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Tremor and Other Hyperkinetic Movements

Reviews

The Role of Dopamine and Dopaminergic Pathways in Dystonia: Insights from Neuroimaging

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Abstract

Background: Dystonia constitutes a heterogeneous group of movement abnormalities, characterized by sustained or intermittent muscle contractions causing abnormal postures. Overwhelming data suggest involvement of basal ganglia and dopaminergic pathways in dystonia. In this review, we critically evaluate recent neuroimaging studies that investigate dopamine receptors, endogenous dopamine release, morphology of striatum, and structural or functional connectivity in cortico-basal ganglia-thalamo-cortical and related cerebellar circuits in dystonia.

Method: A PubMed search was conducted in August 2014.

Results: Positron emission tomography (PET) imaging offers strong evidence for altered D2/D3 receptor binding and dopaminergic release in many forms of idiopathic dystonia. Functional magnetic resonance imaging (fMRI) and diffusion tensor imaging (DTI) data reveal likely involvement of related cerebello-thalamo-cortical and sensory-motor networks in addition to basal ganglia.

Discussion: PET imaging of dopamine receptors or transmitter release remains an effective means to investigate dopaminergic pathways, yet may miss factors affecting dopamine homeostasis and related subcellular signaling cascades that could alter the function of these pathways. fMRI and DTI methods may reveal functional or anatomical changes associated with dysfunction of dopamine-mediated pathways. Each of these methods can be used to monitor target engagement for potential new treatments. PET imaging of striatal phosphodiesterase and development of new selective PET radiotracers for dopamine D3-specific receptors and Mechanistic target of rampamycin (mTOR) are crucial to further investigate dopaminergic pathways. A multimodal approach may have the greatest potential, using PET to identify the sites of molecular pathology and magnetic resonance methods to determine their downstream effects.

Keywords: Dystonia, dopamine, positron emission tomography, functional magnetic resonance imaging, diffusion tensor imaging

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Introduction

Dystonia is the third most prevalent movement disorder and afflicts about 250,000 people in the United States.[1] It comprises a highly heterogeneous group of movement abnormalities, characterized by sustained or intermittent muscle contractions causing abnormal, repetitive movements and postures, or both.[2] Symptoms can develop in children or adults. They can affect a single body part, multiple segments or be generalized. This phenotypical heterogeneity may or may not reflect diverse etiology. Indeed, well-defined monogenic hereditary dystonias have variable age of onset, affected body parts, and rate of progression.[3] A new categorization of dystonia distinguishes those with only dystonia as isolated dystonia. This review focuses primarily on those with isolated dystonia that is either caused by a known genetic mutation or is idiopathic (formerly called primary dystonias).[2] Poor understanding of underlying pathophysiology, inadequate animal models and absence of biomarkers have limited

development of adequate therapeutics for isolated idiopathic or genetic dystonias.

Historically dystonia has been considered a basal ganglia disorder, with numerous lines of evidence suggesting involvement of the dopaminergic system. However, dysfunction of other brain regions and circuits has become increasingly evident. Focal dystonias have been associated with impaired inhibition in the somatosensory cortex and abnormal sensorimotor processing beyond those parts of the brain that represent the symptomatic body part.[4–8] Structural and functional imaging studies show dysfunction of the cerebellum or defects in its connections in isolated idiopathic dystonias.[9–15] Indeed, most researchers agree that dystonia is associated with physiologic abnormalities at multiple levels involving cortico-ponto-cerebello-thalamo-cortical and cortico-basal ganglia-thalamo-cortical pathways.[16–18] Nevertheless, emerging evidence indicates TOR1A, GNAL and ANO3 mutations produce functional changes that converge to affect striatal signal transduction pathways.[19–21] Such findings underscore possible commonalities across at least some of these heterogeneous conditions.

Neuroimaging offers a non-invasive method to examine structural and functional changes in humans. Initially, molecular imaging studies of dopaminergic pathways relied on 6-fluorodopa ([^{18}F]FD), reflecting decarboxylase activity and storage, and non-selective dopamine D2-like receptor radioligands such as [^{18}F]spiperone, [^{11}C]raclopride, and [^{123}I]iodobenzamide. Major advances in molecular imaging, with development of more specific radioligands along with sophisticated analysis methods, permit greater in-depth study of dopaminergic pathways. Similarly, positron emission tomography (PET) and functional magnetic resonance imaging (fMRI)-based blood oxygen level-dependent (BOLD) measures have been used to investigate task-related activation of dopaminergic pathways. Resting state fMRI (rs-fMRI) and diffusion tensor imaging (DTI) studies assess functional and structural connectivity of cortico-basal ganglia-thalamo-cortical circuits. Stronger magnets (3 T and higher) and more advanced data analyses have strengthened these studies. Admittedly, each of these methods provides only a limited indirect view of dopaminergic pathways. In this review, we critically evaluate recent neuroimaging studies that shed light on the involvement of dopaminergic pathways by investigating dopamine receptors, endogenous dopamine release, morphology of striatum and downstream targets, and structural or functional connectivity in cortico-basal ganglia-thalamo-cortical and related cerebellar circuits.

Methods

A PubMed search in August 2014 with keyword combinations dystonia, PET, dopamine; dystonia MRI, dopamine; and dystonia, SPECT, dopamine yielded 141, eight, and 58 entries, respectively. We considered only studies pertaining to the dopaminergic system or relevant pathways in idiopathic or hereditary dystonias.

Dopaminergic pathways

A model of basal ganglia circuitry includes cortical-striato-pallido-thalamic-cortical loops with primary input into striatum (putamen and caudate) from cortical glutamatergic, thalamostriatal glutamatergic, and nigral dopaminergic projections.[22–24] Two major pathways lead from the striatum to the main output nucleus in the basal ganglia internal segment of the pallidum (GPi) and substantia nigra pars reticulate (SNpr): 1) the direct pathway via inhibitory GABAergic fibers, and 2) the indirect pathway, including inhibitory GABAergic neurons to GPe (external segment of GP), inhibitory neurons projecting from GPe to subthalamic nucleus (STN), and excitatory glutamatergic neurons projecting from STN to GPi/SNr. GPi/SNr send inhibitory GABAergic neurons to the ventral anterior thalamus that project via excitatory neurons to cortical areas, including the premotor and motor regions. Multiple studies suggest that the direct pathway selects the desired movement (facilitation), while the indirect pathway suppresses unwanted surrounding movement (inhibition).[25] Dystonia could represent a defect in surround inhibition (abnormal function of the indirect pathway) perhaps coupled with excessive facilitation of the intended movement (overactivation of the direct pathway).[26]

Dopaminergic nigrostriatal input regulates the activity in direct and indirect pathways. Indeed, the nigrostriatal dopaminergic fibers terminate on the shafts of the dendritic spines of the medium spiny neurons (MSNs)[27] and the cortical afferents terminate on the heads of spines, enabling dopamine modulation of the corticostriatal input. Dopamine receptors are G-coupled proteins that divide into D1-like and D2-like families. D1-like (D1, D5) receptors activate and D2-like (D2, D3, D4) receptors inhibit adenylate cyclase.[28,29] Phosphodiesterases are highly expressed in the striatum and control this signaling cascade by regulating the level of cyclic adenosine monophosphate (cAMP).[30] Excitatory D1-like receptors are located exclusively post-synaptically on medium spiny neurons that project to the Gpi/SNpr (direct pathway), while inhibitory D2 receptors (D2R) are located post-synaptically on neurons that project to GPe (indirect pathway). This concept is supported by measurements of D1 receptor (D1R) and D2R mRNA[31] and transgenic mice models with near-complete segregation of D1R and D2R expression.[32,33] D3 receptors (D3R) are expressed in striatum as well. Most data suggest that D3R is predominantly in ventral (limbic) and to a far lesser degree in dorsal (motor) striatum. However, recent autoradiographic studies with a highly D3-selective radioligand have demonstrated a substantial amount of D3R in human dorsal striatum.[34] A small subpopulation of striatal MSN contains both D1R and D2-like receptors,[35,36] and emerging evidence indicates that D1R and D3R can form heterodimers capable of enhancing D1R-mediated activity.[37,38] Nigrostriatal fibers express presynaptic D2R and D3R (autoreceptors) as well, which are inhibitory and their activation reduces the dopamine release at the synaptic cleft between nigrostriatal fibers and medium spiny neurons.

Molecular imaging and dopamine receptors

Many observations suggest that dysfunction of D2-like receptors underlies the pathophysiology of idiopathic and some acquired forms of dystonia. Exposure to drugs that block D2-like receptors can cause acute dystonia.[39–41] Non-human primates treated with intracartoid MPTP (1-methyl-4-phenyl-1,2 3,6-tetrahydropyridine) develop transient dystonia.

The dystonic phase corresponds with a decrease in D2-like striatal receptors as measured *ex vivo* in striatal brain tissue. MPTP selectively destroys dopaminergic neurons, possibly reducing dopamine autoreceptors. The transient nature of this drop in D2-like receptors could either indicate reconstitution of these neurons, which did not occur, or that the D2-like effect was not due to a change in autoreceptors but rather a transient change in post-synaptic receptors.[42] Numerous molecular imaging studies with PET or single-photon emission computed tomography (SPECT) with D2-like radioligands report decreased striatal uptake in various forms of isolated idiopathic dystonias. These include isolated idiopathic hand dystonia, cranial dystonia,[43–45] and cervical dystonia[46] as well as the inherited dystonias caused by mutations in TOR1A/DYT1,[47] THAP1/DYT6,[48] and ε-sarcoglycan/DYT11.[49] However, almost all D2-like radioligands have numerous limitations. They do not distinguish between pre- and post-synaptic dopaminergic receptors and can be displaced by endogenous dopamine. We found reduced striatal [^{18}F]spiperone binding in idiopathic focal dystonia,[44] but this non-specific radioligand also binds to 5-hydroxytryptamine (5-HT) (2A) receptors in primate striatum.[50] Other studies report reduced striatal [^{11}C]raclopride uptake, which has a low selectivity for 5-HT(2A) but near equal selectivity for D2R and D3R[48,51] and can be displaced by endogenous dopamine.[52] Such displacement can confound interpretation of reduced raclopride uptake, which can indicate either reduced D2-like binding sites or increased competition with elevated striatal dopamine. However, subsequent studies with the highly selective D2R radioligand N-methylbenperidol (NMB) did not identify reduced striatal uptake in isolated idiopathic hand or cranial dystonia. Since NMB is 200-fold more selective for D2R than D3R and is not displaced by endogenous dopamine, these findings suggest that previously reported reduced striatal D2-like binding may reflect a reduction in striatal D3R rather than a change in D2R.[53] D3R could play a role in pathophysiology of dystonia through presynaptic autoregulatory receptor sites, a regulatory effect on dopamine transporter, or interaction with D1-like receptors.[54–56] Proof of this hypothesis requires PET studies with D3R-selective radioligands. Such radioligands have been developed and successfully used in non-human primate studies[51] but no studies in humans have yet been reported.

Alternatively, if changes in endogenous dopamine affect dopamine-selective radioligands, an alteration of striatal dopamine concentration could explain apparent differences in striatal radioligand uptake. Reports of post-mortem striatal dopamine levels reveal contradictory results.[57,58] Voxel-wise analysis of task-induced striatal dopamine release revealed decreased [^{11}C]raclopride displacement with a motor task involving the affected body part in patients with laryngeal dystonia compared with healthy controls. In contrast, a motor task of an uninvolved body part elicited an increased striatal [^{11}C]raclopride displacement in the same patients compared with healthy controls.[59] These findings suggest altered striatal dopamine release compared with healthy controls. An analogous study in patients with writer's cramp (another isolated idiopathic dystonia) yielded similar findings, confirming common dopaminergic pathway changes across these two focal isolated idiopathic dystonia subtypes.[59,60] It remains to be determined whether this occurs in other forms of isolated idiopathic dystonia. These studies further suggest somatotopical reduction of striatal dopamine release, as long as the clusters of reduced dopamine release associated with different affected body parts were distinct from each other without any overlap. Interestingly, a [^{18}F]spiperone PET study revealed that changes in striatal D2-like receptors may be somatotopically organized in hand and cranial dystonias.[61]

D1-like receptors primarily influence the direct pathway.[62] Resting metabolic PET studies showing overactivity in the putamen and globus pallidus have been used to support the idea that dystonia may be associated with increased activity in the direct pathway causing excessive disinhibition of motor cortical areas. However, PET studies with [^{11}C]NNC-112, a selective D1-like ligand without displacement by internal dopamine, did not reveal a significant alteration in striatal binding in dopa-responsive dystonia (DRD),[63] or isolated idiopathic focal dystonia (cranial, cervical, arm).[64] Certainly, these findings do not exclude involvement of the direct pathway mediated by changes other than in D1-like receptors.

Molecular imaging and dopaminergic presynaptic integrity

[^{11}C]DTBZ (dihydrotetrabenazine; reflecting vesicular monoamine transporter type 2 [VMAT2]), [^{11}C]MP (methyl-phenidate or other similar radioligands; reflecting dopamine membranous transporter [DAT]) and [^{18}F]FD ([6-fluorodopa; reflecting primarily dopa decarboxylase activity and trapping) provide insight into nigrostriatal fiber and nigral cell integrity (Figure 1).[65] Striatal [^{11}C]DTBZ uptake was increased in L-dopa naive dopa-responsive dystonia (DRD) while [^{11}C]MP and [^{18}F]FD uptake were unchanged, suggesting likely compensatory increased neuronal firing or decreased dopamine competition for VMAT2 binding sites or a combination of both in DRD.[66] This finding was consistent with a SPECT study revealing normal (^{99m})Tc-TRODAT-1 uptake as a measure of DAT in DRD.[67] Other dystonia types in particular isolated idiopathic focal dystonias have not been examined with these ligands.

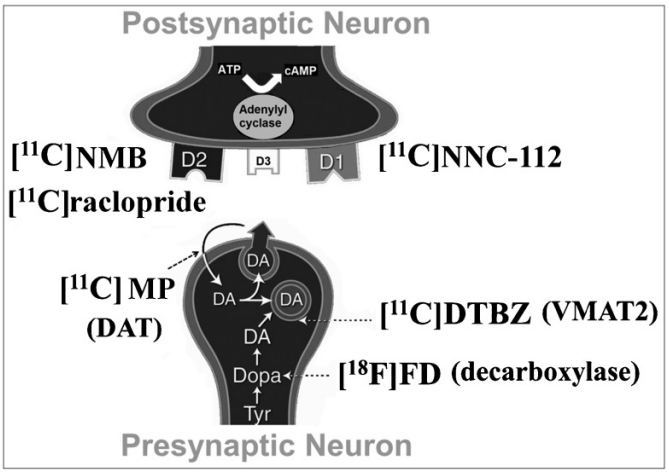

Figure 1. Binding Sites of Relevant Radiotracers at a Dopaminergic Synapse.

Functional imaging and dopamine pathways

Neuroimaging of dopaminergic receptors or dopamine release only provides a limited view of dopaminergic pathways. The downstream functional consequences of such defects may be identified with indirect measures of neuronal functions. This may be achieved with PET or fMRI during task- or drug-induced activation or at rest. Similarly, structural imaging may identify changes in pathways related to dopaminergic systems.

Task-related imaging

Task-related changes in regional brain activity can be used to map brain responses and interrogate relevant brain pathways. [^{18}F]Fludeoxyglucose (FDG) and [^{15}O]H_2O PET studies measure glucose metabolism and regional cerebral blood flow (rCBF), respectively, while fMRI BOLD signals relate to hemodynamic responses that change blood oxygen content. These measures represent a surrogate for increased interneuronal synaptic activity and changes in input to the region.[68,69] Numerous task-related PET and fMRIs have been completed in people with various types of dystonia.[70] Inconsistent findings in basal ganglia, sensorimotor cortex, and cerebellum across many of these studies likely reflect variations in the choice of task, differences in task performance, and presence of dystonia.[71–73] Sensory tasks may or may not have this same confound depending upon whether the sensory task elicits any motor responses. Several studies of vibration-induced brain responses revealed reduced rCBF responses[74,75] that may be influenced by dopaminergic pathways.[76]

Resting state imaging

Similar to task-related imaging, resting state studies can be performed with PET measures of metabolism and blood flow, or with MRI measures of BOLD signals. Resting state studies minimize confounds related to differences in task execution during scanning, which is a major advantage compared with task-related imaging. Many PET FDG studies have revealed involvement of dopaminergic pathways. Galardi et al.[77] demonstrated hypermetabolism in the basal ganglia, thalamus, premotor–motor cortex, and cerebellum in the isolated idiopathic cervical dystonia compared with healthy controls. However, an FDG study of a group including generalized dystonia, hemidystonia, and focal dystonias revealed decreased activity in striatum and globus pallidus.[78] Inclusion of hemidystonia, which is commonly an acquired dystonia, clearly confounds interpretation of these findings. Eidelberg and colleagues[79–82] have applied a principal components analysis method to identify changes in spatial covariance patterns in FDG uptake to define metabolic networks associated with dystonia, and identified increased contributions from posterior putamen, globus pallidus, cerebellum, and SMA (supplemental motor area) in patients with blepharospasm and in *DYT1* and *DYT6* carriers, regardless of the presence of clinical manifestation. A direct comparison of regional glucose metabolism revealed genotype-related metabolic changes including hypermetabolism in the putamen, anterior cingulate, and cerebellum of *DYT1* carriers, and hypometabolism in the putamen and temporal cortex of *DYT6* carriers.[83] Remarkably, the phenotype-related activity pattern in the same study did not include dopaminergic pathways.

rs-fMRI correlations are based on intrinsic fluctuations in the BOLD signal that reflects slow variations in neuronal activity propagating through connected networks. Changes in these fluctuations indicate network dysfunction.[84] Most rs-fMRI studies in isolated idiopathic focal dystonias indicate reduced connectivity in putamen and sensorimotor network regardless of the affected body part (Table 1).[85–89] However, a recent study in focal hand dystonia with extensive cortical, subcortical, and cerebellar seeds did not show any difference in putamenal functional connectivity but instead found changes in functional connectivity of the globus pallidus and cerebellum.[90] While most research has focused on investigating the correlations between low-frequency fluctuations, Zhou et al.[91] analyzed the amplitude of these fluctuations, which revealed increased amplitude in the putamen and globus pallidus and decreased amplitude in the somatosensory region, thalamus, and cerebellum. Overall, these rs-fMRI studies were conducted following various protocols with different levels of quality assurance. Multiple comparison and head motion correction are two major concerns in rs-fMRI analyses. Most studies apply a family-wise error rate to correct for multiple comparisons at the subject level, but only a few perform a Bonferroni correction, which is a far more stringent correction at the group level analysis. Some studies do not apply any correction, or apply only small-volume correction for *a priori* regions (Table 1). It is not surprising that such a heterogeneous level of control over false discovery can contribute to variable and difficult to reproduce data. Motion-induced signal change is another major challenge in analyzing rs-fMRI data, as it causes spurious misleading correlations.[92] Most recent studies try to address this issue by censoring frames with excessive movement and regressing various parameters such as the global signal, or cerebrospinal fluid and white matter signal, in addition to motion parameters. Indeed in many cases excessive frame censoring could lead to exclusion of the subject from data analysis.[93] However, many dystonia studies do not comment on motion correction measures. Interestingly, no study mentions exclusion of subjects due to excessive frame-to-frame movement.[84–90,94] Application of improved analysis and motion correction methods may enhance the quality and reproducibility of findings and reveal new insights into functional consequences of altered dopaminergic pathways as shown in idiopathic Parkinson disease.[93]

Structural imaging and dopamine pathways

Numerous earlier reports showed striatal abnormalities in CT scans of idiopathic or secondary dystonias.[95–98] With advances in MRI, many studies have measured the gray matter volume of relevant structures such as the caudate and putamen, thalamus and sensorimotor cortex in different dystonia subtypes. Nonetheless, the patient population, number of participants, strength of the magnetic field, data acquisition and the processing method have been highly variable among these

Table 1. Functional MRI in Isolated Idiopathic Focal Dystonias without Motor Activation

Study	Idiopathic Dystonia	No. of Cases	Software/Method of Analysis	Movement Correction/ Covariates	Multiple Comparisons	Networks/Seeds	Findings
Dresel et al.[90]	Hand dystonia	15	Spm8 CONN toolbox/seed based and ICA	Six realignment parameters, time series of the averaged CSF and the averaged white matter signal	FWE	Primary motor cortex, SMA, somatosensory cortex, lateral premotor cortex. Based on other studies: left lateral premotor cortex, left thalamus, bilateral GP, cerebello-thalamo-cortical region	↑ FC of cerebellar ROI with pre-SMA and PMd cortex, ↓ FC of cortical seeds to thalamus and GP, ↑ negative cerebello-cortical FC
Hinkley et al.[85]	Hand dystonia	11	SPM5/seed based. A Coh and ICoh map developed for each seed to overcome seed blur causing artifacts			Seed-based definition of networks in healthy controls. 5 mm radius seeds based on previous studies: hand knob, center of mass of putamen, PCC	↓ FC in BG and SMN. No change in DMN
Delnooz et al.[87]	Cervical dystonia	23	FEAT 5.98 (FSL) Using FNIRT/ICA: individual level: dual regression approach Groupwise effects: FSL's randomize tool		FWE for cluster correction and Bonferroni across networks	SMN, DMN, CN, ECN	↓ FC in SMN, ↑ FC in ECN, ↓ FC in PVN
Delnooz et al.[86]	Cervical dystonia	23	FSL/seed based	Time series of averaged CSF and averaged white matter signal scanner drift, time series of non-BG regions	FWE for cluster correction and Bonferroni across networks	Subject-specific functional parcellation of BG based on correlations with SMN, CN, ECN, VN, FPN (Beckmann 2005[114]). Reanalysis with focus on BG: correlation between BG and mean of the RSN	↓ FC from right mid-dorsal putamen/ right GPe to left FPN;
Zhou et al.[91]	Blepharospasm	9	SPM2/ALFF	1.5 mm threshold of frame exclusion	Uncorrected p-value		↑ ALFF in putamen, GP, insula, medial PFC, ↓ ALFF in SSR, thalami, CC, cerebellum,
Mohammadi et al.[88]	Writer's cramp	16	IC 3.09 (FSL)/ICA: individual level: dual regression approach, non-linear image registration	Motion correction	FEW threshold-free cluster enhancement	25 networks as a result of ICA	↓ FC in DMN and in SMA
Castrop et al., [89]	Writer's cramp	12	SPM5/activation study, block design: imagination of hand movement		Small volume correction	primary motor, PM, SMA, and SM1, the thalamus, BG	↓ Activation in SM1, PM, SMA, putamen, and thalamus
Delnooz et al.[94]	Writer's cramp	16	FSL 1.1/Seed based	36 correction parameters EMG, sex, and age	FWE	From prior activation studies: dorsal PFC, BG examined against PMD and PCC as control	↓ FC of superior parietal cortex to PM

↓, Decreased; ↑, Increased; ALFF, Amplitude of Low Frequency Fluctuations; BG, Basal Ganglia; CC, Cingulate Cortex; CONN, A Functional Connectivity Toolbox; CSF, Cerebrospinal Fluid; DMN, Default Mode Network (basal ganglia and cerebellum included); ECN, Executive Control Network; EMG, Electromyography; FC, Functional Connectivity; FEAT, A Software Package in FSL; FNIRT, An FSL Software that Provides Non-linear Image Coregistration; FPN, Frontoparietal Network; FWE, Family-wise Error; FSL, A Comprehensive Library of Analysis Tools for Functional and Anatomical MRI Analysis; GP(e), Globus Pallidus (external); ICA, Independent Component Analysis; ICoh, Imaginary Coherence; PCC, Posterior Cingulate Cortex; PFC, Prefrontal Cortex; PM, Premotor Cortex; PMD: Dorsal premotor; PVN, Primary Visual Network; ROI, Region of Interest; RSN, Resting State Networks; SMA, Supplementary Motor Area; SM1, Sensory Motor Cortex; SMN, Sensory Motor Network; SPM, Statistical Parametric Mapping, a Software Package for Image Analysis; SSR, Somatosensory Region.

studies, which could explain the inconsistent findings. In fact, some showed increased, decreased, or no change in putamenal volume.[60,99,100] Improved magnetization-prepared rapid gradient-echo (MPRAGE) contrast and stronger magnetic fields may improve the reliability of volumetric measurements in future studies.

Diffusion tensor imaging

Another commonly used structural neuroimaging modality is DTI. It is based on diffusion of water molecules in the tissue and provides information about cellularity and integrity of aligned axons. Fractional anisotropy describes the degree of restriction in water molecule diffusion,[101] such that a higher value is associated with aligned axons. Mean diffusivity corresponds to diffusion of water molecules and has higher values as the cellularity of the tissue declines.[102] In particular, diffusion tensor tractography permits *in vivo* mapping of structural connectivity, where white matter fiber trajectories are reconstructed by tracking the direction of fastest diffusion between two targets.

Similar to rs-fMRI, early DTI studies in dystonia show highly inconsistent findings, usually including some elements of the basal ganglia, cerebellum, and sensorimotor cortex.[103] DTI findings depend upon the investigated brain regions of interest (ROI). Many early DTI studies did not include measures of basal ganglia connections. Furthermore, most of these early DTI studies employed magnetic resonance scanners with relatively low field strength of 1.5 T. Fractional anisotropy and mean diffusivity measures vary significantly between 3 T and 1.5 T magnets.[104,105] A stronger magnetic field presumably improves the signal-to-noise ratio at the cost of greater distortion, which must be addressed. Field map corrections attempt to compensate for low distortions, but such corrections have not yet been applied to most studies.[106] In addition, only a few studies have implemented diffusion tensor tractography to determine structural connectivity. Recent DTI studies have defined microstructural changes such as subgyral white matter abnormalities of the sensorimotor cortex and cerebello-thalamic tracts associated with genotype in both manifesting and non-manifesting DYT1 and DYT6 carriers.[107,108] They have further identified somatotopic white matter changes[109] and thalamocortical tract abnormalities[110] related to clinical phenotype. However, none of these studies included basal ganglia as ROI for the tractography analysis, hence diffusion tensor tractography measures of dopaminergic pathways remain to be determined in future studies.

Conclusion

Although specific genetic defects may cause some forms of dystonia, in most cases its etiology remains unknown and treatment options unsatisfactory. Neuroimaging can provide a valuable tool to investigate the pathophysiology of dystonias. Overwhelming functional and structural data suggest the involvement of basal ganglia and related networks in various dystonia types. Increasing evidence also suggests dysfunction of cerebellar pathways as a likely cause of dystonia. In fact, a variety of anatomical and functional studies now suggest that cerebellar and basal ganglia pathways are tightly interrelated.[111] Thus, dysfunction of dopaminergic pathways in basal ganglia could alter cerebellar circuits and vice versa.[93]

Molecular imaging remains an effective neuroimaging modality to investigate dopaminergic pathway involvement. PET imaging offers strong evidence for altered D2/D3 receptor binding yet may miss factors affecting dopamine homeostasis and the dopamine-related subcellular signaling cascade, which also could alter function of these pathways. The effect of dopamine is largely mediated through the cyclic adenosine monophosphate/protein kinase A (cAMP/PKA) signaling cascade and therefore controlled by phosphodiesterases (PDEs). Different PDE isoforms are expressed in striatal dopaminergic terminals, and the medium spiny neurons of direct and indirect pathways. Indeed animal data suggest that PDE10 inhibitors activate an indirect pathway.[112] Novel PET radioligands are available for *in vivo* human PET studies of PDE10A and should be employed in dystonia research.[113] Further, striatal specific protein Rhes can activate striatal mTOR signaling, which is downstream of the *GNAL* dystonia gene. Rhes and mTOR are modulated by dopaminergic pathways and mediate striatal plasticity and could play a role in dystonia.[20] Currently no PET ligands are available for *in vivo* evaluation of these targets.

Functional or structural imaging in isolation cannot discern whether altered basal ganglia network connections are causative, epiphenomenon, or compensatory. However, such studies could help identify network patterns suggestive of disease susceptibility, independent of disease manifestation, and serve as subclinical markers of gene expression. Alternatively, they can be used for monitoring target engagement for disease-modifying therapies if the network pattern correlates closely with the phenotype. In addition, functional and structural neuroimaging data can guide histopathological studies. Finally, combining structural and functional imaging with PET will potentiate their effectiveness. Any region with abnormal radioligand binding could serve as the ROI for rs-fMRI and diffusion tensor tractography and provide information on downstream effects of the molecular change.

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