the (Non-)equivalency of monopolar and bipolar settings for deep brain stimulation fMRI studies of Parkinson's disease patients. *J. Magn. Reson. Imaging* **49**, 1736–1749 (2019).
116. Hesselmann, V. et al. Intraoperative functional MRI as a new approach to monitor deep brain stimulation in Parkinson's disease. *Eur. Radio.* **14**, 686–690 (2004).
117. Knight, E. J. et al. Motor and nonmotor circuitry activation induced by subthalamic nucleus deep brain stimulation in patients with Parkinson disease: Intraoperative functional magnetic resonance imaging for deep brain stimulation. *Mayo Clin. Proc.* **90**, 773–785 (2015).
118. Shen, L. et al. Subthalamic nucleus deep brain stimulation modulates 2 distinct neurocircuits. *Ann. Neurol.* **88**, 1178–1193 (2020).
119. Stefurak, T. et al. Deep brain stimulation for Parkinson's disease dissociates mood and motor circuits: A functional MRI case study. *Mov. Disord.* **18**, 1508–1516 (2003).
120. Chu, C. et al. Subthalamic stimulation modulates motor network in Parkinson's disease: recover, relieve and remodel. *Brain* **146**, 2780–2791 (2023).
121. Chu, C. et al. Subthalamic and pallidal stimulation in Parkinson's disease induce distinct brain topological reconstruction. *Neuroimage* **255**, 119196 (2022).
122. Hanssen, H. et al. Cerebello-striatal interaction mediates effects of subthalamic nucleus deep brain stimulation in Parkinson's disease. *Parkinsonism Relat. Disord.* **67**, 99–104 (2019).
123. Holiga, Š. et al. Resting-state functional magnetic resonance imaging of the subthalamic microlesion and stimulation effects in Parkinson's disease: Indications of a principal role of the brainstem. *Neuroimage Clin.* **9**, 264–274 (2015).
124. Horn, A. et al. Deep brain stimulation induced normalization of the human functional connectome in Parkinson's disease. *Brain* **142**, 3129–3143 (2019).

125. Kahan, J. et al. Deep brain stimulation has state-dependent effects on motor connectivity in Parkinson's disease. *Brain* **142**, 2417–2431 (2019).
126. Mueller, K. et al. Brain connectivity changes when comparing effects of subthalamic deep brain stimulation with levodopa treatment in Parkinson's disease. *Neuroimage Clin.* **19**, 1025–1035 (2018).
127. Saenger, V. M. et al. Uncovering the underlying mechanisms and whole-brain dynamics of deep brain stimulation for Parkinson's disease. *Sci. Rep.* **7**, 1–14 (2017).
128. Zhang, C. et al. Subthalamic and Pallidal Stimulations in Patients with Parkinson's Disease: Common and Dissociable Connections. *Ann. Neurol.* **90**, 670–682 (2021).
129. Li, Z. et al. BOLD frequency–dependent alterations in resting-state functional connectivity by pallidal deep brain stimulation in patients with Parkinson's disease. *J. Neurosurg*. https://doi.org/10.3171/2023.1.JNS221858 (2023).
130. Eraifej, J. et al. Modulation of limbic resting-state networks by subthalamic nucleus deep brain stimulation. *Netw. Neurosci.* **7**, 478–495 (2023).
131. Awad, A., Blomstedt, P., Westling, G. & Eriksson, J. Deep brain stimulation in the caudal zona incerta modulates the sensorimotor cerebello-cerebral circuit in essential tremor. *Neuroimage* **209**, 116511 (2020).
132. Gibson, W. S. et al. Functional correlates of the therapeutic and adverse effects evoked by thalamic stimulation for essential tremor. *Brain* **139**, 2198–2210 (2016).
133. Filip, P. et al. Restoration of functional network state towards more physiological condition as the correlate of clinical effects of pallidal deep brain stimulation in dystonia. *Brain Stimul.* **15**, 1269–1278 (2022).
134. Kokkonen, A., Honkanen, E. A., Corp, D. T. & Joutsa, J. Neurobiological effects of deep brain stimulation: A systematic review of molecular brain imaging studies. *Neuroimage* **260**, 119473 (2022).
135. Ceballos-Baumann, A. O. et al. Thalamic stimulation for essential tremor activates motor and deactivates vestibular cortex. *Neurology* **56**, 1347–1354 (2001).
136. Reich, M. M. et al. Progressive gait ataxia following deep brain stimulation for essential tremor: adverse effect or lack of efficacy? *Brain* **139**, 2948–2956 (2016).
137. Honkanen, E. A. et al. GPi-DBS-induced brain metabolic activation in cervical dystonia. *J. Neurol. Neurosurg. Psychiatry* https://doi.org/10.1136/jnnp-2023-331668 (2023).
138. Wei, X. et al. White matter abnormalities in patients with Parkinson's disease: a meta-analysis of diffusion tensor imaging using tract-based spatial statistics. *Front Aging Neurosci.* **12**, 1–12 (2021).
139. Han, Q., Hou, Y. & Shang, H. A voxel-wise meta-analysis of gray matter abnormalities in essential tremor. *Front Neurol.* **9**, 1–9 (2018).
140. Lin, J., Xu, X., Hou, Y., Yang, J. & Shang, H. Voxel-Based Meta-Analysis of Gray Matter Abnormalities in Multiple System Atrophy. *Front Aging Neurosci.* **12**, 1–12 (2020).
141. Albrecht, F., Ballarini, T., Neumann, J. & Schroeter, M. L. FDG-PET hypometabolism is more sensitive than MRI atrophy in Parkinson's disease: A whole-brain multimodal imaging meta-analysis. *Neuroimage Clin*. 21, 101594 (2019).
142. Darby, R. R., Joutsa, J. & Fox, M. D. Network localization of heterogeneous neuroimaging findings. *Brain* **142**, 70–79 (2019).
143. Weil, R. S., Hsu, J. K., Darby, R. R., Soussand, L. & Fox, M. D. Neuroimaging in Parkinson's disease dementia: connecting the dots. *Brain Commun*. **1**, fcz006 (2019).
144. Sintini, I. et al. Multimodal neuroimaging relationships in progressive supranuclear palsy. *Parkinsonism Relat. Disord.* **66**, 56–61 (2019).
145. Laurencin, C. *et al*. Noradrenergic alterations in Parkinson's disease: a combined 11C-yohimbine PET/neuromelanin MRI study. *Brain* https://doi.org/10.1093/brain/awad338 (2023).
146. Hansen, J. Y. et al. Mapping neurotransmitter systems to the structural and functional organization of the human neocortex. *Nat. Neurosci.* **25**, 1569–1581 (2022).
147. Stephan, K. E., Iglesias, S., Heinzle, J. & Diaconescu, A. O. Translational perspectives for computational neuroimaging. *Neuron* **87**, 716–732 (2015).
148. Langner, R., Rottschy, C., Laird, A. R., Fox, P. T. & Eickhoff, S. B. Meta-analytic connectivity modeling revisited: Controlling for activation base rates. *Neuroimage* **99**, 559–570 (2014).
149. Horn, A. et al. Connectivity Predicts deep brain stimulation outcome in Parkinson disease. *Ann. Neurol.* **82**, 67–78 (2017).
150. Darby, R. R., Joutsa, J., Burke, M. J. & Fox, M. D. Lesion network localization of free will. *Proc. Natl Acad. Sci. USA* **115**, 10792–10797 (2018).
151. Shao, N., Yang, J., Li, J. & Shang, H. F. Voxelwise meta-analysis of gray matter anomalies in progressive supranuclear palsy and Parkinson's disease using anatomic likelihood estimation. *Front Hum Neurosci* **8**, 63 (2014).
152. Middlebrooks, E. H. et al. Neuroimaging advances in deep brain stimulation: Review of indications, anatomy, and brain connectomics. *Am. J. Neuroradiol.* **41**, 1558–1568 (2020).
153. Amunts, K. et al. BigBrain: An ultrahigh-resolution 3D human brain model. *Science (1979)* **340**, 1472–1475 (2013).
154. Vaillancourt, D. E. et al. High-resolution diffusion tensor imaging in the substantia nigra of de novo Parkinson disease. *Neurology* **72**, 1378–1384 (2009).
155. Prodoehl, J. et al. Diffusion tensor imaging of Parkinson's disease, atypical parkinsonism, and essential tremor. *Mov. Disord.* **28**, 1816–1822 (2013).
156. Nagano-Saito, A. et al. Cerebral atrophy and its relation to cognitive impairment in Parkinson disease. *Neurology* **64**, 224–229 (2005).
157. Abe, Y. et al. Occipital hypoperfusion in Parkinson's disease without dementia: Correlation to impaired cortical visual processing. *J. Neurol. Neurosurg. Psychiatry* **74**, 419–422 (2003).
158. Möller, L. et al. Manual MRI morphometry in Parkinsonian syndromes. *Mov. Disord.* **32**, 778–782 (2017).
159. Matthews, D. C. et al. FDG PET Parkinson's disease-related pattern as a biomarker for clinical trials in early stage disease. *Neuroimage Clin.* **20**, 572–579 (2018).
160. Bédard, P., Panyakaew, P., Cho, H. J., Hallett, M. & Horovitz, S. G. Multimodal imaging of essential tremor and dystonic tremor. *Neuroimage Clin* **36**, 103247 (2022).
161. Filip, P. et al. Disruption in cerebellar and basal ganglia networks during a visuospatial task in cervical dystonia. *Mov. Disord.* **32**, 757–768 (2017).
162. Park, S. et al. Changes of regional cerebral blood flow after deep brain stimulation in cervical dystonia. *EJNMMI Res* **12**, 0–4 (2022).

Acknowledgements

Figures for this article were created with BioRender.com.

Author contributions

Conceptualization & Design: J.J. and E.G.E.; Writing – draft preparation: E.G.E., G.M.M., V.K., D.T.C., N.P., M.M.R. and J.J.; Writing – synthesis and editing: E.G.E.; Visualizations: E.G.E. and G.M.M.; Critical revisions: E.G.E., G.M.M., V.K., D.T.C., N.P., M.M.R. and J.J.; Supervision: J.J. The final version of the manuscript was approved by all authors before publication.

Competing interests

E.G.E, G.M.M., and D.T.C., declare no competing financial or non-financial Interests. V.K. serves as an advisory board member of AbbVie Finland and Nordic Infucare AB, has received travel expenses and speaker honoraria from Abbvie Finland, Nordic Infucare AB and Orion Pharma and research funding from the Finnish Alcohol Research Foundation, the Päivikki and Sakari Sohlberg Foundation, the Finnish Cultural Foundation, the

International Parkinson and Movement Disorder Society, and Finnish governmental research funding (VTR). N.P. declares no competing financial interests related to the present article; his contribution to this article reflects entirely and only his own academic expertise on the matter. He has received *Advisory Boards honoraria from: Britannia, Bial, Boston Scientific, Benevolent AI, Roche, Abbvie. 4D Pharma; Speaker Honoraria from: Britannia, Abbvie, GE Healthcare, Boston Scientific, the MDS. He has received research grants from the Independent Research Fund Denmark, Danish Parkinson's disease Association, Parkinson's UK, Center of Excellence in Neurodegeneration (CoEN) network award, GE Healthcare Grant, Multiple System Atrophy Trust, Weston Brain Institute, EU Joint Program Neurodegenerative Disease Research (JPND), the MJFF, and the EU Horizon 2020 research and innovation programme*. M.M.R. reports grant support and honoraria for speaking from Medtronic and Boston Scientific, outside the submitted and was supported by the German Research Foundation (DFG, Project-ID424778381, TRR 295) and the German Federal Ministry of Education and Research (BMBF, 01KG2032_DIPS). J.J. has received research funding from the Finnish Medical Foundation, Sigrid Juselius Foundation, and Finnish Foundation for Alcohol Studies, lecturer honoraria from Lundbeck and Novartis, conference travel support from Abbvie, Abbott and Insightec, and consultancy fees from Summaryx and Adamant Health.

Additional information

Correspondence and requests for materials should be addressed to Elizabeth G. Ellis or Juho Joutsa.