# Eye movements in neurodegenerative diseases

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**Purpose of review**
Abnormalities of oculomotor control accompany the pathological changes underlying many neurodegenerative diseases. Clinical examination of eye movements can contribute to differential diagnosis, whereas quantitative laboratory measures can provide detailed insight into the disease process. In this review of eye movements in neurodegenerative disease, we summarise recent empirical findings and conceptual advances.

**Recent findings**
Oculomotor researchers continue to be particularly prolific in studying Parkinson's disease but there is also substantial activity in Alzheimer's disease and spinocerebellar ataxia. Interesting findings have been reported in Huntington's, motor neuron disease, and glaucoma. Most studies report laboratory-based investigations but useful progress in clinical description continues to be made.

**Summary**
Eye movements remain an active field of investigation across a variety of neurodegenerative conditions. Progress continues to be made at the clinical level as well by using laboratory techniques.

**Keywords**
Alzheimer's disease, dementia, eye movement, neurodegeneration, Parkinson's disease, saccade, spinocerebellar ataxia

## INTRODUCTION

The control of eye movement involves extensive networks of cerebral regions, spanning brainstem to neo-cortex. Therefore, regardless of whether a neurodegenerative process is relatively focal (as in glaucoma) or widespread (e.g. the dementias), effects are therefore likely to be evident in altered oculomotor performance.

Saccades (rapid eye movements) in particular can provide a reliably measurable analogue of the wider effects of a neurodegenerative disease. The review by Gorges *et al.* [1▪] provides excellent graphical examples of eye movement recording measures, using Parkinson's and progressive supranuclear palsy (PSP) cases. For example, saccades in Parkinson's are often hypometric [2▪▪], reflecting the hypokinesia seen in limb and hand movements. Later in the disease, even simple reactive saccades to a target show prolonged latencies, indicative of advanced cognitive impairment (Fig. 1) [3]. The antisaccade task ('look away from, rather than at, the target') is more complicated, and hence recruits more extensive cortical areas. Increased errors (looking at the target) can be found even in early Parkinson's [4] or prior to the onset of Alzheimer's [5], suggestive of early frontal-cortical deterioration. Mobile eye tracking technology is now also enabling insights into oculomotor control in more naturalistic tasks (e.g. Fig. 2).

## PARKINSON'S DISEASE

Diederich *et al.* [7▪▪] propose a fascinating model, in which visual dysfunction in Parkinson's might explain not only hallucinations of presence and passage, but also impairments of saccades and pursuit (although not so readily, vergence and upgaze) and even hypomimia. The affected pathways are proposed to be those that also mediate blindsight, rather than the primary visual pathways, so that such people with Parkinson's are 'blind to blindsight'. Although the model is built mainly upon analogy, the authors propose testable hypotheses,

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## KEY POINTS

- Oculomotor networks, derived from resting-state BOLD MRI, provide an alternative to traditional task-evoked functional MRI and could track progressive neocortical degeneration.
- Oculomotor neurons, selectively preserved in MND, have distinctive protein signatures. This discovery should improve our understanding of the neurodegenerative process and may provide therapeutic targets.
- Oculomotor findings are frequent across the many SCAs, but none are specific enough to be pathognomic.
- Saccadic abnormalities may be markedly more prevalent in PCA than in typical forms of Alzheimer's disease.

and we look forward to seeing if this creative account leads to empirical confirmation.

Trade-off between speed and accuracy of movement is a fundamental principle of motor control. Reward, however, can simultaneously improve 'speed' (expressed as both reduced latency and increased peak velocity) and precision of saccades [8]. In Parkinson's, dopaminergic dysfunction causes both motor impairment and reduced reward sensitivity. Prolonged latencies and slow movements in Parkinson's might be an adaptive mechanism to reduce motor performance variability in the presence of an increased cost for controlling internal noise [8]. The quantitative nature of this model makes it well suited to generate further testable motor control hypotheses, in Parkinson's and beyond.

Studies of the effect of dopaminergic therapy on saccades have been contradictory. This might be because the direction of effects is task-specific. For example, treatment prolongs reactive saccade latencies, whereas memory-guided latencies improve because of medication altering the balance between the direct and indirect basal ganglia pathways [9]. But in a small study of patients with levodopa-induced dyskinesia, reactive saccade latencies clearly 'decreased' [10], with the authors describing this effect and the increased rate of express saccade production as 'superior colliculus dyskinesias'. Although not representative of all

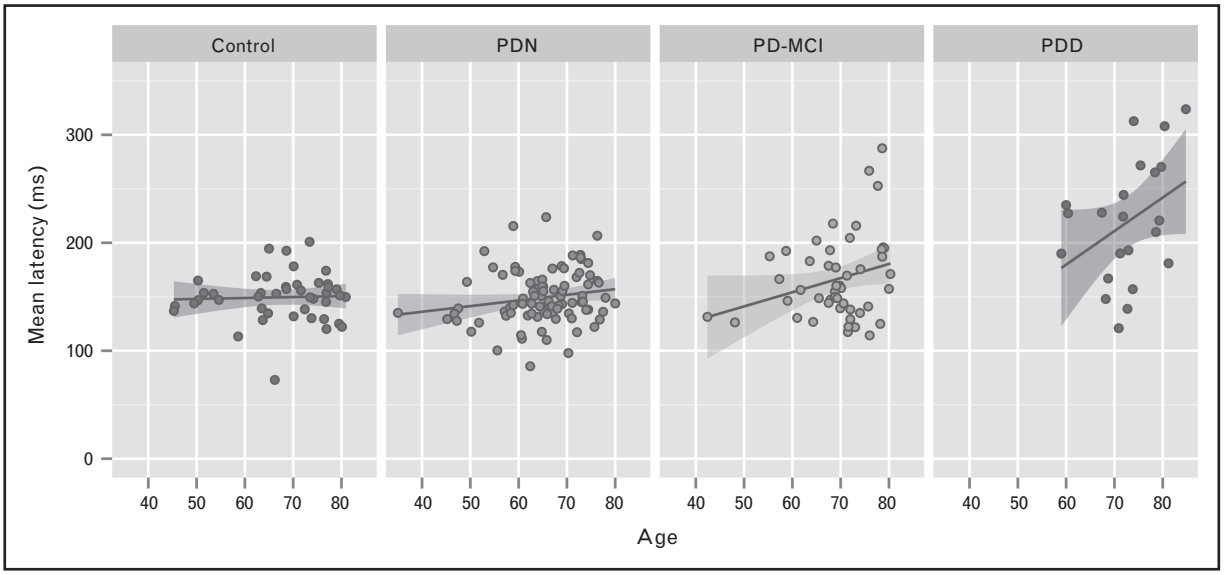


**FIGURE 1.** Laboratory measures of eye movements in response to simple targets offer both precise measurement and manipulation of oculomotor performance in neurodegenerative conditions. For example, the 'gap' task (in which the currently fixated stimulus disappears 200 ms before the onset of the next target) facilitates the disengagement of attention, leading to reduced saccade latencies and an increased rate of 'express' saccade production. In this data from a study of reflexive, visually guided saccades [3], control study participants showed the expected decrease in mean latency (to 150 ms compared with a typical value of 180 ms). This was constant across the age range of controls. Parkinson's disease patients with normal cognitive functioning (PDN) did not differ from controls. Patients with mild cognitive impairment (PD-MCI), however, showed a prolonged latency (15 ms, $P < 0.03$) compared with a mean-aged control (68 years) and a nonsignificant age-related increase (12 ms/decade). Patients with dementia (PDD) showed both a 54 ms increase relative to the average-aged control ($P < 0.0001$), and a strong age-related prolongation of 30 ms/decade ($P < 0.01$). This was an age effect, not because of disease duration. PDD, Parkinson's disease dementia; PD-MCI, mild cognitive impairment in Parkinson's disease.

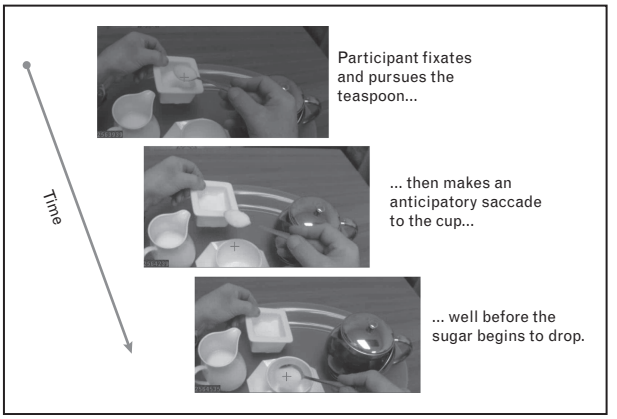


**FIGURE 2.** Mobile eye tracking technology allows investigation of oculomotor strategies in real-world tasks. Above are scene images from a head-mounted SMI HED 200 Hz gaze tracker. The cross shows the current gaze location of a man with Parkinson's disease mild cognitive impairment during part of a tea-making task in our laboratory. The coordination between hand movements and their associated supporting gaze movements was largely preserved in this group while performing this activity [6].

patients, this group may present an avenue to examine dopaminergic dysregulation of oculomotor responses [11].

Parkinsonian gait impairments can be ameliorated by providing visual cues such as stripes on the ground orthogonal to the direction of motion. Vitorio *et al.* [12▪], using simultaneous gaze and gait recordings, found that the stripes act as external targets for both gaze and feet. Classification of oculomotor events during gait tasks poses technical challenges such as the eyes not being stationary during fixations, because of vestibulo-ocular compensation. Stuart *et al.* [13] describe a candidate saccade detection algorithm, tested in a Parkinson's gait study, which attempts to overcome these challenges.

Antoniades *et al.* [4] found that standard antisaccade errors and other executive function measures could discriminate early drug-naive patients from controls. The sample was of nontremor dominant patients, however, who may be particularly prone to early cognitive impairment. de Boer *et al.* [14], meanwhile, found antisaccade performance to be normal in Parkinson's. Increasing the cognitive complexity, however, by adding a simultaneous 'antitapping' instruction, did reveal impairments. Gorges *et al.* [2▪▪] detected most of the accepted oculomotor impairments in a Parkinson's sample (prolonged saccadic latency, reduced gain of saccades and pursuit, increased fixational instability and antisaccade errors). From resting-state blood-oxygen-level dependent (BOLD) MRI data, they then constructed six functional networks, each seeded from a known oculomotor area. Measures of functional connectivity in most of these networks correlated with oculomotor performance, consistent with progressive neocortical degeneration in the course of the disease. Such resting-state connectivity analyses are a useful addition to traditional task-evoked functional MRI.

Owing to manganese toxicity, ingestion of the homemade stimulant ephedrone can lead to a severe, rapidly progressive parkinsonism. Bonnet *et al.* [15▪] found that eye movement impairments were similar to those of idiopathic Parkinson's but a distinguishing feature was relative slowing of horizontal saccade velocity.

Vergence eye movements are impaired clinically in Parkinson's. Hanuska *et al.* [16] showed quantitatively that fast vergence movements in Parkinson's have increased latency. Convergence was otherwise normal, but divergence was slowed and hypometric. Such impaired vergence may contribute to reduced acuity and blurred vision in Parkinson's.

A current controversy is whether hitherto-unrecognized ocular tremor might provide a diagnostic sign of Parkinson's. Whether the phenomenon is real [17,18] or artefactual [19,20] continues to be debated [21▪].

## PROGRESSIVE SUPRANUCLEAR PALSY

Palsy of voluntary vertical gaze is the classic sign distinguishing PSP from other forms of parkinsonism. Anderson [22] provides a video tutorial on detecting this clinically, emphasising the hierarchical process of the examination. There are a number of PSP mimics. Erro *et al.* [23] present a case study of a man with a PSP-like presentation but eventually diagnosed with cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy. Fragile X-associated tremor/ataxia syndrome (FXTAS) can also present similarly to PSP, with additional oculomotor abnormalities [24]. In presymptomatic FXTAS gene carriers, the antisaccade task revealed impaired inhibitory control, indicative of early cognitive impairment [25].

## ALZHEIMER'S DISEASE

Microsaccades, tiny, horizontal rapid eye movements that interrupt periods of fixation, occur at an elevated rate in Alzheimer's [26▪▪]. Human microsaccades are generally horizontal but Kapoula *et al.* [27▪▪] found obliquely-oriented microsaccades to be more common in mild–moderate Alzheimer's and in amnestic mild cognitive impairment (MCI) than in controls. The phenomenon, although subtle,

shows promise as an objective marker of early disease that does not require compliance with a complicated cognitive task.

When reading, information from the current word and the wider context influences upcoming eye movements. For example, saccades are larger when made towards words that are somewhat predictable from their context, compared with saccades towards less predictable words. When reading, saccade amplitudes in Alzheimer's were generally hypometric and showed no beneficial modulation by predictability [28], even when the entire sentence – a well known proverb – was predictable [29]. People with Alzheimer's took longer to read a text, made more fixations, were more likely to reread words, and were much less likely to adaptively skip small and uninformative words [30].

Difficulties in disengaging attention can be examined in the laboratory by comparing saccades with a target that appears 200 ms after the previously fixated stimulus has disappeared (the 'gap' task, which reduces latencies) to those when the previously fixated target remains visible (the 'overlap' task, which induces longer latencies). Crawford *et al.* [31▪▪] reported that compared with controls, latencies in Alzheimer's were longer overall but the magnitude of the overlap effect was similar. In both groups, however, overall latencies decreased slightly at 12-month follow-up, indicating a practice effect even over this timeframe. Crawford *et al.* recommend that eye tracking measures be quantified as a profile of z-scores as in standard neuropsychological test batteries, so that rather than focussing on specific measures, abnormality in an individual is judged by how many scores exceed a threshold. Peltsch *et al.* [5] advocate a similar approach but found that a minimum number of trials exist to yield stable estimates, particularly for antisaccade error measures.

## POSTERIOR CORTICAL ATROPHY

Posterior cortical atrophy (PCA) is an atypical variant of Alzheimer's, in which visuospatial and visuomotor impairments predominate initially [32,33]. Oculomotor abnormalities (primarily saccadic) were detected in 80% of PCA cases, compared with just 17% of typical Alzheimer's, and 5% of controls [26▪▪]. Only 33% of the PCA cases showed clinically apparent deficits, highlighting the sensitivity of laboratory measures. Saccades were of smaller amplitude than in Alzheimer's, with a greater overlap (or 'sticky fixation') effect. People with PCA are less able to appropriately switch between oculomotor strategies when examining photographic scenes for a particular purpose (such as to search for an object, or to describe the scene) [34]. Rather, their fixations were driven by low-level image features rather than task instructions. Oculomotor control whilst reading was also substantially worse than in typical Alzheimer's [35].

When asked to look at which of two scenes contains an animal, healthy observers can make saccades to the target image with very low latencies [36]. This rapid categorization ability involves the frontal eye field, part of the dorsal attentional network that is disrupted by Alzheimer's [37]. Whether detecting animals [37] or making other distinctions (e.g. natural vs. urban scenes, indoor vs. outdoor) [38], Alzheimer's patients made less accurate judgments, whereas lower-level oculomotor parameters (latencies and amplitude) were normal. In PCA, there was even greater impairment relative to Alzheimer's when selecting animals presented within a scene rather than in isolation [33]. People with PCA appeared to benefit less from contextual information and might have impaired figure/ground separation.

## THE PREDEMENTIA PERIOD

Although the concept of MCI as a predementia state remains controversial, visuomotor impairments can precede the development of the pathognomic memory deficits of both amnestic MCI and Alzheimer's disease, and so oculomotor investigations may be useful tools in predicting conversion to dementia [39]. Groups with amnestic MCI and Alzheimer's were similarly impaired on antisaccade performance [5]. Short-latency antisaccade errors correlated negatively with Stroop task scores in MCI and controls, indicating that these might be oculomotor and neuropsychological measures of similar underlying inhibitory difficulties.

The right frontal eye field is a node in a cerebral network supporting the antisaccade task that is particularly vulnerable to neurodegeneration. A hyperactive BOLD signal in this region correlated with worse antisaccade performance even in healthy elderly study participants, indicating that it may be an early marker of cognitive decline [40▪].

## SPINOCEREBELLAR ATAXIA AND CEREBELLAR DISEASE

The cerebellar ataxias have a wide variety of overlapping presentations but a comprehensive review by Rossi *et al.* [41▪▪] brings some order to the field, summarizing 1062 papers covering 12 141 patients with 30 autosomal dominant forms of the disease. Phenotypic descriptions, including eye movement

features, continue to be useful in classifying newly-found genotypes. In a prospective multicentre US study of clinical eye movement features of 301 patients with SCA 1, 2, 3, and 6 [42▪▪], frequencies of specific oculomotor abnormalities varied across subtypes, but none were pathognomic. Slow saccades were rare in SCA 6, whereas nystagmus and pursuit abnormalities were common. In SCA 2, nystagmus and saccadic dysmetria were rare. The lack of dysmetria may result from saccades being so slow that they become nonballistic. That is, their durations are so prolonged that, in response to visual feedback, their trajectories are able to be corrected midflight [43,44]. SCA 1 and 3 had did not have characteristic oculomotor features.

Expression of these disorders varies across populations: SCA 2 being most common in India, SCA 3 in Western countries [45]. In 45 genetically confirmed cases from eastern India, oculomotor abnormalities revealed typical distinctions between SCA 1, 2, 3, 6, and 12 [45]. The prevalence of slow saccades was not, however, useful in distinguishing SCA subtypes 1, 2, 3 and 6 among a sample of 83 Thai patients [46]. In 35 people with SCA 7 from the Haryana region of India, in addition to the characteristic retinal degeneration, slow saccades occurred in 85% [47].

In an oculomotor implementation of the Trail Making Task, seven patients with SCA 2 had performance impaired by low saccadic velocity, whereas in six with late onset cerebellar ataxia, saccadic dysmetria was more relevant [48]. Matsuda *et al.* [49], studying pure cerebellar ataxia (SCA 6 and 31), note that cerebellar impairment can lead to a 'dysmetria of cognition' additional to the more familiar motor impairments. For example, patients took longer than controls to complete a visual search task that required a systematic, serial scanning strategy. When these patients viewed simple drawings, the area they scanned was abnormally large [50], in contradistinction to their earlier findings in Parkinson's, where the explored area was smaller than normal [51]. Falcon *et al.* [52] conducted MR imaging in 14 people with SCA 6 mutations, performing free visual exploration. Cerebral cortex activation was normal but cerebellar activation was abnormal and associated with symptom severity. As disease severity progressed, functional connectivity between cortical and cerebellar regions became markedly abnormal. Reorganization of connections between cortical visual and oculomotor regions, even at preclinical stages, led the authors to question the purely cerebellar characterization of this subtype.

Owing to a founder effect, the prevalence of SCA 2 is extremely high (180/100 000) in Holguín, Cuba. Rodríguez-Labrada *et al.* [53▪] investigated the antisaccade task in 41 symptomatic patients. They showed for the first time that increased error rates and prolonged latencies were related to CAG repeat size. Antisaccade performance was also impaired in 37 presymptomatic SCA 2 mutation carriers (>32 repeats) [54▪] and correlated inversely with projected time to ataxia onset. Saccadic slowing, meanwhile, was slight and evident in only 16%. Thus, high-level cognitive oculomotor impairment might actually be an earlier indicator and marker of the disorder than basic saccade dynamics.

## HUNTINGTON'S DISEASE

Rees *et al.* [55] contend that cerebellar involvement in Huntington's should be given more consideration. From structural MRI of 22 Huntington's disease patients, they demonstrated cerebellar morphological and diffusion abnormalities that correlated with motor performance, including saccade initiation. In a postmortem investigation of eight patients, Rüb *et al.* [56] found neuronal inclusions in the brainstem were more widespread than previously documented, and correlated with the saccadic and vestibulo-ocular impairments. These changes were independent of the more characteristic striatal degeneration. They conclude that Huntington's is a multisystem degeneration that has commonalties with several SCAs.

Grabska *et al.* [57] examined saccades in the juvenile variant of Huntington's, in which onset occurs prior to age 21. Although the clinical presentation is distinctively dominated by bradykinesia and rigidity rather than chorea, saccadic impairments (prolonged latency, decreased velocity, and amplitude) were similar to those seen in adult-onset Huntington's.

## MOTOR NEURON DISEASE

Oculomotor control is relatively spared in motor neuron disease (MND) but is still of research relevance. For example, eye tracking devices are often used as an assistive communication and control technology in advanced stages. Hwang *et al.* [58] showed that these improve self-reported quality of life for patients and reduce caregiver burden because of improved patient autonomy and patient-caregiver communication.

Selective sparing of brainstem oculomotor nuclei provides potential insight into understanding the disease. In an impressive series of postmortem studies of tissue from both mouse models and MND patients, Comley *et al.* [59▪▪] found distinct protein signatures which distinguished vulnerable

**Table 1.** Reviews published during the period

| |
|---|
| General scope: |
| Ocular motor disorders (review of then-current papers only) [21▪] |
| Ocular motor abnormalities in neurodegenerative disorders (historical coverage) [67▪] |
| Alterations of eye movement control in neurodegenerative movement disorders (historical coverage) [1▪] |
| The definitive text, *The Neurology of Eye Movements* by Professors John Leigh and David Zee, was updated to its 5th edition in 2015 [68▪▪]. This is a comprehensive and authoritative resource for everyone interested in the clinical and scientific investigation of oculomotor control, including in neurodegenerative conditions |
| Disease specific: |
| Eye movements in Alzheimer's disease [69] |
| Oculo-visual changes and clinical considerations affecting older patients with dementia [70] |
| Eye movement analysis and cognitive processing: detecting indicators of conversion to Alzheimer's disease [39] |
| The potential utility of eye movements in the detection and characterization of everyday functional difficulties in mild cognitive impairment [71] |
| Saccadic eye movements in Parkinson's disease [72] |
| The measurement of visual sampling during real-world activity in Parkinson's [66] |
| Visual signs and symptoms of multiple system atrophy [73] |
| Supranuclear eye movement disorders [74] |
| The neuropathology of Huntington's disease: classical findings, recent developments, and correlation to functional neuroanatomy [75▪▪] |
| Autosomal dominant cerebellar ataxias: a systematic review of clinical features [41▪▪] |
| Rapid eye movement sleep behaviour disorder and neurodegeneration [64] |
| Two studies in 2014 utilized deep brain stimulation to study eye movements in Parkinson's [76,77], for which we refer the reader to another review in this issue [78] |

and resistant neurons. Preexisting protein expressions of vulnerable neurons are dynamically regulated by the disease process, placing those cells at further risk. These findings have clear implications for identifying disease-modifying targets.

## GLAUCOMA

Glaucoma is a neurodegenerative disease, with disease effects spreading transynaptically beyond the retina to affect central visual pathways [60]. Crabb *et al.* [61] examined eye movement scanpaths during free viewing of television, which were sufficiently distinctive in people with glaucoma to distinguish them from controls via automated analysis. People with glaucoma also show abnormally small eye movements while reading [62]. People with glaucomatous visual field loss can potentially adopt compensatory strategies, when reading such as making more frequent saccades or shifting fixation toward a preserved but eccentric, nonfoveal, retinal location [63].

## RAPID EYE MOVEMENT SLEEP BEHAVIOUR DISORDER

There is a strong link between rapid eye movement sleep behaviour disorder (RBD) and subsequent neurodegeneration. The interested reader is directed to Howell and Schenk [64] for a broad overview. We have not attempted to cover the vibrant literature in this field, as few of these studies focus directly on oculomotor phenomena per se. An exception is the extensive clinical study by Kim *et al.* [65▪▪], who hypothesized that the pathological brainstem changes in RBD could result in nystagmus and ocular flutter. Nystagmus, although not uncommon in multiple system atrophy [17], has not generally been noted in Parkinson's disease. In the largest published oculomotor study in Parkinson's of which we are aware, they assessed 202 patients, 116 of whom also had clinically probable RBD. The proportion of RBD patients who had clinically evident brainstem or cerebellar-like oculomotor findings (24%) was 3.6 times higher than in those without RBD. Though possible explanations include the potential coexistence of other disorders, this surprising observation deserves further exploration.

## CONCLUSION

Oculomotor control remains a vibrant field of research across multiple neurodegenerative conditions. New observations are still being made at the level of clinical description, such as the reported association between RBD and nystagmus [65▪▪] and improved description of conditions that appear to be expressed differently in varying national and

ethnic populations [45–47]. Objective eye tracking recordings are moving beyond measuring responses to simple jumping targets (Fig. 1) to encompass activities such as reading [28], walking [12▪], or other real-world tasks [66] (Fig. 2). The utility of focused, artificial laboratory tasks remains relevant, however, in testing and generating fundamental theories of motor control in general, and the effects of specific neurodegenerative diseases [8]. Readers who wish to learn more about specific disorders, or the field in general, are referred to a number of other reviews that have appeared during the last 18 months (Table 1).

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## Conflicts of interest

*There are no conflicts of interest.*

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- ▪ of special interest
- ▪▪ of outstanding interest

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