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PHYSIOLOGICAL AND PATHOLOGICAL ASPECTS OF SACCADES. NEW APPROACHES TO DIAGNOSIS AND TREATMENT OF SACCADIC ABNORMALITIES.

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Physiological and Pathological Aspects of Saccades
New Approaches to Diagnosis and Treatment of Saccadic Abnormalities

TABLE OF CONTENTS

Part I
Literature Review

Part II
New Approaches to Diagnosis and Treatment of Saccadic Abnormalities

CHAPTER 1

INTRODUCTION

1.1 The Eye Movement System

1.1.1 The Importance of Studying Eye Movements

Several reasons explain the importance of eye movements in the daily clinical practice, as well as in the field of neuroscience research. First of all, abnormalities of eye movements often directly reflect a pathological process at a specific site of lesion in the central nervous system. Therefore, they represent a needful diagnostic tool for the neurologist, provided one knows what to look for. Second, eye movements offer several advantages when used to model normal functioning of neural pathways or pathological disease processes. In fact, as eye movements are essentially restricted to rotations of the globes with almost no linear displacements, they are certainly easier to interpret than movements of the limbs or axial musculature. Also, as the monosynaptic stretch reflex is absent in extraocular muscle,[1] eye rotations directly relate to the discharge of motoneurons. These observations make eye movements generally accessible to precise measurement and quantitative analysis, and explain why they have become such a popular topic in scientific research, as is evident from the number of related yearly publications. Not surprisingly, the study of eye movements has found a number of different applications over the past few years. They have been used to clarify the nature of certain genetic disorders, such as myopathies or cerebellar ataxias.[2,3] Moreover, they have been proved to be helpful when used as a tool to assess the efficacy of new treatments for several neurological

disorders.[4] In fact, neuronal activity related to eye movements can be found in most parts of the brain.[5]

Table 1 shows a functional classification of different classes of eye movements, on the basis of their purpose and physiological properties. This classification is useful for both understanding the biological meaning of eye movements and their clinical importance at bedside examination.

1.1.2 Functional Classes of Eye Movements

Identification of classes of eye movements is based on understanding of their biological functions and the visual needs they must satisfy. The first visual requirement to achieve a good clear vision is that the image of an object of interest be held still on the central region of the retina (the fovea or macula). The area of best foveal acuity falls within 0.5 degrees of the center of the fovea, and visual acuity progressively declines as we move to the retinal periphery.[6,7] If motion of images on the retina is not held below about 5 deg/sec, visual acuity declines[7,8] and oscillopsia, the illusory movement of the visual environment, results. However, small eye movements, such as microsaccades, are actually thought to aid vision by preventing adaptation of retinal photoreceptors, which follows perfect stability of images on the retina and would cause visual fading.

Eye movements can be grouped in two main types, those that stabilize the angle of gaze *(gaze holding)*, and those that bring the fovea on the object of interest *(gaze shifting)*. Gaze-holding eye movements comprise the vestibulo-ocular reflexes and visually mediated reflexes, such as the optokinetic and smooth-pursuit tracking. These reflexes are particularly useful in holding the

fovea on the object of interest during head movements. Gaze-shifting eye movements mainly comprise saccades, which are the rapid eye movements that point the fovea at new features of regard. Smooth-pursuit eye movements hold the fovea on a moving target. Finally, vergence eye movements are necessary to simultaneously place images of a single object of interest on the fovea of each eye. Specific purposes and properties of these classes of eye movements are summarized in Table 1.

The research in this thesis mainly concerns saccades, and an important pre-requisite to understanding their characteristics is the properties of the eyeball and the orbital tissues (often referred to as the ocular motor plant), which is discussed next.

1.1.3 Orbital Mechanics and the Innervation for Saccades

The orbital tissues supporting the eyeball impose viscous drag and elastic restoring forces on the control of gaze. In order to overcome these mechanical constrains, a powerful contraction of the extraocular muscles is required to move the eye. In particular, for rapid eye movements (e.g., saccades) a phasic increase or burst of neural activity must be generated by motoneurons in the ocular motor nuclei (pulse of innervation) (Fig. 1). The pulse command overcomes the viscous drag and is followed by a new tonic level of neural activity (step of innervation). The step command overcomes the elastic restoring forces, and holds the eye in an eccentric position by means of a steady contraction of the extraocular muscles. In fact, without this second innervation command, the orbital elastic forces would return the globe to its central position. Accuracy of saccades and steady fixation of an eccentric target relies on proper match of the pulse (velocity

command) with the step (position command). When pulse and step are mismatched, a variety of clinical disorders may arise. This is the case, for instance, with internuclear ophthalmoparesis (INO) where the adducting eye slowly drifts to the target during execution of a saccade.

The saccades position command (step) is generated by the velocity command (pulse) through a mathematical process of integration with respect to time. In other words, velocity-coded signals must be translated into position-coded signals. This concept applies not just to saccades, but also to all kinds of conjugate eye movements. In fact, neurophysiological evidence suggests that a common neural network, referred to as the neural integrator,[9,10] is responsible for this mathematical process. Moreover, disconjugate eye movements (i.e., vergence) also seem to be generated from velocity and position commands, with the latter being generated by a vergence integrator.[11] The clinical correlate of a defective neural integration process is known as gaze-evoked nystagmus. In this case, the eye cannot be held in its eccentric position after the pulse command is generated, and therefore drifts back to the central position.

Recent discoveries have dramatically changed our knowledge of the organization of the extraocular muscles and the orbital tissues.[12] As I further discuss below, each extraocular muscle consists of outer orbital and inner global layers which, in turn, include different special fiber types with different properties. Despite what previously believed, the outer orbital layer does not insert into the eyeball but rather into a fibrous pulley. The fibromuscular pulley would act as the functional point of origin for the global layer that passes through before it inserts onto the globe. It currently appears that the most important function of the fibromuscular pulleys, is to determine the kinematics of eye

rotations, by simplifying the neural commands sent to the extraocular muscles by the brain.[13]

1.2 The Saccadic System

1.2.1 The Purpose of Saccades

Saccades are the rapid eye movements by which we shift our attention between objects of interest. Saccades can be classified according to a hierarchy of behaviors that includes voluntary saccades as well as their evolutionary precursors, quick phases of nystagmus (Table 2). Such corrective quick phases are essential in compensating for sustained head rotations that cause the eyes to lodge at the corners of the orbit. They do so by moving the eyes in the same direction of head rotation, ultimately assuring the stability of gaze.[14] Quick phases and voluntary saccades share the same anatomic substrate in the paramedian reticular formation of the pons and mesencephalon (Fig. 2). The need for good foveal vision prompted saccades to evolve from the most rudimentary compensatory quick phases to saccades driven by a purposeful behavior.

Saccades are triggered by objects seen or heard, or from memory, or as part of a natural strategy to scan the visual scene. As discussed below, several diseases may cause saccades to become slow, prolonged or inaccurate.

1.2.2 Dynamic Properties of Saccades

Saccadic Velocity and Duration

Size, speed and duration of saccades are consistently related so that the larger the saccade, the greater its top speed and the longer its duration. Ranges

for normal saccades are traditionally defined based on peak velocity or duration as a function of amplitude, commonly referred to as *main sequence relationships*.[15,16] Thus, eye movements falling outside these defined intervals represent either abnormal saccades or non-saccadic eye movements.

Amplitude and *peak velocity* have a linear relationship for saccades smaller than about 20 degrees, whereas a "soft" saturation with asymptotic values of about 500 deg/second affect peak velocity of saccades bigger than 20 degrees. Main-sequence relationships, which also apply to the smallest saccades (microsaccades),[17] is commonly described by the following:

$$\text{Peak velocity} = V_{max} * (1 - e^{-\text{Amplitude}/C})$$

where Vmax is the asymptotic peak velocity and C is a constant.

Saccades *duration* is approximately linearly related to amplitude for movements between 1 and 50 degrees. It is of interest that even large saccades do not last much longer than 100 ms. Since this corresponds to the visual system response time, the visual feedback cannot be used to adjust the size of a saccade once started, but it is rather the brain that must monitor end-point saccadic accuracy and make changes to ensure long-term accuracy. Relationship between amplitude and saccades duration is normally described with the use of power functions.[18-20] Acceleration can also be used to identify saccades,[21] but it tends to saturate for saccades greater than 10 degrees amplitude.

Despite the fact that they are not voluntarily controlled, peak velocity and duration of saccades can be influenced by several factors, such as room light conditions and remembered locations of visual stimuli. In particular, saccade

velocity depends upon the direction of the movement and the initial and final eye position in the orbit.[22-25] Thus, horizontal saccades directed toward the center (centripetal) are faster than centrifugal saccades, and vertical upward saccades made in the visual field's upper portion are slower than upward saccades made in the lower portion.[24] Also, it is debated whether or not saccadic velocity declines with age.[26-30]

Saccadic Waveform

Several measurements of saccadic temporal or velocity waveform have proven useful in characterizing saccades (Fig. 3).

1. *Skewness of saccades.* Also referred to as asymmetry of saccades, it is simply estimated from the ratio of the time to reach maximum velocity (the acceleration phase) to the total duration of the saccade (Fig. 3_middle panel). Small saccades have a skewness ratio of about 0.5 (acceleration and deceleration phases are equal in duration), whereas large saccades show values of about 0.2 (peak velocity is reached earlier relative to the end of the saccade). Skewness increases with saccades made under fatigue or decreased vigilance.[31]

2. *Peak velocity/mean velocity (Q)*.[32-36] This ratio, mainly related to the velocity waveform, has a value of about 1.6 in humans, and typically does not change even for slow saccades made by fatigued subjects and some disorders of saccades (Fig. 3).

3. P*hase-plane plots.* This approach allows examination of eye position versus eye velocity or acceleration (see chapter 3). Such plots have been used to investigate abnormally disconjugate saccades, saccadic-vergence eye movements, and corrective saccades in patients with vestibular hypofunction.[37]

The main advantage of using binocular phase planes is to remove saccadic onset latency differences between the eyes.

Saccadic Conjugacy

The eyes do not move perfectly together, especially during horizontal saccades.[23,24] In fact, the abducting eye shows a larger, faster, and more skewed movement than the adducting eye, leading to a transient intrasaccadic divergence. Vertical saccades tend to be more conjugate because the eyes are better yoked in the vertical plane.

A brief drift of the eyes normally follows a horizontal saccade. Such *post-saccadic drift*, also referred to as *glissade*,[38] has both disjunctive (vergence) and conjugate (version) components, and it has been attributed to a pulse-step mismatch of the saccadic command. They are more frequent in fatigued subjects.[39]

Occasionally, an oppositely directed small fast movement occurs at the end of a saccade. These so called *dynamic overshoots* are more frequent after small saccades or saccadic intrusions, such as square-wave jerks,[40] but can also occur in patients who show larger saccadic oscillations such as ocular flutter. They may be conjugate or disconjugate, being sometimes more evident in the abducting eye.[41-43] Dynamic overshoots might arise because of the mechanical properties of orbital tissues or, more likely, from a transient reversal of the central saccadic command.[44-46]

Saccadic Reaction Time (Latency)

A time delay of about 200 ms normally separates the presentation of a visual stimulus from the actual onset of a saccadic eye movement. This time interval is probably necessary for neural processing of visual information in the retina, cerebral cortex, superior colliculus and the cerebellum. As a convention, this interval relates to the time by when the eye exceeds a speed threshold of about 30 deg/second. Saccadic latency depends upon modality and temporal properties of stimulus presentation, but it is also influenced by other factors, such as the subject's motivation and attention, or physical properties of the stimulus itself (e.g., luminance, size, contrast). When analyzing eye movements, an inter-ocular time latency component should also be taken into account, since saccades do not start at the exact same time in the two eyes.[47] This is true even for normal subjects, and more evident in patients with disorders of saccadic conjugacy (e.g., INO) (see Chapter 3).

1.2.3 Examination of Saccades

Bedside Examination

The best way to examine saccades at the bedside is by asking the patient to alternately switch fixation between two targets, such as the tip of a pen and the examiner's nose. Horizontal, vertical, and oblique saccades should be examined in each direction, paying particular attention to velocity, initiation, accuracy and conjugacy.

A typical example of saccadic slowing is the adducting eye lag in patients with internuclear ophthalmoplegia (INO). In order to detect saccadic slowing, it is sometimes useful to induce quick phases with a hand-held "optokinetic" drum

or tape. In this way, it is possible to appreciate how quick phases of the affected eye are smaller and slower. By having the subject alternately look between two diagonally placed targets, a slowing of saccades in one plane of movement can be easily detected. In fact, the normal component of the diagonal saccades would be completed before the abnormal component, and the eye movement would have a curved trajectory.

Saccadic latency can be appreciated by noting the time between the stimulus presentation and the moment the patient initiates the saccade. Good judgment of saccadic accuracy is crucial in identifying several disorders of eye movements. A saccade is generally considered accurate or eumetric when, in response to a target appearance, it rapidly brings and stops the eye on target. At the bedside, the examiner should look for saccadic inaccuracy or dysmetria, both in the way of overshooting (hypermetria) and undershooting (hypometria) the target. Some degree of saccadic hypometria is observed in normal individuals for saccades made between distant targets, whereas overshoots may occur normally for centripetal and downward saccades. The persistence of dysmetria with repetitive refixations between the same targets should prompt the examiner to consider serious conditions of saccadic inaccuracy, such as pathologies that involve the cerebellum.

Once a saccade abnormality is detected, a good approach is to localize the disturbance by examining saccades according to their hierarchical organization (i.e., quick phases, reflexive saccades and so forth). For instance, loss of quick phases usually implies a brainstem process affecting premotor burst neurons, and loss of voluntary saccades with retention of reflexive saccades and quick phases

is typical of acquired ocular motor apraxia. More volitional "predictive" types of saccades may be compromised in Parkinson's disease.

Accompanying head movements or blinks should also be looked up for if saccadic initiation is impaired, since they can facilitate the ability to initiate saccades,[48] speed-up slow saccades,[49] or induce saccadic oscillations.[50] Asking the patient to repetitively refixate between two targets or to sustain gaze for several seconds on an eccentric target, can be useful when looking for the effects of fatigue on saccadic eye movements, like in myasthenia gravis.

Finally, the examiner should always observe for the occurrence of extraneous saccadic eye movements during attempted steady fixation (e.g., saccadic intrusions, see below). This is best appreciated during ophthalmoscopy.

Measurement of Saccadic Eye Movements

In order to appreciate subtle degrees of changes in saccadic velocity, initiation, and accuracy, analysis by eye movement recordings is sometimes necessary.

The search coil and corneal reflection techniques usually meet the requirements for reliable recordings of saccade trajectories, along with offering adequate sensitivity (<0.1 deg), and linear range (± 20 deg). On the other hand, the electro-oculography (EOG) is a less reliable method because of numerous artifacts induced by movement of the lid, movement of the opposite eye, and a muscle action potential spike at the onset of the saccade.[51] When eye movements are recorded using either the search-coil or the infrared reflection techniques, the

speed of adducting saccades appears to be lower than that of abducting saccades, while the opposite is the case with the EOG.

The conventional measure of saccadic accuracy is the ratio of saccade amplitude to target amplitude (saccadic gain). Position of the eye at the beginning of the saccade and when the saccadic pulse is finished are used to define saccadic amplitude. As mentioned above, saccade onset is defined by eye velocity exceeding an arbitrary value, such as 30 deg/second, and saccade pulse offset by the dropping of eye velocity below that value. Saccadic dynamics is traditionally measured using peak velocity and duration, as they are plotted as a function of amplitude *(main-sequence relationships)*.

Some examples of saccadic abnormalities that are best detected or confirmed with eye movement recordings include: post-saccadic drifts, saccadic waveforms observed in myasthenia gravis, internuclear ophthalmoparesis, and some types of ocular oscillations. Also, study of saccades under special paradigms of stimulation (e.g., gap-overlap tasks, antisaccades, predictive saccades, saccades on command) requires quantitative measurements of eye movements. Since properties of saccades can be influenced to some extent by some factors, such as luminance and attention, and possibly by the age of the patient, it is essential to compare measurements in any patient with 95% confidence limits from an age-matched control group, under similar testing conditions.

1.3 The Neural Substrate for Conjugate Saccadic Eye Movements

In this section I review the neural machinery that generates the command for saccades and the functional structures that influence saccadic control, with particular attention to the brainstem and the cerebellum.

The brain must transform the visual stimulus, which is "spatially-coded" within the primary visual cortex (different parts of the cortical map correspond to different locations on the retina), into a "temporally-coded" saccadic command in the ocular motoneurons (third, fourth, and sixth cranial nerves nuclei). This latter command is encoded in terms of frequency and duration of discharge, and the size of the saccade is proportional to the total number of discharge spikes. The oculomotor nuclei cause the extraocular muscles to move the eyes with respect to the head, in craniotopic coordinates. A transformation of retinal coordinates into craniotopic coordinates is also required. Thus, while the retinal coordinates are two-dimensional, the eye rotates about three axes.[52]

1.3.1 Brainstem Pathways for Saccades

Burst neurons and omnipause neurons are the two functional components of the brainstem network that generates premotor commands for saccades. The neural integrator, which includes the cerebellum and the perihypoglossal and vestibular nuclei, is responsible for holding the eye in an eccentric position after a saccade has been generated.

Burst neurons for horizontal saccades lie within the paramedian pontine reticular formation (PPRF) in the caudal pons, while burst neurons for vertical and torsional saccades lie within the rostral interstitial nucleus of the medial

longitudinal fasciculus (riMLF) in the rostral mesencephalon. The omnipause neurons lie in the nucleus raphe interpositus (RIP), in the midline of the pons (Fig. 2). For the purpose of this thesis, I will focus especially on the neurophysiological control of horizontal saccades.

Pontomedullary Burst Cells for Horizontal Saccades

Excitatory and inhibitory burst neurons for horizontal saccades lie within the pontomedullary region of the brainstem.

The *excitatory burst neurons* (EBN), whose discharge frequency is temporally related with the horizontal component of all types of saccades and quick phases,[42,53] lie in the PPRF, rostral to the abducens nucleus, at the level of the medial part of the nucleus reticularis pontis caudalis.[54,55] EBN discharge activity represents the premotor command that generates the pulse of activity for horizontal ipsilateral saccades. Instantaneous EBN firing relates with instantaneous eye velocity,[42,56] and total number of spikes in the burst of activity is proportional to the amplitude of the saccades. Electrophysiological evidence suggests that some individual EBN in the PPRF encode saccades monocularly,[57] and that EBN also discharge during vertical and oblique saccades.[42] Thus, unilateral lesions within the PPRF cause horizontal saccadic gaze palsy, with loss of ability to generate ipsilateral saccades,[58] while bilateral PPRF lesions not only abolish horizontal saccades but also cause slowing of vertical saccades.[58,59] The EBN project directly to the ipsilateral abducens nucleus, where they contact two populations of motoneurons: the abducens motoneurons and the internuclear neurons. The pulse of innervation travels from the abducens motoneurons

through the abducens nerve to the lateral rectus muscle, and from the abducens internuclear neurons to the medial rectus subgroup of the contralateral oculomotor nucleus, through the contralateral MLF (Fig. 2). In normal subjects, the result is a contraction of the ipsilateral lateral rectus and the contralateral medial rectus muscles that turn the eyes rapidly together, as a "conjugate saccade." The EBN also project to the following structures: the perihypoglossal and vestibular nuclei, which participate in the pulse-step integration process; the cell groups of the paramedian tracts, which relay a copy of all ocular motor commands to the cerebellum; the ipsilateral inhibitory burst neurons.

Inhibitory burst neurons (IBN) for horizontal saccades lie in the nucleus paragigantocellularis dorsalis of the dorsomedial portion of the rostral medulla, caudally to the abducens nucleus.[60,61] The IBN are under inhibitory control of the omnipause neurons and the contralateral IBN, and receive contralateral excitatory inputs from the superior colliculus.[62] During ipsilateral saccades, the IBN inhibit contralateral abducens motoneurons and interneurons, in the contralateral abducens nucleus. They also project to structures of the neural integrator, such as the vestibular nuclei and the nucleus prepositus, and to cell groups of the paramedian tracts.[60] The IBN are thought to have two main roles in generation of horizontal saccades: to silence the antagonist muscles activity (Sherrington's law of reciprocal innervation); and to help end the saccade when the eye is on target.[63] The pontomedullary neuronal network formed by EBN and IBN, in which IBN inhibits IBN, is potentially unstable, and may lead to high-frequency saccadic oscillations, such as ocular flutter.[64]

Midbrain Burst Cells for Vertical Saccades

Vertical and torsional components of saccades are encoded by the EBN in the riMLF.[65-68] For vertical saccades, while excitatory upward EBN in the riMLF project bilaterally to CN III and CN IV nuclei motoneurons, downward EBN project only ipsilaterally. For torsional saccades, the EBN seem to discharge most vigorously for those eye movements that rotate the eyeball in a plane parallel to that of a pair of reciprocally acting vertical semicircular canals (for example, right anterior and left posterior canals).[67] For instance, EBN in the right riMLF increase their discharge when the right eye extorts and the left eye intorts. Only bilateral lesions in the riMLF abolish all vertical and torsional saccades,[69] while unilateral lesions affect vertical saccades only slightly, but abolish ipsilateral torsion. This can be explained with the fact that, while the direction of torsion is fixed for EBN on each side, the direction of vertical rotation is upward in some and downward in others. The equivalent of IBN for vertical and torsional saccades have been located outside the riMLF, in the adjacent interstitial nucleus of Cajal and surrounding reticular formation.[70]

Projections from the vertical EBN to the interstitial nucleus of Cajal are also important because the latter contains burst-tonic neurons, which contribute to the velocity-to-position (pulse-step) integration for vertical and torsional eye movements.

Omnipause Neurons

The nucleus raphe interpositus, located in the midline between the rootlets of the abducens nerves, contains the omnipause cells.[71,72] *Omnipause*

neurons have a predominant inhibitory function, and use glycine as their neurotransmitter.[73] Omnipause neurons cease their continuous discharge immediately prior to and during saccades in any direction, and also during blinks.[74] They exert their inhibitory control by projecting, mainly through crossed pathways, to the EBN in the pons, the IBN in the medulla, and the riMLF neurons.[75,76] They receive projections from the rostral pole ("fixation zone") of the superior colliculus,[77-79] the frontal eye fields,[80] the supplementary eye fields,[81] the central mesencephalic reticular formation, the long-lead burst neurons in the rostral pons and midbrain,[82] and the fastigial nucleus.[83] Experimental evidence suggest that omnipause cells tonically inhibit all burst cells, and that they must, in turn, be inhibited to permit burst cells to discharge when a saccadic command is generated. Thus, if omnipause cells are stimulated in the monkey, the ability of making saccades or quick phases in any direction is lost, while other types of eye movements are preserved.[84] Accordingly, if omnipause neurons are stimulated during a saccade, the eye decelerates abruptly in mid-flight.[85,86]

In other words, the omnipause cells guarantee the synchronization of burst neurons activity, so that the eyes can be rapidly turned during the saccade and kept still when the saccade is over. The omnipause cells function of gating visually mediated eye movements, is probably not limited only to saccades, but may also extend to the visual fixation system performance.[87]

Somewhat surprising is the experimental finding that lesions in the omnipause region cause slow horizontal and vertical saccades,[88,89] and not uncontrollable saccadic oscillations, such as opsoclonus. To account for this finding, the paradoxical influence of omnipause cells on burst neurons should be

considered. Glycine, apart from being utilized for inhibiting burst neurons, can also facilitate N-methyl-D-aspartate (NMDA) receptor currents.[90] Moreover, when burst neurons are triggered both by a signal from long-lead burst neurons (discussed next) and the cessation of omnipause discharge, the result is a post-inhibitory rebound that produces the high acceleration typical of saccades.[91,92] Based on these two observations, a lesion of the omnipause cells will cause a lack of glycine, and therefore there will be no post-inhibitory rebound (i.e., glycine can not enhance the NMDA receptor currents). As a result, saccades will be slower since they depend solely on inputs from long-lead burst neurons.

Before a saccade is initiated and throughout its duration, the omnipause neurons are probably inhibited by inputs from the rostral pole of the superior colliculus. Following this initial inhibition, the level of membrane hyperpolarization of the omnipause neurons is probably sustained by discharge of excitatory burst neurons, via local inhibitory neurons called latch neurons. These latch neurons are thought to be located in the PPRF,[87] and their malfunction would be associated with a premature deceleration of the eye during a saccade (see Prematurely Terminated Saccades).[93,94]

Long-Lead Burst Neurons (LLBN) and the cMRF

LLBN lie in the midbrain and discharge about 40 ms before the onset of saccades, and during saccades to their "movement field." They receive projections from the superior colliculus,[82] and project to pontine EBN, medullary IBN, omnipause neurons, and to the nucleus reticularis tegmenti pontis (NRTP).

The central mesencephalic reticular formation (cMRF), which lies just lateral to the CN III nucleus,[95] contains neurons that have reciprocal connections with the superior colliculus.[96,97] These neurons, which also start to discharge more than 40 ms before saccades,[98] receive projections from the supplementary eye fields and the fastigial nucleus, and project largely to omnipause neurons and NRTP. Experimental lesions of the cMRF cause hypermetria of contralateral and upward saccades and hypometria of ipsilateral and downward saccades. Also, large saccadic intrusions that disrupt fixation may arise.[99] Vertical saccades can also be impaired if the MRF is inactivated more rostrally.[100]

The NRTP contains other LLBN that are mainly connected to the cerebellum and the PPRF.[82] In conclusion, LLBN probably serve more than one function. For instance, the LLBN that receive inputs from the superior colliculus may have a role in synchronizing the onset and end of saccades, because of their projections to omnipause and premotor burst neurons.[56,82]

1.3.2 Higher-Level Control of Saccades

I now briefly discuss the influence of higher-level structures on saccades, with particular attention on the role of the cerebellum in saccadic control.

Among the several distinct cortical areas involved in the voluntary control of saccades, the cortical eye fields have the largest connections to the superior colliculus and the pontine nuclei, especially NRTP, which project, in turn, to the cerebellum. On the other hand, direct projections to the PPRF and riMLF are smaller.

The superior colliculus may play a role in coordinating the discharge of burst and omnipause neurons. While inactivation of collicular burst neurons blocks the effects of frontal eye field stimulation,[101] destructive lesions in this region are not permanently associated with loss of voluntary saccades.[102,103] Therefore, the cortical projection to NRTP and the cerebellum also seems important in saccadic control. Conversely, saccades can still be made after destructive frontal eye field lesions. Bilateral lesions of the frontal eye fields and the superior colliculus determine a severe, sustained deficit of voluntary saccades,[104] as is the case with combined bilateral lesions of the frontal and parietal eye fields.[105]

In conclusion, parallel descending pathways are involved in generating voluntary saccades, and it appears that each one of them is capable of performing spatial-to-temporal and retinotopic-to-craniotopic transformations of neural signals.

1.3.3 The Cerebellar Control of Saccades

The cerebellum has an important role in the control of saccades. Thus, beside direct projection from the cortical eye fields to the cerebellum via the pontine nuclei, several brainstem saccade-related structures also project to the cerebellum. In this review, I focus on the two main cerebellar areas involved in the programming and control of saccades, the dorsal vermis and the caudal fastigial nucleus, and a pontine nucleus that is a major relay for saccadic commands to the cerebellum.

Nucleus Reticularis Tegmenti Pontis (NRTP)

The NRTP lies ventral to the rostral PPRF and contains neurons that discharge in relation to a variety of eye movements, including saccades.[106] It receives inputs from the frontal and supplementary eye fields,[107,108] and the superior colliculus.[109] It projects to the dorsal vermis and caudal fastigial nucleus.[110,111] The NRTP also contains long-lead burst neurons, which project to the cerebellum and PPRF.[112]

The main function of neurons in the NRTP is to encode the three-dimensional eye displacement vectors, ultimately ensuring that saccadic eye movements obey Listing's law.[113] This influence of NRTP on the three-dimensional control of eye movements may actually depend on its connection with the cerebellum.[114] Other neurons in the NRTP are concerned with pursuit and vergence eye movements, which would make the NRTP a possible site for coordination of different ocular motor subsystems.

The Dorsal Vermis

Saccades produced by dorsal vermis stimulation have an ipsilateral component,[115] as Purkinje cells discharge about 15 ms before saccades in a preferred direction.[116] A topographic organization is also evident.[117] Within the "ocular motor vermis", stimulation of lobule V evokes saccades that range from upward to horizontal, while stimulation of lobules VI and VII evokes saccades that range from horizontal to downward. While saccadic direction is dictated by the anatomic location of stimulation in the cerebellum, just as it is in the frontal eye fields and in the superior colliculus, saccades evoked by cerebellar

stimulation are also graded in amplitude and direction, as a function of stimulus intensity.

One main "saccadic" role of the cerebellum is probably the feedback control of the amplitude of individual saccades.[118,119] Thus, saccadic dysmetria, as marked ipsilateral hypometria and mild contralateral hypermetria, is the result of unilateral pharmacological decortication of the dorsal vermis.[120] The latter also causes a gaze deviation away from the side of the inactivation. Similarly, ablative lesions of the dorsal vermis cause saccadic dysmetria that is mainly hypometria.[121] Dysmetria from dorsal vermis lesions concerns the saccadic pulse, with no associated post-saccadic drift, which is the case with ablation of the cerebellar flocculus and paraflocculus,[122] or total cerebellectomy.[123] With both symmetrical and asymmetrical lesions of the dorsal vermis, saccadic latency is also affected.[121] Finally, abnormal saccadic waveforms and impaired ability to adapt saccades to visual demands are seen after lesions of the dorsal vermis.[121]

In conclusion, the dorsal vermis (lobule VII), through its projections to the caudal part of the fastigial nucleus, plays a key role in governing the accuracy of saccades. It is the Purkinje cells of the dorsal vermis that encode the time when a saccade must stop to land on target.[124] Thus, amplitude of saccades become more variable after dorsal vermis lesions.[121]

The Fastigial Nucleus

The caudal part of the fastigial nucleus, which represents the fastigial oculomotor region (FOR), receives inputs from Purkinje cells of the dorsal vermis. It also receives a copy of the saccadic commands, relayed by NRTP from the frontal eye fields and superior colliculus.[110] The main fastigial nucleus

projections cross within the fellow fastigial nucleus, enter the uncinate fasciculus in the dorsolateral border of the superior cerebellar peduncle, and reach the brainstem. Important projections are also directed to omnipause neurons, IBN in the rostral medulla, EBN in the PPRF and riMLF, the cMRF, and the rostral pole of the superior colliculus.[125]

The fastigial nucleus is thought to provide an early drive to premotor burst neurons during contralateral saccades, and a late brake during ipsilateral ones.[126] Thus, with contralateral saccades, caudal fastigial nucleus neurons discharge about 8 ms prior to onset of the eye movement, while they discharge towards the end with ipsilateral saccades.[126-128] The role of fastigial nucleus in generation and control of saccades has been clarified by using muscimol to obtain pharmacological inactivation. After unilateral injections, all-sizes ipsilateral saccades are hypermetric (typical gain 1.3) with increased acceleration, while contralateral saccades are hypometric (typical gain of 0.7)[129] with decreased acceleration. Vertical saccades also show diagonal trajectory towards the side of inactivation (ipsipulsion). After bilateral injections, horizontal and vertical saccades are hypermetric.[129]

A severe degree of saccadic pulse dysmetria with very hypermetric saccades as well as postsaccadic drifts (pulse-step mismatch dysmetria) follow complete cerebellectomy in trained monkeys.[123] Saccadic hypermetria may even results in macrosaccadic oscillations.

In conclusion, the main function of the dorsal cerebellar vermis with the underlying fastigial nuclei is probably the control of saccadic pulse's size, while the flocculus and paraflocculus are likely to be involved in accurately matching the saccadic step to the pulse.

Control of Saccadic Metrics

Here, we propose a hypothetical scheme of function of the saccadic metrics control by the dorsal vermis and the fastigial nucleus.

The initial eye acceleration at the beginning of a saccade is due to early activity in one fastigial nucleus; the later activity in the other fastigial nucleus is probably responsible for stopping the eye on target. In fact, when the later, decelerating fastigial activity is disrupted, saccades become hypermetric because the eye does not decelerate and stop on target.

Since saccades are brief and vision cannot be used to guide the eye to the target, it is essential that the brain monitor its own motor commands, also called corollary discharge or efference copy. The cerebellum is the structure probably involved in monitoring the corollary discharge and stopping the eye when it is calculated to be on target. For horizontal saccades, the corollary discharge is most likely provided to the cerebellum by the cell groups of the paramedian tracts (PMT), which encode all ocular motor signals. In fact, the PMT cell groups, which are distributed throughout the brainstem, receive inputs from all premotor ocular motor structures,[130] and project to the cerebellum. Other mossy fiber projections from pontine nuclei might also contribute in providing the cerebellum with the corollary discharge. For vertical saccades, a similar role is attributed to the posterior interpositus nucleus, which receives inputs from the ventral paraflocculus.[131] Such motor signals feedback requires that eye velocity signals be converted to a representation of current eye position by a resettable integrator.[132,133]

The reported scheme can be used to explain saccadic hypermetria following fastigial nucleus lesions, where the feedback signals required to stop the eye on target could arrive late to the fastigial nucleus itself.[134]

In conclusion, neurophysiologycal evidence suggests that the cerebellum controls saccadic accuracy (amplitude and direction), and corrects for position-dependent changes in the mechanical properties of eye muscles and orbital tissues. The cerebellum exerts this function both in an "on-line" fashion, since cerebellar dysmetria immediately follows fastigial nuclei inactivation, as well as in the long-term. To further address the role of the cerebellum in the control of saccades, it is worth stressing that neither frontal eye field or superior colliculus lesions alone cause enduring changes in saccadic metrics. This observation, along with the evidence reported, leaves the cerebellum as the best candidate in computing the size and dynamics of saccades.

1.3.4 The Ocular Motor Periphery

The anatomy of the extraocular muscles and orbital tissues has gone through a dramatic revision over the last few years. A few discoveries have changed the way we think of the structure and function of extraocular muscles, and cast new light on mechanisms of common neurological disorders that affect the ocular motor plant. I here summarize the main concepts concerning the orbital tissues and eye rotations, the unique properties and function of extraocular muscles, and the neuromuscular junction.

Orbital Tissues and Eye Rotations

All the extraocular muscles but the inferior oblique arise from the apex of the orbit, in the annulus of Zinn. The inferior oblique originates from the inferior nasal aspect of the orbit. While the four recti insert into the sclera *anterior* to the equator of the globe, the two oblique muscles approach the globe from its anterior and medial aspect and insert *posterior* to the equator of the globe.

Each rectus muscle is composed by two layers:[135] an inner global layer, which directly inserts on the globe of the eye, and an outer orbital layer which inserts into a fascial component of Tenon's capsule, which suspends the eye in the orbit (Fig. 4).[136-138] The tendons of the four recti originating from the inner global layer pass through sleeve-like fibromuscular pulleys. These pulleys, each consisting of an encircling ring of collagen, lie within peripheral Tenon's capsule and are located about 10 mm behind the insertion sites of the muscles. They attach to the wall of the orbit, the adjacent extraocular muscles and the Tenon's fascia by means of sling-like bands containing collagen, elastin, and smooth muscle.[139] The inferior oblique orbital layer inserts into inferior rectus and lateral rectus pulleys, while superior oblique orbital layer inserts into the superior rectus pulley.[140]

The discovery of the fibromuscular pulleys has changed the functional significance of ocular anatomy. The pulleys change the point of origin of the rectus muscles, just as the trochlea changes the functional point of origin of the superior oblique muscle. By doing that, they exert at least a couple of critical functions: to limit sideslip movement of the rectus muscles during eye rotations, and probably to constraint the eye axes of rotation during visually guided movements to Listing's plane, which is perpendicular to the fixation line in

primary position.[141] Experimental evidence suggest that the fibromuscular pulleys may actually simplify for the brain the job of governing 3-D eye rotations, although there is evidence that neural factors also play a role.[142] In sum, according to the "active pulleys hypothesis", the eye axis of rotations is determined by the pulleys displacement,[137] although some anatomical evidence argue against this.[138]

While the clinical impact of the fibromuscular pulleys is still being determined, the discovery of their role in extraocular muscles contraction and eye rotation, has already provided new approaches to evaluate eye movement disorders.[137] For example, some forms of congenital strabismus have been attributed to congenital misplacement of pulleys,[143] and even systemic diseases affecting the connective tissues (e.g., Marfan's syndrome) may cause increased mobility of the pulleys with resulting strabismus.[144]

Properties of Extraocular Muscles

Extraocular muscles have unique anatomical, physiological, and immunological features that distinguish them from limb muscles.[145-147] Their fibers are smaller, more variable in size, more richly innervated, and could have properties of very fast contraction, yet remaining fatigue-resistant.[148] The extraocular muscles contain twitch and non-twitch fibers. Twitch fibers have a single endplate per fiber and can generate an all-or-none propagating response (action potential), while non-twitch fibers cannot generate action potentials and show graded contractions to trains of electrical pulse stimuli.[149,150] The non-twitch fibers of the global layers have the unique feature of stretching the whole

length of the muscle.[151] Other intermediate fibers also exist that still generate slow action potentials.[150]

Extraocular muscles virtually express all known striated muscle isoforms of myosin heavy chain, including embryonic isoforms in the proximal and distal portions of muscle fibers in the orbital layers.[147,152,153] This preservation of embryonic myosin has been proposed to account for the different ways extraocular muscles respond to changes in innervation and disease states.[154] Moreover, both orbital and global fibers have the ability to contract quickly, as myosin expression may vary along the length of single muscle fibers, with "fast" forms being more prominent in the central region of most fibers.[155]

Extraocular muscles show biological differences from skeletal muscles, as they show a low content in enzymes and regulators related to glycogen metabolism, which points to important differences in energy metabolism.[154] They are also different from skeletal muscles under other aspects, such as transcriptional regulation, sarcomeric organization, excitation-contraction coupling, intermediary metabolism and the immune response.[153]

Extraocular muscles are more susceptible than skeletal muscles to some pathological processes, such as myasthenia gravis,[145,156,157] and more resistant to others, such as Duchenne's dystrophy.[147,158,159] Several factors could account for these differences. First of all, the safety factor (the amount by which the endplate potential exceeds the threshold required to trigger an action potential) is smaller in extraocular than skeletal muscles. This is due to less prominent synaptic folds and, possibly, less acetylcholine receptors on the post-synaptic membrane of extraocular muscles.[157] Second, extraocular muscles express lower levels of decay accelerating factor, which is an inhibitor of complement mediated

responses.[160] This might partly explain a more severe involvement of extraocular muscles in myasthenia gravis.[161]

In chapter 3, I further discuss extraocular muscles fibers involvement in pathological processes, such as myasthenia gravis and chronic progressive external ophthalmoplegia.

Structure and Function of Extraocular Muscle Fiber Types

The two distinct layers of each extraocular muscle (Fig. 5) lie in two concentric zones near the origin of each muscle, and form two parallel zones as the muscle is traced anteriorly.[153] These are the central global layer and the peripheral orbital layer. While each layer contains fibers more suited for either sustained contraction or brief rapid contraction, the orbital zone is richer in fatigue-resistant twitch fibers. Six types of fibers have been described in the extraocular muscles (Fig. 5).[146,152,162,163]

About 80% of the *orbital layer* fibers are singly innervated, while the remaining 20% are multiply innervated. The singly innervated fibers are typically fatigue-resistant, as they have fast-type myofibrillar ATPase, and high oxidative activity with numerous mitochondria. They are not found in skeletal muscle or the eyelid, and are probably the main contributors to sustained muscle tone.[146,164] The multiply innervated fibers, on the other hand, have twitch capacity near the center of the fiber, and non-twitch activity proximal and distal to the end plate band.

In the *global layer,* four type of fibers have been described: about 33% are singly innervated, fast-twitch, and fatigue-resistant fibers; another 33% are pale, singly innervated fibers with fast-twitch properties but low fatigue resistance; about

25% are singly innervated fibers with fast-twitch properties, numerous mitochondria, and an intermediate level of fatigue resistance; the remaining 10% are multiply innervated fibers, with synaptic end plate along their entire length, as well as at the myotendinous junction, where there are palisade organ proprioceptors.[165] These last fibers are believed to possess tonic properties.

The levator palpebrae superioris contains singly innervated fibers and a true slow-twitch fiber type. The multiply innervated fiber types and the fatigue-resistant singly innervated type seen in the orbital layer are absent.

Scott and Collins found that orbital fibers are active throughout nearly the entire range of movement except during fixation, while global fibers are recruited only as the eye is called into the field of action of that muscle.[166] This would support the hypothesis that the singly innervated, fatigue-resistant orbital fibers play a key role in sustaining eye position and maintaining extraocular muscle "tone" in any eye position. Moreover, both global and orbital fibers are activated during saccades, with the latter being able to guarantee a sustained contraction, while the activity of global fibers may subsequently fall. Taken together, these findings point to the presence of more fatigue-resistant fibers in the orbital layers. Moreover, the "fast fatigable" muscle fibers have also been shown to be the strongest,[149] so that global fibers may be best able to generate rapid eye movements.

Finally, electrophysiological evidence suggest that, although each fiber can potentially contribute to all classes of eye movement, orbital, fatigue-resistant twitch fibers are most important for holding the eye in steady fixation, whereas global, pale, twitch fibers have a role in moving rapidly the eye to a new orbital position. On the other hand, multiply innervated tonic fibers are linked non-twitch motoneurons that receive inputs predominantly from the pretectal area and

medullary structures concerned with gaze-holding. Hence, these fibers may be more concerned with vergence and gaze-holding, and also contribute to proprioceptive feedback of the extraocular muscles, along with the pallisade endings.

Possible clinical implications of extraocular muscles structure and function, along with hypothetical mechanisms of disease, are further discussed in chapter 3.

The Neuromuscular Junctions of the Extraocular Muscles

Fibers with single and multiple nerve end plates have different acetylcholine receptor isoforms. Thus, while adult skeletal muscles and the levator of the eyelid possess only the adult isoforms of the acetycholine receptor, extraocular muscles express the adult epsilon isoform in singly innervated fibers, and the fetal gamma subunit in multiply innervated fibers.[167] As mentioned above, in most types of extraocular fibers, synaptic folding is sparse if compared to skeletal muscle, with a resulting low "safety factor". This would make the extraocular muscle fibers more susceptible to neuromuscular fatigue in myasthenia gravis. Only the pale global fibers, which are responsible for the large acceleration of saccades, have well developed synaptic folding.[135] Finally, as I further discuss below, electromyographic studies indicate that global fibers discharge mainly for saccades, but are not as active as orbital layer fibers during eccentric gaze holding.[168]

1.4 Saccadic Abnormalities

Fig. 6 summarizes classification of saccadic abnormalities using a pathophysiological approach. In particular, they can be divided into disorders of

the saccadic pulse, disorders of the saccadic step, or saccadic pulse-step mismatch. For instance, a change in the amplitude (size) of the pulse command would cause saccades to become dysmetric, whereas a decrease in the height of the pulse command would cause saccades to become slow. A pulse-step mismatch generates a post-saccadic drift or glissades at the end of the movement. Finally, a defective step command would cause the eye drifts back toward the central position after an eccentric saccade, creating gaze-evoked nystagmus.

Disorders of Saccadic Velocity

The normal peak velocity-amplitude relationship (main sequence) is conventionally used to determine if a saccade is too slow or too fast. Abnormalities of saccadic velocities can be grouped in four main categories:

1. *Fast small-amplitude saccades.* This situation is typical of myasthenia gravis, where saccades can be interrupted in mid flight and do not reach the final position failing to bring the eye on target.[169,170] These saccades are not really faster than normal, but appear so on the peak velocity-amplitude relationship because they are in fact too small. Orbital tumors or other conditions that cause restriction of the globe motion can also determine similar abnormalities.
2. *Fast normal-amplitude saccades.* These are mainly observed in patients with macrosaccadic oscillations,[173] flutter and opsoclonus,[171,172] in patients with prematurely terminated saccades,[93] and in subjects affected by a form of hereditary ataxia (see chapter 4).

3. *Slow small-amplitude saccades*. Such saccades are often seen in patients with disorders that localize to the ocular motor periphery, such as extraocular muscle or ocular motor nerve paresis, or to the medial longitudinal fasciculus (e.g. INO).
4. *Slow normal-amplitude saccades*. This finding normally points to a central neurological disorder. Usually, slow saccades with normal ocular motor range can be due to one of these situations: a direct lesion of the brainstem burst neurons that generate the saccadic command; a lack of excitatory inputs to the burst neurons from higher level structures (e.g., cerebral hemispheres or superior colliculus);[174,175] a defect in the brainstem omnipause cells that normally cease inhibiting the burst neurons when a saccade needs to be generated.

   From a diagnostic point of view, it is useful to remember that selective slowing of horizontal saccades normally indicates pontine disease (PPRF), whereas selective slowing of vertical saccades suggests upper midbrain dysfunction (riMLF).[176]

Disorders of Saccadic Accuracy

Inaccuracy of saccadic pulse is normally referred to as dysmetria, which include hypermetria, and hypometrya. *Hypermetric saccades* are very likely to be caused by cerebellar disease. The lesion can be localized to the fastigial nucleus, the olivocerebellar climbing fibers within the medulla or within the inferior cerebellar peduncle (Wallenberg's syndrome), and to the superior cerebellar peduncle. From a clinical point of a view, it is important to observe the

direction of the hypermetric saccade and the usually associated opposite directed hypometric saccade, in order to determine site and side of the lesion. When saccadic hypermetria is severe, patients may even show macrosaccadic oscillations, with a series of hypermetric saccades about the target position.[177,178] Saccadic hypermetria can also reflect an adaptive response to a peripheral ocular motor deficit,[179] and occur after edrophonium injection in patients with disorders of the neuromuscular junction (i.e., myasthenia gravis).[180]

Hypometric saccades can occur with both cerebellar and brain stem disorders. Postsaccadic drift, reflecting pulse-step match dysmetria, has been shown in patients with both central and peripheral ocular motor disorders. Visual field defects, such as hemianopia, may lead to saccadic hypermetria and hypometria, in order to keep the target within the intact part of the visual field.[181-183] A posterior parietal-temporal cortex lesion may cause dysmetria exclusively for moving targets.[184] Ipsilateral hypermetria and contralateral hypometria are also associated with large unilateral lesions of the cerebral hemispheres.[185]

Prematurely Terminated Saccades

Saccades can be prematurely terminated before the programmed movement is even completed. For instance, patients with Parkinson's disease may show very hypometric movements when making either memory-guided saccades,[186] or self-generated saccades.

Velocity records of large saccades can show transient decelerations, especially in patients with some disorders of brainstem and cerebellum, such as

late-onset Tay-Sachs disease and Wernicke's encephalopathy.[93,94] These disorders are possibly attributed to a disorder of the "latch" circuit that normally inhibits omnipause neurons until completion of the planned saccade.[93]

Disorders of Saccadic Initiation

Latency of saccades may physiologically vary with the patient's age, state of consciousness, and level of attention. Visual abnormalities such as amblyopia,[187] and focal hemispheric lesions may cause saccades with increased latencies. Ocular motor apraxia is a severe defect of voluntary saccades initiation caused by bilateral frontoparietal lesions.[188]

Patients with disease of the basal ganglia also show increased saccadic latencies. In Huntington's disease, saccades made on command and during predictive tracking are typically affected,[189] whereas self-paced saccades between two visible targets have abnormal high latencies in patients with Parkinson's disease.

Patients with Alzheimer's disease show greater variability of saccadic reaction times, probably due to difficulties with sustaining attention and suppressing reflexive movements.[190]

Certain disorders, such as progressive supranuclear palsy (PSP), can actually be associated with decreased saccadic latencies.[191]

Inappropriate Saccades: Saccadic Intrusions and Oscillations

Normal subjects can suppress regular saccades during steady fixation, and even the smallest saccades (microsaccades) when a specific task needs to be performed.

Saccadic intrusions are inappropriate involuntary movements that disrupt normal fixations, by taking the eye away from the target (Fig. 7).

Small (typically 0.5 degrees), horizontal saccades that take the eyes off the target, followed by a corrective re-foveating saccade, are commonly referred to as *square-wave jerks.* Typically, an intersaccadic interval of about 250 ms separates the two saccadic movements. Square-wave jerks may be encountered in normal individuals at frequencies of 20 per minute or greater,[192] without any accompanying disorders of saccadic control.[193] However, the finding of square-wave jerks on clinical examination should always prompt the physician to look for other associated neurological findings, especially cerebellar, as they are common in disorders such as Friedreich's ataxia and progressive supranuclear palsy (PSP). Involvement of the superior colliculus or its inputs, which controls saccades generation, is thought to be the cause of square-wave jerks in these disorders. Thus, reciprocal connections of the superior colliculus with the central mesencephalic reticular formation might explain the common finding of square wave jerks in patients with PSP.

Less often, saccadic intrusions can be larger in amplitude (>5 degrees) with an intersaccadic interval of about 80 ms. These are usually called macrosquare-wave jerks and can occur in patients with multiple sclerosis and multiple system atrophy.

Another disorder that disrupts steady fixation is *macrosaccadic oscillations*, which are thought to be an extreme form of saccadic hypermetria, and consist of horizontal saccades occurring in runs with an intersaccadic interval of 200 ms. They are encountered in cerebellar disease that involves the fastigial nucleus or its output,[177] or with discrete pontine lesions that involve the omnipause neurons.[178]

Back-to-back horizontal saccades without an intersaccadic interval include ocular flutter and opsoclonus. *Ocular flutter* is characterized by oscillations occuring only in the horizontal plane, whereas oscillations occuring in all directions define *opsoclonus.* Flutter and opsoclonus are associated with brainstem and cerebellar disease, and reflect inappropriate, repetitive, alternating discharge pattern of different groups of burst neurons. Different factors may contribute to saccadic oscillations without an intersaccadic interval, including the inherently high discharge rates (gain) of saccadic burst neurons, the existence of central processing delays that make a system susceptible to oscillations, and a dysfunction of the omnipause neurons, which normally inhibit burst neurons during fixation.[171] This hypothesis is supported by the fact that some patients show transient saccadic oscillations in association with blinks,[50] or vergence movements,[194] both of which inhibit omnipause neurons. Ocular flutter has also been reported due to a pontine demyelinative lesion in a patient with multiple sclerosis exacerbation, with subsequent resolution of the oscillations as the patient recovered.[195] On the other hand, autopsy studies of some patients with flutter or opsoclonus did not show abnormalities in the region of the omnipause cells,[196] and pharmacological activation of the omnipause cell region in monkeys does not produce oscillations but slow saccades.[88,89]

Alternately, saccadic oscillations without intersaccadic interval may be attributed to the synaptic organization of premotor burst neurons, in which a predisposition to oscillations could be due to positive feedback loops and post-inhibitory rebound properties of burst neurons.[91,92,66] Also, cerebellar disease might indirectly increase the likelihood of saccadic oscillations, through projections of the fastigial nucleus to the premotor burst neurons.

CHAPTER 2

RECORDING METHODS

2.1 Summary of Techniques Available for Recording Eye Movements

Several techniques are available to study the rotations of the two eyes and obtain information about the dynamics of eye movements. However, among these techniques, only the video-based systems and the magnetic search coil technique represent a reliable measure for both horizontal and vertical eye movements. Nonetheless, they carry some disadvantages as well, and other methods can be successfully used and provide a good standard of accuracy in studying especially horizontal eye movements. Some of these include the D.C. electro-oculography (EOG), the infrared differential limbus reflection techniques, and the Purkinje image tracker.

The video-based systems that track pupil or reflected corneal images, have high potentials for more reliable eye movement measurements in 3-D, and are not invasive when compared to search coil techniques, which require the patient to wear a contact lens (Fig. 8). However, most of these devices still suffer from certain limitations, particularly the inability to track the eye during blinks and vertical saccades (they lose the eye-tracking signal when the eyelid closes).

Recording and analysis of eye movements for the research presented in this thesis were mainly focused on the study of horizontal saccades. The majority of subjects and patients were recorded using the search coil system, but in a few cases (n=5 patients) we did use the infrared reflection technique. This chapter

summarizes aspects of recording and analyzing eye movements that are pertinent to the current experiments.

2.2 The Magnetic Search Coil Technique

The magnetic search coil technique is still widely regarded as the most reliable and versatile method for measuring eye movements of many animal species and human eye movements.[5] This technique allows measurement of eye rotations in all three axes, with sensitivity greater than 1 minute of arc and a potential linear range of 180 degrees. The standard deviation of system noise is typically less than 0.02 of a degree. It also offers a bandwidth of 0-500 Hz, minimal drift, insensitivity to translation of the eye, and an unlimited field of view. The main disadvantage of the technique is that the subject must wear a "contact lens" (Fig. 8), a silastic annulus with imbedded coils of fine wire; this scleral search coil is placed after applying topical anesthetic eye drops. Although it is often assumed that wearing such an annulus is uncomfortable, the experience of the Daroff-Dell'Osso Ocular Motility Laboratory of the Cleveland VA Medical Center (based on studying over 1000 individuals) is that it is well tolerated for periods of ~30 minutes by most human subjects. A disadvantage is the potential for corneal abrasion, but the incidence in the laboratory is reported to be less than 1 in 500. The search coil method is especially valuable for measuring eye movements in patients who cannot reliably point their eyes at calibration targets (e.g. due to nystagmus or restricted/slow eye movements), since the scleral annulus that the patient wears can be pre-calibrated on a protractor device. Comparison of the search coil technique suggests that saccadic

peak velocities may be mildly slow, but also less variable, than with other available methods.

2.2.1 The Search Coil System Used for this Research

The magnetic search coil system used in the Daroff-Dell'Osso laboratory (CNC Engineering, Seattle, WA) consists of a 6-foot cubic enclosure. The subject sits on a chair inside this cube so that his head and eyes are at the center of the magnetic field in the cube. The magnetic field enclosure consists of a 60 kHz rotating magnetic field in the horizontal plane and a static vertical field, oscillating at 90 kHz. A special contact lens containing a coil of wire (search coil) is inserted on the subject or patient's eye (Fig. 8). When the eye (and therefore the search coil) moves horizontally, there is a change in the phase of the voltage induced in the search coil. The difference in phase of the signal in the search coil and that in a stationary reference coil is linearly related to the angle of the search coil in the horizontal plane, thus allowing an accurate measurement of horizontal movements of the eye. The angle of the eye in the vertical plane induces a voltage in the search coil whose amplitude is proportional to the size of the movement. These voltage signals are fed to phase detectors that demodulate and provide eye position signals. The cross-talk between the horizontal and vertical coil signals is typically less than 2.5%.

2.2.2 Data Acquisition and Analysis

Signals from these phase detectors were low-pass filtered using a 4-pole Butterworth filter (Model 3364, Krohn-Hite Corp., Avon MA) with a cutoff

frequency of 150 Hz, less than half the digitization rate of 500 Hz. These signals were then digitized using the AT-MIO-16XE-50 data acquisition board (National Instruments, Austin, TX).

Visual stimuli were provided by a laser-target that was back-projected onto a tangent screen, made of translucent plastic. This screen was placed just outside the magnetic field enclosure, about 1.2 m from the subject. The laser-target's motion on the screen was produced by relaying the beam via an X-Y mirror galvanometer (Model XY 2026V, CX660 Scanner Control, General Scanning Inc.). This latter was controlled by a D/A board (AT-AO-6, National Instruments, Austin, TX). Data collection and the control of visual stimuli were performed in LabVIEW, and synchronized by means of buffered acquisition. The control signals for the visual stimuli were generated in LabVIEW itself, or read in through files that had been previously generated using another package such as MATLAB (The MathWorks, Natick MA). Data analysis was then carried out using interactive programs written in MATLAB, and using graphing and statistical software such as SigmaPlot (SPSS Inc., Chicago, IL).

More details about specific data analysis for each of the two reported studies in this thesis can be found respectively in chapter 3 and 4 (see also Appendix).

2.3 The Infrared Differential Limbus Reflection Technique

The infrared differential limbus reflection technique is a photoelectric method that tracks the limbus (scleral-iris edge) of the eye by measuring the amount of scattered light. This method is generally more sensitive and reliable

than EOG, but provides a limited linear range, especially for vertical eye movements. Its main advantage is that it does not require a contact lens device and is therefore suitable for measurement of eye movements in children. In general, most photoelectric systems use photodectors that must be mounted close to the eyes, so they may restrict the field of view. Photoelectric methods also suffer from potentially large errors if there is lateral motion of the sensors relative to the eye.

To sum up, the infrared corneal reflection technique provides an eye movement recording method that is non-invasive, causes minimal discomfort, with a resolution of 0.5 degrees or better, and very little noise. On the other hand, its main disadvantage is that it has a limited linearity range (±20 degrees horizontally and ±10 degrees vertically).

2.3.1 The Infrared System Used for this Research

Horizontal eye movements were recorded in five patients (2 with horizontal saccadic gaze palsy from brainstem stroke, 2 with INO, 1 with abducens nerve palsy) using the infrared reflection technique (Skalar IRIS IR Eyetracker, Cambridge Research Systems Ltd., Rochester, England). This system uses a mountable helmet equipped with infrared emitting and detecting diodes. The infrared signal from each eye was calibrated with the other eye behind cover to obtain accurate position information. Eye positions and velocities (obtained by analog differentiation of the position channels) were displayed on a strip chart recording system (Beckman Type R612 Dynograph). The total system bandwidth (position and velocity) was 0-100 Hz. The patients seated in a vestibular chair

with headrest and a stabilizing headband, at a distance of about 1 meter from an arc of red LEDs, which were alternately lit at different gaze angles between 0° and ±20° in order to study horizontal saccades.

2.3.2 Data Acquisition and Analysis

The acquired signals were digitized (500 Hz with 12-bit resolution) using the AT-MIO-16XE-50 data acquisition board (National Instruments, Austin, TX), and data collected using LabVIEW (see above). Data calibration, analysis and filtering if necessary, were performed using software written in MATLAB (The MathWorks, Natick MA).

More details about specific data analysis for each of the two reported studies in this thesis can be found respectively in chapter 3 and 4 (see also Appendix).

CHAPTER 3

CONJUGACY OF HORIZONTAL SACCADES: APPLICATION OF BINOCULAR PHASE PLANES

3.0 Abstract

Background: Clinicians are interested in detecting abnormal disconjugacy, especially of horizontal saccades, which may identify internuclear ophthalmoparesis (INO). Prior approaches to detecting disorders such as INO have compared peak velocity, peak acceleration or change in position of each eye after a specified time interval. However, other disorders, such as myasthenia gravis, can mimic central disorders such as INO and lead to misdiagnosis. Moreover, these approaches have not been applied to the study of other disorders that can cause horizontal saccades to be disconjugate.

Methods: We recorded horizontal saccades in 22 patients with disease affecting the brainstem reticular formation, the abducens nucleus motoneurons, the medial longitudinal fasciculus, the abducens nerve, the neuromuscular junction and the extraocular muscles, and in 10 age-matched controls. We used the phase-plane technique, to plot the velocity difference between the two eyes against the position of the eye with the smallest displacement. We also applied the technique to disjunctive saccades made by normal subjects, as they switched fixation between two points, at different distances, that were aligned on one eye.

Results: We found that patients with disorders of the brainstem or the cranial nerves show abnormal velocity disconjugacy in the first 10% of the displacement. Patients with myasthenia gravis do not show early disconjugacy, but may do so later in the course of the saccade. Patients with disease affecting

the extraocular muscles show only minor initial disconjugacy. Disjunctive saccades made by normal subjects do not show abnormal velocity disconjugacy in the first 10% of eye displacement.

Conclusions: Along with conventional measures of saccades, such as peak velocity, phase-planes provide a useful diagnostic tool to detect abnormal disconjugacy. In particular, they can be used to differentiate INO and cranial nerve palsies (i.e. abducens nerve) from myasthenia. Preservation of conjugacy of the initial saccadic movement on binocular phase planes in myasthenia and chronic progressive external ophthalmoplegia, as well as in normal subjects during disjunctive saccades, suggests that the pale global fibers drive the initial, high-acceleration component of saccades.

3.1 Introduction

3.1.1 Methods for the Study of Horizontal Saccadic Conjugacy

Conjugacy of saccadic eye movements is required for peripheral targets to fall on corresponding points of the two retinas (foveation), hence to allow a clear vision. In particular, horizontal saccades conjugacy depends on integrity of the brainstem machinery and ocular motor periphery (Fig. 2), which was reviewed in Chapter 1. For example, disorders that affect the brainstem, such as internuclear ophthalmoparesis (INO), may cause horizontal saccades to become more disjunctive than those of normal subjects. INO results from a lesion in the medial longitudinal fasciculus (MLF) in the dorsomedial brainstem tegmentum of either the pons or the midbrain.[5] The MLF connects the abducens internuclear neurons with the medial rectus motoneurons of the oculomotor nucleus, being ultimately responsible for eyes coordination during horizontal saccades. Clinically, it results in slowing of the adducting eye when the patient performs horizontal saccades between two points of fixation (see also Chapter 1).

Different methods have been proposed in order to objectively identify disruption of horizontal saccadic conjugacy, specifically to identify INO. The need for reliable measurements arises from the fact that INO can be difficult to identify at the bedside, especially if the range of eye adduction is normal, with the eye velocity only being abnormally reduced. Thus, in a study of the ability of experienced clinicians to detect INO from cases presented on a video tape, substantial numbers of errors were made compared with INO confirmed with eye movement measurements.[197]

Bird and Leech were among the first to utilize comparison of peak angular saccadic velocities of the two eyes, in patients with INO.[198] More recent

studies have provided evidence to support the value of the versional dysconjugacy index (VDI) in identifying ocular dysconjugacy in INO.[199, 200] The VDI is a ratio of abducting to adducting eye movements for peak velocity, peak acceleration, latency, and eye displacement (amplitude). The use of the VDI has the advantage of eliminating the inter- and intra-individual variability of measurements based on monocular saccadic parameters.[201]

Another technique utilized to diagnose INO is the first-pass amplitude (FPA), which is the ratio of the abducting to the adducting eye position, when the abducting eye first reaches an eccentric target of fixation.[202] This method has been proved to be more sensitive than the simple amplitude ratio computed when both eyes reach the target at the end of the saccade (final-amplitude, FA). In fact, many patients with INO still retain the ability to ultimately achieve an eccentric target with both eyes.

Frohman and colleagues implemented both the peak velocity-VDI and the FPA-VDI measures using a statistic (the Z score), in order to compare the degree of INO in patients with Multiple Sclerosis (MS) to the mean VDI from a population of normal controls. Briefly, the Z score represents a standardized number that indicates the proximity of a test result to the mean value derived from a standard or reference population, and is expressed in units of standard deviation.

$$Z_{INO} = VDI_{INO} - \text{Mean}\,(VDI_{NC})/SD\,(VDI_{NC})$$

In other words, when applied to patients with INO, the Z score represents the number of standard deviations that separate the VDI value of a single patient

with INO from the mean VDI value derived from a reference population, and does not depend on units of measurement. The VDI velocity Z score was found to be more reliable than the VDI acceleration Z score because, even if more sensitive, horizontal saccadic VDI for acceleration has a higher degree of variability on repeated measures analysis.[201] Furthermore, peak acceleration saturates for saccades greater than about 5 degrees, making it unsuitable for comparing large movements. Frohman and colleagues also suggested that the Z score analysis could be useful for linking the INO level of severity with neuroradiological abnormalities in the region of the MLF, in patients with MS.[201,203] Recently, internuclear ophthalmoparesis has been also used to model the effects of body temperature changes on axonal conduction in patients with MS.[204]

However, these reported techniques for the study of horizontal saccadic conjugacy carry some limitations that will be summarized:

1) When using the peak velocity-VDI to assess ocular conjugacy, possible differences in the saccade onset and time course between the two eyes are not taken into account. When a saccadic command is generated, the two eyes do not move exactly together but there is always a time latency component, even in normal subjects.[47] This de-synchronization becomes obvious when one eye is slowed down because, for instance, of a lesion at the MLF site causing INO. If eye position is plotted against time (time plot) for a saccade of a patient with INO (Fig. 9), it can be appreciated that the eyes do not reach the peak velocity at the same time (i.e., the eyes do not move together because the saccadic pulse for the adducting eye is smaller than the one for the abducting eye).

2) The FPA computes the eye displacement ratio between the abducting and the adducting eye, at the very moment when the normal eye achieves the target.[202] However, in patients with INO the abducting eye often overshoots the target, as a consequence of Hering's law of equal innervation and mechanisms of central nervous system adaptation (Fig. 10).[208] Therefore, the use of this technique potentially carries some risk of inaccuracy if not performed at the exact required eye position.

3) All these methods have been mainly used to detect INO, especially in patients affected by MS. However, some other ocular motor system disturbances can cause horizontal saccades to appear disconjugate at the bedside. For instance, disorders of the ocular motor periphery, such as Myasthenia Gravis (MG) can imitate INO (pseudo-INO) or cranial nerve palsies, leading to misdiagnosis. Similarly, Miller Fisher syndrome, a disorder affecting the ocular motor nerves, can imitate INO. Peak velocity-VDI and FPA-VDI Z-scores have not been used in patients with MG or other disorders of horizontal saccadic conjugacy.

3.1.2 Saccadic Disconjugacy in Patients with Myasthenia Gravis

A previous study of two myasthenic patients who presented with pseudo-INO suggested that the clinical appearance of INO was not due to the initial eye acceleration, but to subsequent disconjugacy during the course of the saccade.[205] Furthermore, in myasthenic pseudo-INO, the adducting eye was shown to reach the peak velocity before the abducting eye, whereas the converse was the case in true INO due to MS. The technique of plotting saccades as binocular phase planes of eye velocity versus eye displacement (position) was used to remove latency differences between the responses of each eye. This approach made it

possible to graph horizontal saccades as if the eyes were moving together with almost no difference in the timing of onset, and to calculate the velocity difference between the eyes at each desired position point (velocity disconjugacy). On phase planes, normal subjects and myasthenic patients showed a similar initial movement of the abducting and the adducting eye, whereas patients with INO showed an early abnormal velocity disconjugacy.[205]

3.1.3 Saccadic Disconjugacy in Normal Controls

Onset of saccades can be slightly asynchronous in the two eyes even in normal subjects.[47] Under natural conditions we generate disjunctive saccades, when shifting gaze between objects that lie in different directions and at different depths in the visual environment. The dynamics of horizontal saccadic disconjugacy and the interaction of saccades with vergence-eye movements has been previously investigated.[206] In their study Ramat and colleagues demonstrate that, despite the different change in eye position during combined saccadic-vergence movements, the acceleration peaks of the saccadic component are very similar in the two eyes. Thus, the two eyes receive equal pulses even during disconjugate horizontal saccades. Thus, Hering's law of equal innervation applied if the initial part of the saccade (corresponding to the pulse of innervation – see Chapter 1) were compared.

3.2 Objectives

The goal of our study was to evaluate the phase-plane approach as applied to patients with a range of disorders affecting the ocular motor saccadic system at different sites of lesions, from the brainstem to the periphery. This

brainstem machinery for saccades is well studied, so much of its anatomy, physiology, and pharmacology have been worked out (see Chapter 1). We also applied the phase-plane technique to disjunctive saccades made by normal subjects, as they switched fixation between two points, at far and near, that were aligned on one eye.

In particular, we tested the following hypotheses:

1) Horizontal saccades can be disconjugate as a result of lesions at more than one ocular motor site, from the brainstem to the extraocular muscles.
2) The phase plane technique is a sensitive and reliable method for identifying subtle disturbances of horizontal saccadic conjugacy.
3) The phase plane technique is a useful diagnostic tool for differentiating central from peripheral ocular motor disorders. In particular, it can be utilized to characterize those disorders of the neuromuscular junction (e.g., MG), which can mimic INO or cranial nerve palsies.
4) On binocular phase planes, the initial component of disjunctive saccades made by normal subjects does not show an abnormal difference in velocity values (velocity disconjugacy) between the two eyes.
5) As a unifying concept, the initial component of saccades represents contraction of pale global extraocular muscle fibers, which closely obey Hering's law of equal innervation. In order to test this last hypothesis, we applied the phase plane method to two pathological conditions (MG and Chronic Progressive External Ophthalmoplegia, CPEO), which are likely to spare the pale global fibers.

3.3 Subjects

We studied a group of twenty-two patients (range 22 – 70 years, 4 female) with abnormal saccades who had a range of disorders:

- Horizontal saccadic gaze palsy (2 from brainstem stroke)
- Horizontal gaze palsy (1 due to abducens nucleus infarction); post-cardiac surgery gaze palsy (2)
- INO due to MS (7), to brainstem stroke (2) and episodic ataxia type 2 (EA2 – 1)
- Abducens nerve palsy (2)
- Myasthenia gravis (3)
- Chronic progressive external ophthalmoplegia (CPEO – 2)
- We also studied ten age-matched (range 30 – 60 years), healthy control subjects (3 female).

All patients and control subjects gave informed written consent, in accordance with the Declaration of Helsinki and the Institutional Review Board of the Cleveland Veterans Affairs Medical Center.

3.4 Experimental Paradigms

Subjects made horizontal saccades in response to 5 – 40 degrees jumps of a visual target located at 1.2 m on a tangent screen (approximately equidistant targets). Testing was performed during monocular viewing with each eye in turn, and during binocular viewing. In addition, we applied the Müller paradigm to induce disjunctive saccades in normal subjects by presenting two targets aligned on one eye (the dominant), at distances of 15 cm (near) and 1.2 m (far) (unidirectional targets).

3.5 Recording Methods

We measured horizontal and vertical positions of each eye using the magnetic search coil technique. One important advantage of this technique is that the contact lenses that the subject wears (Fig. 8) can be calibrated prior to placing on the subject's eye. Thus, there is no need to make the assumption that the subject is looking at the visual target during calibration (and this assumption may be erroneous in patients with limited ocular motor range).

3.6 Data Analysis

Coil signals were filtered (0-150 Hz) prior to digitization at 500 Hz; eye velocity and acceleration were computed as previously described.[209] To compare corresponding peak velocity values (saccadic pulse) of each eye, we used the phase-plane technique. By offsetting the initial eye position to a value of zero, this method allowed us to eliminate any latency difference in saccade onset, between the two eyes. The functions "getPhasePlane.m" and "calPhasePlane.m", written in Matlab (The MathWorks, Natick MA), were used to calculate and plot the binocular phase-plane for each saccade (see program code in Appendix A). First, the saccade onset and ending were selected on the basis of an acceleration threshold of 2000 degrees/second^2. For each eye, the maximum displacement (position) and velocity were calculated; the eye with the smaller displacement was called "weak eye", and the eye with the larger displacement was called "strong eye". Position and velocity of both eyes were then normalized, assigning a value of 1.0 to the maximum position and velocity values of the "strong eye". The plot of normalized eye velocity versus normalized eye position (phase-plane) was truncated at the maximum position value of the "weak eye".

Standardized position samples were identified, in steps of 1% of the maximum displacement values for the "weak eye" position range. These desired points were ultimately used to interpolate the velocity values of the "strong eye" to the position of the "weak eye", using a cubic-spline method. The interpolation process was necessary because the eye-coil signals were sampled at fixed time intervals (0.002 s bins, corresponding to the digitization rate) and thus, the positions of each eye were not necessarily matched. In this way, we were able to compare the velocity of each eye for the same eye displacement values, and plot the difference of normalized eye velocity between the two eyes ("velocity disconjugacy"). For each patient, the average "velocity disconjugacy" for at least 10 saccades was plotted versus the normalized position of the "weak eye" (velocity disconjugacy plots). Finally, we defined 95% prediction intervals based on pooled data of ~1400 saccades, from ten age-matched normal subjects, and determined whether patients' data fell outside of those intervals.

An important test for our method was to determine if the size of saccades affected ocular conjugacy on phase planes. This was an important concern, since larger saccades have more skewing of their velocity profiles than do smaller saccades.[210] When we grouped saccades of different sizes from two normal control subjects (age 30 and age 60 respectively) and plotted the velocity difference between the eyes (velocity disconjugacy) against the normalized "weak eye" position, we found that different sized-saccades had a similar velocity profile for both subjects, until at least 60% of eye displacement (Fig. 22). Therefore, it seemed justified to apply the phase-plane approach to saccades of different sizes, at least until up to 60% of eye displacement (Fig. 22).

3.7 Results

A representative phase plane plot for a single saccade (equidistant target) from a normal control is shown in Fig. 11 (top panel); the phase plane for each eye and the velocity difference or disconjugacy curve is plotted against the normalized "weak-eye" position. Figure 16 (top panel) summarizes the average velocity difference curves for each of the ten normal subjects, along with 95% prediction intervals for the grand total of 1,400 saccades, which served as a benchmark against which to test the saccades of the patients we studied. We found that disruption of horizontal saccades conjugacy is possible for lesions at several distinct sites of the ocular motor system (Fig. 2).

Two patients with post-cardiac surgery gaze palsy due to presumed lesion of the brainstem burst and omnipause neurons,[59,207] were found to have disconjugate horizontal rightward saccades. Figure 12 (top panel) shows a representative phase plane plot (1 saccade) from one of these patients. In figure 17 (top panel) the average of ~10 saccades velocity difference between the eyes (velocity disconjugacy) is plotted against the normalized "weak-eye" position; 95% PI from 10 normal subjects is displayed. Similarly, saccades from one patient with horizontal saccadic left gaze palsy due to brainstem stroke were found to be disconjugate between 20% and 50% of eye displacement (Fig. 12_middle panel, 17_middle panel), whereas saccades from another patient with mild horizontal saccadic right gaze palsy also due to brainstem stroke, fell mostly within the normal range (Fig. 17_middle panel). Saccades from a patient with a pure left abducens nucleus lesion did not show abnormal velocity disconjugacy (Fig. 12_bottom, 17_bottom). These differences are addressed in the Discussion.

Figure 13 (top panel) shows a representative phase plane plot (1 saccade) from a patient with left INO due to MS. Horizontal saccades from all patients with INO (7 due to MS, 2 due to brainstem stroke, 1 with EA2) showed early velocity diconjugacy, which remained abnormal throughout the whole eye displacement (Fig. 18_top panel).

Saccades from two patients with abducens nerve palsy were also found to be disconjugate early on. Figure 13 (bottom panel) shows a representative phase plane plot (1 saccade) from a patient with left abducens nerve palsy. Figure 18 (bottom panel) shows the average of ~10 saccades velocity difference between the eyes (velocity disconjugacy) from a patient with severe (patient 1), and one with mild abducens nerve palsy (patient 2).

The initial component of horizontal saccades from three patients with MG (site of lesion: neuromuscular junction) was found to be similar to controls. Figure 14 displays a representative phase plane plot (1 saccade) from one patient with right pseudo-INO (top panel) and one with right pseudo-abducens nerve palsy (bottom panel), both due to MG. All these three patients showed varying degrees of horizontal disconjugacy only later in the course of the saccades (Fig. 19_top panel).

Of the two patients with CPEO (site of lesion: extraocular muscles), only the one with advanced stage of disease (patient 2) showed abnormal horizontal saccadic conjugacy. Representative phase plane plots (1 saccade), and ~ 10 saccades velocity disconjugacy plots are shown (Fig. 15, 19_bottom).

A summary of findings for different groups of patients is shown in figure 20. We found that patients with lesions at the MLF site (i.e., INO) or at cranial nerves site (i.e., abducens nerve palsy) show abnormal velocity disconjugacy in

the first 10% of the eye displacement (Fig. 21_top panel). On the other hand, patients with lesions at the neuromuscular junction site (i.e., MG) do not show abnormal disconjugacy in the first 10% of the eye displacement, but did so later in the course of the saccade (Fig 21_bottom).

We found that even for saccades of different size and direction (disjunctive saccades) made by normal subjects, there is no abnormal velocity disconjugacy in the first 10% of the eye displacement. A representative phase plane plot from a normal control (1 saccade, unidirectional targets) is shown in figure 11 (bottom panel). In figure 16 (bottom panel), the average of 79 saccades velocity difference between the eyes (velocity disconjugacy) from nine normal subjects during Müller paradigm, is plotted against the normalized "weak-eye" position (velocity disconjugacy plot).

3.8 Discussion

The main finding of this study is that binocular phase-plane analysis of horizontal saccades provides a sensitive means to identify the location of lesions causing disconjugate eye movements. Although some saccadic disconjugacy was evident for most of the patients we studied, disconjugacy evident on velocity difference curves within the first 10% of the movement was specific for INO or cranial nerve palsies. To interpret what these results mean, we first comment on the findings for each group of patients, and then examine our hypothesis that seeks to account for the findings in terms of involvement of the pathway innervating the pale global extraocular muscle fibers.

We studied two patients who acutely presented with selective saccadic gaze palsy after cardiac surgery.[207] This clinical picture is presumed to be due to focal

neuronal necrosis at the level of median and paramedian pons, based on one case who came to autopsy[57] and recent applications of mathematical models for the brainstem generation of saccades. In these patients, both horizontal and vertical saccades were slow and hypometric, suggesting involvement of the omnipause neurons.[207] Phase plane technique analysis revealed horizontal leftward saccades to be disconjugate in both patients (Fig. 17_top panel). Although it is possible that the pathological process might have not uniformly affected the brainstem ocular motor neurons that generate saccades, associated vergence eye movements might also play a role in causing horizontal saccades to be disconjugate in these patients. Thus, both patients were studied some months after their surgery, and it seems possible that compensatory mechanisms, such as substituting vergence movements for saccades, may have cause the phase planes that we measured. The same mechanisms may account for the findings in one of the two patients with horizontal saccadic gaze palsy due to brainstem stroke, who exhibited abnormal velocity disconjugacy between 20% and 50% of eye displacement (Fig 17_bottom). In contrast, a patient with a presumed lesion affecting her left abducens nucleus[211] showed conjugate saccades on phase planes, indicating commensurate involvement of abducens motoneurons and abducens internuclear neurons. In her case, slow leftward movements from right gaze back to the midline may simply reflex visco-elastic forces applied by the orbital tissues, after the sustained (step) innervation ended.

When we compared horizontal saccades of patients with INO or abducens nerve palsy with those of patients with MG (pseudo-INO and pseudo-abducens nerve palsy), we found that occurrence of abnormal velocity disconjugacy in the first 10% of eye displacement can distinguish between these conditions (Fig. 21).

If patients with MG show abnormal velocity disconjugacy between the eyes, they do so later in the course of the saccade. Similarly, when we induced disjunctive saccades in normal controls by using the Müller paradigm, we did not found abnormal velocity disconjugacy in the first 10% of eye displacement (Fig. 16_bottom). Of note, we showed that horizontal saccades of patients with CPEO are likely not to be disconjugate until later in the course of the disease, when other factors may cause saccades to become disjunctive (Fig. 19_bottom), such as fibrosis of the extraocular muscles.

Can our hypothesis – that the pale fibers of the extraocular muscles global layer are responsible for driving the initial acceleration component of saccades – account for our findings? Current evidence, reviewed in chapter 1, suggests that the pale global fibers are spared in MG and CPEO, and are therefore able to induce fast saccades, ultimately assuring the two eyes conjugacy at least in the beginning of the eye movement. As discussed in chapter 1, each extraocular muscle comprises clearly distinguished outer orbital and inner global layers, which, in turn, contain fibers more suited for either sustained contraction or brief rapid contraction.[135] About 80% of the orbital layer fibers are singly innervated, and fatigue-resistant to contraction. These fibers are probably the main contributors to sustained muscle tone. The remaining 20% are multiply innervated, with non-twitch properties. In the global layer, about a third of fibers are pale, singly innervated fibers with fast-twitch properties but low fatigue resistance. Another third are singly innervated, fast-twitch, and fatigue-resistant. About a quarter are singly innervated fibers with fast-twitch properties, numerous mitochondria, and an intermediate level of fatigue resistance. The remaining 10% are multiply innervated

fibers, with synaptic endplates along their entire length, as well as at the myotendinous junction, where there are palisade organ proprioceptors.[165]

There are two reasons to suspect that the pale global fibers will be relatively spared in ocular myasthenia. The first is an old observation, based on electromyographic studies of the extraocular muscles, that pale global fibers contract less frequently than the orbital fibers, being active mainly during saccades but less so while the eyes are sustained at an eccentric position in the orbits.[166] A second, more recent finding, based on electron microscopic studies of extraocular muscle, is that endplates show a notable paucity of post-junctional folds for all fiber types *except* the pale global singly innervated fibers, which do show substantial post-junctional synaptic folding.[165] These morphological differences suggest that, compared with other extraocular fiber types, the pale global fibers have a higher safety factor – the degree of endplate depolarization beyond that required to generate an action potential. We propose that the clinical appearance of ocular disconjugacy some patients with MG might exhibit, is due to involvement of not-pale fibers that cause the saccades to be disconjugate later during the eye movement. The main reason to suspect that pale global fibers are relatively spared in CPEO is that they are relatively poor in mitochondria, when compared to the orbital fibers. Our finding of relatively preserved saccadic velocity conjugacy in one patient with CPEO supports this evidence.

Moreover, we provide evidence that the initial acceleration saccadic component of combined eye movements (saccadic-vergence) is conjugate in normal controls, when analyzed using the phase plane technique. This finding is in accordance with previous report that extraocular muscles receive similar

saccadic pulses, even when the size of movement is quite different between the two eyes.[209]

It seems possible, therefore, that a pathway from pre-motor burst neurons in the brainstem projects to the pale global extraocular fibers, and that this pathway ensures that the high-acceleration part of saccades is conjugate. It is interesting, in this regard, to consider microsaccades, which have recently been confirmed as playing a useful role in preventing fading of the periphery of vision. Microsaccades are indeed small, but have high accelerations, and are conjugate. Thus, there may be a need for similar signals to be generated by each eye for the visual system to use the information to prevent adaptation and fading of vision.

3.9 Concluding Remarks

We propose that binocular phase-plane analysis could be a clinically useful technique in disorders that cause disjunctive movements of the eyes. We have shown it to be a sensitive method to detect even subtle disorders, such as mild INO, that are difficult to diagnose at the bedside, and to distinguish between central and peripheral disorders of ocular motility (i.e., true INO vs pseudo-INO) that can present with a similar clinical picture. Furthermore, we proposed that the initial conjugate component of saccades is generated by the global pale fibers of the extraocular muscles, for which medial and lateral rectus receive very similar commands (Hering's law of equal innervation). We suggest that the evolutionary pressure for conjugate contraction of pale global fibers is to generate conjugate

high-acceleration eye movements that serve as a prompt to the visual system that a gaze shift has occurred.

CHAPTER 4

TREATMENT OF SACCADIC INTRUSIONS IN HEREDITARY ATAXIA WITH MEMANTINE

4.0 Abstract

Background: Spinocerebellar ataxia with saccadic intrusions (SCASI) is a rare form of hereditary ataxia that is also associated with peripheral neuropathy. Despite a normal visual function is observed in patients with SCASI, instability of visual fixation precludes reading and reading-related daily activities. **Methods:** Two patients from a family affected by SCASI were treated with memantine, an uncompetitive glutamate antagonist, at a dose of 20 mg per day. Eye movements were recorded before and after treatment, using the search coil technique. **Results:** Before treatment with memantine, both patients showed spontaneous horizontal macrosaccadic oscillations that disrupted steady fixation; saccades were faster than normal and generally hypermetric. After treatment, the frequency of saccadic intrusions was reduced of about 50% in both patients, while amplitude was decreased in only one patient. Speed and accuracy of voluntary saccades were little changed. **Conclusions:** It is hypothesized that saccadic intrusions in SCASI patients occur when excitatory inputs from mossy fiber collaterals to deep cerebellar nuclei are not suppressed by inhibition from cerebellar cortex. Memantine may reduce the excitatory effect of mossy fiber collaterals on cerebellar deep nuclei, thereby reducing the probability of an unwanted saccade. Saccadic hypermetria, wich is also related with loss of processing in the cerebellar cortex, is not ameliorated by memantine. Memantine

may only suppress certain types of saccadic intrusions, and clinical trials are required to define its therapeutic role.

4.1 Introduction

4.1.1 Neurobiological Bases for Saccadic Intrusions and Oscillations

As reviewed in chapter 1, several types of "saccadic intrusions" may disrupt visual fixation (Fig. 7). The most common form of saccadic intrusions is "square-wave jerks," which consist of small horizontal saccades (about 0.5 degrees) that take the eye away from the target and, after an intersaccadic interval of about 250 ms, during which the eye is still, return it to the visual target.[192] Square-wave jerks are commonly encountered in normal subjects, when they normally do not degrade vision. They represent a cardinal clinical finding of certain neurological disorders, such as progressive supranuclear palsy (PSP) and spinocerebellar ataxias.[5] Saccadic intrusions that are larger (greater than 2 degrees) and oscillate the eye around the desired point of fixation may also degrade vision and make visual tasks difficult.[212] Such larger intrusions are commonly called "macrosaccadic oscillations" and occur with midline cerebellar lesions,[177] which also cause marked overshooting (hypermetria) of voluntary saccades. Thus, even small saccades overshoot the fixation point, as do the attempts at correction. Like square-wave jerks, macrosaccadic oscillations show intersaccadic intervals of about 250 ms, and are distinct from saccadic oscillations such as ocular flutter and opsoclonus, which consist of back-to-back saccades without intersaccadic intervals. Recent basic studies have provided a biological basis for some of these saccadic intrusions and oscillations.[212] Thus, high-frequency oscillations have been attributed to an instability of the reciprocal inhibition of inhibitory burst neurons (IBN) on other contralateral IBN in the brainstem. Macrosaccadic oscillations occurring during gaze-shifts have been proposed to represent a severe form of saccadic hypermetria, as they are usually

encountered with midline cerebellar lesions, which would cause a delay in the "choke" signal that stops saccades. On the other hand, no model is available to account for the occurrence of macrosaccadic oscillations during fixation, or to explain the nature of the most common square-wave jerks.

4.1.2 Saccadic Abnormalities in Patients with SCASI

Swartz et al. previously described a family in which 5 of 14 sibs had autosomal-recessive spinocerebellar ataxia with saccadic intrusions and neuropathy (SCASI), with linkage to chromosome 1p36.[3,134] Affected patients had normal visual examinations but were unable to read because of frequent horizontal saccadic intrusions and marked saccadic hypermetria. Macrosaccadic oscillations occurred in these patients with each gaze-shift, but also intruded on steady fixation. Saccadic gain and peak velocities of large saccades were generally increased in these patients. A conduction deficit in cerebellar parallel fibers, as well as in long axons, was hypothesized to explain both the saccadic abnormalities and the sensorimotor neuropathy. Thus, they proposed that slow conduction in the parallel fibers would cause a delay in the fastigial nucleus (CFN) signal used to stop ipsiversive saccades on target. Their theory of delayed cerebellar feedback, supported by experimental observation of the effects of CFN lesions in monkeys, would explain both the hypermetria and the abnormally increased velocity of saccades in SCASI patients. However, it does not explain the occurrence of macrosaccadic oscillations especially during fixation, which was proposed to be triggered by microsaccades instead.

4.1.3 Use of Memantine in Clinical Practice

Memantine is an uncompetitive (channel-blocking) N-methyl-D-aspartate (NMDA) receptor antagonist, which has been used to treat patients with Alzheimer's disease (AD) and vascular dementia.[213] It is typically effective if administered orally in a daily dose of 20 mg, and is generally well tolerated. Starck et al. successfully treated with memantine 11 patients affected by MS, presenting with long-lasting acquired pendular nystagmus (APN).[214] However, a unifying hypothesis to explain the efficacy of memantine in APN treatment is still lacking. On the other hand, the pathogenesis of APN is also not fully understood, while an underlying mechanism has been proposed to explain most types of saccadic intrusions.

4.2 Objectives

The goal of this study was to evaluate the efficacy of memantine in treating saccadic intrusions in two patients affected by SCASI. A model is proposed to explain occurrence of macrosaccadic oscillations in the studied patients, both during gaze shifting and during visual fixation. Finally, a hypothetical mechanism of action of memantine in the treatment of saccadic intrusions is presented.

4.3 Subjects

Two patients (males, Patient 1 age 54 years and Patient 2 age 58 years), from the previously described family affected from Spinocerebellar Ataxia with Saccadic Intrusions and Neuropathy (SCASI),[3,134] were treated with memantine 20 mg daily. The disease, characterized by progressive ataxia, corticospinal

signs, axonal sensorimotor neuropathy and disruption of vision by saccadic intrusions, has an autosomal recessive inheritance with linkage to chromosome 1p36. Screening for Friedreich's ataxia, spinocerebellar ataxia (SCA) 1-3 and 6-8, and Unverricht-Lundborg progressive myoclonic epilepsy (EMP1), was negative.

Both patients reported onset of symptoms in their early twenties, consisting of gait unsteadiness and difficulty reading. Eventually, they developed gait, trunk, and limb ataxia, as well as pyramidal tract signs with increased reflexes and Babinski plantar responses. They now both use walking aids. Myoclonic jerks were also noted, but electroencephalography has shown no evidence of epilepsy. Nerve conduction studies showed findings consistent with axonal sensorimotor neuropathy, with evidence of active denervation in the distal muscles of the lower limbs. Magnetic resonance imaging scans showed mild cerebellar atrophy, with involvement of the dorsal vermis. The visual and auditory-evoked potential studies were within normal limits except for the visual N105 wave, which was delayed or poorly formed, possibly an artifact due to eye movements.

The optic fundi, visual fields, and corrected visual acuity (20/20) were normal in both patients. Reading was barely possible but slow and tedious because of saccadic intrusions and hypermetria (*e.g.,* when attempting to move along a line of print or jump to the beginning of the next line) (see Fig. 28).

4.4 Methods

Eye movements of each patient were measured using the magnetic field/search coil technique,[5] before and 1 month after the treatment with

memantine at a dose of 20 mg/day. Their eye movements were compared with a previously reported group of 10 normal subjects, age range 24-65 years.[34] All patients and subjects gave informed consent in accordance with the Institutional Review Board of Cleveland Veterans Affairs Medical center and the Declaration of Helsinki.

During all experiments, patients sat in a vestibular chair, with their heads braced against a headrest; head stability was monitored using a search coil attached to their foreheads. The following were tested: attempted steady fixation of a laser spot at a viewing distance of 1.2 m for 3 minutes with ambient room lighting, and visually guided saccades in response to jumps of the laser spot at 0.4 Hz in non-predictable directions, through 5° – 50° in the horizontal or vertical planes. It has been previously documented that the SCASI patients have normal vestibular, pursuit, vergence, and gaze-holding functions (*i.e.,* no nystagmus).[3] Coil signals were filtered (bandwidth, 0-150Hz) before digitization at 500Hz with 16-bit resolution. Onset and offset of the saccades were defined using a velocity criterion of 40 degrees/sec.[34] Microsaccades were detected using the two-dimensional algorithm developed by Engbert and Kliegl,[215] computing the horizontal and vertical components of each movement.

4.5 Results

Prior to treatment, both patients had similar disturbances of eye movements, which were more marked in Patient 1. The most striking finding was a marked inability to hold steady fixation because of horizontal macrosaccadic oscillations around the target (Fig. 23-24), accompanied by hypermetric saccades, overshooting the target. This was especially evident for leftward

saccades in Patient 2 (Fig. 25). As previously noted,[3] larger saccades were faster than normal (greater than 95% prediction intervals for the control subjects), with peak velocities up to 700 deg/sec (Fig. 26). Rightward and leftward gain of saccades was increased in both SCASI patients when compared with the controls (Fig. 27).

After treatment with memantine, both patients reported a "tremendous" improvement in reading-associated daily activities. Patient 1 has benefited from memantine for 1 year, and patient 2 for 2 years. Measurements indicated that the frequency of saccades that disrupted steady fixation dropped by about 50% in both patients: from 154/min to 69/min in Patient 1 (Fig. 23), and from 168/min to 89/min in Patient 2 (Fig. 24). The amplitude of these saccadic oscillations was significantly decreased only for Patient 2 ($p < 0.001$) (Fig. 24); in Patient 1, saccadic oscillations were reduced in frequency but, when they occurred, were just as big as before treatment (Fig. 23). The peak velocity/amplitude (main sequence) relationships remained unchanged in both patients (Fig.26). The gain of visually guided saccades was reduced only for leftward saccades in Patient 2, whereas there was no significant change for Patient 1 (Fig. 27). Microsaccades were also compared in each patient prior to and during memantine therapy. The frequency of microsaccades was reduced by about 22% in Patient 1 and 33% in Patient 2 during treatment; however, their magnitude and peak velocity/amplitude relationships showed no consistent changes (Fig. 26). Figure 28 shows the effect of memantine on reading activity in Patient 2.

4.6 Discussion

Memantine halved the frequency of saccadic intrusions in two patients with a form of recessive spinocerebellar ataxia (SCASI). Before treatment, reading and reading related daily activities were precluded because of frequent saccades about the position of attempted fixation (macrosaccadic oscillations), which disrupted vision. After taking memantine 20 mg/day, both patients reported that they were able to read more easily. Although memantine reduced the frequency of saccadic oscillations in both patients, it only decreased their size in Patient 2. Visually guided saccades became more accurate to the left in Patient 2 (Fig. 25, 27B), improving his reading ability (Fig. 28). However, Patient 1 showed no difference in gain of saccades before and after treatment (Fig. 27A). The main sequence (peak velocity/amplitude) relationships were unchanged in both patients (Fig. 26). Similarly, even if frequency of microsaccades was somewhat reduced in both patients, their size and peak velocity/amplitude relationships did not change (Fig. 26).

Currently, memantine, which is an uncompetitive NMDA receptor channel blocking drug, is mainly used for treatment of early stage Alzheimer's disease, because it can promote synaptic plasticity, preserve or enhance memory, and it may reduce excitotoxicity of low levels of glutamate.[213] Memantine has been considered for the treatment of two patients with macrosaccadic oscillations because it had been reported to improve vision in another eye movement disorder – acquired pendular nystagmus (APN) in patients affected by MS.[214] However, it is worth stressing that these two disorders have quite different hypothetical underlying mechanisms (see above). In the two SCASI patients, memantine seems to have had its main effect on the mechanism that normally suppresses

saccades until a decision is made to shift gaze. On the other hand, effects on saccadic hypermetria were smaller.

I will now discuss the likely pathogenesis of saccadic abnormalities in patients with SCASI, and explain how memantine could have worked in reducing the frequency of saccadic intrusions.

4.6.1 Saccadic Hypermetria and Macrosaccadic Oscillations

As discussed in chapter 1, saccades are generated by premotor burst neurons in the reticular formation of the brainstem that fire intensely during saccades, but are silent at other times. Excitatory and inhibitory burst neurons (EBN and IBN) for horizontal saccades lie in the paramedian pontine reticular formation (PPRF), while those concerned with vertical saccades lie in the rostral interstitial nucleus of the medial longitudinal fasciculus (RIMLF).[5] Both horizontal and vertical burster areas receive glycinergic inhibition from omnidirectional pause neurons (OPN) that lie in the nucleus raphe interpositus (RIP) in the midline pons. Starting a saccade requires the cessation of the OPN activity. Once started, saccades can stop for two reasons: 1) the caudal part of the ipsilateral cerebellar fastigial nucleus fires the brainstem's contralateral IBN and chokes off the drive to the motor neurons,[63] or 2) the OPN restart and inhibit the premotor burst neurons. This interpretation is based on observations that inactivation of the caudal fastigial nucleus causes pronounced saccadic hypermetria,[129] but saccades remain accurate, although slow, after inactivation of the OPN.[89]

Thus, macrosaccadic oscillations might arise from a deficit in the midline cerebellum that also causes hypermetric saccades (Fig. 29). Occurrence of

saccadic hypermetria in SCASI patients has been attributed to a late arrival of a "stop" signal on parallel fibers of the dorsal vermis, and thence to the ipsilateral fastigial nucleus.[3] As a consequence, once started, saccades overshoot the target, and, after a normal delay, are followed by a corrective saccade that also overshoots the target. This mechanism may explain *macrosaccadic oscillations associated with a change in fixation* in the two patients with SCASI.

4.6.2 Increased Velocity of Saccades

Saccades are faster than normal for their size in the SCASI patients (Fig. 26). The higher than normal acceleration observed suggests that the output of the fastigial nucleus must also be larger than normal. Because the cerebellar cortex (e.g., vermis) is damaged in patients with SCASI, it would therefore exert less inhibition (through Purkinje cells) on the deep cerebellar nuclei (e.g., fastigial nuclei). During an eye movement, excitation arrives at the cerebellar cortex and deep nuclei via mossy fibers and their collaterals (Fig. 29). The inhibitory output of the cortex prevents the fastigial neurons from firing. If the cerebellar disease in these patients reduced the efficacy of the cerebellar cortex, it would remove inhibition from the fastigial neurons and cause them to fire more strongly than usual, which would result in faster than normal saccades.

4.6.3 Macrosaccadic Oscillations during Fixation

Although macrosaccadic oscillations are usually induced by a gaze shift, they can also occur during attempted fixation,[5] as in the SCASI patients. Current models, when made hypermetric, can generate oscillations when triggered by a gaze shift, but no model is available to explain how oscillations can start during

fixation, although spontaneously occurring microsaccades have been suggested to trigger larger saccades.[5]

Why then, do unwanted saccades intrude during fixation? Changes in our visual field and our desire to search the visual field continually give rise to potential eye movements. These potential movements are normally suppressed by the frontal eye fields in favor of fixating on the object of interest.[216] However, the fixation command is not so strong that electrical stimulation of superior colliculus or cerebellar vermis in monkeys can not cause saccades during fixation.[217, 218] We assume that when signals related to potential saccades occasionally arrive on the mossy fibers, the output of the deep cerebellar nuclei is suppressed by the inhibition from the cerebellar cortex, so that there is little or no output from the cerebellum to disturb fixation. In the SCASI patients, the disease affecting the cerebellar cortex likely reduces the inhibition on the deep nuclei. When the potential saccade signals arrive on the mossy fiber collaterals, the deep nuclei generate a substantial output. This output goes to the brainstem, and just like the signal evoked by electrical stimulation in monkeys, causes a saccade.

Since memantine reduced the frequency of saccadic intrusions during attempted fixation, without much affecting their amplitude or speed, we hypothesize that macrosaccadic oscillations are initiated by output from the deep cerebellar nuclei that is normally suppressed by the cerebellar cortex. The oscillations are sustained by the usual mechanisms for saccadic hypermetria (loss or delay of the choke signal caused by failure of the cerebellar cortex to propagate the stop signal to the ipsilateral fastigial nucleus).

One aspect of saccadic oscillations in SCASI that remains unexplained is why it is predominantly horizontal in direction. Projections from the fastigial nucleus run in the contralateral superior cerebellar peduncle to reach neurons of the PPRF, RIMLF, superior colliculus and the omnipause neurons.[5] Such cerebellar inhibition of burst neurons may use different pathways, or different neurotransmitters,[212] for horizontal and vertical saccades, thereby leading to the predominantly horizontal intrusions encountered in the two SCASI patients. Control of vertical saccades may also be more widely distributed through the cerebellar cortex than for horizontal saccades,[115,131] making it less susceptible to disruption in cerebellar disease.

4.6.4 Memantine Mechanism of Action

NMDA receptors are present at mossy fiber synapses on cerebellar nuclei,[219] and this could be a site where memantine exerts its glutamate-antagonist effect. In the SCASI patients, I hypothesize that saccades are hypermetric because the cerebellum generates the choke signal too late. However, this assumes that the input to the saccadic system is normal. If the memantine reduces the effective excitation of the brainstem premotor burst neurons, large saccades will be a little slower, and thus less hypermetric than before. This may explain the small effect of memantine on saccade gain in patient 2. Of note, small saccades are affected less by post-inhibitory rebound and more by glutamate than large saccades.[92] This explains the effect of memantine on saccade gain in patient 2, and could also account for the effect of memantine in reducing the magnitude of microsaccades (Fig. 26).

The major effect of memantine, however, was to reduce the frequency of occurrence of the saccadic intrusions in both patients. I propose that this is caused by a reduction in the strength of the mossy fiber input to the fastigial nuclei. Thus, the random signals that initiate the saccadic intrusions, when cerebellar cortical inhibition is reduced, are less effective. Assuming that the remaining inhibition from cerebellar cortex sets a threshold below which these random signals cannot elicit a saccade, the effect of memantine is to reduce more of the mossy fiber inputs below that threshold.

4.7 Concluding Remarks

In conclusion, evidence is provided that memantine suppresses saccadic intrusions in one form of recessive spinocerebellar ataxia. I hypothesize that saccadic intrusions are caused by random inputs on mossy fiber collaterals to fastigial nuclei after loss of inhibition from the cerebellar cortex. Saccadic hypermetria is caused by loss or delay of the stop signal generated within the cerebellar cortex. Memantine may act by reducing the strength of inputs to the deep nuclei from mossy fiber collaterals, reducing the probability of incidence of saccadic intrusions, but not their size.

Further work is needed to determine whether memantine could be helpful in other cerebellar disorders, such as Friedreich's ataxia or destructive processes that cause abnormal saccades that disrupt steady fixation. Further studies are also required to investigate the possible effect of memantine on microsaccades.

CHAPTER 5

CONCLUSIONS AND SUGGESTIONS FOR FURTHER RESEARCH

In this thesis project I reviewed the neuroanatomical machinery that generates rapid eye movements (i.e., saccades), and I particularly focused on properties and anomalies of horizontal saccades. We showed that binocular phase-plane analysis could be a clinically useful technique in the diagnosis of disorders that disrupt horizontal saccadic conjugacy. In particular, we found it to be helpful in differentiating between peripheral and central oculomotor disorders. This method allows a comparison of the two eyes throughout the course of the whole eye movement, both in terms of position and velocity values, whereas current measures of saccadic conjugacy provide mostly a one-point instantaneous assessment. Further studies could extend the application of the phase planes to other diseases that can cause saccades to be disconjugate (e.g., Miller-Fisher's syndrome). Also, application of phase planes to disorders of vertical saccadic conjugacy (e.g., fourth cranial nerve palsy) might provide new insights on the mechanisms that subtend coordination of vertical eye movements. Moreover, by comparing the velocity profiles of the two eyes in peripheral and central disturbances of saccades, we had come to the conclusion that the extraocular pale global fibers might be responsible for the initial acceleration of saccadic eye movements. More direct proof of the pale global fibers role in saccadic dynamics would be needed in the near future.

By studying saccadic anomalies in two patients with a form of spinocerebellar ataxia, we provided new insights on the mechanisms that might cause some oculomotor disorders associated with cerebellar lesions. In particular, we proposed a new model to account for the occurrence of macrosaccadic oscillations during fixation in patients with SCASI. Recent electrophysiological evidence is likely to confirm some of our findings.[220] We also showed how memantine is effective in reducing the frequency of saccadic intrusions in the reported patients. However, a specific mechanism of action to account for these effects can only be hypothesized. More studies are required to evaluate the efficacy of memantine in treating other types of saccadic intrusions, such as the most common *square-wave jerks*, and to better define its potential therapeutic role in eye movement disorders.

APPENDIX

MATLAB Codes

calPhasePlane.m

```
% Calculate difference for face plate.
% input are two eyes' normalized information
% with the first column and third column being position and velocity for one eye,
% and the second and forth column being position and velocity for the other eye.

function [result1 result2] = calPhasePlane(pone, ptwo, vone, vtwo)

%close all;
% Get the max range, p1 always is the one with smaller range
% max is the range that difference should be calculated.

max1 = max(pone);
max2 = max(ptwo);
if (max1 > max2)
    p1 = ptwo;
    p2 = pone;
    v1 = vtwo;
    v2 = vone;
    smax = max2;
else
    p1 = pone;
```

```
    p2 = ptwo;
    v1 = vone;
    v2 = vtwo;
    smax = max1;
end




% cut them at the maximum position of the weaker eye
sac_end_loc1=find(p1>=smax);
sac_end_loc2=find(p2>=smax);

% clear noise at the begining of p2.
%v2diff = diff(v2);
thres = 0.1;
%thres = 0;
sac_start_loc1=find(v1>=thres);
sac_start_loc2=find(v2>=thres);



p1cut = p1(sac_start_loc1(1):sac_end_loc1(1));
v1cut = v1(sac_start_loc1(1):sac_end_loc1(1));

p2cut = p2(sac_start_loc2(1):sac_end_loc2(1));
```

```
v2cut = v2(sac_start_loc2(1):sac_end_loc2(1));



% calculate the difference for each point on p1cut
% standarize position samples where interpolation will be done
% in step of 1% of maximum position
stdPs = [0.01:0.01: max(p1cut)];
v2interp = interp1(p2cut,v2cut,stdPs,'cubic');
v1interp = interp1(p1cut,v1cut,stdPs,'cubic');
vdiff = v2interp - v1interp;

% find two point around the desired position
% v2interp = interp1(p2cut,v2cut,p1cut,'spline');
% vdiff = v2interp - v1cut;

% % calculate the difference for each point on p1
%
% % find two point around the desired position
% v2interp = interp1(p2,v2,p1,'spline');
% vdiff = v2interp - v1;

% lenP = length(p1cut);
%
% maxbin = 0;
% for (i=1:lenP)
```

```
%
%     right_pt_arr = find(p2>=p1cut(i));
%     right_pt  = right_pt_arr(1);
%     left_pt = right_pt - 1;
%     if(left_pt >= 1 )
% %         vdiff(i) = v2(right_pt) - (v2(right_pt) - v2(left_pt)) ...
% %         * (p2(right_pt) - p1cut(i))  / (p2(right_pt) - p2(left_pt)) ...
% %         - v1(i);
%
%         tempBin = abs(p2(right_pt) - p2(left_pt));
%         if(tempBin > maxbin)
%             maxbin = tempBin;
%         end
%     end
%
% end


% fprintf('  Verlocity difference between two eyes: \n');
% [zeros(sac_start_loc1(1)-1,1); vdiff]
% fprintf('  Max Size of the bin used in interpolation is: %6.3f\n', maxbin);


% plot the face plate
% vinter = vdiff' + v1cut;
figure(2);
```

```
plot(p1cut, v1cut,'*-', p2cut, v2cut,'+-', stdPs, vdiff, stdPs, v2interp, 'r+', stdPs,
v1interp, 'g*');
legend('weaker eye', 'stronger eye', 'velocity difference', ...
   'stronger eye interpolated points', 'weaker eye interpolated points');
grid on;


xlabel('normalized eye position');
ylabel('normalized eye velocity');
title('Phase Plane Plot');



result1 = [stdPs' v1interp' v2interp' vdiff'];
result2 = [p2 v2];
```

getPhasePlane.m

```
%function getPhasePlane
% extract phase plane information from lab files.
% calculate velocity difference, acceleration difference.

% steps: 1. Click the start point that is before but close to when vel
% surpasses the threshold.
%       2. Get 10 samples before the clicked point, and calculate mean and
%       standard deviation. set mean + 3*sd as the new threshold.
%       3. Select end point. calculate max position for each eye, and
%       normalize them according to bigger max position. Also normalize
%       the velocity according to bigger max acceleration.
%       4. Call calphaseplane to calculate the actual phase plane for
%       velocity and acceleration difference.
%       5. write result into files.

fprintf('Choose the file you want to analyze. \n');
rdlab
fprintf('Reading file...done. \n');
fprintf('Choose the array you want to use:\n');
fprintf('  1: rh and lh\n  2: rv and lv\n  3: hh and hv\n');
choice = input('Enter choice [1-3]:');
if choice==1 arr1=rh; arr2=lh;
elseif choice==2 arr1=rv; arr2=lv;
elseif choice==3 arr1=hh; arr2=hv;
```

```
end

fprintf('Choose the direction of the saccades:\n');
fprintf('  1: right/up\n  2: left/down \n');
choice = input('Enter choice [1-3]:');
if choice==1
   idir = 1;
   fn=strrep(filename,'.lab','_up.asc');
else idir = -1;
   fn=strrep(filename,'.lab','_dn.asc');
end
fn=strcat(path,fn);
fprintf('\nFollow instructions on graph.\n');


arr1_v=derivata(arr1,smpf);
arr1_a=derivata(arr1_v,smpf);
arr1_af=remezfilt(arr1_a,55,60,smpf);
arr2_v=derivata(arr2,smpf);
arr2_a=derivata(arr2_v,smpf);
arr2_af=remezfilt(arr2_a,55,60,smpf);

figure(1),plot(t,[arr1 arr2 arr1_v/10 arr2_v/10], t, ones(size(t))*2,...
   t,-ones(size(t))*2,t,zeros(size(t)));
```

```
grid on;
legend('eye1', 'eye2', 'Vel1/10', 'Vel2/10');



% fid=fopen(fn,'a');
% fprintf(fid,['\t pos1\t vel1\t pos2\t vel2\t vel diff\n']);
% fclose(fid);
saccount = 0;
choice='y';
while ~strcmpi(choice,'n')
    figure(1);
    title('Zoom into the area of interest, and press a key when ready');
    zoom; pause;
    zoom off;
    title('0. Click before the start of saccade.');
    [at0,y0]=ginput(1);pause;
    title('1. Click before the end of saccade.');
    [at1,y1]=ginput(1); % at1=t1 approximated
%     title('2. Click the end of drift.');
%     [at2,y2]=ginput(1); % at2=tdrift
%     title('2. Approximate time of pk sacc vel');
%     [at2,y2]=ginput(1);


%    accthresh=2000;
%    Get 10 samples before the clicked point, and calculate mean and
```

```
%    standard deviation. set mean + 3*sd as the new threshold.
    sacaccarray1 = arr1_v(round(at0*smpf):round(at1*smpf));
    samplearray1 = arr1_v(round(at0*smpf)-9:round(at0*smpf));
    thres1 = mean(samplearray1) + idir*3*std(samplearray1);
    sac_start_loc1 = find(abs(sacaccarray1)>=abs(thres1));


sacaccarray2 = arr2_v(round(at0*smpf):round(at1*smpf));
    samplearray2 = arr2_v(round(at0*smpf)-9:round(at0*smpf));
    thres2 = mean(samplearray2) + idir*3*std(samplearray2);
    sac_start_loc2 = find(abs(sacaccarray2)>=abs(thres2));

    % make sure they have same size
    if sac_start_loc1(1) > sac_start_loc2(1)
        lenofarr = length(sacaccarray2) - sac_start_loc2(1);
    else
        lenofarr = length(sacaccarray1) - sac_start_loc1(1);
    end

%
%     vel1 = arr1_v(round(at0*smpf)+sac_start_loc1(1)
1:round(at0*smpf)+sac_start_loc1(1)+lenofarr);
%     pos1 = arr1(round(at0*smpf)+sac_start_loc1(1)-
1:round(at0*smpf)+sac_start_loc1(1)+lenofarr);
%     pos1 = pos1 - pos1(1);
```

```
%     acc1 = arr1_af(round(at0*smpf)+sac_start_loc1(1)-
1:round(at0*smpf)+sac_start_loc1(1)+lenofarr);
%
%
%     vel2 = arr2_v(round(at0*smpf)+sac_start_loc2(1)-
1:round(at0*smpf)+sac_start_loc2(1)+lenofarr);
%     pos2 = arr2(round(at0*smpf)+sac_start_loc2(1)-
1:round(at0*smpf)+sac_start_loc2(1)+lenofarr);
%     pos2 = pos2 - pos2(1);
%     acc2 = arr2_af(round(at0*smpf)+sac_start_loc2(1)-
1:round(at0*smpf)+sac_start_loc2(1)+lenofarr);


   vel1 = arr1_v(round(at0*smpf)+sac_start_loc1(1)-1:round(at1*smpf));
   pos1 = arr1(round(at0*smpf)+sac_start_loc1(1)-1:round(at1*smpf));
   pos1 = pos1 - pos1(1);
   acc1 = arr1_af(round(at0*smpf)+sac_start_loc1(1)-1:round(at1*smpf));



   vel2 = arr2_v(round(at0*smpf)+sac_start_loc2(1)-1:round(at1*smpf));
   pos2 = arr2(round(at0*smpf)+sac_start_loc2(1)-1:round(at1*smpf));
   pos2 = pos2 - pos2(1);
   acc2 = arr2_af(round(at0*smpf)+sac_start_loc2(1)-1:round(at1*smpf));
```

```
%   3. Select end point. calculate max position for each eye, and
%   normalize them according to bigger max position. Also normalize
%   the velocity according to bigger max acceleration.
    maxpos = max(max(abs(pos1)), max(abs(pos2)));
    maxvel = max(max(abs(vel1)), max(abs(vel2)));
    pos1_n = idir*pos1 / maxpos;
    pos2_n = idir*pos2 / maxpos;
    vel1_n = idir*vel1 / maxvel;
    vel2_n = idir*vel2 / maxvel;

    [data1 data2] = calPhasePlane(pos1_n, pos2_n, vel1_n, vel2_n);
%     fig2 = figure;
%     plot(data1(:,1), data1(:,2),'*-', data2(:,1), data2(:,2),'+-', data1(:,1),
data1(:,4), data1(:,1), data1(:,3), 'r*');
%     legend('weaker eye', 'stronger eye', 'velocity difference', 'interpolated
points');
%     grid on;
%
%     xlabel('normalized eye position');
%     ylabel('normalized eye velocity');
%     title('Phase Plane Plot');

    keep=input('Do you want to keep these points? [(y)/n]','s');
%    disp(strcat(keep, '.end.'));
    keep = strtrim(keep);
```

```
    regRsl = regexp(keep, '[nN]');
%    length(regRsl)
    if (length(regRsl) == 0)
        % Writing data to file
        fid=fopen(fn,'a');
        saccount = saccount + 1;
        fprintf(fid,['Saccade NO%d :\n'], saccount);
        fprintf(fid,['\t t start\t t end\t max pos\t max vel\n']);
        fprintf(fid,['\t %8.3f\t %8.3f\t %8.3f\t %8.3f\n'],...
            at0, at1, idir*maxpos, idir*maxvel);
        fprintf(fid,['\t pos1\t vel1\t pos2\t vel2\t vel diff\n']);
        if size(data1,1) > size(data2,1)
            nMax = size(data1,1);
        else
            nMax = size(data2,1);
        end
        for i=1:size(data1,1)
            if i > size(data2,1)
                fprintf(fid,['\t %8.3f\t %8.3f\t %8.3f\t %8.3f\t %8.3f\n'],...
                data1(i, 1), data1(i, 2), 0, 0, data1(i, 4));


            elseif i >= size(data1,1)
                fprintf(fid,['\t %8.3f\t %8.3f\t %8.3f\t %8.3f\t %8.3f\n'],...
                0, 0, data2(i, 1), data2(i, 2), 0);
            else
```

```
            fprintf(fid,['\t %8.3f\t %8.3f\t %8.3f\t %8.3f\t %8.3f\n'],...
            data1(i, 1), data1(i, 2), data2(i, 1), data2(i, 2), data1(i, 4));
        end
    end
    fclose(fid);
  else
    fprintf('Ok....points discarded.\n');
%       hold on;
%
plot(t0,arr_af(round(t0*smpf)+1)/1000,'w+',t1,arr_af(round(t1*smpf)+1)/1000,...
%           'w+',tdrift, pdrift, 'w+',
t2,pksacvel/10,'w*',tpkacc,pksacacc/1000,'w*',tpkdec,pksacdec/1000,'w*');
%
plot(t0,arr_af(round(t0*smpf)+1)/1000,'r',t1,arr_af(round(t1*smpf)+1)/1000,...
%           'r',tdrift, pdrift,
'r',t2,pksacvel/10,'r',tpkacc,pksacacc/1000,'r',tpkdec,pksacdec/1000,'r');
  end
  close(2);
  choice=input('Do you want to continue? [(y)/n]','s');
  choice=strtrim(choice);
end
fprintf('Done.\n');
```

Table 1

FUNCTIONAL CLASSES OF HUMAN EYE MOVEMENTS

Class of Eye Movement	*Main Function*
Vestibular	Holds images of the seen world steady on the retina during brief head rotations or translations
Visual Fixation	Holds the image of a stationary object on the fovea by minimizing ocular drifts
Optokinetic	Holds images of the seen world steady on the retina during sustained head rotation
Smooth Pursuit	Holds the image of a small moving target on the fovea; or holds the image of a small near target on the retina during linear self-motion; with optokinetic responses, aids gaze stabilization during sustained head rotation
Nystagmus quick phases	Reset the eyes during prolonged rotation and direct gaze towards the oncoming visual scene
Saccades	Bring images of objects of interest onto the fovea
Vergence	Moves the eyes in opposite directions so that images of a single object are placed or held simultaneously on the fovea of each eye

(Reproduced courtesy of Dr. Leigh RJ.[5])

Table 2

CLASSIFICATION OF SACCADES

Classification	**Definition**
VOLITIONAL SACCADES	Elective saccades made as part of purposeful behavior
Predictive, anticipatory	Saccades generated in anticipation of or in search of the appearance of a target at a particular location.
Memory-guided	Saccades generated to a location in which a target has been previously present (Fig. 3-2C).
Antisaccades	Saccades generated in the opposite direction to the sudden appearance of a target (after being instructed to do so – Fig. 3-2D).
To command	Saccades generated on cue.
REFLEXIVE SACCADES	Saccades generated to novel stimuli (visual, auditory or tactile) that unexpectedly occur within the environment.
EXPRESS SACCADES	Very short latency saccades that can be elicited when the novel stimulus is presented after the fixation stimulus has disappeared (gap stimulus – Fig. 3-2B)
SPONTANEOUS SACCADES	Seemingly random saccades that occur when the subject is not required to perform any particular behavioral task.
QUICK PHASES	Quick phases of nystagmus generated during vestibular or optokinetic stimulation or as automatic resetting movements in the presence of spontaneous drift of the eyes.

(Reproduced courtesy of Dr. Leigh RJ.[5])

Figure 1

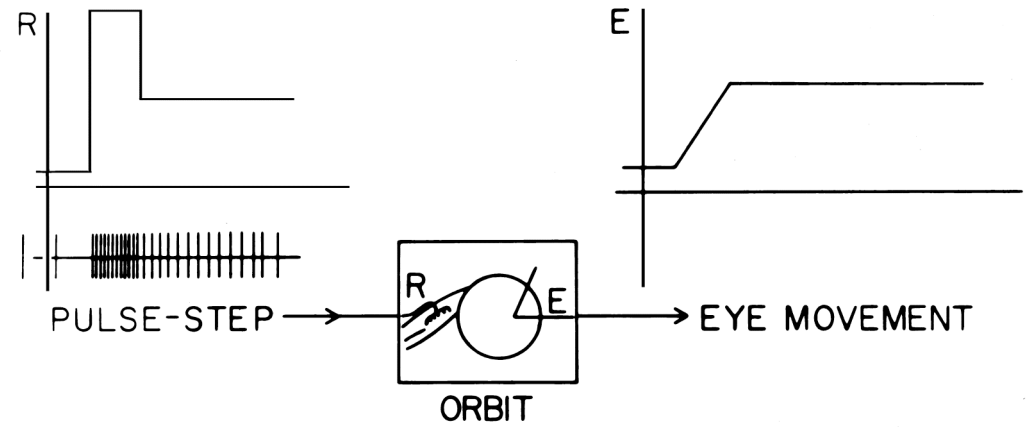


Figure 2

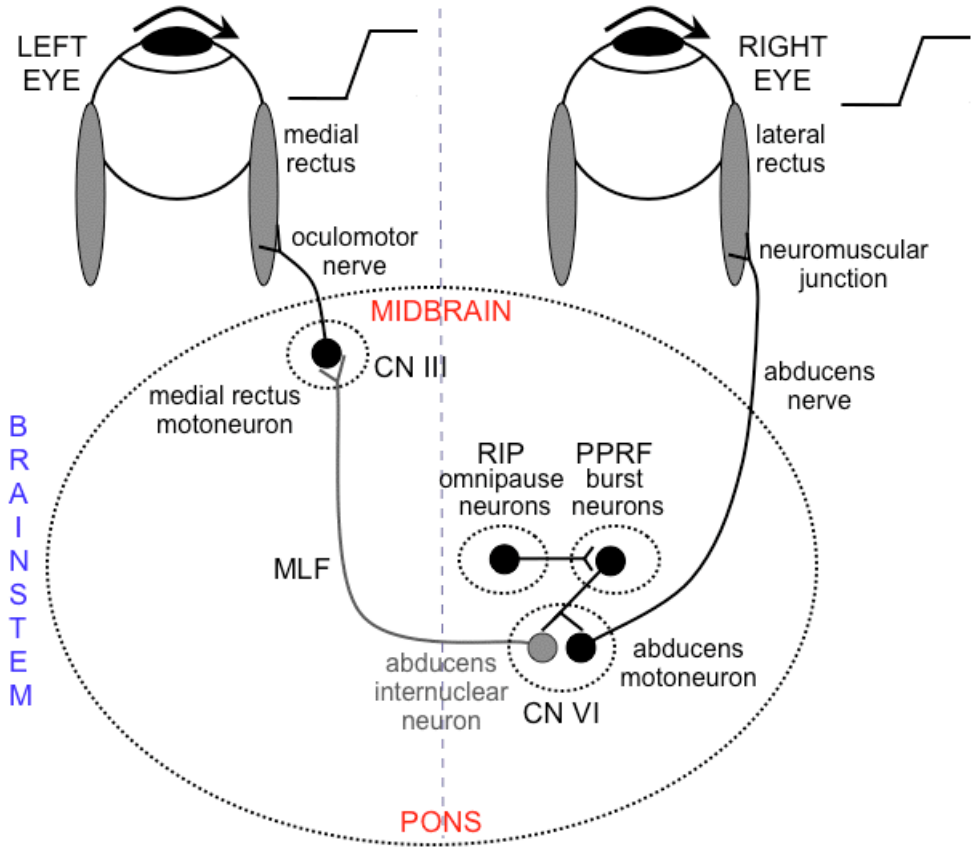

LEFT EYE
medial rectus
oculomotor nerve
RIGHT EYE
lateral rectus
neuromuscular junction
MIDBRAIN
CN III
medial rectus motoneuron
abducens nerve
BRAINSTEM
RIP omnipause neurons
PPRF burst neurons
MLF
abducens internuclear neuron
abducens motoneuron
CN VI
PONS

Figure 3

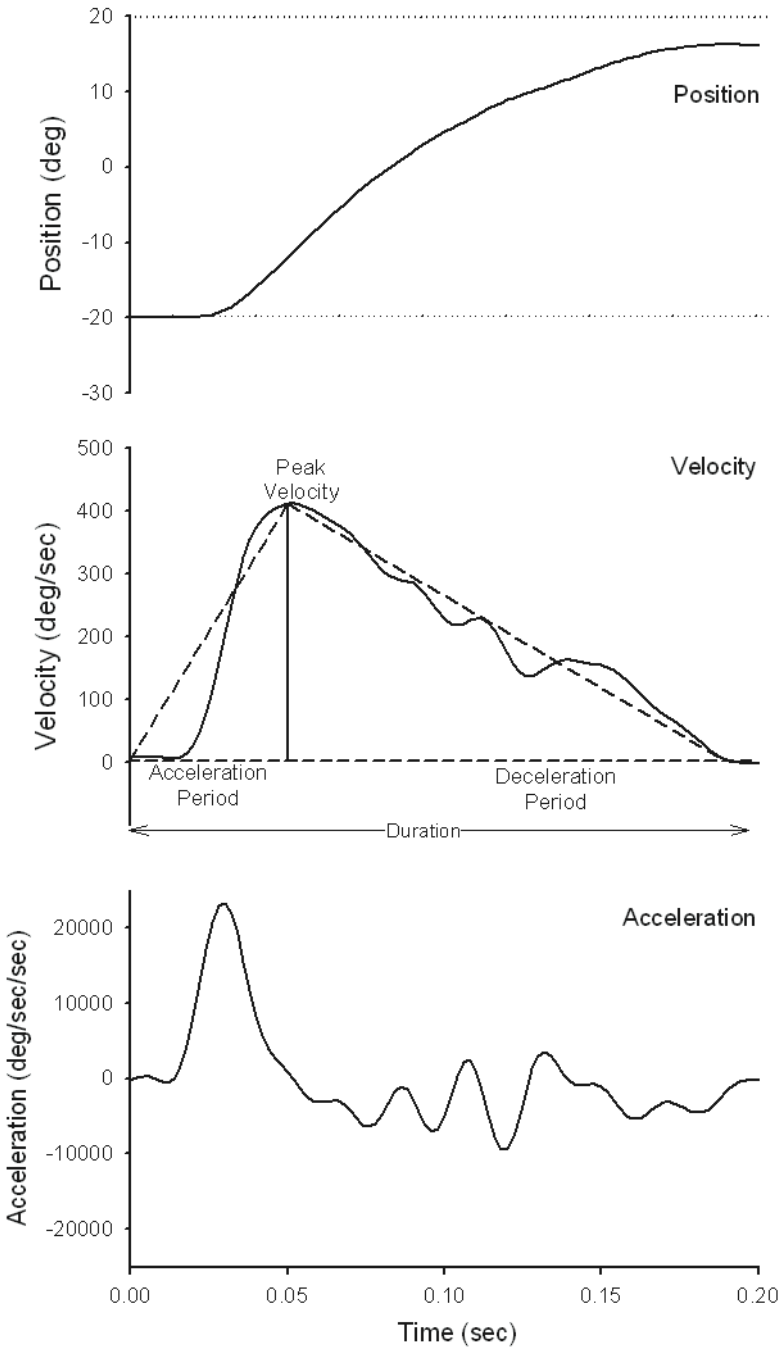

Position
Position (deg)
20
10
0
-10
-20
-30
Velocity
Velocity (deg/sec)
Peak
Velocity
500
400
300
200
100
0
Acceleration
Period
Deceleration
Period
Duration
Acceleration
Acceleration (deg/sec/sec)
20000
10000
0
-10000
-20000
0.00
0.05
0.10
0.15
0.20
Time (sec)

Figure 4

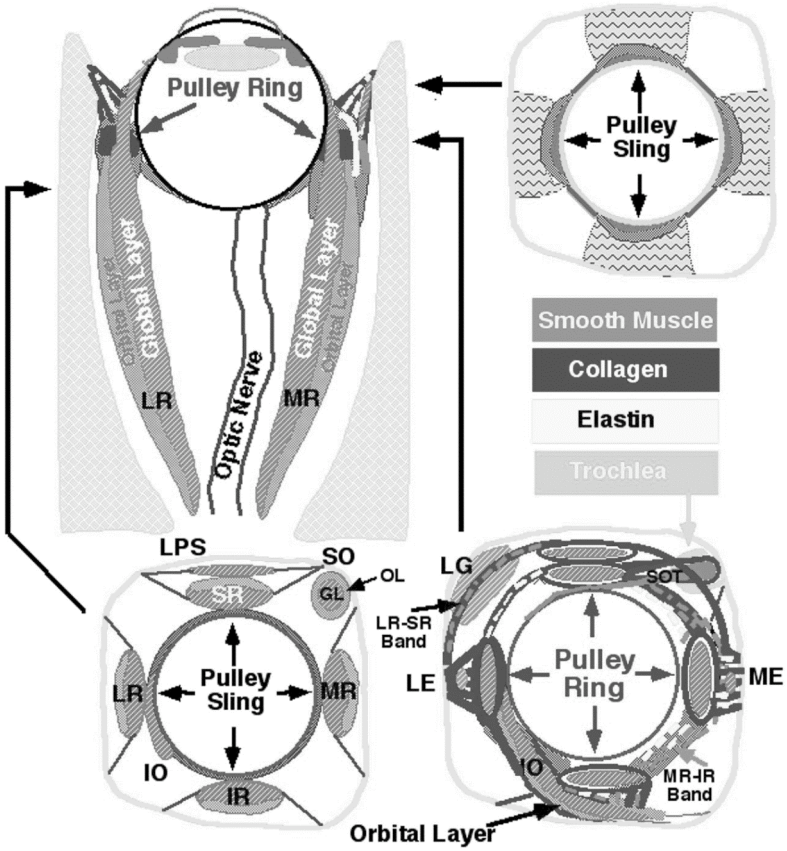


Figure 5

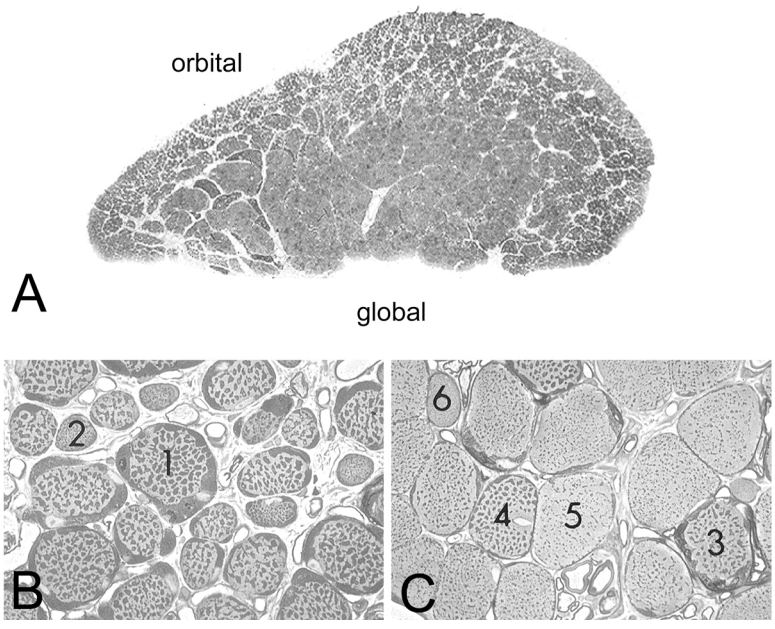


Figure 6

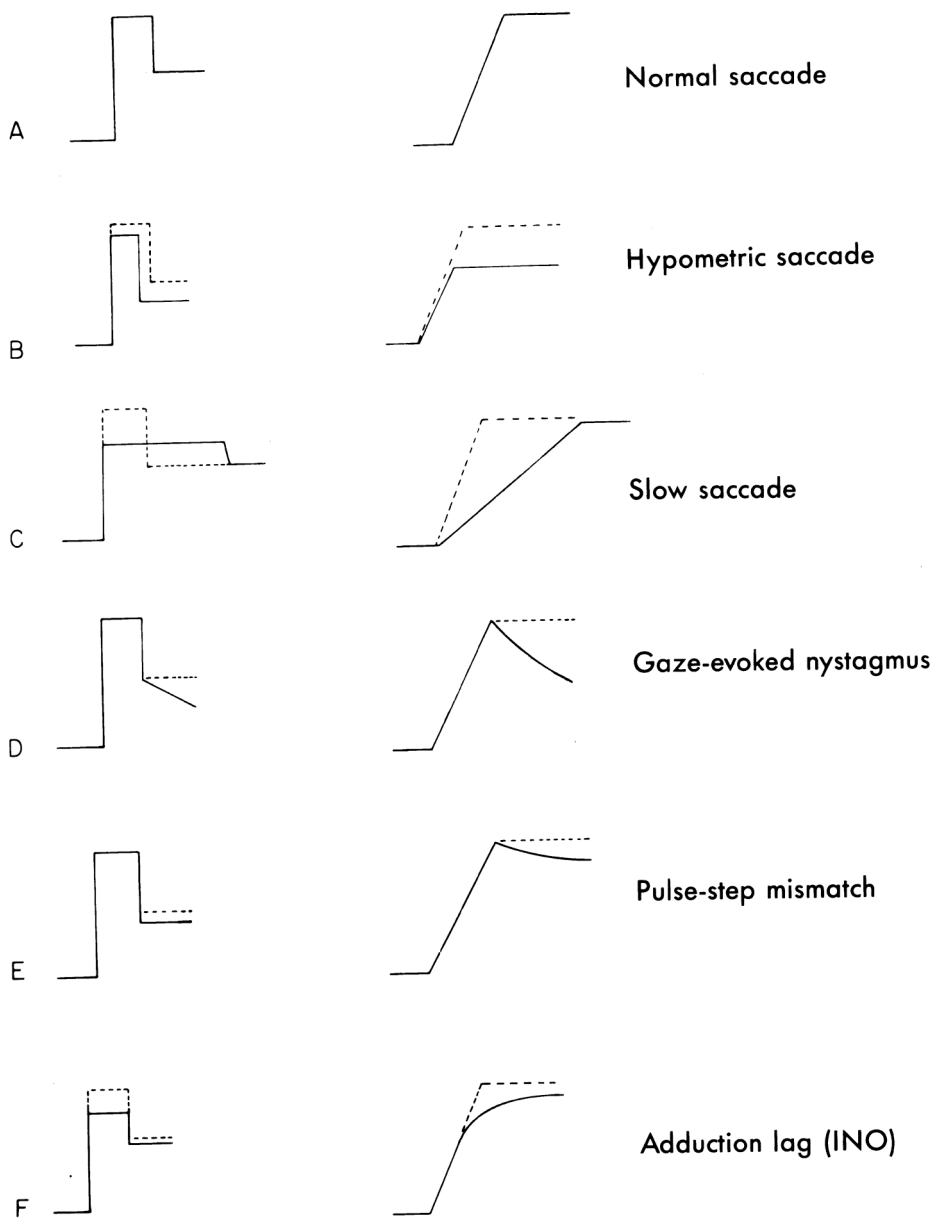

A
Normal saccade
B
Hypometric saccade
C
Slow saccade
D
Gaze-evoked nystagmus
E
Pulse-step mismatch
F
Adduction lag (INO)

Figure 7

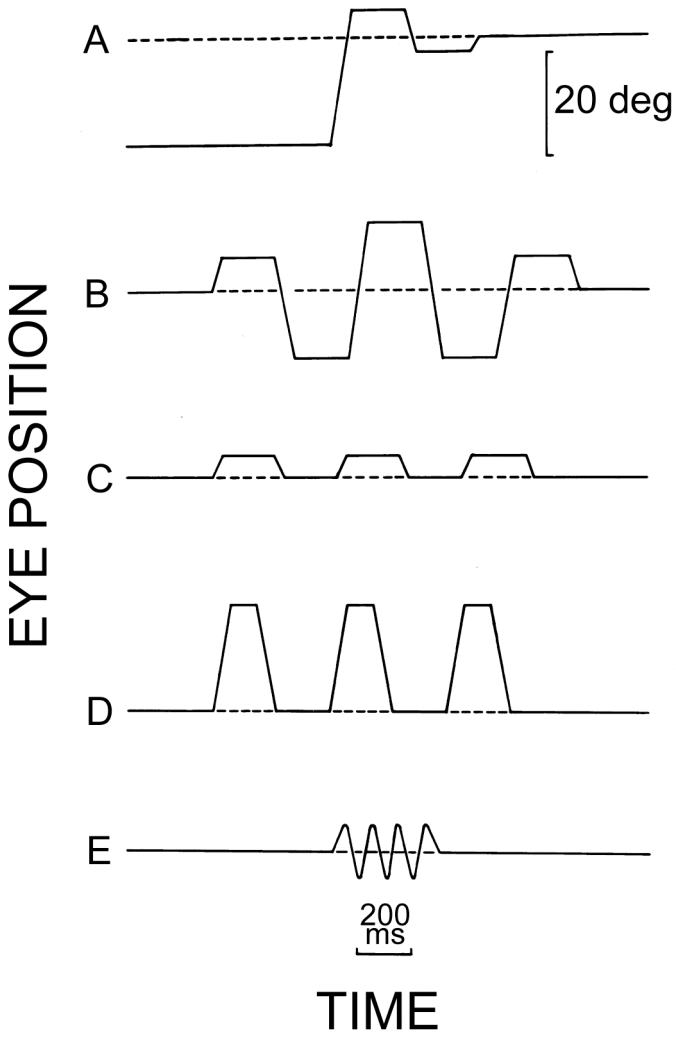


Figure 8

Figure 9

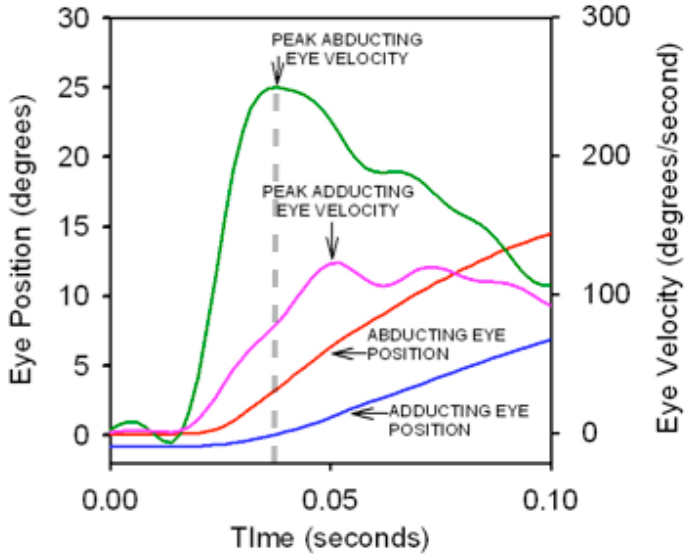


Figure 10

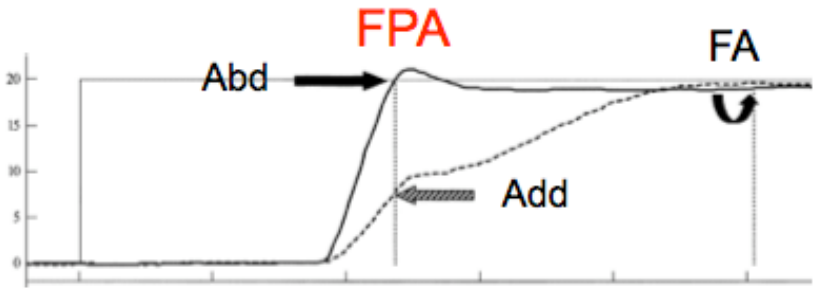
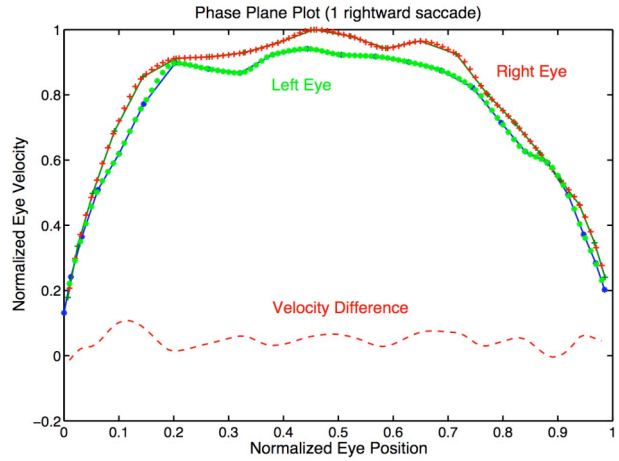


Figure 11


Phase Plane Plot (1 rightward saccade)
Right Eye
Left Eye
Velocity Difference
Normalized Eye Velocity
Normalized Eye Position

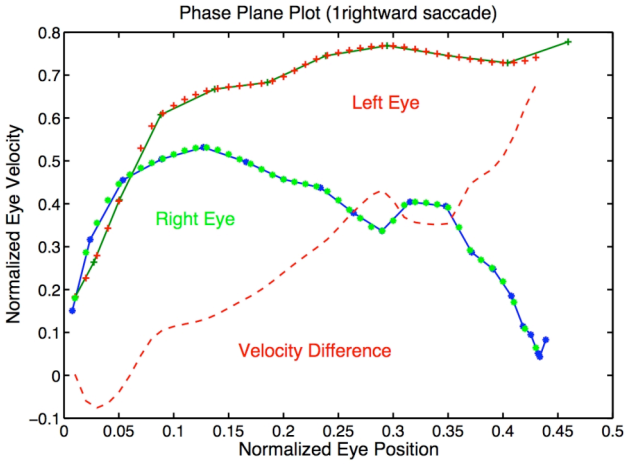

Phase Plane Plot (1rightward saccade)
Left Eye
Right Eye
Velocity Difference
Normalized Eye Velocity
Normalized Eye Position

Figure 12

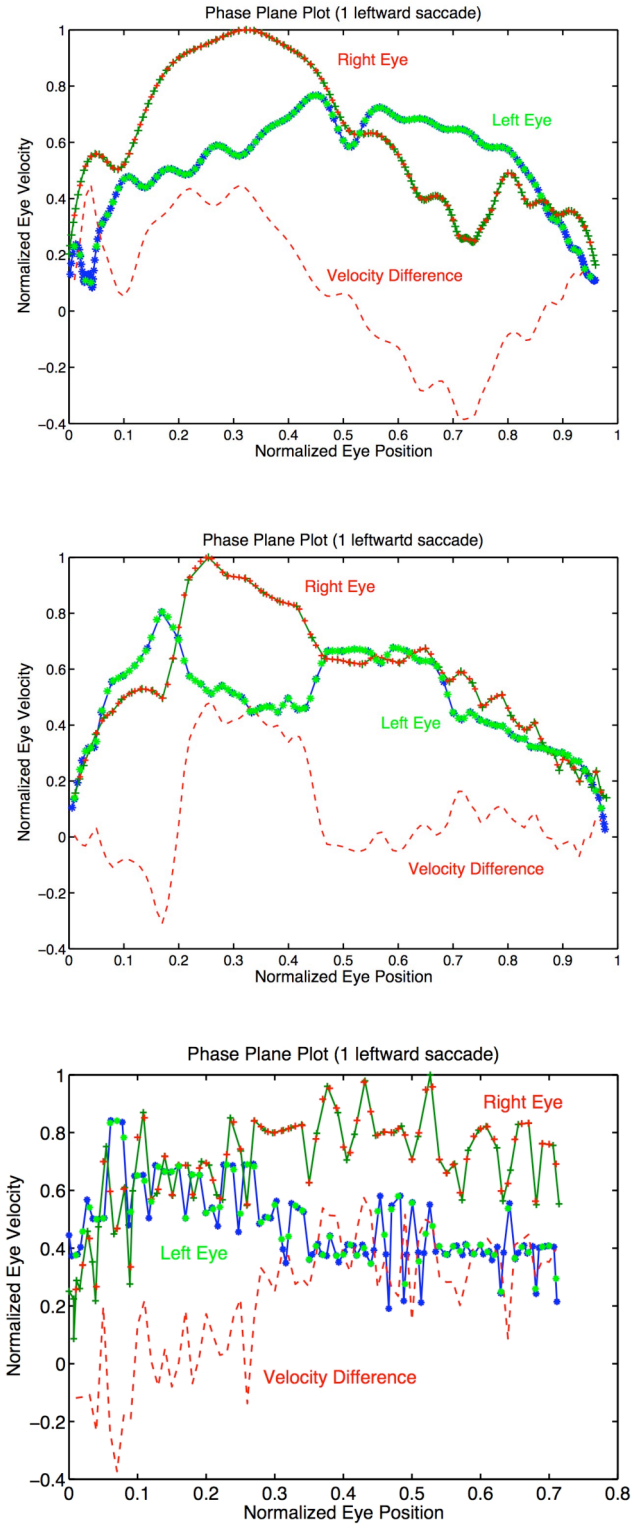
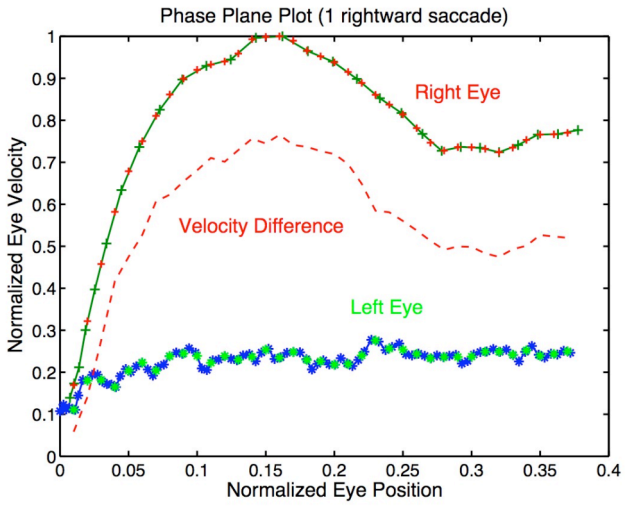

Phase Plane Plot (1 leftward saccade)
Right Eye
Left Eye
Velocity Difference
Normalized Eye Velocity
Normalized Eye Position
Phase Plane Plot (1 leftwartd saccade)
Right Eye
Left Eye
Velocity Difference
Normalized Eye Velocity
Normalized Eye Position
Phase Plane Plot (1 leftward saccade)
Right Eye
Left Eye
Velocity Difference
Normalized Eye Velocity
Normalized Eye Position

Figure 13


Phase Plane Plot (1 rightward saccade)
Right Eye
Velocity Difference
Left Eye
Normalized Eye Velocity
Normalized Eye Position
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1
0.05
0.15
0.25
0.35

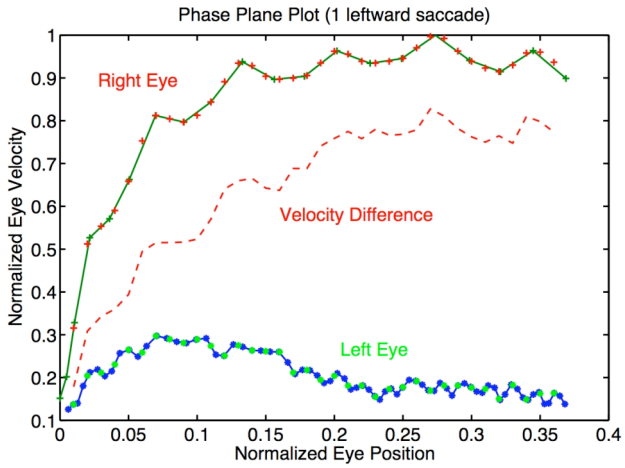
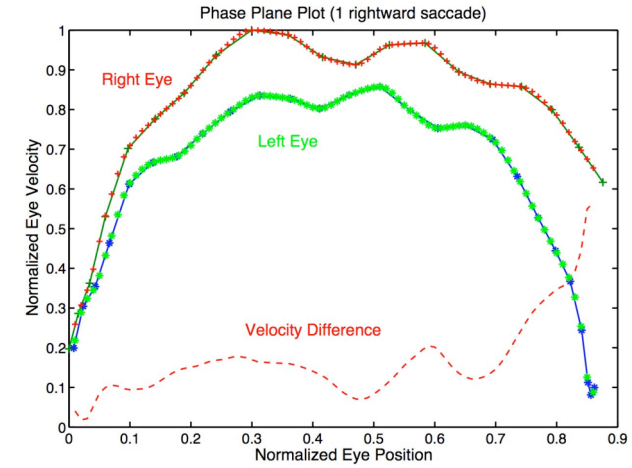

Phase Plane Plot (1 leftward saccade)
Right Eye
Velocity Difference
Left Eye
Normalized Eye Velocity
Normalized Eye Position
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1
0
0.05
0.1
0.15
0.2
0.25
0.3
0.35
0.4

Figure 14


Phase Plane Plot (1 rightward saccade)
Right Eye
Left Eye
Velocity Difference
Normalized Eye Velocity
Normalized Eye Position

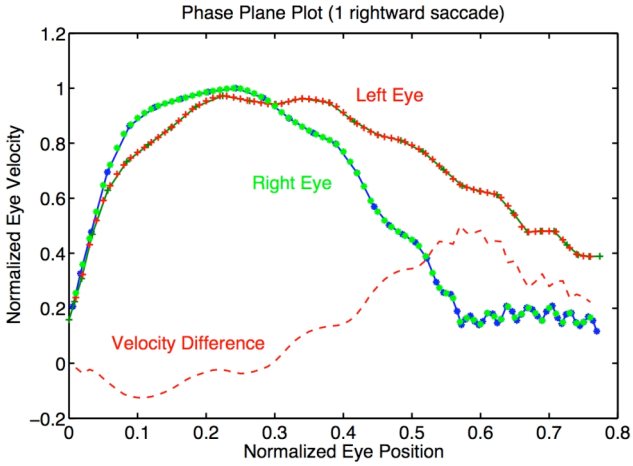
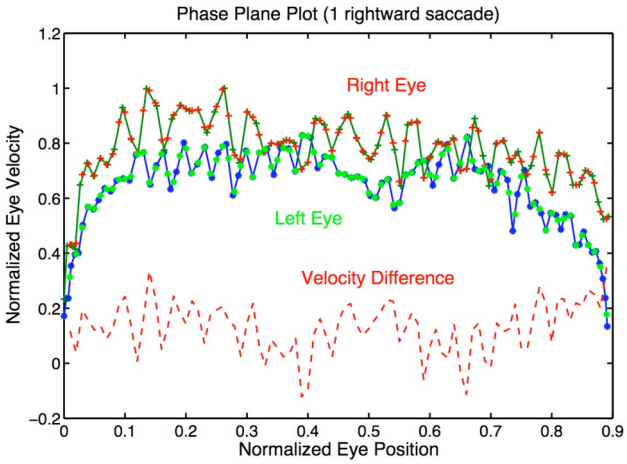

Phase Plane Plot (1 rightward saccade)
Left Eye
Right Eye
Velocity Difference
Normalized Eye Velocity
Normalized Eye Position

Figure 15


Phase Plane Plot (1 rightward saccade)
Right Eye
Left Eye
Velocity Difference
Normalized Eye Velocity
Normalized Eye Position

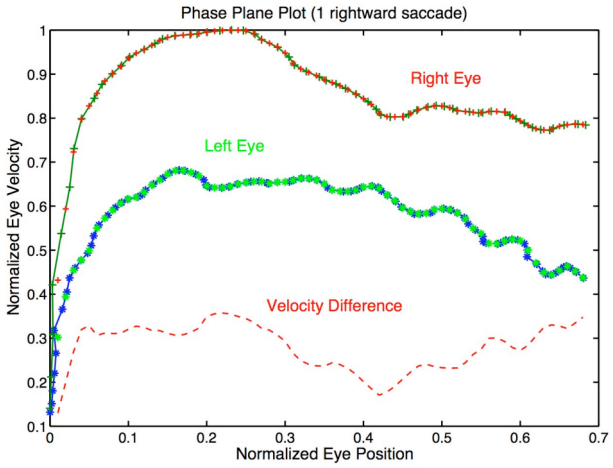
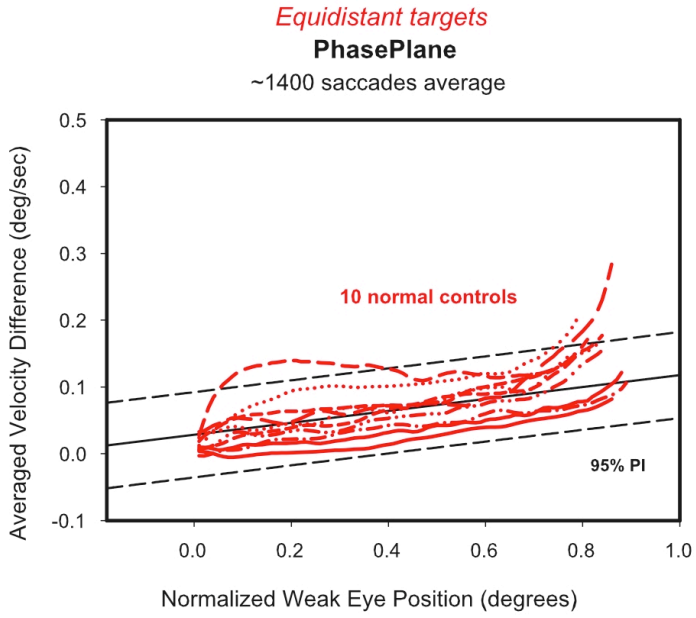

Phase Plane Plot (1 rightward saccade)
Right Eye
Left Eye
Velocity Difference
Normalized Eye Velocity
Normalized Eye Position

Figure 16


Equidistant targets
PhasePlane
~1400 saccades average
Averaged Velocity Difference (deg/sec)
0.5
0.4
0.3
0.2
0.1
0.0
-0.1
10 normal controls
95% PI
0.0
0.2
0.4
0.6
0.8
1.0
Normalized Weak Eye Position (degrees)

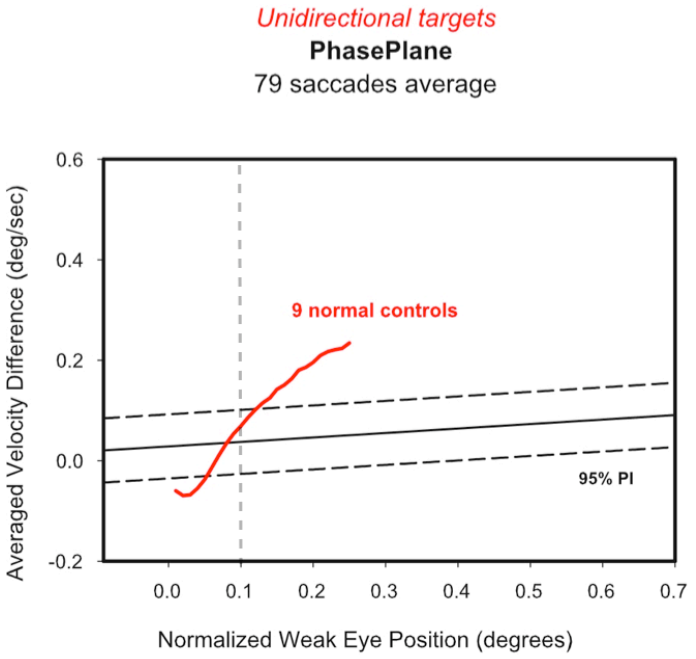

Unidirectional targets
PhasePlane
79 saccades average
Averaged Velocity Difference (deg/sec)
0.6
0.4
0.2
0.0
-0.2
9 normal controls
95% PI
0.0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
Normalized Weak Eye Position (degrees)

Figure 17

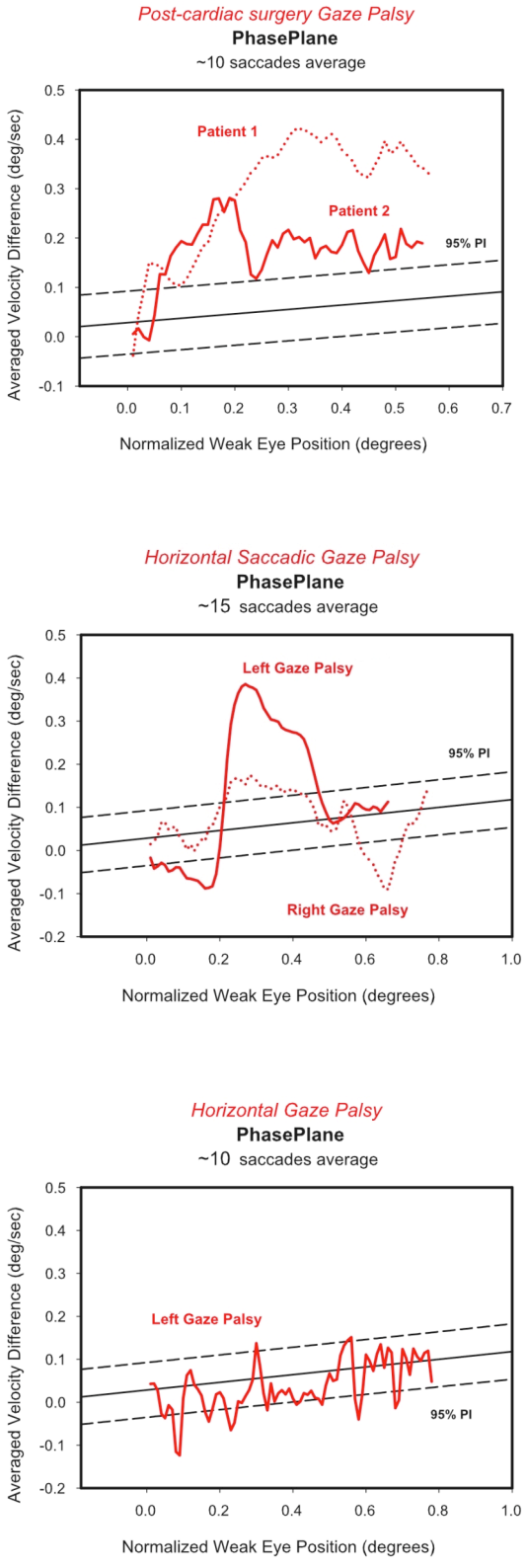
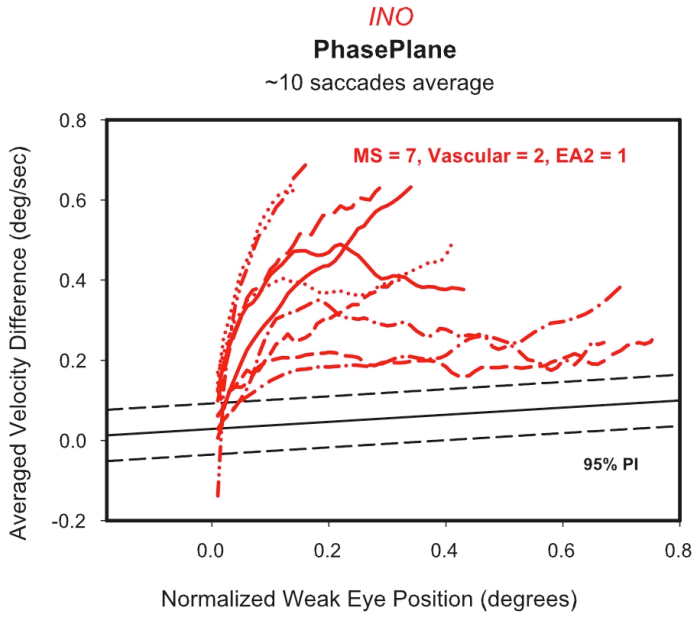

Post-cardiac surgery Gaze Palsy
PhasePlane
~10 saccades average
Patient 1
Patient 2
95% PI
Averaged Velocity Difference (deg/sec)
Normalized Weak Eye Position (degrees)
Horizontal Saccadic Gaze Palsy
PhasePlane
~15 saccades average
Left Gaze Palsy
Right Gaze Palsy
95% PI
Averaged Velocity Difference (deg/sec)
Normalized Weak Eye Position (degrees)
Horizontal Gaze Palsy
PhasePlane
~10 saccades average
Left Gaze Palsy
95% PI
Averaged Velocity Difference (deg/sec)
Normalized Weak Eye Position (degrees)

Figure 18


INO
PhasePlane
~10 saccades average
MS = 7, Vascular = 2, EA2 = 1
95% PI
Averaged Velocity Difference (deg/sec)
Normalized Weak Eye Position (degrees)
0.8
0.6
0.4
0.2
0.0
-0.2
0.0
0.2
0.4
0.6
0.8

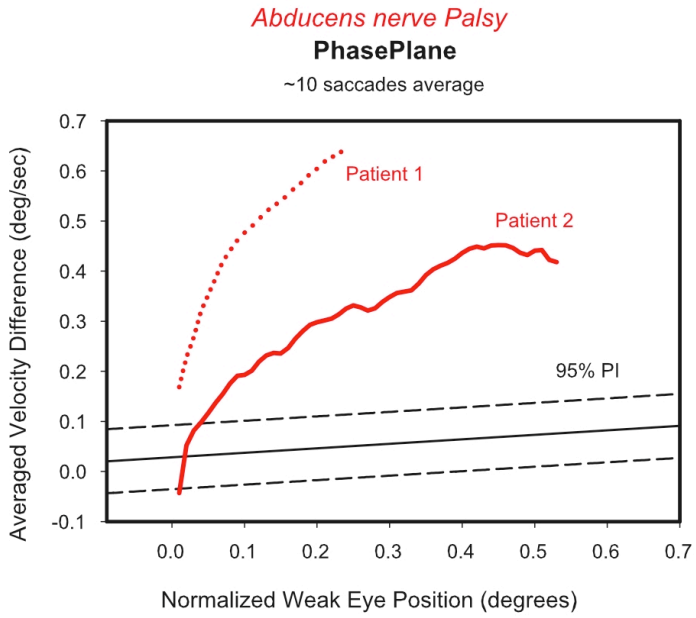
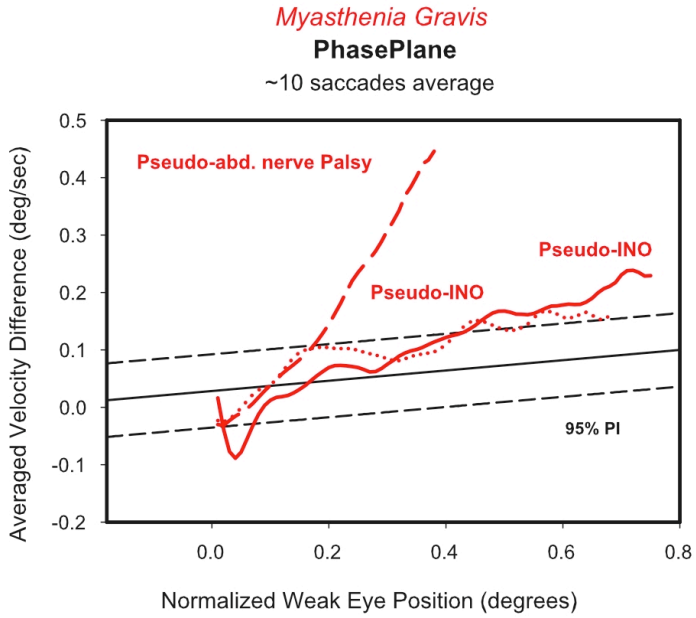

Abducens nerve Palsy
PhasePlane
~10 saccades average
Patient 1
Patient 2
95% PI
Averaged Velocity Difference (deg/sec)
Normalized Weak Eye Position (degrees)
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
-0.1
0.0
0.1
0.2
0.3
0.4
0.5
0.6
0.7

Figure 19


Myasthenia Gravis
PhasePlane
~10 saccades average
Pseudo-abd. nerve Palsy
Pseudo-INO
Pseudo-INO
95% PI
Averaged Velocity Difference (deg/sec)
Normalized Weak Eye Position (degrees)
0.5
0.4
0.3
0.2
0.1
0.0
-0.1
-0.2
0.0
0.2
0.4
0.6
0.8

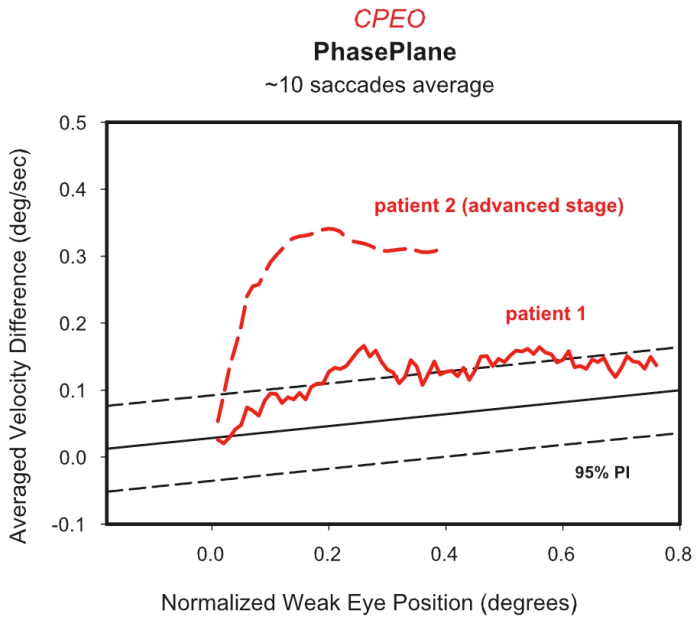

CPEO
PhasePlane
~10 saccades average
patient 2 (advanced stage)
patient 1
95% PI
Averaged Velocity Difference (deg/sec)
Normalized Weak Eye Position (degrees)
0.5
0.4
0.3
0.2
0.1
0.0
-0.1
0.0
0.2
0.4
0.6
0.8

Figure 20

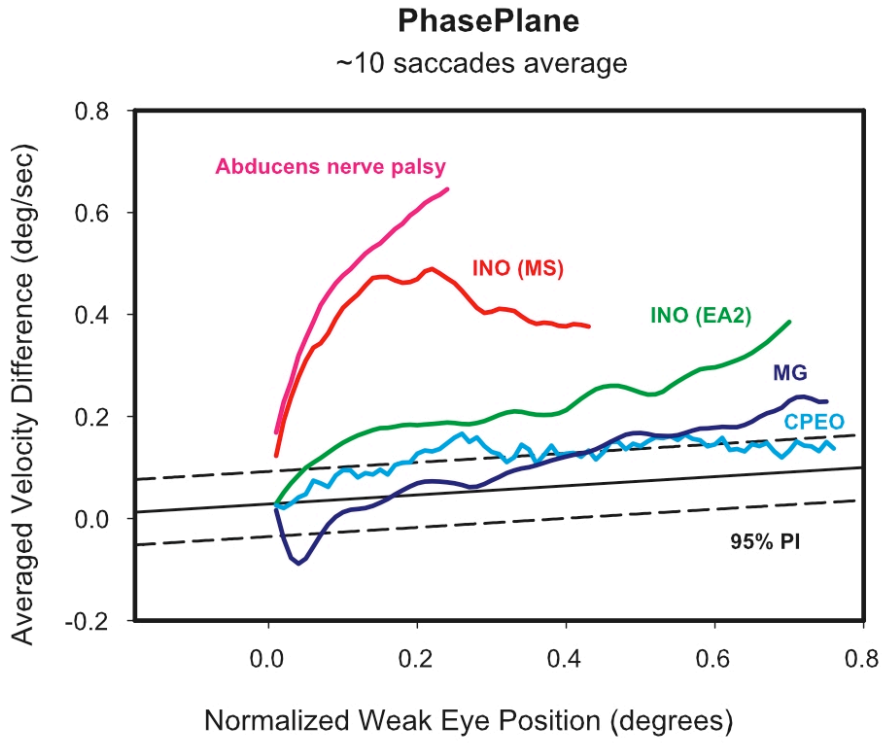
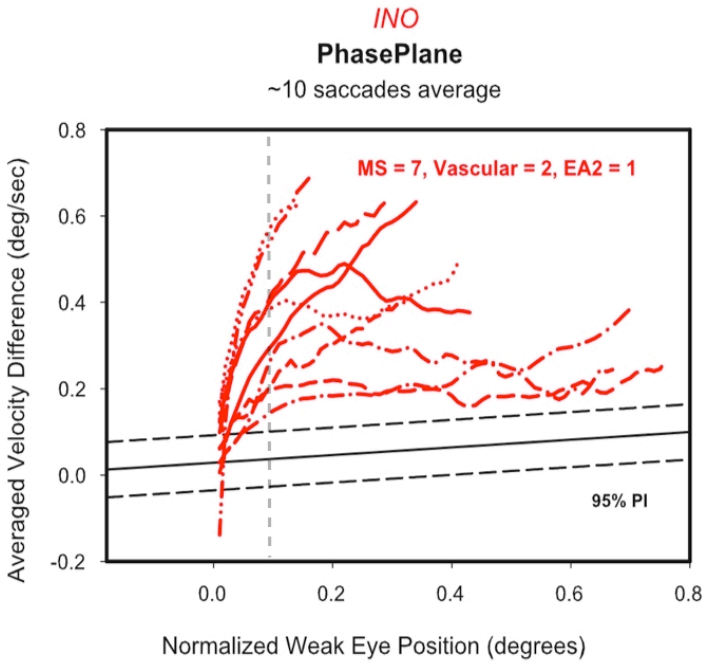

PhasePlane
~10 saccades average
Abducens nerve palsy
INO (MS)
INO (EA2)
MG
CPEO
95% PI
Averaged Velocity Difference (deg/sec)
0.8
0.6
0.4
0.2
0.0
-0.2
0.0
0.2
0.4
0.6
0.8
Normalized Weak Eye Position (degrees)

Figure 21


INO
PhasePlane
~10 saccades average
MS = 7, Vascular = 2, EA2 = 1
95% PI
Averaged Velocity Difference (deg/sec)
0.8
0.6
0.4
0.2
0.0
-0.2
0.0
0.2
0.4
0.6
0.8
Normalized Weak Eye Position (degrees)

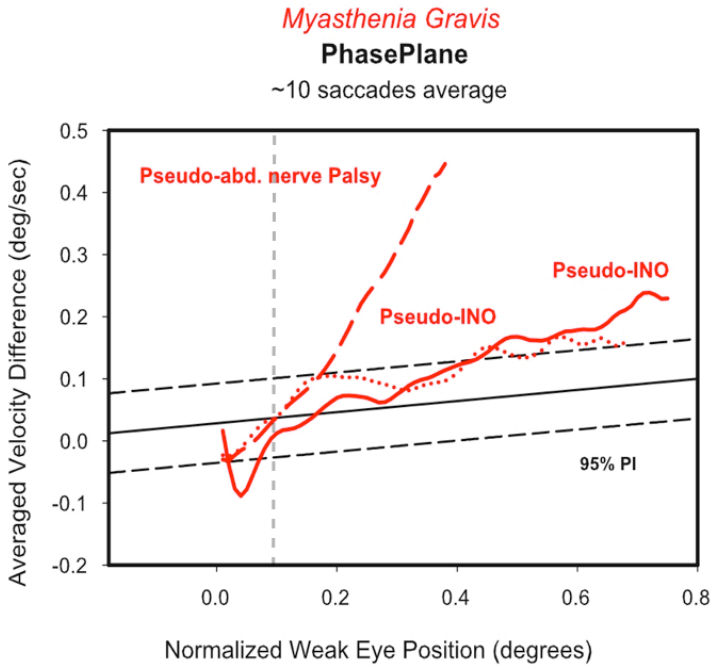
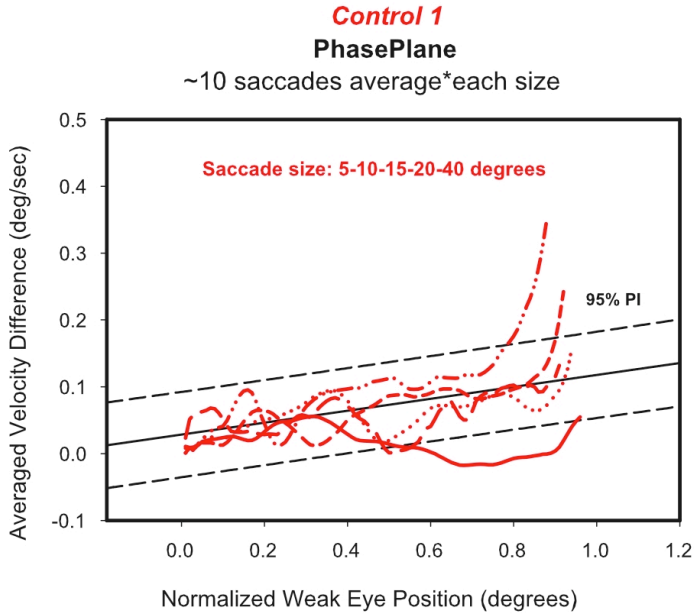

Myasthenia Gravis
PhasePlane
~10 saccades average
Pseudo-abd. nerve Palsy
Pseudo-INO
Pseudo-INO
95% PI
Averaged Velocity Difference (deg/sec)
0.5
0.4
0.3
0.2
0.1
0.0
-0.1
-0.2
0.0
0.2
0.4
0.6
0.8
Normalized Weak Eye Position (degrees)

Figure 22


Control 1
PhasePlane
~10 saccades average*each size
Saccade size: 5-10-15-20-40 degrees
95% PI
Averaged Velocity Difference (deg/sec)
0.5
0.4
0.3
0.2
0.1
0.0
-0.1
0.0
0.2
0.4
0.6
0.8
1.0
1.2
Normalized Weak Eye Position (degrees)

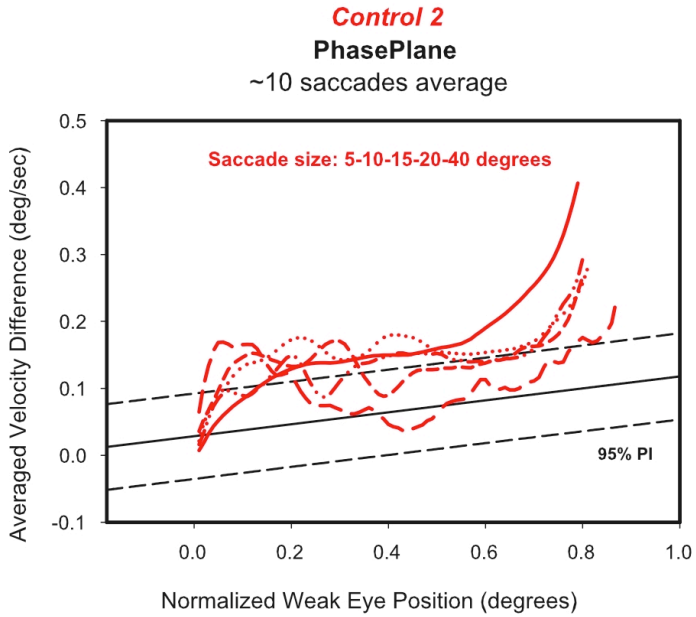

Control 2
PhasePlane
~10 saccades average
Saccade size: 5-10-15-20-40 degrees
95% PI
Averaged Velocity Difference (deg/sec)
0.5
0.4
0.3
0.2
0.1
0.0
-0.1
0.0
0.2
0.4
0.6
0.8
1.0
Normalized Weak Eye Position (degrees)

Figure 23

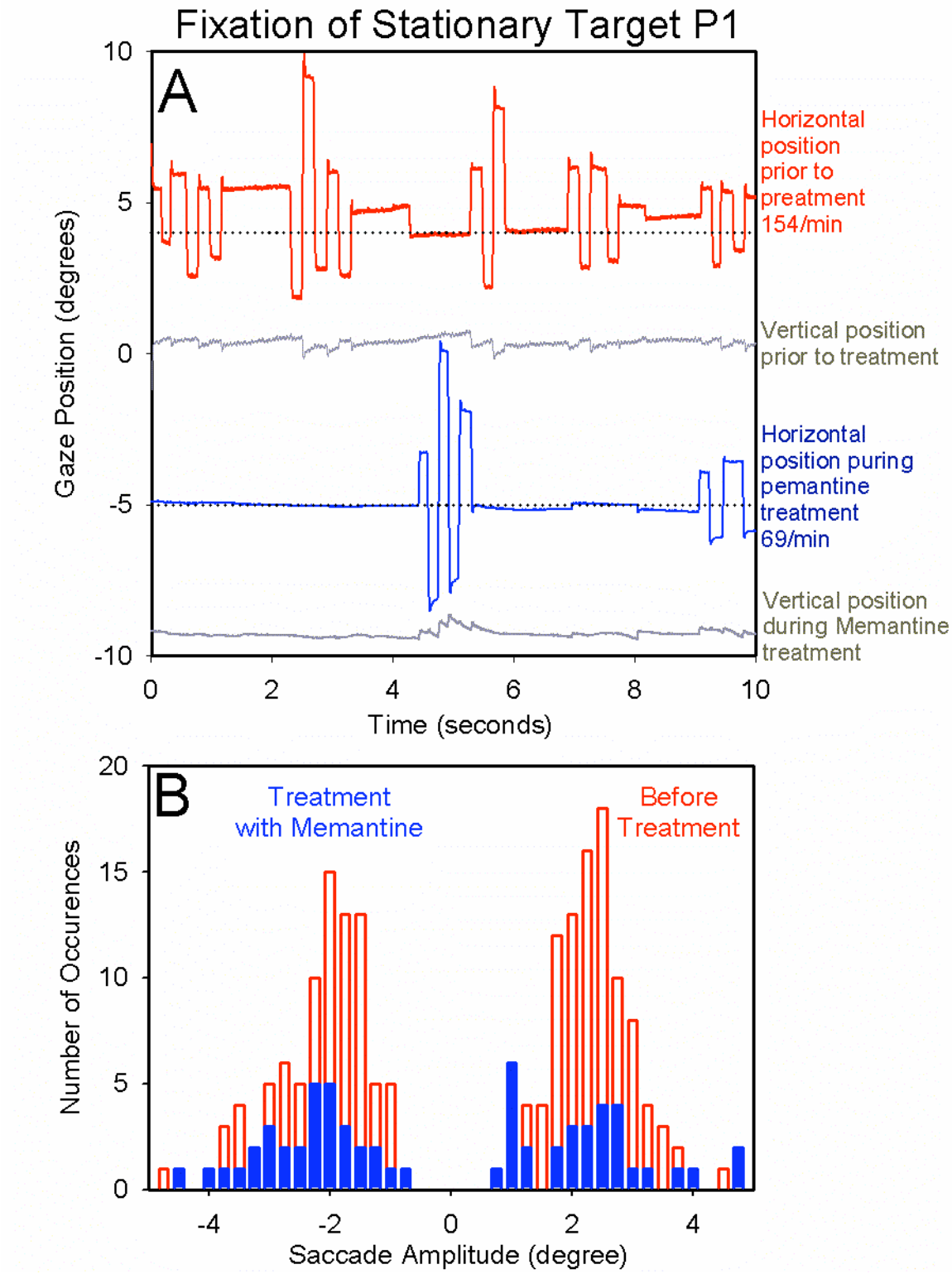

Fixation of Stationary Target P1
A
Gaze Position (degrees)
Time (seconds)
Horizontal position prior to preatment 154/min
Vertical position prior to treatment
Horizontal position puring pemantine treatment 69/min
Vertical position during Memantine treatment
B
Treatment with Memantine
Before Treatment
Number of Occurences
Saccade Amplitude (degree)

Figure 24

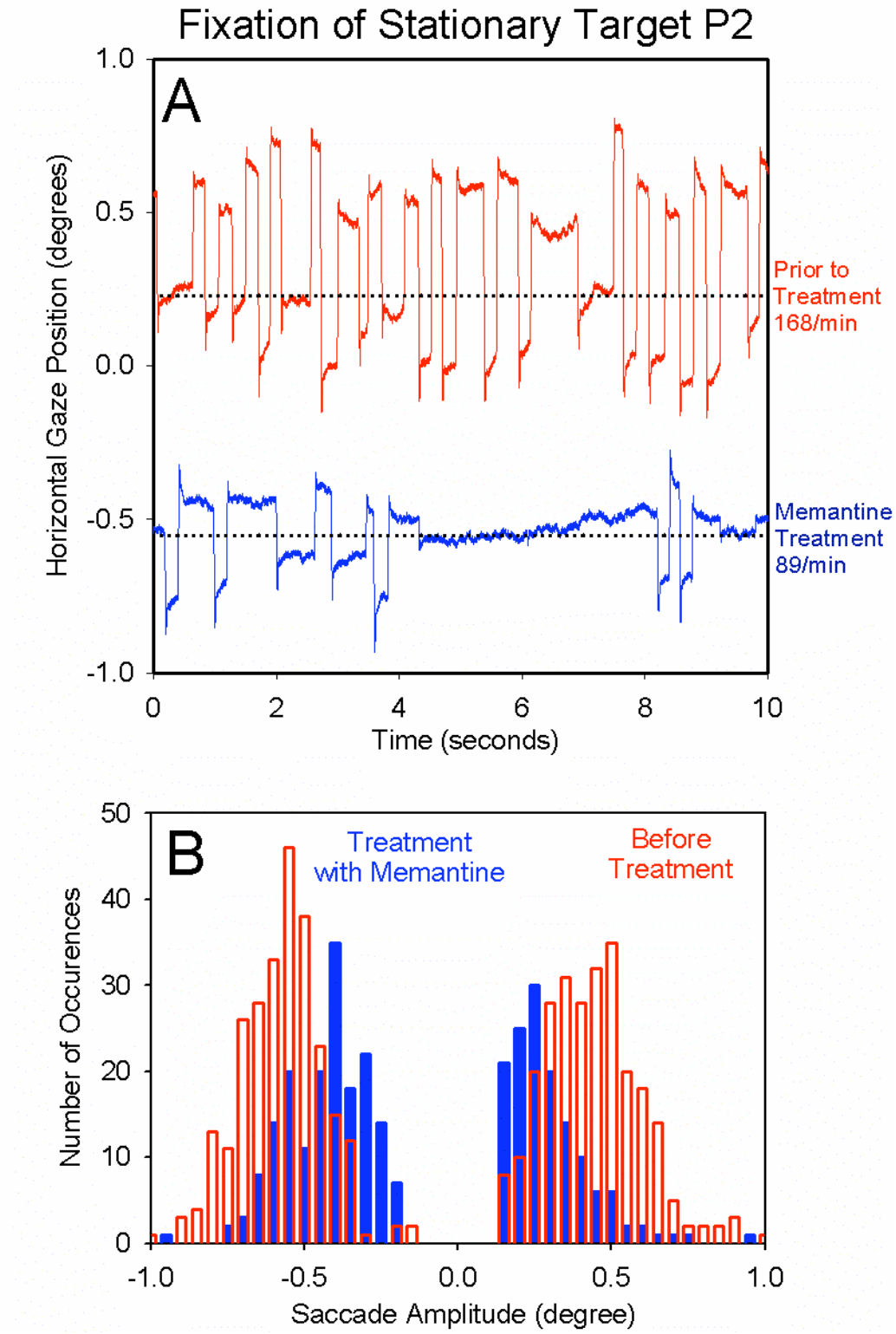

Fixation of Stationary Target P2
A
Horizontal Gaze Position (degrees)
1.0
0.5
0.0
-0.5
-1.0
0
2
4
6
8
10
Time (seconds)
Prior to Treatment 168/min
Memantine Treatment 89/min
B
Number of Occurences
50
40
30
20
10
0
-1.0
-0.5
0.0
0.5
1.0
Saccade Amplitude (degree)
Treatment with Memantine
Before Treatment

Figure 25

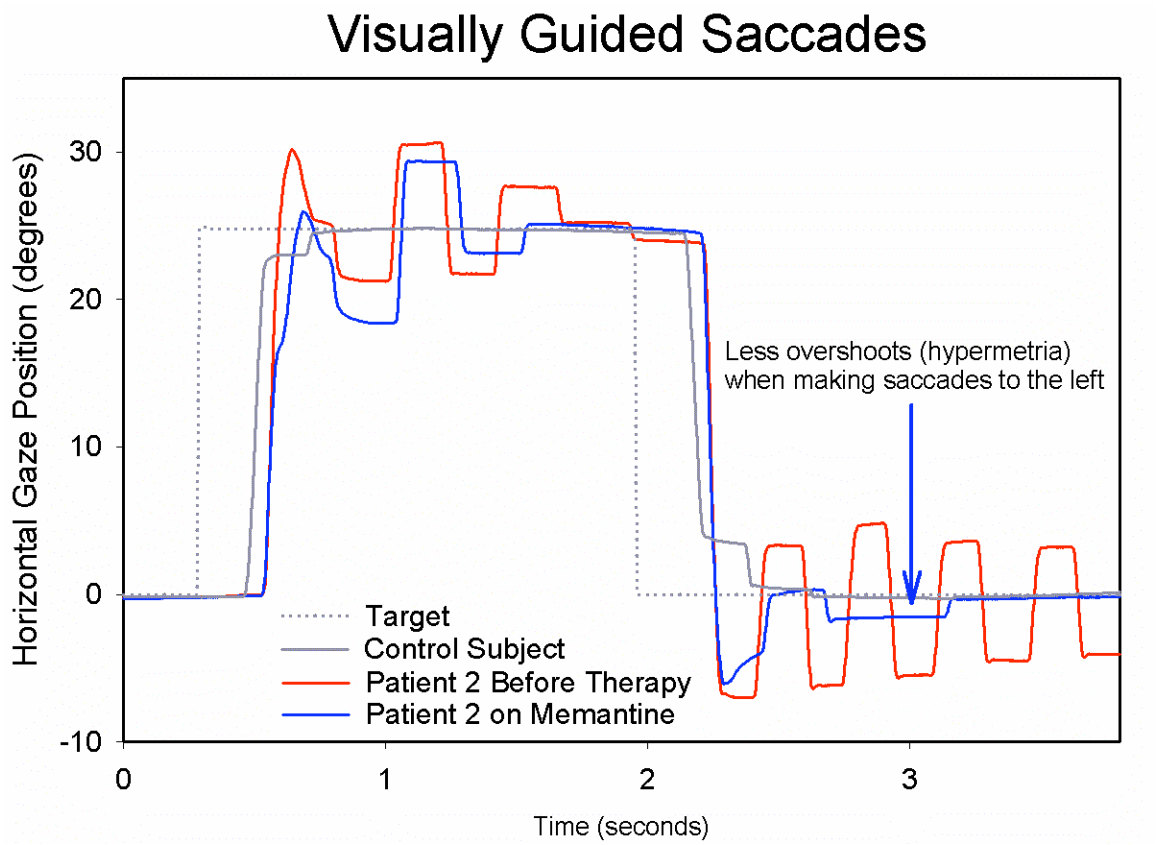

Visually Guided Saccades
Horizontal Gaze Position (degrees)
30
20
10
0
-10
0
1
2
3
Time (seconds)
Less overshoots (hypermetria)
when making saccades to the left
Target
Control Subject
Patient 2 Before Therapy
Patient 2 on Memantine

Figure 26

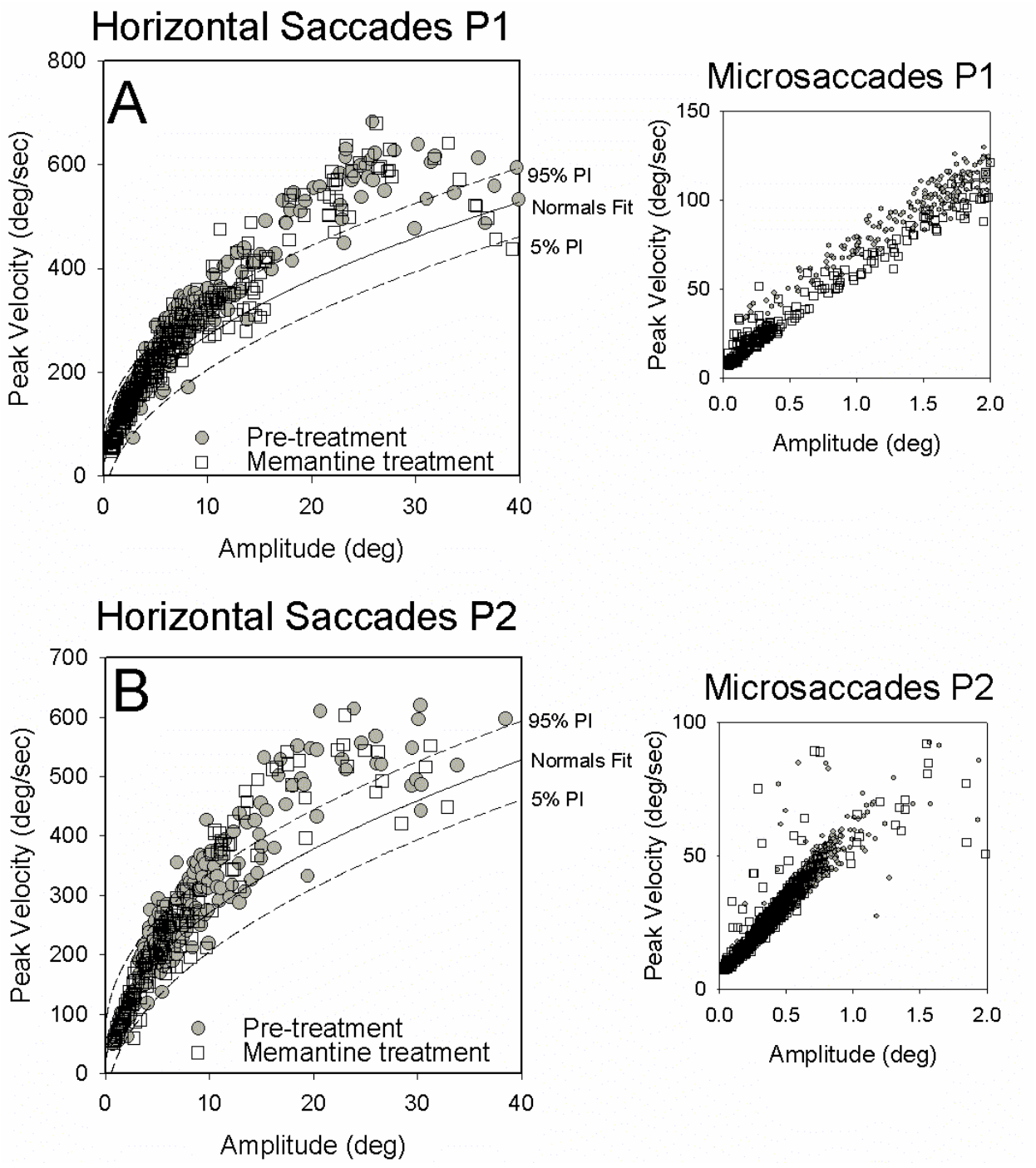

Horizontal Saccades P1
A
Peak Velocity (deg/sec)
Amplitude (deg)
95% PI
Normals Fit
5% PI
Pre-treatment
Memantine treatment
Microsaccades P1
Peak Velocity (deg/sec)
Amplitude (deg)
Horizontal Saccades P2
B
Peak Velocity (deg/sec)
Amplitude (deg)
95% PI
Normals Fit
5% PI
Pre-treatment
Memantine treatment
Microsaccades P2
Peak Velocity (deg/sec)
Amplitude (deg)

Figure 27

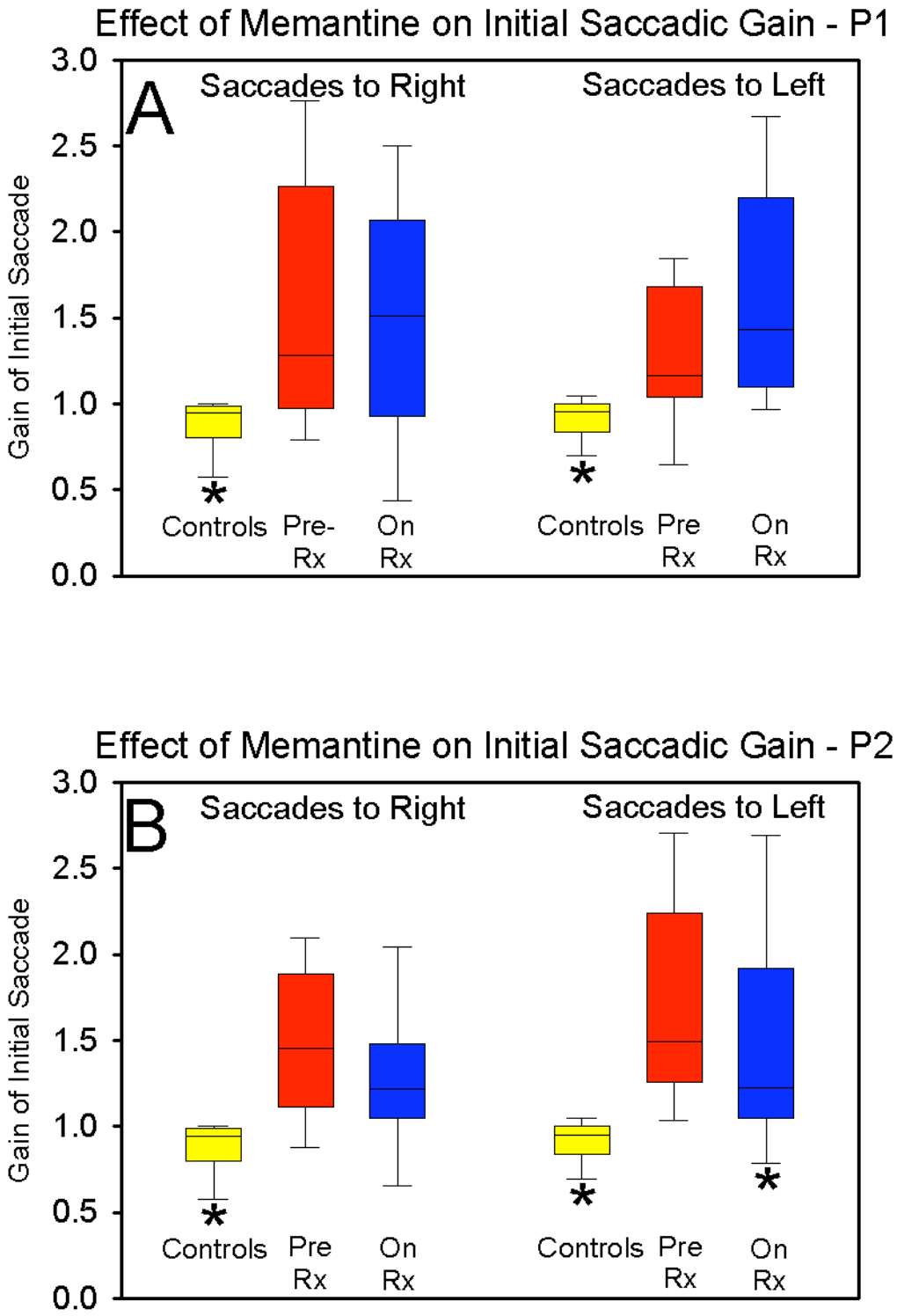

Effect of Memantine on Initial Saccadic Gain - P1
A
Saccades to Right
Saccades to Left
Gain of Initial Saccade
3.0
2.5
2.0
1.5
1.0
0.5
0.0
Controls
Pre-Rx
On Rx
Controls
Pre Rx
On Rx
Effect of Memantine on Initial Saccadic Gain - P2
B
Saccades to Right
Saccades to Left
Gain of Initial Saccade
Controls
Pre Rx
On Rx
Controls
Pre Rx
On Rx

Figure 28

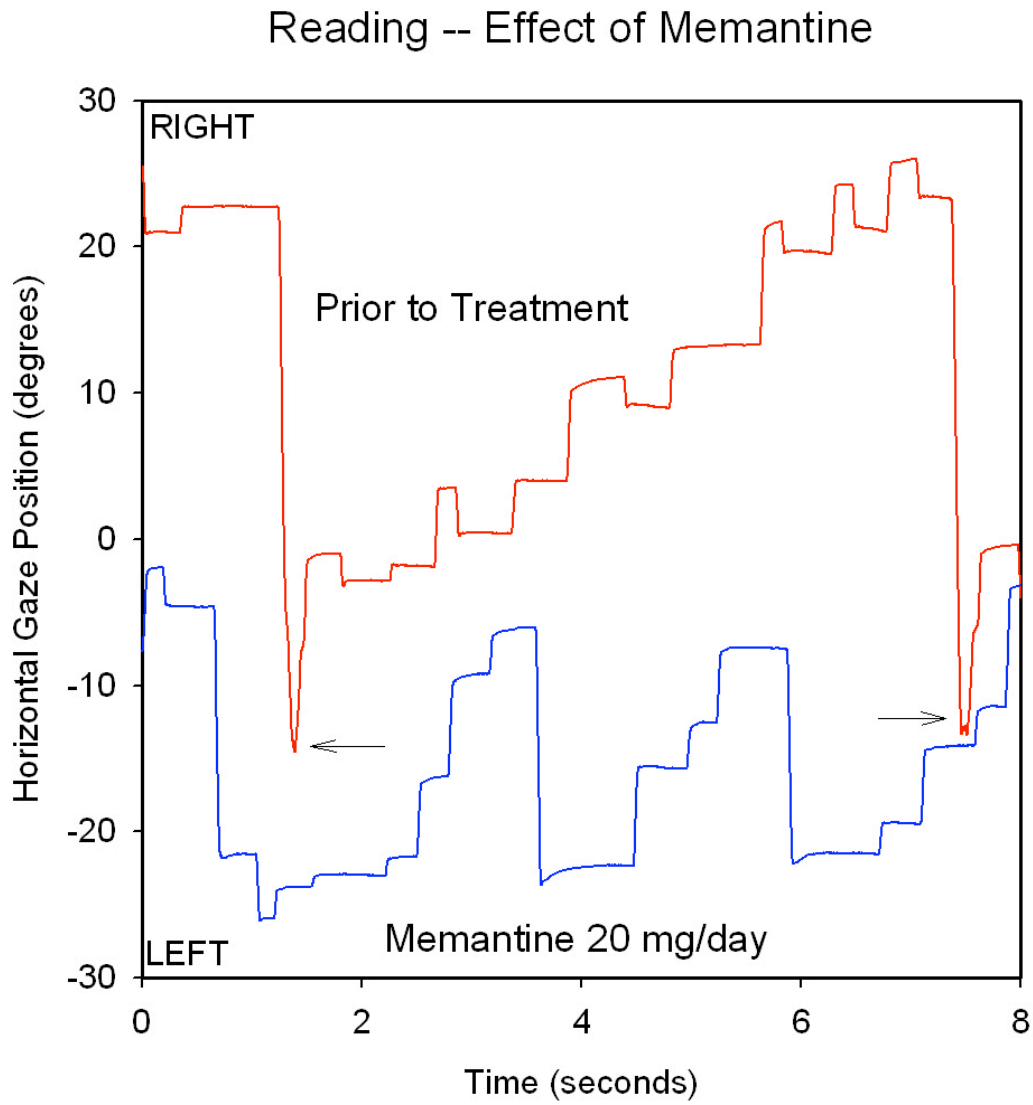

Reading -- Effect of Memantine
RIGHT
Prior to Treatment
LEFT
Memantine 20 mg/day
Horizontal Gaze Position (degrees)
Time (seconds)
30
20
10
0
-10
-20
-30
0
2
4
6
8

Figure 29

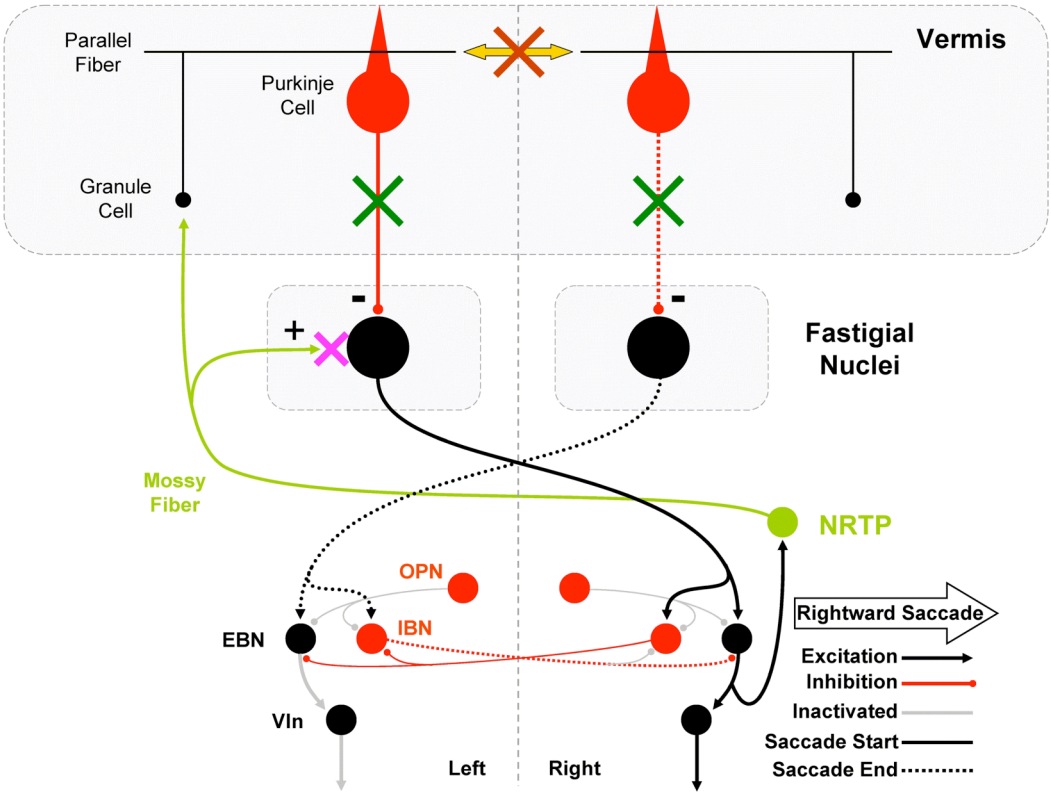

Parallel Fiber
Purkinje Cell
Granule Cell
Vermis
Fastigial Nuclei
Mossy Fiber
NRTP
OPN
IBN
EBN
VIn
Left
Right
Rightward Saccade
Excitation
Inhibition
Inactivated
Saccade Start
Saccade End

FIGURE LEGENDS

Figure 1

The pulse-step command for a saccade. The eye movement is shown on the right. E is eye position in the orbit: the abscissa scale represents time. On the left, the neural signal sent to the extraocular muscles to generate the saccade is shown. Vertical lines represent the occurrence of action potentials of an ocular motoneuron. This graph is a plot of the neuron's discharge rate (R) against time (firing frequency histogram). The pulse (velocity command) is followed by the step (position command). Reproduced courtesy of Dr. Leigh RJ.[5]

Figure 2

Summary of model for horizontal saccades. Premotor burst neurons, lying in the paramedian pontine reticular formation, are inhibited by omnipause neurons in the RIP. When a saccade needs to be generated, this inhibition ceases. Premotor burst neurons project a pulse of innervation to the abducens nucleus (CN VI). Abducens motoneurons project the pulse of innervation via the sixth nerve to the right lateral rectus, which contracts rapidly to generate an abducting saccade of the right eye. Abducens internuclear neurons project the pulse of innervation, via the medial longitudinal fasciculus (MLF, internuclear pathway) to medial rectus motoneurons that, in turn, innervate the left medial rectus via the third nerve, to generate a fast adducting saccade of the left eye. Comparison of the initial acceleration of the abducting and adducting eyes (shown schematically to the right of each eyeball) provides direct information about transmission of high-frequency signals (pulses of innervation) in the MLF. Not shown is the step of

innervation that follows the pulse, which holds the eye in its new position. Vertical gray line indicates the midline.

Figure 3

Representative record of a 36-degree horizontal saccade made by a normal subject in response to a 40-degree target jump (dotted lines in top panel). Corresponding position, velocity, and acceleration records for this saccade are shown. In the middle panel, components of the velocity waveform are shown, including the acceleration period and total duration, the ratio of which gives a measure of the skewing of the velocity waveform. Positive values correspond to rightward movements. Reproduced courtesy of Dr. Leigh RJ.[5]

Figure 4

Schematic representation of orbital connective tissues. GL: global layer; IR: inferior rectus; LPS: levator palpebrae superioris; LR: lateral rectus; M: medial rectus; OL: orbital layer; SO: superior oblique; SOT: superior oblique tendon; SR: superior rectus. The three coronal views correspond to the levels indicated by arrows in the horizontal section. In the horizontal section, note the attachment of the globe to the orbit by the anterior part of Tenon's capsule (collagen and elastin) through which the extraocular muscles pass in sleeves, which serve as pulleys. Note also bands of smooth muscle and collagen between the LR and SR, and between the MR and IR. (Reproduced, with permission, from Demer, J.L. Anatomy of strabismus. In *Pediatric Ophthalmology and Strabismus*, third edition. Edited by Taylor D. and Hoyt C. London: Elsevier, 2005. pp 849-861.)

Figure 5

Histological profiles of the EOM layers (A) and fiber types (B,C) in the monkey lateral rectus muscle. Note general fiber type size differences, with the c-shaped orbital layer containing smaller diameter fibers. Profiles of the SIFs (1,3-5) and MIFs (2,6) in the orbital (B) and global (C) layers are indicated. Phase contrast light photomicrographs of semithin (1 μm) sections highlight differences in mitochondrial content of different muscle fiber types. 1, orbital SIF; 2, orbital MIF; 3, global red SIF; 4, global intermediate SIF; 5, global white SIF; 6, global MIF. Reproduced courtesy of Dr. John D. Porter.[153]

Figure 6

Disorders of the saccadic pulse and step. Innervation patterns are shown on the left, eye movements on the right. Dashed lines indicate the normal response. (A) Normal saccade. (B) Hypometric saccade: pulse amplitude (width × height) is too small but pulse and step are matched appropriately. (C) Slow saccade: decreased pulse height with normal pulse amplitude and normal pulse-step match. (D) Gaze-evoked nystagmus: normal pulse, poorly sustained step. (E) Pulse-step mismatch (glissade): step is relatively smaller than pulse. (F) Pulse-step mismatch due to internuclear ophthalmoplegia (INO): the step is larger than the pulse, and so the eye drifts onward after the initial rapid movement. Reproduced courtesy of Dr. Leigh RJ.[5]

Figure 7

Schematic of saccadic intrusions and oscillations. (A) Dysmetria: inaccurate saccades. (B) Macrosaccadic oscillations: hypermetric saccades about the position of the target; (C) Square-wave jerks: small, uncalled-for saccades away from and back to the position of the target; (D) Macrosquare-wave jerks or macrosaccadic pulses: large, uncalled-for saccades away from and back to the position of the target; (E) Ocular flutter: to-and-fro, back-to-back saccades without an intersaccadic interval. Reproduced courtesy of Dr. Leigh RJ.[5]

Figure 8

A method for precise measurement of horizontal, vertical and torsional eye rotations. The subject is wearing a silastic annulus embedded in which are two coils of wire, one wound in the frontal plane (to sense horizontal and vertical movements) and the other wound in effectively the sagittal plane (to sense torsional eye movements). When the subject sits in a magnetic field, voltages are induced in these search coils that can be used to measure eye position. Reproduced courtesy of Dr. Leigh RJ.[5]

Figure 9

Representative time plot of a 15-degree rightward saccade from a patient with left INO. Note the latency between the times the two eyes reach their own peak velocity (grey dashed line). Red line: right eye position. Blue line: left eye position. Green line: right eye velocity profile. Magenta line: left eye velocity profile.

Figure 10

Representative time plot of a 20-degree rightward saccade from a patient with left INO. Note how the abducting right eye (solid line) initially overshoots the target, and how the adducting left eye (dotted line) eventually lands on target. FPA: first pass amplitude. FA: final amplitude. Reproduced courtesy of Dr. Frohman EM.[202]

Figure 11

Representative 1 saccade-phase plane plot from a normal control for equidistant targets (top), and during Müller paradigm (unidirectional targets) (bottom). Normalized eye velocity is plotted against normalized "weak-eye" position. During the regular saccade (top) the right and the left eye velocity profiles are very similar, and the velocity difference between the eyes is about a value of 0 (i.e., the eyes are conjugate). During the disjunctive saccade, the right and the left eye velocity profiles are very similar in the first part of the movement. Red dashed line: velocity difference between the eyes. Green solid line with red interpolated points: right eye. Blue solid line with green interpolated points: left eye.

Figure 12

Representative 1 saccade-phase plane plot from a patient with post-cardiac surgery gaze palsy (top), a patient with left horizontal saccadic gaze palsy due to brainstem stroke (middle), and a patient with left horizontal gaze palsy due to abducens nucleus infarction (bottom). Normalized eye velocity is plotted against normalized "weak-eye" position. In the first two plots there is some velocity

disconjugacy between the eyes, especially between about 20% and 50% of eye displacement. In the third plot, at least up to 30% of eye displacement, the two eyes show no abnormal velocity difference. Not that the signal level is noisy in the third plot. Red dashed line: velocity difference between the eyes. Green solid line with red interpolated points: right eye. Blue solid line with green interpolated points: left eye.

Figure 13

Representative 1 saccade-phase plane plot from a patient with left INO, due to MS (top), and a patient with left abducens nerve palsy (bottom). Normalized eye velocity is plotted against normalized "weak-eye" position. In both plots, the eyes appear to be disconjugate early on and throughout the course of the saccade. Red dashed line: velocity difference between the eyes. Green solid line with red interpolated points: right eye. Blue solid line with green interpolated points: left eye.

Figure 14

Representative 1 saccade-phase plane plot from a patient with MG presenting with left pseudo-INO (top), and a patient with MG presenting with right pseudo-abducens nerve palsy (bottom). Normalized eye velocity is plotted against normalized "weak-eye" position. The plots show that the eyes are conjugate in the first part of the movement, with some abnormal velocity disconjugacy later on in the course of the saccade. Red dashed line: velocity difference between the eyes. Green solid line with red interpolated points: right eye. Blue solid line with green interpolated points: left eye.

Figure 15

Representative 1 saccade-phase plane plot from two patients with CPEO. Normalized eye velocity is plotted against normalized "weak-eye" position. The first plot (top) shows a saccade from a patient with mild CPEO, with no appreciable velocity disconjugacy between the eyes. In the second plot (bottom) a rightward saccade from a patient with advanced CPEO is shown; the eyes are disconjugate with the left eye being slower. Red dashed line: velocity difference between the eyes. Green solid line with red interpolated points: right eye. Blue solid line with green interpolated points: left eye.

Figure 16

Top. Velocity disconjugacy plot from ten normal controls for equidistant targets. The average of the velocity difference of several saccades (total 1418) from each normal control is plotted against the normalized "weak-eye" position. 95% prediction interval is displayed. Bottom. Velocity disconjugacy plot from nine normal controls during Müller paradigm (unidirectional targets). The average of the velocity difference of 79 saccades from all the controls is plotted against the normalized "weak-eye" position. 95% prediction interval is displayed. Disjunctive saccades induced in normal controls do not show an abnormal velocity difference profile in the first 10% of eye displacement.

Figure 17

Velocity disconjugacy plots from two patients with post-cardiac surgery gaze palsy (top), two patients with horizontal saccadic gaze palsy due to brainstem stroke (middle), and one patient with horizontal gaze palsy due to abducens

nucleus infarction (bottom). The average of the velocity difference of ~10-15 saccades from each patient is plotted against the normalized "weak-eye" position. 95% prediction interval is displayed. Saccades of patients with post-cardiac surgery gaze palsy fall mostly outside the normal range, whereas only saccades of one patient with saccadic gaze palsy due to brainstem stroke are disconjugate, mostly between 20% and 50% of eye displacement. Saccades of the patient with horizontal gaze palsy from abducens nucleus infarction fall in the normal range.

Figure 18

Velocity disconjugacy plots from ten patients with INO, seven due to MS, two due to brainstem stroke, one due to EA2 (top), and two patients with mild (solid line) and severe (dotted line) abducens nerve palsy (bottom). The average of the velocity difference of ~10 saccades from each patient is plotted against the normalized "weak-eye" position. 95% prediction interval is displayed. Saccades of patients with INO and abducens nerve palsy, either mild or severe, are disconjugate early on and stay disconjugate throughout the course of the eye movement.

Figure 19

Velocity disconjugacy plots from three patients with MG, two presenting with pseudo-INO (solid and dotted lines) and one with pseudo-abducens nerve palsy (dashed line) (top), and two patients with mild (solid line) and advanced (dashed line) CPEO (bottom). The average of the velocity difference of ~10 saccades from each patient is plotted against the normalized "weak-eye" position. 95%

prediction interval is displayed. Saccades of patients with MG are not immediately disconjugate, but may become so later in the course of the saccade. Saccades of patients with CPEO may be disconjugate at an advanced stage of the disease (patient 2).

Figure 20

Summary of findings in different groups of patients. The average of the velocity difference of ~10 saccades from each patient is plotted against the normalized "weak-eye" position; 95% prediction interval is displayed (Velocity disconjugacy plot). Saccades of patients with INO, either due to MS or EA-2, or abducens nerve palsy are abnormally disconjugate. Saccades of patients with MG or CPEO fall mostly in the normal range.

Figure 21

Velocity disconjugacy plots from ten patients with INO (seven due to MS, two due to brainstem stroke, one due to EA2) (top), and from three patients with MG [two presenting with pseudo-INO (solid and dotted lines) and one with pseudo-abducens nerve palsy (dashed line)] (bottom). The average of the velocity difference of ~10 saccades from each patient is plotted against the normalized "weak-eye" position. 95% prediction interval is displayed. Note how saccades from patients with INO (site of lesion: MLF) are abnormally disconjugate in the first 10% of eye displacement (vertical dashed line), whereas saccades from patients with MG (site of lesion: neuromuscular junction) are not.

Figure 22

Velocity disconjugacy plots from two normal controls (1_age 30, 2_age 60). The average of the velocity difference of ~10 saccades of different sizes (5-10-15-20-40 degrees) is plotted against the normalized "weak-eye" position. 95% prediction interval is displayed. In both subjects, saccades of different sizes show similar velocity difference profiles, at least up to about 60% of eye displacement.

Figure 23

Patient 1. **A.** Fixation of stationary target at center position for a 10-second time interval. Frequency of macrosaccadic oscillations dropped by about 50% from 154/min before treatment with memantine 20 mg/day (red, solid line) to 69/min after treatment (blue, solid line). Vertical position prior to treatment is also displayed (grey, solid line). Traces have been offset from 0 degrees position for display purposes. **B.** Number and amplitude of macrosaccadic oscillations, before (red) and after treatment (blue). Amplitude of oscillations is not significantly decreased in Patient 1 ($p = <0.718$).

Figure 24

Patient 2. **A.** Fixation (similar conventions to Fig. 22). Frequency of macrosaccadic oscillations drops of about 50% from 168/min before treatment with memantine 20 mg/day (red, solid line) to 89/min after treatment (blue, solid line). **B.** Number and amplitude of macrosaccadic oscillations, before (red) and after treatment (blue). Amplitude of oscillations is significantly decreased in Patient 2 ($p = <0.001$).

Figure 25

Example of horizontal saccades made by a normal subject (gray, solid line) and Patient 2 with SCASI before (red, solid line), and after treatment with memantine 20 mg/day (blue, solid line). Saccades are made in response to a 25-degree target jump (gray, dotted line) from center position to right 25 degrees. After a reaction time, the normal subject makes an initial hypometric saccade, followed by a small corrective saccade to the target. A similar pattern is observed when the target returns to center. The patient shows hypermetria, overshooting the target when it jumps to the right, and especially when it jumps back to the center, following which there are macrosaccadic oscillations of about 5-10 degrees around the point of fixation. After treatment with memantine, saccades are less hypermetric and both the frequency and the size of oscillations are diminished, especially for leftward saccades (arrow). Positive values correspond to rightward movements.

Figure 26

Main sequence relationship: plots of the relationship between the amplitude and peak velocities of saccades from P1 and P2, before (gray circles) and after treatment with memantine (open boxes) 20 mg/day. Also, 5%, mean, and 95% prediction intervals for controls are displayed. Larger horizontal saccades made by both patients often exceed the 95% prediction interval for normal subjects, i.e. large saccades are faster than normal. This finding is not affected by the treatment with memantine. Microsaccades (shown in plots at right) showed minor and inconsistent differences in peak velocity due to memantine, but their frequency and magnitude were reduced by this drug.

Figure 27

Effect of memantine on initial saccadic gain. **A.** In Patient 1 both rightward and leftward saccades show a significant increase ($P < 0.05$, asterisk) in gain (red) with respect to controls (yellow). Gain is not significantly changed during treatment with memantine. **B.** In patient 2 both rightward and leftward saccades (red) show significantly increased gain with respect to controls (yellow). During treatment with memantine (blue), saccades to the left have significantly reduced gain compared with prior to treatment.

Figure 28

Effect of memantine on reading in Patient 2. Prior to treatment (red), leftward saccades directed towards the beginning of the next line overshot (horizontal arrows). During treatment with memantine (blue), these leftward overshoots were much reduced (vertical arrows), allowing the patient to move from the end of one line to the beginning of the next. Also note that saccadic intrusions were reduced during memantine therapy.

Figure 29

Schematic of cerebellar circuitry. Cortical Purkinje cells receive input on parallel fibers from granule cells. The Purkinje cells inhibit the deep nuclear cells. Input from the outside is brought to the granule cells on mossy fibers, which also send bilateral collaterals to the deep nuclei. The main role of the vermis is to set the timing (indicated by the gold arrow) between the contralateral side (firing early) and the ipsilateral side (firing late). We propose that in the two SCASI patients, that path is blocked (brown x), causing saccades to be hypermetric. Normally,

mossy fiber input to the nuclear cells is blocked by corresponding inhibition from the Purkinje cells. However, we propose that path is also blocked (green x), causing saccades to accelerate more at onset. Because inhibition is blocked, saccadic intrusions can occur whenever a large enough signal arrives on the mossy fibers. I hypothesize that memantine (magenta x) reduces the probability of a saccadic intrusion by weakening the mossy fiber inputs due to its inhibition of NMDA receptors at this site.

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Why does the eye see a thing more clearly in dreams than the imagination when awake?

Leonardo da Vinci, 1452-1519