Structural and Functional Brain Mapping Correlates of Impaired Eye Movement Control in Parkinsonian Syndromes: A Systems-Based Concept

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The investigation of the human oculomotor system by eye movement recordings provides an approach to behavior and its alterations in disease. The neurodegenerative process underlying parkinsonian syndromes, including Parkinson's disease (PD), progressive supranuclear palsy (PSP), and multisystem atrophy (MSA) changes structural and functional brain organization, and thus affects eye movement control in a characteristic manner. Video-oculography has been established as a non-invasive recording device for eye movements, and systematic investigations of eye movement control in a clinical framework have emerged as a functional diagnostic tool in neurodegenerative parkinsonism. Disease-specific brain atrophy in parkinsonian syndromes has been reported for decades, these findings were refined by studies utilizing diffusion tensor imaging (DTI) and task-based/task-free functional MRI—both MRI techniques revealed disease-specific patterns of altered structural and functional brain organization. Here, characteristic disturbances of eye movement control in parkinsonian syndromes and their correlations with the structural and functional brain network alterations are reviewed. On this basis, we discuss the growing field of graph-based network analysis of the structural and functional connectome as a promising candidate for explaining abnormal phenotypes of eye movement control at the network level, both in health and in disease.

Keywords: magnetic resonance imaging, diffusion tensor imaging, "resting-state" functional magnetic resonance imaging, neurodegenerative movement disorder, video-oculography, Parkinson's disease, progressive supranuclear palsy, multisystem atrophy

INTRODUCTION

More than half a century ago, Carl F. List concluded in his essay that abnormal oculomotor function frequently gives valuable information of both the localization and the pathoanatomy of an underlying disease process (1). Although eye movements in the diseased brain have been extensively studied since then, it has been only recently that several multimodal studies support an increasingly coherent understanding of the structural and functional brain organization correlates. Characteristic disturbances of eye movement control accompany ongoing pathology (2) and include saccade disturbances, e.g., gaze palsy (3), saccadized smooth pursuit (4), or executive oculomotor dysfunctions, e.g., increased anti-saccade errors (5).

This narrative review links current experimental evidence of human behavior as observed from eye movement recordings in parkinsonian syndromes, including Parkinson's disease (PD),

progressive supranuclear palsy (PSP), and multisystem atrophy (MSA) to what is known from neuroimaging studies in structural and functional brain architecture. Moreover, we discuss how the growing field of graph theory-based investigations of the structural and functional connectome might provide a more elaborated approach to the principles of functional architecture underlying human behavior.

THE OCULOMOTOR SYSTEM AND ITS RELATION TO HIGHER COGNITIVE PROCESSES
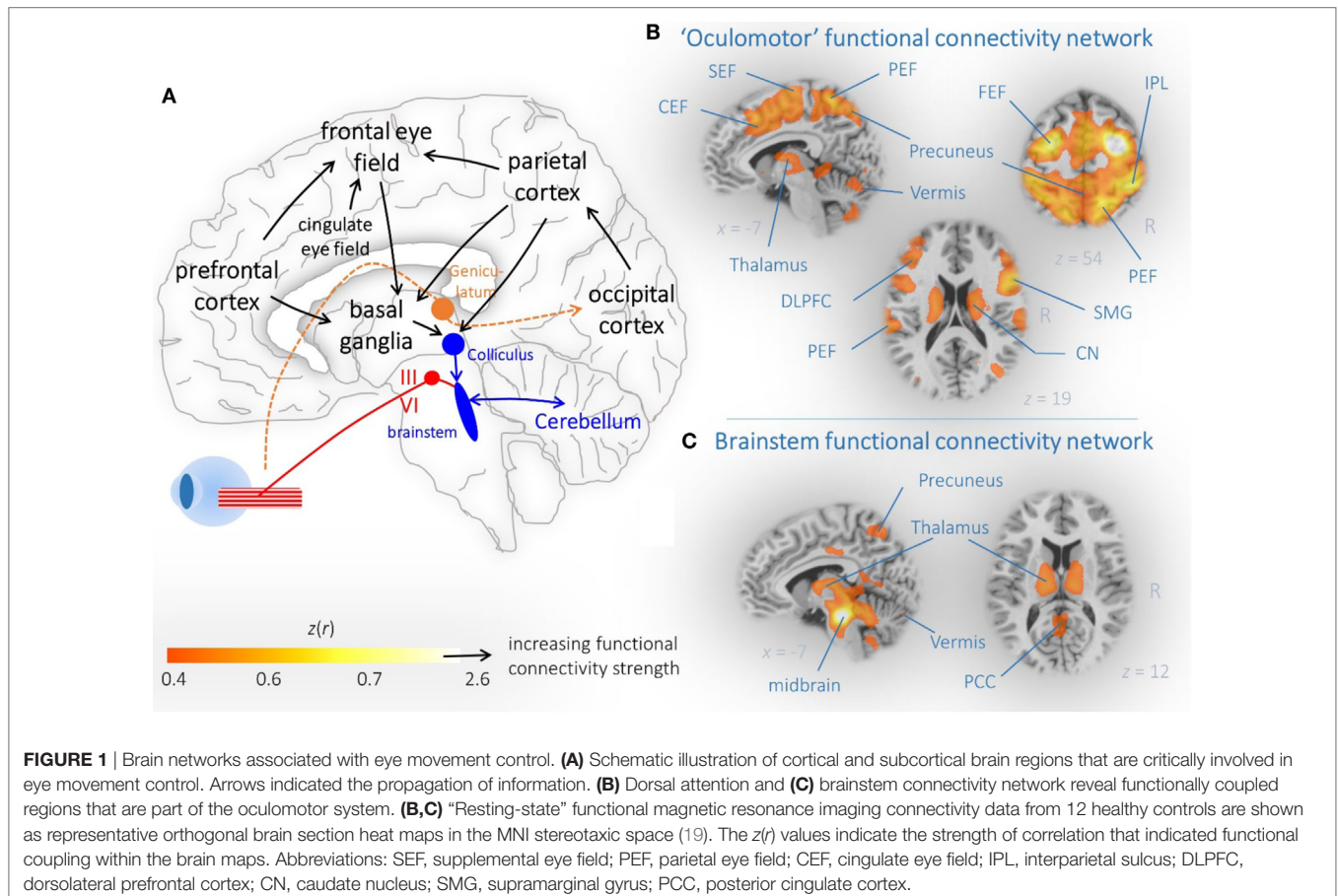
Human cognition is related to sensorimotor activation including oculomotion—a position that nowadays makes many researchers term eye movements as a window to complex forms of human behavior (6) and cognitive processes (7, 8). Subjects facing a choice between multiple stimuli tend to repeatedly look at them and more toward the option they are going to choose (8), presumably implementing a comparison process between different items (9). Brain structures and neural pathways which are involved in the control of eye movements have been reported in a multitude of studies (6, 10), as depicted in **Figure 1**. Brain mapping of eye movement control has been extensively studied in healthy human subjects including evidence from structural imaging (11), diffusion tensor imaging (DTI) (12), "task-evoked"

(13), and "task-free" functional magnetic resonance imaging (fMRI) (14). These studies revealed that the control of eye movements involves multiple networks spanning the brainstem to the neocortex (15, 16). It is well known that parkinsonian syndromes present with progressive impairment of structural and functional brain networks (17), and it is a growing field of neuroimaging research how these brain alterations are linked with the respective oculomotor phenotype. In this context, getting subtle clues from abnormal eye movement control often requires standardized eye movement recordings with dedicated techniques, e.g., by means of video-oculography (18).

BRAIN MAPPING OF OCULOMOTOR PHENOTYPES IN NEURODEGENERATIVE PARKINSONISM

Video-Oculographic Recordings of Eye Movements

Tracking eye movements with state-of-the-art video-based techniques is non-invasive and allows for precise and quantifiable measures of horizontal and vertical movements of the eye (20). Video-oculographic recordings have emerged as a tool in the diagnostic framework of vertigo (21) and especially of neurodegenerative movement disorders (22). Video-oculographic

FIGURE 1 | Brain networks associated with eye movement control. **(A)** Schematic illustration of cortical and subcortical brain regions that are critically involved in eye movement control. Arrows indicated the propagation of information. **(B)** Dorsal attention and **(C)** brainstem connectivity network reveal functionally coupled regions that are part of the oculomotor system. **(B,C)** "Resting-state" functional magnetic resonance imaging connectivity data from 12 healthy controls are shown as representative orthogonal brain section heat maps in the MNI stereotaxic space (19). The z(r) values indicate the strength of correlation that indicated functional coupling within the brain maps. Abbreviations: SEF, supplemental eye field; PEF, parietal eye field; CEF, cingulate eye field; IPL, interparietal sulcus; DLPFC, dorsolateral prefrontal cortex; CN, caudate nucleus; SMG, supramarginal gyrus; PCC, posterior cingulate cortex.

measurements are usually performed in a dedicated laboratory environment which is darkened, optically and acoustically shielded and provides a standardized experimental setup. The subject is comfortably placed in front of a screen with the head stabilized by a chin rest (18, 23). Infrared based light-weighted miniature cameras are mounted on a head band or helmet-like aperture and allow either binocular or monocular eye movement imaging (20). These recorded images are then automatically processed online or offline by a preconfigured computer that is usually an integral component of the eye tracking device (24). The computer provides orthogonal (i.e., horizontal and vertical) eye movement traces that can be analyzed in consideration of the presented stimuli. The stimulus design can incorporate smooth pursuit testing [e.g., by trapezoidal (25) or sinusoidal target motion (26)], reactive saccade testing (e.g., "jumping" target) (27), and executive function tests [e.g., anti-saccades (28)]. Smooth pursuit eye movement traces are analyzed for saccades that interrupt smooth pursuit. Recordings from reactive saccades, i.e., the performance of tracking a "jumping" target, are analyzed with respect to the primary saccades [with an eye amplitude of about 90–95% of the target amplitude (29)] and the reaction times, saccadic gain (i.e., saccade distance divided by target distance), and peak eye velocity. Executive functions testing such as anti-saccades address erroneous response (relative to number of elicited anti-saccades), i.e., pro-saccades toward the target are counted as an error because the subject is asked to immediately shift the gaze into the opposite direction with respect to the eccentric presentation of a visual target (28). Taken together, phenotyping of eye movement control allows for quantification of most useful parameters (such as peak eye velocity or smooth pursuit gain) which can potentially give clues to the clinician early in the course of a disease even when characteristic disease-defining symptoms are not overt (30).

Characteristic but Non-Specific Eye Movement Patterns

Figure 2 illustrates a possible concept of mapping patterns of eye movement disturbances to brain structure and function. Oculomotor control examination is ideally performed at the time of MRI investigations in a dedicated oculomotor laboratory which allows a detailed investigation of eye movement control using state-of-the-art video-oculographically based tracing of eye movements in an acoustically shielded atmosphere (31) Deficits in eye movement control are generally present in parkinsonian syndromes (32). The patterns are characteristic for the phenotype but not disease-specific (22); under this prerequisite, quantification of eye movements is increasingly used as a functional investigation tool in the differential diagnostic framework (18).
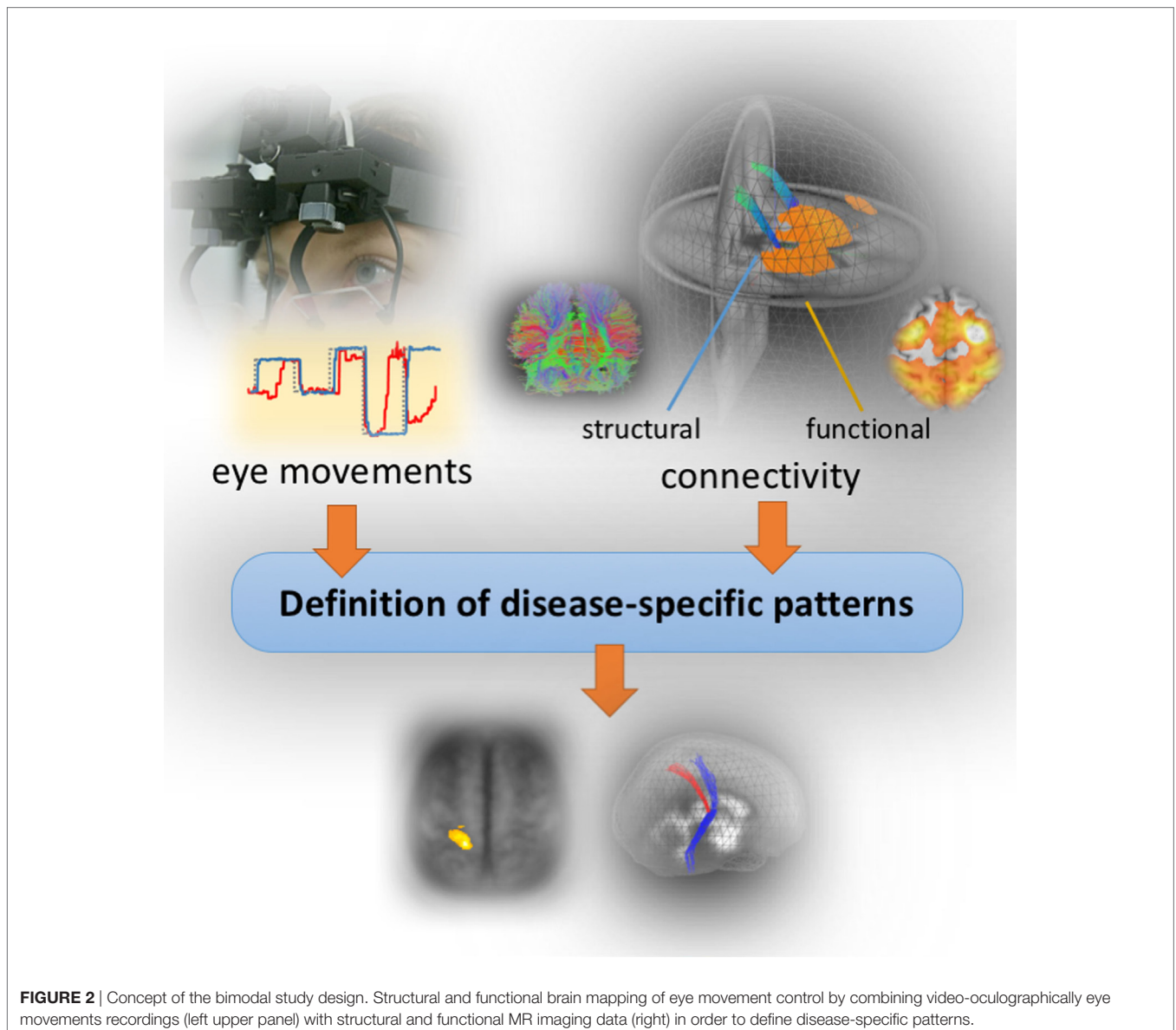
Brain Structural Correlates of Eye Movement Control

A multitude of widely distributed brain regions, including the brainstem (33), basal ganglia (34), and higher centers covering almost the entire neocortex (35, 36) exerts ultimate control over both voluntary and involuntary eye movements (**Figure 1A**). Using a bimodal or multimodal approach of video-oculography

and neuroimaging, morphological alterations in association with deficits in oculomotor control can be addressed in order to see whether distinct brain regions are attributable to eye movement performance (11). Formerly, the voxel-based morphometry approach, a well-known technique to detect region-specific gray matter atrophy (37), was often used for voxel-based lesion symptom mapping (38). Absolute quantification by volumetric techniques such as atlas-based volumetry (ABV) of high-resolution three-dimensional MRI (39) provides a valuable alternative approach. ABV is a dedicated unbiased computer-based technique for absolute regional brain volume quantification at the individual level (39) that allows for fully automated classification of patients with parkinsonian syndromes (40). Using a bimodal analysis of ABV and video-oculographically recorded eye movements allows to identify the relationship between impaired eye movement control and regional brain atrophy in neurodegenerative parkinsonism (41). As a different methodological approach, DTI allows for the *in vivo* investigation of the brain's microstructure within cerebral networks (42) and provides a more subtle measure on microstructural alterations as compared to morphometric or volumetric analysis (43). Disruption of microstructural tissue integrity has been reported in many studies in neurodegenerative Parkinson syndromes and may prove valuable in supporting the diagnosis of PD, PSP, and MSA (44). In association with eye movement control, DTI allows to determine axonal bundles that propagate information on eye movement control (45).

Brain Functional Correlates of Eye Movement Control

Functional magnetic resonance imaging has enabled researchers to investigate functionally activated regions when performing a task as compared to a baseline ("rest") condition (46). The fMRI signals during the performance of saccadic eye movement experiments exhibit a consistent spatial pattern of co-activated brain regions, including fronto-subcortical-parietal regions, thalamus, striatum, and intraparietal cortex (13). Smooth pursuit eye movement performance activated the common oculomotor network (47) including dorsal cortical eye fields and cerebellum (48). "Task-based" fMRI studies have supported the notion that cognitive functions and sensorimotor eye movements are closely interacting with each other and have helped to develop a better understanding of network-level brain abnormalities in neurodegenerative disorders (49). The "classic" "task-evoked" fMRI concept, i.e., simultaneous eye movement recordings and visual stimulus presentation in the MRI scanner, have limitations including the restriction of MRI-dedicated eye movement recording devices and the "noisy" and uncomfortable environment. Some concepts have emerged that to overcome these limitations of eye movement recordings in the scanner by running the fMRI scan afterward or before performing extensive eye movement assessment in a dedicated oculomotor lab (50, 51). The observed activation patterns in these studies revealed regions that are on the one hand part of the well-known oculomotor network and on the other hand regions that are known to be functionally disrupted in PD (50, 52). The activation patterns in association with saccades impairment in PSP demonstrated that not only in

FIGURE 2 | Concept of the bimodal study design. Structural and functional brain mapping of eye movement control by combining video-oculographically eye movements recordings (left upper panel) with structural and functional MR imaging data (right) in order to define disease-specific patterns.

the brainstem, but also cortical neuronal networks contributed to impaired saccadic eye movements in PSP (51).

Functionally involved brain regions in eye movement control can be accurately captured by "task-free" or "resting-state" fMRI experiments, where subjects quietly "rest" in the scanner (53, 54). Resting-state (rs)-fMRI has gained substantial insights into the organization of intrinsic activity patterns of the human brain (54–56), after the discovery of temporally coherent patterns of ongoing low-frequency BOLD fluctuations under "resting" conditions (53). These patterns, i.e., intrinsic functional connectivity networks, remarkably resemble the maps of task-evoked coactive brain regions (57) and reveal a more general picture of the functional brain organization (58). Some substantial advances in understanding brain architecture have emerged from the observation of spontaneous "ongoing" brain activity as measured indirectly *via* the rs-fMRI signal while subjects lying quietly in the

scanner (56). Understanding eye movement control on the basis of functionally interacting brain regions topologically organized as functional connectivity networks put forward the understanding of underlying pathology of impaired eye movement control and behavioral interpretations of these intrinsic connectivity networks (59).

BRAIN NETWORKS AND OCULOMOTOR DISTURBANCES IN PARKINSONIAN SYNDROMES

Parkinson's Disease

Parkinson's disease is now recognized as an age-related multisystem disorder with cardinal motor symptoms that manifest years after the initial onset of pathogenesis—a process that is virtually

self-promoting in a well predictable distribution pattern and not subject to remission (60, 61). A broad spectrum of oculomotor disturbances comprising impaired smooth pursuit, hypometric saccades, prolonged latencies, increased anti-saccade errors that accompany the cardinal motor symptoms (2, 62, 63). In particular, PD-associated oculomotor deficits (2, 64, 65) were shown to be predominantly attributable to executive impairment, because PD patients present substantial difficulties in suppressing unwanted gaze shifts by frequently moving their eyes away from the target in the absence of any distractor, but almost instantaneously correct these involuntary eye movements by re-foveating the target (63). This behavior is typically observed during visually guided reactive saccade performance and can be quantified as the rate of saccadic intrusions (63). Correlation analysis indicated a significant relationship between an increased rate of saccadic intrusions and overall cerebral brain atrophy but not with specific brain regions (41). This result at the structural level is supported by DTI-based investigations which were utilized in order to delineate the axonal organization of the brain at the microstructural level (42). In PD, however, the whole-brain-based analysis of diffusion patterns did not reveal significant correlations between eye movement parameters, e.g., between the rate of saccadic intrusions as a measure for executive control, and regional microstructural damage (41). The correlation analysis between brain structure and eye movement control in PD thus suggested that the executive dysfunctions are more likely attributed to a cortical network disorder (63, 66), rather than to regional brain atrophy or regional microstructural damage.

These findings raised the question whether functional connectivity between interconnected gray matter regions is correlated with oculomotor deficits. In a network-based rs-fMRI study in PD, a pronounced pattern of increased functional connectivity in cognitively unimpaired patients and a pattern of decreased functional connectivity in demented patients could be demonstrated (67). The pattern of abnormal functional connectivity is, in addition, related to abnormal oculomotor performance as revealed by a study of rs-fMRI and video-oculography in PD patients ranging from mild cognitive impairment to dementia (63). In particular, impaired executive oculomotor functions are correlated with a functional connectivity loss in the cognition-related default mode functional network. Taken together, these results allow for the development of a hypothetical model that links oculomotor performance and macro- and microstructural brain changes. Here, oculomotor performance markedly declined in the course of PD and functional connectivity appears to decrease after a critical cell loss has been reached; **Figure 3** illustrates a hypothetical model of PD-associated alterations of functional connectivity together with executive eye movement control changes. The suggested course of functional connectivity is somewhat speculative, but many studies in the field of functional brain mapping try to establish a connection between neurodegeneration and adaptive mechanisms in relation to clinical phenotypes (68). We did not find any correlation between oculomotor parameters and volumetric, structural, and functional measures in ponto-cerebellar structures, midbrain or brainstem in PD—this may indicate that
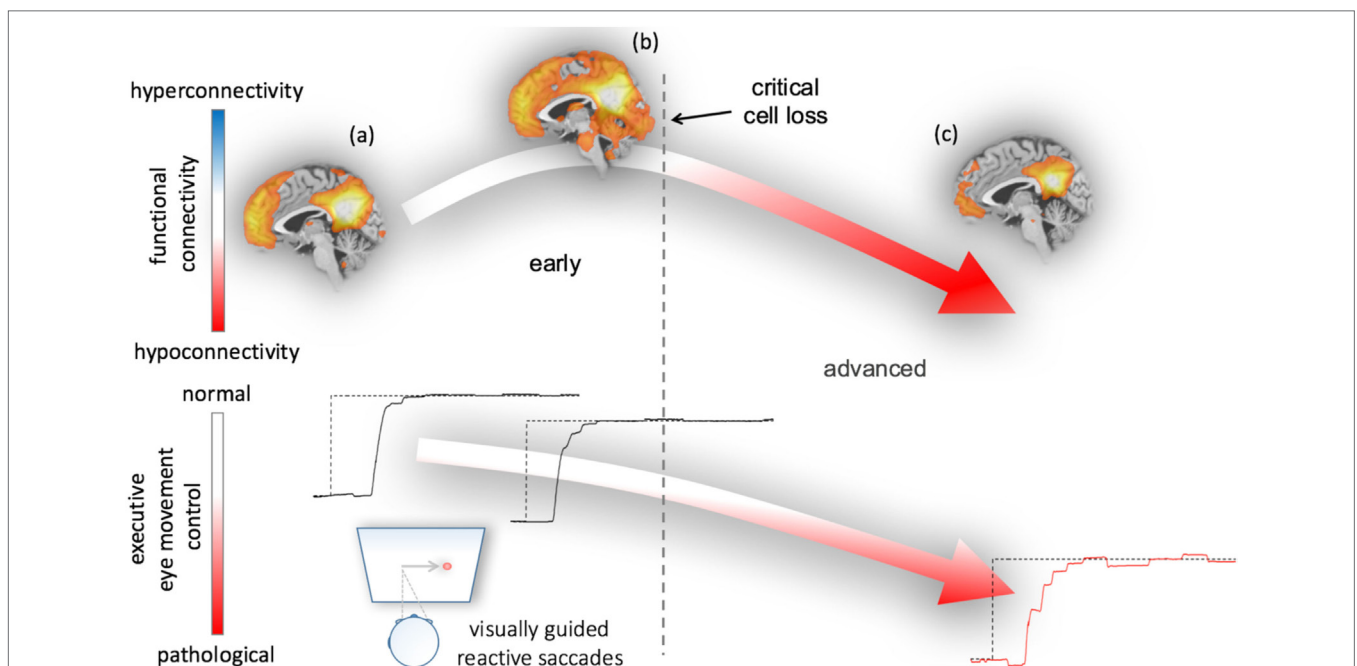

FIGURE 3 | Hypothetical model of functional connectivity alterations in association with executive eye movement control in Parkinson's disease (PD). The model results from correlations between functional connectivity data and eye movement impairment in early and advanced patients with PD (63). Neural damage due to the ongoing PD-associated pathological process from **(A)** healthy or premotor to **(B)** clinically manifest disease status paradoxically results in increased functionally connectivity early in the course of the disease upon a critical cell loss is reached. During this phase, executive oculomotor function gradually worsens as evidenced from visually guided reactive saccade performance (lower row)—remarkably, neuropsychological assessment in these patients revealed cognitively unimpaired "normal" performance (67). **(C)** In the final stages of PD, patients most patients met the criteria of PD-associated dementia and have developed a function disconnection syndrome (decreased functional connectivity) that is associated with a pattern of severely impaired eye movement control (right lower panel).

oculomotor deficits are not associated with disturbed ponto-cerebellar circuits or impaired oculomotor brainstem nuclei.

Previous studies supported the notion of a possible cerebellar involvement in PD (69) which has been recently strengthened by reports of α-synuclein aggregation in precerebellar structures (70). Connectivity studies in macaques (71) and DTI studies in humans (72) indicated that the cerebellum is part of a cerebello-cortico-basal ganglia network that is affected in PD. However, the role of this network and its alterations due to possibly impaired connectivity with respect to oculomotor function has not been systematically disentangled yet. Our oculomotor experience revealed a tendency toward a pattern of a "pontocerebellar type" of smooth pursuit disturbance in PD patients in an advanced disease state, most frequently accompanied by dementia. This observation leads to the speculative conclusion that the cerebellum, if ever, becomes involved later in the course of the disease as proposed by Braak and Del Tredici (60).

Given that, in PD, pathology progresses in different disease stages (60, 73) and eye movement performance worsen over time (30), various MRI techniques, i.e., volumetry, DTI, and task-based and rs-fMRI, allow to map cerebral correlates of oculomotor disturbances. This is specifically important to address the underlying disease-specific pathology both at a structural and functional level. According to the promotion of molecular pathology as suggested for PD (74), raises the question what has happened to the brain when oculomotor deficits manifest. Are these deficits driven by functional decline or structural damage or both? And which diseased brain regions are suspect to be associated with a particular pattern of eye movement disturbances? These questions cannot be fully addressed yet, but systematic studies investigating eye movement control and brain connectivity (75, 76) may indicate that network-based functional connectivity alterations are associated with worsened executive oculomotor function and that functional abnormalities may precede microstructural and macrostructural changes. Although the primary visual cortex in PD appears to be spared by the pathological process (60), a broad spectrum of visuo-oculomotor dysfunctions including color vision (77) and diplopia have been reported (78). Impaired color vision seems to be predictive to developing cognitive problems in PD (79) which could be most likely due to a network dysfunction involving vison-associated structures. Diplopia is frequently reported by PD patients and has been investigated in non-demented PD patients (78). From a clinical perspective, one might speculate that reporting diplopia in association with PD might be predictive for cognitive decline, but diplopia in association with the risk of developing cognitive dysfunctions remains to be investigated on a systematic basis.
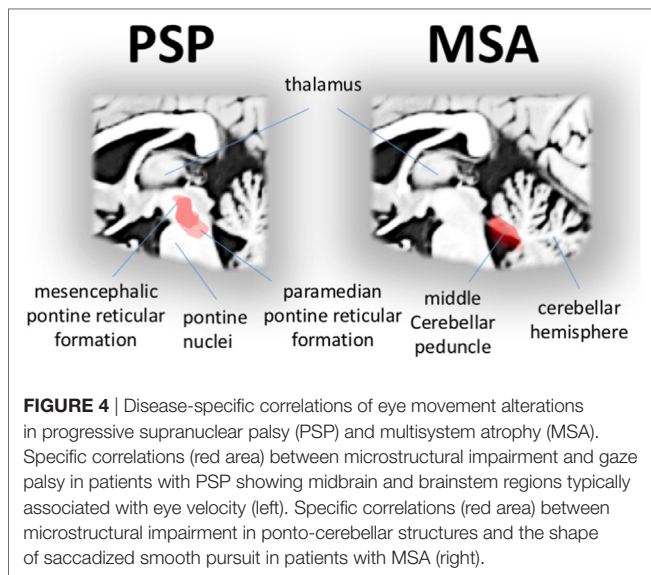
Antiparkinsonian treatment including deep brain stimulation of the subthalamic nucleus was reported to improve oculomotor inhibition control and to facilitate saccade initiation (80), most likely due to compensatory mechanisms (81), whereas other groups reported no significantly improved oculomotor performance (62). Apparently, improvement of oculomotor performance due to antiparkinsonian treatment depends on the disease state, i.e., patients early in the course are more likely to improve eye movement performance (18). Future prospective studies are required to unravel the effect of treatment on eye movement performance in association with brain connectivity.

Other Neurodegenerative Parkinsonism

Progressive supranuclear palsy and MSA are other parkinsonian syndromes (82–85) which comprise a characteristic spectrum of oculomotor dysfunctions (65). In contrast to PD patients who predominantly show oculomotor dysfunctions that are attributable to executive dysfunctions, PSP and MSA patients were shown to present predominantly "genuine" oculomotor dysfunctions (31). Impaired "genuine" oculomotor function comprised reduced peak eye velocity feature in PSP (3) which is used for diagnostic differentiation between PSP and both PD and MSA (30). Reduced peak eye velocity is the hallmark oculomotor feature in PSP patients (86) which is present at different levels from normal saccade velocity toward gaze palsy which has become increasingly relevant in the diagnostic guidelines for PSP (85). Earlier studies suggested that deficient generation of the motor command by midbrain burst neurons is most likely the cause of slowed vertical saccades in PSP (87).

Progressive supranuclear palsy is considered a neuropathologically defined disease presenting with a broad spectrum of clinical phenotypes besides the "classical" phenotype Richardson syndrome [PSP-RS (88)], including the Parkinsonian subtype (PSP-P), corticobasal syndrome subtype, and frontotemporal dementia subtypes (89) besides further variants which are of limited importance for oculomotor control. Slowed saccades in all subtypes of PSP are due to the paucity in burst generation at the excitatory burst (90). The PSP-RS and PSP-P subtypes show an almost identical oculomotor phenotype, hence, eye movement recordings do not allow to distinguish between PSP-PS and PSP-P (91). There are no systematic data for eye movement alterations associated with the other variants yet. It might be of note in that context that, in patients with frontal lobe degeneration, saccadic and smooth pursuit eye movements are impaired (92), and multimodal morphological studies revealed a link between atrophy in frontal brain regions and executive oculomotor performance (93). In the search of an imaging correlate of slowed saccades in PSP (including both PSP-RS and PSP-P patients), it could be demonstrated that the characteristic deficits in eye movement control were associated with regional macrostructural (41) and microstructural white matter alterations (94) (**Figure 4**, left). In particular, the hallmark oculomotor feature in PSP, a pathologically reduced peak eye velocity in both horizontal and (predominantly) vertical direction is associated with midbrain and brainstem pathology including the oculomotor nuclei responsible to "drive" the extra-ocular eye muscles. In addition, a recent "resting-state" fMRI study in both PSP-RS and PSP-P could also demonstrate correlations between midbrain functional connectivity and brainstem gaze centers (95). This finding is in agreement with the fact that on the one hand degeneration of neurons in the midbrain gaze centers in PSP-RS leads to progressive slowing of saccades (3) but that on the other hand slowed vertical saccades are not necessarily present in an early state of each subtype of PSP. In the tauopathy corticobasal degeneration as defined by Armstrong and coworkers in 2013 (96), it is mentioned that eye movement abnormalities may be present in

FIGURE 4 | Disease-specific correlations of eye movement alterations in progressive supranuclear palsy (PSP) and multisystem atrophy (MSA). Specific correlations (red area) between microstructural impairment and gaze palsy in patients with PSP showing midbrain and brainstem regions typically associated with eye velocity (left). Specific correlations (red area) between microstructural impairment in ponto-cerebellar structures and the shape of saccadized smooth pursuit in patients with MSA (right).

about 60% of corticobasal degeneration cases, but data are sparse and heterogeneous, partly describing increased saccadic latency and abnormal antisaccade performance. However, studies on neuroimaging correlates are lacking. Taken together, this group of neurodegenerative disorders often overlaps clinically, and future studies have to investigate well-defined samples.

Multisystem atrophy can be distinguished in a cerebellar subtype (MSA-C) and a MSA-P. The oculomotor phenotype in MSA-C and MSA-P is almost identical (4) and does not allow to separate both subtypes—a finding that is supported by a recent bimodal MRI and VOG study that investigated functional connectivity and smooth pursuit performance in MSA-C and MSA-P patients (97).

Smooth pursuit eye movement is the ability to perfectly stabilizing the image of a continuously moving object onto the fovea (36). In MSA, smooth pursuit eye movement is disturbed throughout a reduced gain (i.e., eye velocity/target velocity <1), resulting in an offset between target and eye position, i.e., the target continuously slips away from the center of the fovea (18). This offset is almost instantaneously corrected by a "catch-up" saccade that centers the fovea back onto the target—an adaptive process that results in a staircase pattern without episodes of perfect smooth pursuit (4). The presence of catch-up saccades interrupting smooth pursuit is a common oculomotor feature in patients with ponto-cerebellar impairment like in MSA (4) and contributes to the differential diagnosis (18).

Lesion studies in animals that targeted vital elements of the smooth pursuit pathways including the cerebellar vermis and precerebellar nuclei, indicate that these structures are responsible for catch-up saccades (36). Consistent with this finding, severe macro- and microstructural damage in the bilateral middle cerebellar peduncles in MSA patients is correlated with smooth pursuit impairment (**Figure 4**, right). In particular, pontine volume loss is strongly related to the shape of saccadized smooth pursuit as demonstrated in a study of video-oculographically recorded eye movements and ABV-based volumetry (41). These findings are further strengthened by correlating performance measures

of smooth pursuit with DTI-based measures of microstructural impairment. The degree of microstructural impairment in the middle cerebellar peduncle was strongly correlated with the shape of "catch-up" saccades during smooth pursuit in MSA (94). Moreover, abnormal functional connectivity within the ponto-cerebellar network is also strongly correlated with the shape of characteristically impaired smooth pursuit as revealed in rs-fMRI study in MSA patients compared to controls (97).

These findings, at a broader scope, may allow to generally speculate about brain structure and function in association with oculomotor phenotyping in parkinsonian syndromes. Disease-characteristic patterns of impaired oculomotor control gradually worsen over time and are apparently closely related with ongoing region-specific macrostructural and microstructural damage. The pattern of network-dependent functional connectivity alterations is more complex. As suggested, the pattern of functional connectivity increases and then gradually declines toward a disconnection syndrome. The development of functional connectivity in the course of the disease is well explained by the concept of adaptive changes (i.e., hyperconnectivity) that aims to compensate for ongoing cell loss in the sense of cortical network reorganization up to a point in time where a critical cell loss is reached (68, 98). From this point in time, compensation is no longer possible and the cognitive reserve is exhausted (99, 100). A limitation of the suggested model is the lack of information from longitudinal studies.

A PERSPECTIVE ON CONNECTOMICS AND EYE MOVEMENT CONTROL

The brain is an efficient representation of a complex system (101, 102) which consists of spatially distributed and functionally specialized regions that continuously share information with each other (103). Graph-theoretical approaches for the analysis of both structural and functional networks enable to quantify properties of the brain's functional system together with the underlying wiring (104). A network is defined in graph-theory as a set of nodes, i.e., anatomically segregated brain regions, and edges, i.e., a connectivity measure, between two nodes (105). Many measures of useful properties that characterize the network organization can be computed, including basic concepts, measures of segregation, integration, motifs, resilience, and other concepts such as "network small-worldness" (106). These measures are to be correlated with behavioral parameters including quantitative measures of eye movement control. For instance, the saccadic reaction times are prolonged in parkinsonian syndromes, but there is no report about any specific regions of the brain which are structurally or functionally correlated with reaction times (41, 63, 94). It appears that there is no single "region" associated with latency; rather, reaction time could be hypothesized to reflect network efficiency computable in a graph-based framework. Thus, modeling the brain connectivity as a graph, with nodes being segregated brain modules and edges being "region-to-region" connectivity strengths, opens a new avenue for investigating brain organization in association with the respective oculomotor phenotype in parkinsonian syndromes. Recent evidence strongly suggests that the anatomical connections determine whether they are

vulnerable to degeneration in neurodegenerative parkinsonism (107). It remains to be investigated whether eye movements provide a window into the status of neurodegeneration (disease stage) or even allow to serve as a prognostic marker.

CONCLUDING REMARKS

The oculomotor analysis of a patient using gaze-tracking technology might help clinicians to gain insights into the brain function and disease status. In addition, the reviewed studies pave the way toward the development of a standardized protocol for video-oculographic assessment in the differential diagnostic frame aiming at establishing a technical surrogate marker. In neurodegenerative parkinsonism, worse oculomotor performance in the disease-specific domain was shown to be associated with more severely impaired regional macro- and microstructure and altered regional functional connectivity in disease-specific brain structures. These findings increase our pathophysiological knowledge of the underlying parkinsonism-associated network

pathology. Finally, brain mapping of impaired eye movement control as shown for parkinsonian syndromes should be investigated in a broader context of brain diseases in order to find out whether the demonstrated findings could be generalized to neurodegenerative diseases beyond parkinsonism.

AUTHOR CONTRIBUTIONS

MG and JK drafted the manuscript. H-PM revised the manuscript for intellectual content. All authors performed literature search, agreed to be accountable for the content of the work, and finally approved the manuscript.

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