Published in final edited form as:

Expert Rev Ophthalmol. 2017 ; 12(6): 457–473. doi:10.1080/17469899.2017.1395695.

Basic and translational neuro-ophthalmology of visually guided saccades: disorders of velocity

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Abstract

Introduction: Saccades are rapid, yoked eye movements in an effort to direct a target over fovea. The complex circuitry of saccadic eye movements has been exhaustively described. As a result clinicians can elegantly localize the pathology if it falls on the neuraxis responsible for saccades. Traditionally saccades are studied with their quantitative characteristics such as amplitude, velocity, duration, direction, latency and accuracy.

Areas covered: Amongst all subtypes, the physiology of the visually guided saccades is most extensively studied. Here we will review the basic and pertinent neuro-anatomy and physiology of visually guided saccade and then discuss common or classic disorders affecting the velocity of visually guided saccades. We will then discuss the basic mechanism for saccade slowing in these disorders.

Expert commentary: Prompt appreciation of disorders of saccade velocity is critical to reach appropriate diagnosis. Disorders of midbrain, cerebellum, or basal ganglia can lead to prolonged transition time during gaze shift and decreased saccade velocity.

Keywords

eye movements; saccade; saccade velocity

1.0 Introduction

Saccades are rapid, simultaneous movements of both eyes by which we shift our line of sight in order to point the fovea at the object of interest [1]. Behavioral classification of saccades are used to categorize them into various paradigms [1] (Table 1). Various subclasses of

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Declaration of interest

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saccades are often implemented collectively in gauging the function of the central nervous system as each class has specific neural correlate.

An important type of saccade known as visually guided saccades are internally generated towards the intended target. Reflexive saccades are made to an unexpected appearance of a target leading to a reflexive refixation of gaze. Memory guided saccades are those made to the remembered location of the target; while antisaccades include suppression of the movement in the direction of the target but instead make a saccade of equal amplitude in the opposite direction. Table 2 provides a brief description of the saccade classes.

Although generated at various cortical locations, and modulated by distinct subcortical nuclei, the different classes of saccades are processed by a final common pathway in the brainstem. Independent of the class, important parameters of a saccade include velocity, amplitude, duration, direction, accuracy and latency. Saccadic movements manifest with a relatively invariant direct relationship between their amplitude and peak velocity. The velocity of large saccades may exceed 500 degrees per second and a typical duration of 20–100 ms. A commonly described equation for the relationship between amplitude and peak velocity is:

$$\text{Peak Velocity} = V_{\max} \left(1 - e^{-\text{amplitude}/c} \right).$$

Interestingly, the saccadic speed and duration are not under voluntary control. Because of the short duration of the movement, visual information cannot influence the movement once they have begun. Disorders of saccades include abnormalities of velocity, accuracy, initiation, premature termination, saccadic intrusions and oscillations.

Pathology of the orbit and muscle dysfunction may affect all the parameters of a saccade. In contrast, disorders of the central nervous system might selectively spare one or more of such parameters. Electrophysiological, inactivation and classical lesion studies in primates and functional imaging and transcranial magnetic stimulation in humans have provided us with insights on the localization and networking of the cortical and subcortical areas responsible for different phases of saccades [1]. This review focuses on the disorders of the central nervous system affecting the velocity of visually guided saccades. Table 4 summarizes the effects of clinical disorders discussed in this article on the peak velocity of visually guided saccades.

2.0 Applied Anatomy and Physiology

2.1 Cortex:

The cerebral hemispheres direct instructions for saccades via parallel descending pathways to the superior colliculus [2, 3]. One of the parallel pathways has origin in the frontal eye field, supplementary eye field, and the dorsolateral prefrontal cortex [4, 5, 6]. The second parallel cortical projections begin from the parietal eye field in the posterior parietal cortex [2, 3] (Fig. 1). Stimulation of frontal eye field evokes contralaterally directed horizontal or oblique saccade whose amplitude depends upon the area of stimulation [7, 8]. Pathological,

or pharmacologically induced inactivation of frontal eye field with muscimol causes slowing of visually-guided saccades and a gaze shift towards the side of the inactivation [9, 10]. Indeed stimulation or inactivation induced gaze shifts are considered classic clinical signs to diagnose hyperacute disorders such as seizure or stroke. With chronic lesions, subtle changes in visually guided saccades are observed which include impaired latency and decreased amplitude of saccade [11, 12] (Table 3). However these cortical insults do not directly impair saccade velocity[12].

2.2 Basal ganglia:

Basal ganglia functions as a relay for indirect projections from frontal and parietal eye fields to the superior colliculus [13, 14]. Frontal lobe projections to caudate nucleus are from the frontal eye field, supplementary eye field and dorsolateral prefrontal cortex [14] (Fig. 2A). The caudate nucleus sends direct, inhibitory fibers to substantia nigra pars reticulata [15] which in turn maintains tonic GABAergic inhibition over superior colliculus [16, 17]. The caudate nucleus also projects indirectly to the subthalamic nucleus via external segment of globus pallidus [15] (Fig. 2A). Such a neuronal circuitry ensures that a transient cessation of these neurons lead to timely saccade initiation [18, 19]. Lesions of the caudate nucleus decrease velocity and amplitude of saccades [20]. Pharmacological inhibition of substantia nigra pars reticulata after muscimol injection results in contralaterally directed spontaneous saccades [21] (Table 3). Electrical stimulation of the substantia nigra pars reticulata causes reduced latency and hypometric visually guided saccades [22].

2.3 Cerebellum:

Cerebellum plays an important function in accuracy [23, 24] and calibration of the saccade amplitude [25, 26]. Cortical eye fields project to the cerebellum via pontine nuclei [27, 28, 29, 30] (Fig. 1A). Dorsal vermis, a medial cortico-nuclear zone of cerebellum and fastigial nucleus, a deep cerebellar nucleus serve an important function in the control of saccadic eye movements. Dorsal vermis receives fibers from the nucleus reticularis tegmenti pontis and projects to the caudal part of fastigial nucleus [31] (Fig. 1). In addition to dorsal vermis, the caudal part of fastigial nucleus also known as fastigial oculomotor region (FOR) also receives projections from the superior colliculus and frontal eye fields [32]. FOR sends efferents to omnipause neurons, inhibitory burst neurons (IBN), excitatory burst neurons (EBN) [33]. FOR thus modulates saccades by stimulating the burst neurons during contralateral saccades and providing inhibition during ipsilateral saccades [34, 35].

Total cerebellectomy or lesions of vermis has been shown to produce saccadic dysmetria [23, 24, 36]. Similar to frontal eye fields and superior colliculus, stimulation of dorsal vermis produce an ipsilateral saccade [40]. Furthermore, unilateral pharmacological inactivation of the dorsal vermis causes a marked ipsilateral hypometria in addition to a mild contralateral hypermetria [41]. Lesions of fastigial nucleus produces a significant hypermetria [42, 43, 44, 45, 46]. In addition, unilateral pharmacological inactivation causes hypermetria of ipsilateral saccades and a hypometria of contralateral saccade [47] (Table 3). Isolated lesions of cerebellum therefore do not affect saccade velocity.

2.4 Superior Colliculus:

Superior colliculus is a multi-layered structure located in the midbrain. The major role of superior colliculus is considered to be in selecting a target of foveation [48], movement initiation [49] and modulating its velocity [50]. Most contemporary theories postulate that the superior colliculus functions as a bottleneck and a 'final common pathway' during visually guided saccades [51–53]. Superior colliculus receives excitatory inputs from the cortex and inhibitory fibers from substantia nigra pars reticulata [54, 55] (Fig. 1). The ventral layers of the superior colliculus consists of a motor map carrying information concerning the eye movement parameters [56, 57] (Fig. 1). A distinct neuronal population directly involved in saccade generation has been demonstrated on electrophysiological studies. [60, 61]. The ventral layer of the superior colliculus projects to the midbrain and pontine reticular formation [62] where the premotor structures involved in the saccade generation are located. These include the horizontal gaze center paramedian pontine reticular formation (PPRF) and the vertical gaze center rostral interstitial medial longitudinal fasciculus (riMLF).

Superior colliculus ablation abolishes contralateral saccade generation which later recovers but with a prolonged latency [11, 63] (Table 3).

2.5 Omnipause Neurons:

The commands for saccades converge onto omnipause neurons (OPNs) in the nucleus raphae interpositus (RIP) of the midline pons [33, 64, 65]. The direct pathway from the cortex signals to the OPNs via superior colliculus [66, 67, 68]. The indirect pathway projects via basal ganglia [69] to cerebellum before innervating the OPNs [32] (Fig 1). (Fig. 1, Fig. 2A). The omnipause neurons are tonically active which inhibits the activity of both horizontal and vertical saccade burst generators (Fig. 2B) [71, 72]. The suppression of OPNs initiates a saccadic eye movement [70]. Electrical stimulation of omnipause neurons can stop a saccade in mid-flight [73].

Pharmacologic lesion of oculomotor neurons by ibotenic acid decreases peak saccade velocity and consequently increasing the saccade duration [74, 75].

2.6 Premotor Burst Complex:

Several groups of burst neurons have been described. Excitatory burst neurons (EBNs) in the paramedian pontine reticular formation (PPRF) relay monosynaptically to oculomotor neurons for horizontal saccadic eye movements while EBNs in the rostral interstitial nucleus of the Medial Longitudinal Fasciculus (riMLF) present in the prerubral fields of the dorsal midbrain are responsible for vertical saccades [72, 76, 77] (Fig 2B). As mentioned above, the OPNs inhibit the activity of both horizontal and vertical saccade generators (Fig. 2B) [71, 72]. EBNs are silent at all times except during saccades [77]. The saccadic eye velocity is determined by the strength in firing rate of EBN [76, 78]. Any pathology affecting the EBN can affect strength of the burst leading to slow velocity of the saccades [78, 79]. Experimental or clinical lesions of the PPRF and riMLF results in a selective loss of vertical saccades but other ocular movements are intact [80, 81]. Table 3 summarizes the major abnormalities observed with lesions at different segments of the saccadic pathway.

3.0 Disorders of Basal Ganglia

3.1 Parkinson's Disease

Parkinson's disease is a common neurodegenerative disorder of basal ganglia manifesting with a number of clinical features, commonly including bradykinesia, rest tremor, shuffling gait, masklike facies, and increased muscle tone [82, 83]. A number of eye movement abnormalities have been reported in Parkinson's disease. Large amplitude visually guided saccades in Parkinson's disease present with an increased latency [99]. The saccadic initiation defect is marked in the vertical plane, especially in the upward direction [91]. A study measuring kinematics of visually guided saccades revealed increasing prevalence of hypometria, compared to healthy controls, especially if the saccadic amplitude exceeded 20 degrees [88]. Asymmetry of hypometria was evident in subjects with asymmetric Parkinson's disease, the saccades were more hypometric towards the more symptomatic side [102]. The trajectory of hypometric saccades appear like a staircase as these movements are typically corrected to shift gaze to its target [103, 104]. While staircases increase the time taken to reach target of interest, it does not imply reduction in the saccade velocity [96]. Nevertheless, there is higher variability of the peak velocity of visually guided saccades in subjects with Parkinson's disease; only in advanced cases there is saccade slowing [87, 91, 105]. Some studies have found a correlation between ocular motility abnormalities and freezing of gait in Parkinson's disease [98, 106, 107]. Saccade latency is increased in Parkinson's disease with freezing of gait [107]. In contrast, other symptoms of PD such as tremor, rigidity and bradykinesia [98].

L-DOPA and dopamine agonists, which are central to the treatment of Parkinson's disease, surprisingly, increase the latency of the visually guided saccades [108, 109]. These results are however controversial; an independent study found an improvement in the amplitude and latency of the visually guided saccades [88]. High-frequency deep brain stimulation improves motor symptoms in Parkinson's disease and it also decreases the latency in all types of saccades [100, 110]. However, the deep brain stimulation does not affect the saccade velocity.

The basal ganglia via serial inhibitory projections inhibits extraneous saccades during attempted gaze holding, while facilitating timely voluntary saccades (Fig. 3A)[14, 19, 69]. In pathological states such as the Parkinson's disease, the superior colliculus remains in inhibited state due to hyperactive substantia nigra pars reticulata (Fig. 3A). Therefore, it is expected that the abnormalities in visually guided saccades could be due to excessive inhibition of the superior colliculus. There are still fundamental questions remain unanswered. One question is whether hypometric saccades in subjects with Parkinson's disease are "interrupted" due to excessive phasic inhibitory discharge transmitted through the substantia nigra pars reticulata, or they are "mal-programmed" due to involvement of basal ganglia and as well as midbrain and brainstem saccade generators, or they are slow? The second question is whether Parkinson's disease differentially affects horizontal and vertical saccades? Answers to these questions will address an important dichotomy concerning saccade abnormalities in Parkinson's disease: whether there is an excessive

inhibition of the superior colliculus or an involvement of brainstem saccade generators that are distinct for horizontal and vertical saccades.

3.2 Progressive supranuclear palsy

Progressive supranuclear palsy is a sporadic neurodegenerative condition classified as a tauopathy - an abnormal accumulation of microtubule-associated protein, which is a main constituent of neurofibrillary tangles responsible for neuronal injury and atrophy. Typical clinical features of progressive supranuclear palsy include postural instability, supranuclear gaze palsy, axial rigidity, and bulbar palsy [111, 112].

Studies of eye movements have important contribution in diagnosis and tracking the course of Progressive supranuclear palsy. Both amplitude and velocity of a visually guided saccade is characteristically abnormal in progressive supranuclear palsy. Oblique saccades in progressive supranuclear palsy have a prominent curvature with relatively faster horizontal component that may assist in distinguishing progressive supranuclear palsy from other forms of atypical parkinsonism and Parkinson's disease [87]. A characteristic phenotype vertical saccades follow is a curved pathway called "round the houses sign" [114]. With increasing severity, complete vertical gaze palsy occurs wherein vertical saccades are lost [115]. Remarkably, vertical saccades with small amplitude have normal velocities [113]. Interestingly, horizontal saccades are hypometric in early disease and with disease progression, become slower [116].

Slowing of vertical saccades and vertical gaze limitation is the hallmark of the classic progressive supranuclear palsy subtype called Richardson syndrome [118, 119]. Supranuclear gaze palsy restricts vertical gaze in both directions [87, 120]. Since the restriction of upward eye movement is common in normal healthy elderly due to age-related changes in the orbital tissue [90], a mild upgaze limitation may not be specific in progressive supranuclear palsy during the early disease course. However, the limitation of downward gaze is a more specific finding [115, 121]. Progressive supranuclear palsy also presents with increased latency for saccade initiation in both horizontal and vertical directions of eye movement, which is more prominent with vertical saccades [119].

In typical forms of PSP, the most prominent autopsy changes are found in the substantia nigra pars compacta of basal ganglia, mesencephalon, diencephalon, and brainstem reticular formation involving rostral interstitial nucleus of medial longitudinal fasciculus [126, 127, 128] which correlates with slow or absent vertical saccades (Fig. 3B). Dysfunction of the omnipause neurons lead to impairment in horizontal and vertical saccades; but in progressive supranuclear palsy there is asymmetric involvement and selective deterioration of vertical saccades. Several phenomenologies describe saccade slowing in progressive supranuclear palsy. One reason for slowing is reduced peak velocity. Premature interruption of ongoing saccade can also increase transit time. Progressive supranuclear palsy is known to cause selective deficits of vertical saccades generators [126]. Various mechanisms describe such premature interruption of the saccades. The fastigial nucleus activates the omnipause neurons and inhibitory burst neurons leading to cessation of the saccades. The spontaneous pathological premature discharges in the fastigial nucleus or the omnipause neurons could therefore prematurely interrupt saccades. Such mechanism describes interruptions in both

horizontal and vertical saccades. In addition to interruptions, saccades in progressive supranuclear palsy have substantial curvature and irregularity. The orientation of the redirected saccades is dependent upon the coordinates of the stimulated site in the fixation zone of superior colliculus [129].

3.3 Dementia with Lewy Bodies

Dementia with Lewy Bodies presents with cognitive impairment, parkinsonism, visual hallucinations, fluctuating mental state, autonomic dysfunction, and prominent sleep disorders [130, 131]. Dementia with Lewy-bodies causes several clinical abnormalities that may help in distinguishing it from Parkinson's disease and other known causes of dementia [131][130]. A slowing and hypometria of both horizontal and vertical saccades is a known abnormality but it is not a diagnostic hallmark [132]. Rarely dementia with Lewy bodies present with a vertical gaze palsy [133, 134]. Patients with dementia with Lewy body also have a prolonged latency of saccade initiation, a decreased latency of visually guided saccades [132, 135]. In laboratory evaluation of eye movements, the parameters of saccade latency and velocity in dementia with Lewy body were comparable to Parkinson's disease with dementia [135].

3.4 Corticobasal Syndrome

Corticobasal syndrome or cortico-basal ganglionic degeneration is an akinetic-rigid neurodegenerative disorder with characteristic clinical features such as asymmetric limb rigidity, bradykinesia, dystonia, myoclonus, tremor, gait abnormalities with postural instability and falls and one or more of the cortical features: apraxia, cortical sensory deficits, or the alien limb phenomenon [136, 137, 138]. Saccade latency is consistently increased in corticobasal syndrome [87, 105]; the slowing of saccade is an occasional finding [87, 137]

3.5 Huntington's Disease

Huntington's disease is a CAG triplet repeat disorder with an autosomal dominant pattern of inheritance. The increases in triplet repeat leads to a defect in protein huntingtin, which is responsible for the progressive degeneration involving caudate nucleus and frontal lobe. The classic clinical features include choreoathetosis, behavioral changes, and cognitive decline correlated with the distribution of degeneration [140, 141, 142].

Huntington's disease affect multiple aspects of eye movements [143, 144, 145, 146, 147, 148] which correlate with the distribution of neuropathology [149, 150, 151]. Saccade abnormalities are a sensitive marker of Huntington's disease [152]. Therefore, laboratory measurements of eye movements can serve as an important biomarker of preclinical disease [153] and disease progression [154, 155, 156, 157]. Prolonged saccade latency and hypometria are common findings early in the disease course [158] [156] which worsen with disease progression [152, 159, 160]. Because of increased latency of saccade initiation in advanced diseases, a patient may have to rely on blinking or head thrust to initiate a gaze shift [161]. In advanced stages of the disease, hypometria manifests in both horizontal and vertical planes [159, 162, 163]. Slow saccades, in either horizontal or vertical plane, are a

common feature during late stages of the disease; however, it may also be present early [159, 162, 163].

Several eye movement phenotypes have stark contrasting features determined by the age of onset of Huntington's disease. In early onset disease, usually in age group of less than 30-year-old patients, a drastic reduction in peak saccade velocity without prolonged latency contrasts is observed. However, with later-onset Huntington's disease, usually in age group greater than 30 years, only a mild reduction in peak saccade velocity with a markedly increased latency has been reported [163][158].

Substantia nigra pars reticulata by its inhibition of superior colliculus via the nigro-striatal projection controls voluntary saccades. Substantia nigra pars reticulata in turn, is inhibited by frontal lobe and caudate nucleus. Subsequent to frontal lobe and caudate nucleus degeneration, hyperactivity of substantia nigra pars reticulata results in difficulty in initiating voluntary saccades (Fig. 3c)[88, 168, 169]. Finally, it has been suggested that slowing of saccades in Huntington's disease may reflect involvement of saccadic burst neurons in the brainstem reticular formation [170, 171].

4.0 Disorders of Mid-Brain

4.1 Late-Onset Tay Sachs Disease

Tay-Sachs disease, a metabolic storage disorder, is an autosomal recessive GM2 gangliosidosis due to a mutation in the enzyme hexosaminidase A causing progressive neurodegeneration. The age at the onset of neurologic symptoms determines the classification of the disease as infantile or late-onset. Late-onset Tay Sachs has a progressive course with a variable clinical picture of ataxia, signs suggestive of motor neuron disease, and psychiatric symptoms [172].

Reduction in saccade velocity, putatively due to supranuclear pathologies, and coarse saccades have been described in case studies [173]. Hypometria and a slowing of vertical and horizontal saccades are reported in both infantile as well as late-onset Tay-Sachs disease [174, 175].

Objective measures of hypometric saccades in late-onset Tay-Sachs reveal transient deceleration and premature, abrupt saccade termination (Fig. 4)[175]. It is proposed that premature activation of the omnipause neurons leads to a mid-saccade cessation [175]. Alternate explanation is the abnormal premature activation of the inhibitory burst neurons leading to a dysregulated saccadic behavior [174, 176].

4.2 Niemann-Pick Disease

Niemann-Pick disease is an autosomal recessive metabolic storage disorder. Deficiency of acid sphingomyelinase is responsible for Niemann-Pick Type A and B whereas a mutation in NPC1 or NPC2 gene cause a type C variant [177]. The onset of Niemann-Pick disease is usually in adolescence and it presents with dysarthria, ataxia and intellectual disability. The disease also manifests with characteristically prominent disorders of eye movements [178]. With disease progression, multiple abnormalities can be seen [182]. A selective slowing of

vertical saccades (vertical supranuclear gaze palsy) has been described in early phase of the disease [179, 180] however, a slowing of horizontal saccades is also known [181]. Histopathological examination reveals a completely normal interstitial nucleus of Cajal and ocular motoneurons [184]. Glial fibrillary lesions are found in the posterior commissure signifying neuronal injury and neuronal loss is noted in rostral interstitial nucleus of medial longitudinal fasciculus [182]. The pontine-to-midbrain ratio on brain magnetic resonance imaging is inversely correlated with the slowing of saccade [186].

4.3 Gaucher's Disease

Gaucher's disease, a lysosomal glycolipid storage disease, is an autosomal recessive disorder due to a deficiency of the enzyme glucocerebrosidase. Gaucher's disease comprises three phenotypic variants [187, 188]. Type 1 is the most common and lacks neurological features. Type 2 (infantile) and type 3 (juvenile) are the neuronal types. Type 2 form of the disease is lethal and death occurs in early childhood, in contrast to type 3, which has a milder course [189].

The hallmark characteristic of Gaucher's disease type 3 is the predominant involvement of horizontal saccades [190]. One of the earliest eye movement abnormalities is prolonged saccade latency [191] which is greater in horizontal direction than vertical [190]. Slowing of saccades is a prominent finding in adult patients [192, 193] which is more marked with horizontal saccades [190]. Additionally, with vertical saccades downward movements are slower than upward movements [190]. Although type 1 Gaucher's disease does not have any neurologic symptoms, abnormal saccade velocity was reported in one study [188]. Large saccades in Gaucher's disease may show intermittent slowing during their course, suggesting malfunctioning brain stem omnipause neurons [175].

4.4 Micro-Infarcts after Cardiac and Large Thoracic Vessel Surgery

There is an increasing recognition of the association between aortic or cardiac surgery and disorders of saccade. A wide spectrum of ocular movement impairments have been reported [194, 195, 196, 197, 198, 199]. Characteristic findings range from slow or hypometric saccades in both horizontal and vertical directions to complete saccade palsy [200, 201, 202]. Quick phases of both optokinetic and vestibular nystagmus are slow to absent [197, 203]. The pathophysiology is not well understood however, a likely mechanism is the selective loss of omnipause and premotor burst neurons in the paramedian pons with sparing of cerebral hemisphere and other parts of the neuraxis [200]. No neuroimaging abnormalities were identified. However, it has been proposed that the loss of cerebellar Purkinje cells [198] or perineuronal nets (PN) dysfunction, due to their vulnerability to ischemia, are responsible for the saccadic palsy [204, 205, 206]. It is postulated that the abnormality is likely to be due to a brainstem process that singles out the saccadic burst generation in pons and mesencephalon. Rarely, bihemispheric cerebral infarction can occur leading to paralysis of any voluntary eye movement [194].

5.0 Disorders of Cerebellum

5.1 Spinocerebellar Ataxia Type 2

Spinocerebellar ataxia type 2 is an autosomal dominant disorder due to an unstable expansion of a polyglutamine domain within ataxin-2 [207] which is a cytoplasmic protein found in many body tissues and neurons. The disorder is characterized clinically by a progressive cerebellar ataxia, dysarthria, action tremor, early neuropathy, and slowing of saccades [208]. Slowing of saccade velocity can be strongly correlated with the polyglutamine expansion, but not with disease duration, age of onset or the gender of the subject [209]. An interesting observation is the inverse correlation between the severity of ataxia and slowing of saccade [209]. Slowing is present even before manifestation of other clinical features of the disease [210]. Therefore, saccade velocity is a sensitive and specific marker of disease activity [211] and can be used as a surrogate marker of disease severity [212] even before the onset of ataxia [210]. Other eye movement abnormalities include vertical and horizontal gaze palsy [213]. Figure 5 depicts pathophysiology of saccade slowing in spinocerebellar ataxia type 2.

5.2 Spinocerebellar Ataxia Type 3

Spinocerebellar ataxia type 3, also known as Machado-Joseph disease is an autosomal dominant disorder occurring due to CAG triplet repeat expansion [214, 215, 216]. It presents with progressive gait, stance, limb, and truncal ataxia, dysarthria, somatosensory deficits, dystonia and occasionally parkinsonism, dysphagia, and a varying degree of eye movement disorders [217, 218, 219].

Eye movement abnormalities such as impaired smooth pursuit, optokinetic nystagmus, gaze evoked nystagmus, saccadic dysmetria and horizontal vestibulo-ocular reflex dysfunction are well known deficits of spinocerebellar ataxia type 3 [221, 222, 223, 224, 225, 226]. The saccades in some spinocerebellar ataxia type 3 patients may have dynamic overshoot of the target, however, those without dynamic overshoot have saccades with low peak velocity [228]. In comparison to spinocerebellar ataxia type 2, the inferior olive in spinocerebellar ataxia type 3 is rarely affected. Diffuse atrophic changes in the nervous system are observed on MRI with marked changes in the cerebellar vermis, superior cerebellar peduncle, pontine tegmentum, and frontal lobes [229, 230]. Histopathological studies have shown a degeneration of reticulotegmental nucleus of the pons [231] and the omnipause neurons of nucleus raphe interpositus [232] which may be responsible for the abnormal horizontal saccades [232, 233].

6.0 Disorders of lower brainstem and spinal cord

6.1 Amyotrophic Lateral Sclerosis

Amyotrophic Lateral Sclerosis is a progressive neurodegenerative disorder of the upper and lower motor neurons involving the primary motor cortex, brainstem and spinal cord [234, 235]. For instance, other motor neuron diseases (e.g. Kennedy disease, X-linked spinobulbar muscular atrophy), cervical spondylotic myelopathy, benign fasciculation syndrome, multifocal motor neuropathy cause symptoms similar to amyotrophic lateral sclerosis but

they lack any eye movement abnormalities [236]. Hence, examining eye movements is important as it may provide clues to diagnosis when other differentials cannot be ruled out.

Upward gaze restriction is observed in some patients [239]. A defect in smooth pursuit [240, 241, 242, 243] can also be found in patients with a prominent frontal lobe involvement [243]. Increased saccade latency and slowing have been described [241, 242, 244, 245, 246]. With disease progression, vertical gaze palsy may develop due to supranuclear ophthalmoplegia [246, 247, 248]. These impairments are associated with bulbar involvement and cognitive dysfunction [243]. The vertical saccade palsy can be correlated with histopathological changes in the rostral interstitial nucleus of medial longitudinal fasciculus [248].

6.2 Wernicke's Encephalopathy

Wernicke's encephalopathy is caused by a nutritional deficiency of thiamine and is commonly encountered in alcoholics. The classic triad of Wernicke's encephalopathy is ophthalmoplegia, mental confusion, and gait ataxia [249]. Early ocular motor finding in Wernicke's encephalopathy include gaze-evoked and upbeat nystagmus that may switch to downbeat nystagmus with convergence [250, 251].

Horizontal vestibulo-ocular response impairment occurs early, which progresses to abduction impairment, inter-nuclear ophthalmoplegia (impaired adduction during conjugate gaze shift), horizontal and vertical gaze palsies, and eventually complete ophthalmoplegia [252, 253, 254]. Wernicke's disease can progress to Korsakoff's syndrome, which manifests with a severe memory loss and psychiatric symptoms. Significant saccadic abnormalities include hypometria and slow and inaccurate saccades [255, 256].

7.0 Immune Disorders

7.1 Adult-Onset Still's Disease

Adult-onset Still's disease is an idiopathic, systemic inflammatory disorder. Clinical features on presentation include high, spiking fever accompanied by systemic manifestations such as arthralgia, fever, skin rash, lymphadenopathy, and hepatosplenomegaly [258].

Eye movement disorders in adult-onset Still's disease have not been comprehensively investigated. There are rare studies investigating ocular motility disorders in adult-onset Still's disease showing periodic horizontal micro-saccadic oscillations and periodic rapid clockwise torsional eye movements with subsequent counterclockwise torsional drifts [259]. Such disorders are associated with increased velocity of horizontal saccades [259].

The hypothesis is that the immune-mediated pathological hyperexcitability of the burst neurons leads to the observed micro-saccadic oscillations [259]. It is known that saccadic burst neurons, excitatory burst neurons and inhibitory burst neurons are reciprocally innervated [51, 260].

Their membranes are characterized by the property of post-inhibitory rebound [261] which leads to a sudden depolarization after a momentary external inhibition [262, 263, 264]. The

reciprocal innervation and post-inhibitory rebound together are responsible for the oscillatory property of the network the same network when physiologically functioning results in normal saccade velocity [75, 265, 266].

7.2 Syndrome of anti-GAD antibody

Glutamic acid decarboxylase (GAD) is an enzyme important in the nervous system for catalyzing the conversion of glutamic acid to γ aminobutyric acid (GABA) - an inhibitory neurotransmitter [267]. Autoantibodies directed against GAD (anti GAD-Ab) have been described in patients with insulin-dependent diabetes mellitus, stiff-person syndrome, epilepsy and in a few patients with late-onset cerebellar ataxia [268, 269, 270, 271].

Increased muscle tone, episodic spasms, and cerebellar ataxia are known clinical manifestations of syndrome of anti-GAD antibody [269, 272, 273, 274, 275]. Saccadic abnormalities in patients with syndrome of anti-GAD antibody include, slow vertical saccades, prolonged latency, and saccadic dysmetria [276, 277, 278, 279]. Case reports of Periodic Alternating Nystagmus [280], and opsoclonus myoclonus [281] have also been described. A study in Stiff-Person Syndrome with cerebellar degeneration described rare saccade abnormalities in the vertical direction. A downward gaze showed multiple hypometric saccades with a normal velocity profile, whereas with upward gaze there was a single saccade with abrupt slowing [278].

The exact role of anti-GAD-Ab and GABAergic neurotransmission in the pathogenesis of the neurological manifestations is not fully understood, however the presence of these autoantibodies suggests an underlying autoimmune pathophysiological mechanism [272, 282]. It has been proposed that the clinical features might be due to a decrease in inhibitory GABA, which leads to hyperexcitability of burst neurons [271, 283].

8.0 Infections

8.1 Whipple's Disease

Whipple's disease, or intestinal lipodystrophy, is a chronic systemic infectious disorder caused by *Tropheryma whippelii*. Patients present with weight loss, arthralgia, diarrhea, and abdominal pain. On biopsy; the presence of periodic-acid-Schiff positive *T. whippelii* is diagnostic [284, 285, 286, 287]. CNS infection by *T. whippelii* has been well described [288, 289, 290] can present with supranuclear vertical gaze palsy [289] which mimics progressive supranuclear palsy. Measurements of eye movements reveal a slowing of vertical saccades with an absence of square wave jerks [291]. In addition, oblique saccades follow a curved trajectory [291]. In a severe case, saccade slowing was present in all directions [292].

8.2 HIV Encephalopathy

Central nervous system infection with HIV can be complicated by a syndrome known as HIV encephalopathy [293]. Reports concerning abnormalities in eye movements are conflicting. A drastic reduction in saccade velocity has been reported in association with increased duration of saccades [294], however, another study did not find any difference in velocity [295]. Instead, an increase in saccade latency was observed which was more

prominent in the vertical direction[295, 296] which did not agree with another study that did not observe any deficits of saccade initiation [294].

8.3 Creutzfeldt-Jakob Disease

Creutzfeldt-Jakob disease is the commonest subtype of human prion disease causing a transmissible spongiform encephalopathy. The characteristic neuropathology of Creutzfeldt-Jakob disease consists of spongiform changes, astrocytosis and microgliosis, and poorly defined neuronal loss [299, 300]. The eye movement abnormalities in Creutzfeldt-Jakob disease reflect involvement of cerebellar and brainstem systems [301]. Patients with Creutzfeldt-Jakob disease may show slowing of pursuits [302], slow vertical saccades, saccadic pursuits [301, 303] suggesting involvement of reticular formation [303]. As the disease progresses, the eye movements eventually deteriorate with complete loss of saccades [301]. The characteristic nystagmus seen with Creutzfeldt-Jakob disease includes centripetal nystagmus [304] and periodic alternating nystagmus [301, 303] which by themselves are very rare.

9.0 Drug Induced

9.1 Benzodiazepines and other sedatives

Benzodiazepines and other sedatives are known to affect saccadic eye movements [23, 307, 308, 309, 310, 311, 312] and they can be used as a biomarker of the effects of benzodiazepines in humans [313]. Several studies have reported a direct relationship between the drug dose and saccade velocity [313]. Sedation can significantly increase the tonic firing of the saccadic omnipause neurons and decreases the activity of burst neurons [314]. With sustained eye closure, the saccade duration is found to be extremely prolonged and velocity is reduced due to decline in OPNs firing [315]. For comparable level of sedation, propofol and midazolam but not dexmedetomidine increased the saccade latency and decreased the saccade velocity indicating a drug specific effect on oculomotor dynamics [312]. Diazepam and thiopental reduce the peak velocity of voluntary saccades [309, 310]. However, in this study there was no correlation between serum levels of benzodiazepine and the saccade velocity suggesting that reduction of voluntary saccades could be due to both general sedation of nervous system as well as having a direct effect on saccade burst generators [309]

Expert Commentary: Eye movement analysis provide a readily accessible means of localizing deficits in disease states which can be employed to localize a lesion. The study of neural substrates encoding their kinematics are an exciting branch of neurosciences. Differential, yet overlapping pathways have been defined for saccades in either horizontal, vertical or oblique directions. Multiple experimental paradigms have been defined to explore subtle deficits brain pathology. Disorders that affect the pathway for saccades influence, amongst other characters, the velocity of these movements. Various degenerative, congenital, genetic, metabolic, infectious, immune-mediated and environmental insults of the central nervous system have been described which alter the saccadic velocity profile. A thorough investigation of the saccadic velocity profiles in a disease state can serve as an important clinical tool in diagnosis, staging and treatment.

Five-year review: We anticipate several important advances to take place utilizing saccade velocity as a tool to guide diagnosis and treatment. Saccade velocity has been shown to be a fairly sensitive marker of disease onset and progression for only a limited number of disorders. We expect more studies would be performed which would extend the concept of saccade velocity as a biomarker to more neurologic diseases. The development of portable eye trackers would enable monitoring of eye movement profile for a more accurate evaluation of the velocity impairment. Furthermore, studies will be performed to correlate the velocity with more comprehensive imaging modalities to ascertain a better localization of abnormalities in the pathway. Such an approach would assist in delineating novel surgical techniques. Lastly, we foresee an increased appreciation of saccade velocity deficits in evaluation of movement disorders in clinics.

Acknowledgments

Funding

This work was supported by career development award funded through Dystonia Medical Research Foundation and the National Institute of Neurological Disorders and Stroke U54 TR001456–08.

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Key issues

- Several saccade paradigms have been described and visually guided saccade have been most extensively explored.
- The study of neural substrates encoding their kinematics are an exciting branch of neurosciences.
- Measurement of velocity profile in visually guided saccades affords a means to further define the clinical impairments.
- Saccade velocity measures can be objective biomarker of conditions affecting the central nervous system.

Fig 1.

A schematic figure of the neural structures that project to the brainstem saccade generator (premotor burst neurons in the PPRF and riMLF). Instructions for saccades originate from frontal and parietal cortex through parallel direct or indirect pathways, via caudate nucleus, onto superior colliculus and omnipause neurons. The caudate nucleus inhibits the substantia nigra pars reticulata (SNpr), which itself tonically inhibits the SC. Caudate nucleus excitation, therefore disinhibits superior colliculus and triggers voluntary saccades. Frontal eye fields also send projections to cerebellum via pontine nuclei which calibrates the amplitude of saccadic eye movements. The kinetics of saccadic eye movement are under control of distinct neuronal populations in the brainstem (Scudder, Kaneko et al. 2002) and the cerebellum (Robinson and Fuchs 2001).

STN = subthalamic nucleus, SNpr = Substantia Nigra pars reticulata, PPRF = Paramedian Pontine Reticular Formation, riMLF = rostral interstitial nucleus of Medial Longitudinal Fasciculus

Red: Excitatory

Blue: Inhibitory

The thickness of the line corresponds with the degree of influence of the projections from a structure to its downstream components

Fig 2.

A Block diagram of the macro circuits of basal ganglia network in saccadic eye movements and interaction with cortical eye fields. Striatum and STN are the principal input nuclei of basal ganglia. Substantia nigra pars compacta (SNpc) send inhibitory (blue) and excitatory (red) projections to the striatum. The striatum projects via direct and indirect pathways to the output nuclei of the basal ganglia. The excitatory inputs to the striatum continue, via direct pathway as inhibitory projection to Globus Pallidus pars interna (GPI) and Substantia Nigra pars reticulata (SNpr). Parallel to these, the inhibitory inputs to the striatum continue, via indirect pathway as inhibitory projection to Globus Pallidus pars externa (GPe) and Subthalamic Nucleus (STN). B A schematic figure of the midbrain network involved in saccadic eye movements. Inhibitory projections (blue) from the omnipause neurons present in the pontine nucleus raphe interpositus (RIP) on to the burst neurons inhibit saccadic eye movements. Burst neurons located in the midbrain are disinhibited when the initial trigger for saccade turns off the omnipause neurons. Burst neurons in the Paramedian Pontine Reticular Formation (PPRF) project to nuclei of Abducens nerve (Cranial Nerve VI) and Oculomotor Nerve (Cranial Nerve III) which innervate the medial and lateral recti to generate horizontal saccades. Burst neurons in the rostral interstitial nucleus of the Medial Longitudinal Fasciculus (riMLF) project to nuclei of Abducens nerve (Cranial Nerve VI) and Oculomotor Nerve (Cranial Nerve III) which innervate the superior and inferior recti to generate vertical saccades.

Red: Excitatory Blue: Inhibitory

The thickness of the line corresponds with the degree of influence of the projections from a structure to its downstream components

Fig 3.

A Degeneration of dopaminergic SNpc in Parkinson's Disease produce a cascade of changes in the basal ganglia, which ultimately results in reduced inhibition of GPi and SNr. The net effect is an increased output from GPi and SNr leading to inhibition of Superior Colliculus.

B Vertical gaze impairment manifesting as slow, hypometric saccades is characteristic of Progressive Supranuclear Palsy (PSP). Early involvement of brainstem reticular formation containing riMLF is responsible for the vertical motion abnormalities. With disease progression, complete vertical gaze palsy develops.

C The characteristic pathoanatomy of Huntington's disease includes caudate nucleus degeneration and frontal lobe atrophy. It leads to decreased inhibitory projection to SNpr resulting in excessive inhibition of the Superior Colliculus. Frontal lobe atrophy decreases the excitatory projections to the Superior Colliculus. Collectively, decreased outflow from the Superior Colliculus results in impaired gaze in both horizontal and vertical directions.

Red: Excitatory Blue: Inhibitory

The thickness of the line corresponds with the degree of influence of the projections from a structure to its downstream components. Dotted line indicates pathologically decreased outputs.

Fig 4.

Hypometric saccades with slowing and occasional abrupt cessation in Late-Onset Tay Sachs disease presumably due to premature activation of omnipause neurons.

Red: Excitatory

Blue: Inhibitory

The thickness of the line corresponds with the degree of influence of the projections from a structure to its downstream components. Dotted line indicates pathologically decreased outputs.

Fig 5.

Slowing of saccades and dysmetria in patients with Spinocerebellar Ataxia correlates with cerebellar atrophy and pontine nuclei degeneration.

Red: Excitatory

Blue: Inhibitory

The thickness of the line corresponds with the degree of influence of the projections from a structure to its downstream components. Dotted line indicates pathologically decreased outputs.

Table 1:

Functional classes of eye movements

Fixation	Holds the image of a stationary object on the fovea by minimizing ocular drifts
Vestibuloocular Reflex (VOR)	Holds images on the retina during brief head rotations or linear movements
Ocular following responses (OFR)	Short-latency response to motion on the visual scene, represents early motion processing
Optokinetic Reflex	Hold images steady on the retina during sustained head rotation
Smooth pursuit	Holds the image of a small moving target on the fovea
Nystagmus quick phases	Reset the eyes during prolonged rotation and direct gaze towards the oncoming visual scene
Saccades	Rapidly brings the object of interest onto the fovea
Vergence	Eyes move in the opposite directions so that the images of a single object are placed or held simultaneously on the fovea

Table 2:

Classes of saccade

Classification	Definition
Spontaneous	Random saccades when the subject is not required to perform any special behavioral task
Voluntary saccade	Elective saccade made as a part of purposeful behavior or to a verbal command
Memory-guided saccades	Saccades generated to the location in which a target has been previously present
Antisaccades	Saccades generated voluntarily in the opposite direction to the sudden appearance of a target
Reflexive	Saccades generated to novel stimuli (visual, auditory or tactile) that unexpectedly occur within the environment
Microsaccades or fixational saccades	Small amplitude saccades that occur spontaneously during attempted visual fixation

Table 3:

Summary of effects of lesions on saccadic eye movements

Anatomic structure	Effect on eye movements
Cortex	Prolonged latency, decreased amplitude
Basal Ganglia	Difficulty initiating voluntary saccades
Cerebellar fastigial nucleus	Saccadic hypometria
Cerebellar dorsal vermis	Saccadic dysmetria
Omnipause neurons	Saccadic oscillations (opsoclonus and flutter). Slow horizontal and vertical saccades
Premotor Burst Neurons:	Slow saccades
PPRF	Horizontally
riMLF	Vertically

Table 4:

Visually Guided Saccade velocity in clinical disorders

Disorder	Visually Guided Saccade	
	Horizontal Saccade	Vertical Saccade
Parkinson's Disease	Normal	Not studied extensively
Progressive Supranuclear Palsy	Slow, hypometric late in disease	Slow, hypometric
Dementia with Lewy Body	Slow, hypometric	Slow, hypometric
Corticobasal Degeneration (CBD)	Slow	Variable slowing
Huntington's disease	Slow, hypometric	Slow, hypometric
Late-onset Tay Sach's (LOTS)	Slow, hypometric	Slow, hypometric
Niemann-Pick Disease	Slow	Markedly Slow
Gaucher's Disease	Markedly Slow	Slow
Micro-infarcts after cardiac surgery	Variable Slow	Variable slowing
SCA2	Slow	Slow
SCA3	Slow	Slow
Wernicke-Korsakoff Syndrome	Slow	Slow
Adult onset Still's disease	Increased	Not described
Syndrome of anti-GAD antibody	Slow in upwards gaze, hypometric, but normal velocity in downward gaze	Slow
HIV encephalopathy	Conflicting data	Conflicting data
Whipple's Disease	Normal, hypometric	Slow (mimics PSP)
CJ Disease		Slow
Benzodiazepines, and other sedatives	Slow	Slow