Multiple Saccadic Abnormalities in Spinocerebellar Ataxia Type 3 Can Be Linked to a Single Deficiency in Velocity Feedback

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Purpose. The purpose of the current research is to understand if the different eye movement abnormalities in patients with the same neurologic disease are related to varied disease processes or, alternately, do different patients adopt different strategies to overcome a singular brain deficiency.

Methods. Using a magnetic search coil, we measured saccade dynamics, that is position and velocity waveforms, for patients diagnosed with spinocerebellar ataxia type 3 (SCA-3), also known as Machado-Joseph disease (MJD).

Results. We observed that the saccadic waveform of the majority of the SCA-3 patients (7 of 10) exhibited dynamic overshoot, with the eye passing the desired endpoint and making a rapid correction before coming to rest. Patients with normal waveforms, that is with no dynamic overshoot, had saccades with relatively low peak velocity.

Conclusions. Velocity feedback in a closed loop control system is essential for providing a fast response without overshoot. Lack of a velocity feedback or an imbalance between position and velocity gains yields a tradeoff between response time and overshoot. While the goal of a saccade is to get to the desired position, models based on animal research suggest that the saccadic control also incorporates a velocity feedback. Results presented here indicated that all SCA-3 patients had deviations in the saccadic waveform, albeit of two types, either slow saccades or dynamic overshooting saccades. Using saccadic models based on animal research can explain how a single deficit, that is a mismatched velocity control of the motor error due to the disease, can yield these two different abnormalities in human patients. (*Invest Ophthalmol Vis Sci.* 2013;54:731–738) DOI:10.1167/iovs.12-10689

The short duration of a saccade (tens of milliseconds) makes it impossible to achieve closed loop control using the relatively slow visual system. While saccades are triggered and programmed based on visual information, in-flight, saccades are controlled by an internal motor feedback control mechanism. This mechanism minimizes an error signal between the current gaze position and an efferent copy of the motor command. Supporting evidence for this model is based on experiments in primates in which saccades were interrupted mid-flight by electrical stimulation of the omnipause neuron region and still achieved accuracies similar to normal saccades even in the absence of visual input. [1] This led to a model in which the feedback control system uses motor velocity information in addition to position information. Generally, in control systems, using a velocity feedback, that is the rate of change, in addition to position enables the system to achieve a smoother dynamic, specifically minimizing the dynamic overshoot (DO) in systems where a fast reaction is required.

Comparing eye movement abnormalities observed in patients to given models can help differentiate between pathology in the ocular motor periphery and problems in higher level internal control mechanisms. Conversely, the validity of eye movement models based on electrical neurophysiology in primates can be tested against eye movement abnormalities found in humans.

Various saccadic abnormalities occur in many neurodegenerative diseases, including spinocerebellar ataxia type 3 (SCA-3), also known as Machado-Joseph disease (MJD). MJD, the most common form of autosomal dominant cerebellar ataxia, is an expanded repeat disease with "CAG" repeats in the *ATXN3* gene. Magnetic resonance imaging (MRI) studies reveal diffuse central nervous system (CNS) atrophic changes, particularly in the cerebellar vermis, superior cerebellar peduncle, pontine tegmentum, and frontal lobes.[2] Despite the common pathology of the disease, the clinical manifestations of MJD can be highly variable, even among affected persons in the same family.

The prevalence of the disease is highest among people of Portuguese/Azorean descent. Interestingly, in Israel the only population known to have MJD is a Yemenite Jewish subpopulation that has been found to have a genetic isolate of SCA-3 characterized by a relatively large number of homozygotes for the CAG trinucleotide repeat expansion at the *MJD1* gene.[3–5]

Ocular motor functions were examined previously in patients with various spinocerebellar ataxias, including SCA-3. Gordon et al. found various degrees of gaze-evoked nystagmus and bilateral loss of the horizontal VOR in SCA-3.[5] Additional ocular-motor abnormalities, such as reduced smooth pursuit gain and VOR interactions, were documented in SCA-3 patients.[6] There is a discrepancy in the literature regarding abnormalities of saccades in SCA-3 patients. Gordon et al. reported amorphous "saccade abnormalities," including "saccade accuracy" and "saccade velocity,"[5] Bürk et al. reported mild reduction of saccade velocity in approximately one-third of patients,[7,8] while Buttner et al.[9] and Rivuad-Pechoux et al.[10]

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didn't find any significant change in saccade velocity relative to healthy controls.

We examined the saccadic abnormalities found in MJD, and used them to propose a single ocular motor deficit that can explain the observed abnormalities and the discrepancy in the literature regarding the velocity of the saccades in patients with SCA-3. At the same time, our model buttresses the standard saccade generation model that includes velocity feedback.

Methods

Subjects

All patients included in our study were examined in the neurologic outpatient clinic of Meir Medical Center, Kfar Saba, Israel, and were diagnosed clinically and genetically as having SCA-3 (MJD). Ataxia score of the MJD patients was evaluated according to the SARA scale.[11]

There were 10 SCA-3 (MJD) patients and 10 healthy controls. Among the 10 patients 7 were female and 3 male, with an average age of 48.6 (14.9). The average age of the healthy controls was 46.1 (14.4), which was a close match with the average age of the MJD patients.

The protocol of the experiment was approved by the Ethics Committee (Institutional Review Board) of Meir Medical Center, Kfar Saba, Israel, and followed the tenets of the Declaration of Helsinki. Before each testing session a written, informed consent was signed by the subject.

Eye Movement Recordings

Horizontal gaze of the left eye was measured using the magnetic search coil technique[12] with 6-foot field coils (CNC Engineering, Seattle, WA) using a scleral search coil embedded in a Silastic ring (Skalar, Delft, Netherlands). This method still is the best and fastest method of recording saccades. The coil was placed on the eye after the application of a local anesthetic (benoxinate HCl 0.4%). Coil signals were low pass filtered (bandwidth 500 Hz) before digitization at 1000 Hz, with 16 bit resolution (NI-USB-6221; National Instruments, Austin, TX). The visual stimulus was a dim (3 mW), red laser spot (1.5 mm diameter) rear-projected onto a semitranslucent screen situated 1.1 meters in front of the subject. The position of the laser spot was controlled by an X-Y galvanometer (model number DSC-2000, X-Y mirrors model Z1913; General Scanning, Inc., Billerica, MA). The fly-time of the mirrors is 2 to 3 ms, and they settle to their final location within 5 to 6 ms. The subject sat in front of the semitranslucent screen in a dark room and was given time to adjust to the dark. The subject's head was immobilized with a head restraint device attached to the chair. An additional coil was attached to the forehead of the subject to record head position and to verify that there was no head movement.

Experimental Paradigm

Each session consisted of several runs, each 8 to 16 trials long. Trials started with the target at the center of the screen for a random duration of between 1 and 2 seconds. It then jumped to one of four locations on the horizontal axis: 10 degrees right or left, or 20 degrees right or left. The target stayed at the off-center location for a random duration between 1 and 2 seconds before jumping back to the center.

Data Analysis

Using an interactive graphic program written using MATLAB (version 2010b; MathWorks, Natick, MA), the beginning and end of each saccade was determined manually. The MATLAB application has a graphic user interface (GUI) that allows zooming in and out on the traces of eye position versus time, and eye velocity versus time. The user located the stationary points before and after a saccade with amplitudes greater than 5 degrees by placing markers at the points at which the velocity of the eye was above the noise level.

Statistical Analysis

The statistical significance of the results was validated by performing a parametric test. Using a *t*-test, we examined the hypothesis that for each patient, there exists at least one saccadic parameter that differs significantly from the expected normal value. For peak velocity of the saccades, we tested the hypothesis that the peak velocity ratio was significantly smaller than 1.0. The peak velocity ratio was calculated for each saccade. The peak velocity ratio is the ratio between the measured peak velocity of the saccade and the expected peak velocity of a saccade, based on its amplitude and the main sequence of the controls. For DO, we used a *t*-test to test the hypothesis that the percentage of the overshoot relative to the amplitude of the saccade is significantly larger than 2.0%.

The nonparametric Kolmogorov–Smirnov test (K-S test) was used to compare the peak velocity ratio between the healthy control subjects and various groups of patients. The K-S test was used to check the significance of the prior assumption that those with MJD have lower peak velocities, that is slow saccades. Differences were considered significant at $P < 0.05$.

Results

The Table lists the sex, age, and ataxia score for each patient. Typical traces of eye position and eye velocity versus time during horizontal saccades for MJD patients and a healthy subject are given in Figure 1. The eye position and eye velocity traces of the MJD patients showed two abnormalities. For some patients we observed a DO, while for other patients we observed a relatively slow peak velocity, that is slowness of saccades. In the following paragraphs, these two abnormalities will be quantified. The slowness of the saccades were analyzed using the saccade main sequence and the DO was measured from the traces of the position versus time.

Dynamic Overshoot

Position traces of saccades of some of the MJD patients showed DO, that is the eye passes the desired position endpoint and makes a rapid correction, with velocity in the opposite direction, before coming to rest. In DO, the corrective motion is an integral part of the motor process of the initial saccade. This differs from a hypermetric saccade in which there also is overshooting of the target, but in which the corrective saccade is initiated after the eye has come to a complete rest. In hypermetric saccades, the corrective motion is a result of a new motor process.

Figure 2 shows the overshoot as a percentage of saccade size for all patients and controls. The overshoot in percentage is the angular distance the eye moves past the endpoint relative to the desired saccade amplitude.

A subset of 7 of 10 of the MJD patients had a significantly larger DO relative to the healthy controls. In contrast, none of the 10 healthy controls had an overshoot that is significantly larger than 2%. It is worth noting that due to the very short duration of this DO, it usually cannot be seen without recording eye movements at a relatively high temporal frequency and, thus, often is missed during a clinical examination.

Therefore, these patients can be divided into 2 subgroups: a group of patients with DO (7 of 10), and a group of patients without a significant overshoot (3 of 10). We were not able to correlate the presence of an overshoot with any other of the patients' clinical parameters listed in the Table.

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Table. Summary of Patient Characteristics for All 10 Patients

Patient ID	Age	Sex	Symptomatic, y	SARA	Saccade Peak Velocity Ratio	Slow Saccade	Overshoot, %	Significant Overshoot
01	33	Female	1	4.0	0.88	*	0.7	
02	75	Female	7	25.0	0.90	*	11	*
03	29	Female	6	10.0	1.37		17	*
04	50	Female	4	6.0	0.94	*	6.4	*
05	40	Male	14	11.5	0.80	*	0.3	
06	44	Male	3	5.0	1.36		5.6	*
07	65	Female	12	10.0	0.90	*	8.8	*
08	52	Female	4	17.0	0.94		20	*
09	61	Female	2	14.0	0.81	*	0.4	
10	37	Male	8	10.5	1.21		14	*

* Indicates a significant difference at the level of $P < 0.05$.

Saccade Main Sequence

The saccadic main sequence quantifies the peak velocity and duration of saccades versus the saccade amplitude. Saccades with larger amplitude have a higher peak velocity compared to saccades with smaller amplitudes. In addition, the duration of the saccade is longer for larger saccades. When evaluating saccadic peak velocity or duration, it is essential to relate the measured values to the amplitude of the saccade. This is done by plotting the measured peak velocity or the measured duration of the saccade as a function of saccadic amplitude. This function is referred to as the saccadic main sequence.

The peak velocity versus amplitude curves, that is the main sequences, of horizontal saccades for all MJD patients are shown in Figure 3. As can be seen from the main sequence plots, only a subset of the MJD patients had slowness of saccades. To divide the patients into subgroups of those with slow saccades and those with normal peak velocity, we introduced the variable peak velocity ratio, which quantifies the slowness of the saccade. It is calculated for each saccade, and is the ratio between the measured peak velocity of the saccade and the expected peak velocity of a saccade with the same amplitude. The expected peak velocity of a saccade was estimated based on the measured main sequence of the healthy controls. The average and confidence interval of the peak velocity ratio for the ten MJD patients and ten healthy controls are given in Figure 4. Slowness of saccadic eye movements, significantly lower than the nominal value of 1.0, was seen only for a subset of 7 of the 10 MJD patients. These 7 patients had a peak velocity ratio that was significantly lower than 1.0, although within the range of 2 SD of the healthy controls. For the age-matched healthy control subjects, we found that 3 of 10 had a peak velocity ratio significantly lower than 1.0. The observation that healthy controls had a peak velocity ratio not equal to 1.0 can be explained by the large peak velocity variation of saccades observed in healthy controls.[13]

The data in the Table indicate that there is a correlation between the slowness of the saccades and the DO. Slowness of the saccades was found for all 3 patients with no DO. Thus, each of the SCA-3 patients had a saccade flaw, either slowness and/or overshoot.

To examine the correlation between the velocity of the saccade and the overshoot further, we compared the mean peak velocity of the healthy controls to different subgroups of

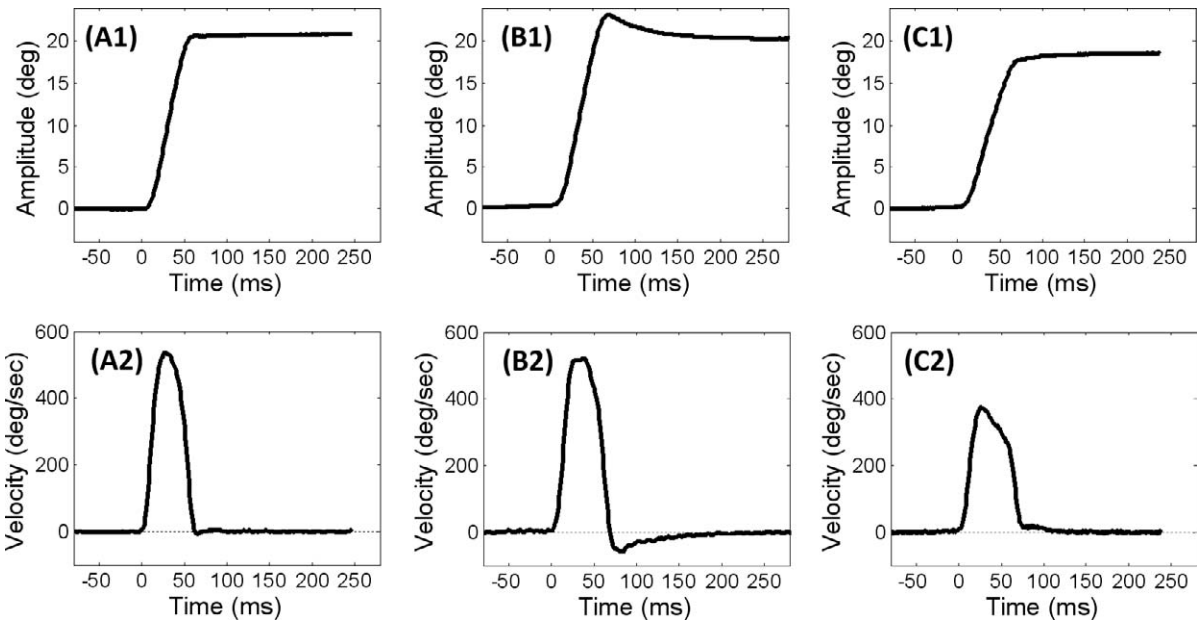

Figure 1. Position and velocity profiles of typical saccades for a healthy subject and two MJD patients. Saccade amplitude for all examples is 20 degrees. (**A1**, **A2**) Healthy subject, peak velocity = 536 deg/sec and no overshoot. (**B1**, **B2**) MJD patient with peak velocity comparable to the healthy subject, 519 deg/sec, but with a 13.8% DO. (**C1**, **C2**) MJD patient with slow saccade, peak velocity = 315 deg/sec, and no DO.

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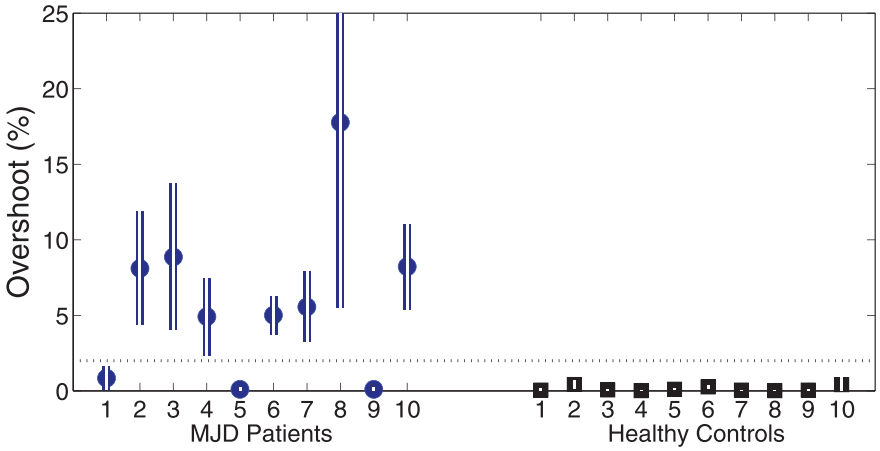

Figure 2. DO in percentage for each of the 10 MJD patients and 10 healthy controls. The *bars* indicate the confidence interval of the mean overshoot according to the *t*-test with $P = 0.05$. The *blue circles* indicate the mean overshoot for each MJD patient and the *black squares* indicate the mean overshoot for the healthy controls. Note that for the healthy controls the confidence intervals are smaller than the marker of the mean. For all 10 healthy controls the overshoot is significantly ($P < 0.05$) smaller than 2%. In contrast, for 7 of the 10 MJD patients, the mean overshoot is significantly ($P < 0.05$) larger than 2%.

patients. According to the K–S test, the mean peak velocity ratio of the 3 MJD patients with no DO (patient IDs 1, 5, and 9 in the Table) was significantly lower ($P < 0.005$) relative to the mean peak velocity of the 10 healthy controls. In contrast, the mean of the peak velocity ratio of all MJD patients was not significantly different from the healthy controls.

Discussion

Eye movements of patients with SCA-3 (MJD) have been examined in the past, with mixed reports about their saccadic velocity. Our results attempted to explain this disparity by dividing the MJD patients into two subgroups: those with significant DO and those with no DO. Patients with normal velocity saccades all had significant overshoot.

The earliest models of the saccadic system[14] from almost 40 years ago assumed a ballistic system lacking any feedback. Within a few years it was understood that there exists some form of feedback, and a feedback loop using an efference copy of the eye position was added to the saccadic model. This position signal was thought to be based on an efference copy of the eye velocity that passed through a resettable integrator. Subsequent models incorporated velocity feedback as well. These models were supported by computer simulations[15] and animal studies.[1]

We propose that the data from our SCA-3 patients can bolster the contention that the saccadic system uses velocity feedback, and we suggest that all SCA-3 patients share a common deficit in the velocity feedback, despite the appearance of there being two types of saccadic abnormalities.

Dynamic Overshoot

An early analysis of DO was done by Bahill et al.,[16] and the topic received sporadic attention over the years. In contrast to MJD patients, the DO observed in healthy subjects was less frequent and of smaller size. In addition, previous reports have shown that DO is prominent for saccades smaller than five degrees and is rare for larger saccades. Nonetheless, here we observed DO for saccades with amplitude of 10 and 20 degrees, something usually not seen healthy controls.

Bahill et al., based on IR recordings, described DO as being "quite capricious."[16] That is, there can be much DO one day and little another day, or there can be a run of saccades with DO followed by a few without at random intervals. They reported DO to be more common and more prominent in small saccades, and typically only 2% to 3% in large saccades. They further reported that DO often is a monocular phenomenon. They postulated that DO is generated by nonrandom and nonaccidental reversals in the neuronal control signals sent to the extraocular muscles. In general, the antagonist resumes its activity only after the agonist ceases its burst of activity. In DO there is a reversal at the end of the controller signal. Bahill et al. argue that this reversal is precisely the second-order time optimal controller signal required to enable the eye to arrive and stay within one central foveal radius of the target in the least possible time.[16]

Several years later, Kapoula et al. examined the prevalence and properties of DO using search coils.[17] While their findings were similar to those of Bahill et al.,[16] they in general found DO to be less common and of smaller amplitude. As discussed below, this difference may relate to the recording method used. They found an overall rate of DO of approximately 13%, being more frequent for smaller saccades, and occurring more often in the abducting eye.

Bötzel et al. reported a great deal of variability between subjects in the incidence of DO, but observed that it was a common occurrence.[18] Of significance is that the size of the DO usually was small, with an average size of 1.6% for all subjects. Study co-author Rottach (personal communication) observed that their study was done with an infrared system which, when compared to a coil system, shows too many and too large DO. Thus, it is fair to say that DO is not rare, but is of small amplitude. The neuronal mechanisms of DO are not clear, but it is assumed not to be a passive phenomenon, but rather due to the braking of saccades. Further support for this is the fact that the incidence of DO rises significantly when the saccade is accompanied by a blink.[19]

Control Theory Models

Control theory explains that there is a trade-off between rise time and overshoot. In this trade-off, a low gain produces slow rise time and minimal overshoot, while high gain gives a fast rise time but significant overshoot. It is possible to achieve faster rise time without overshoot (Fig. 5A) in a linear control system by including feedback about the rate of change of the signal, that is the velocity, in addition to position feedback. We

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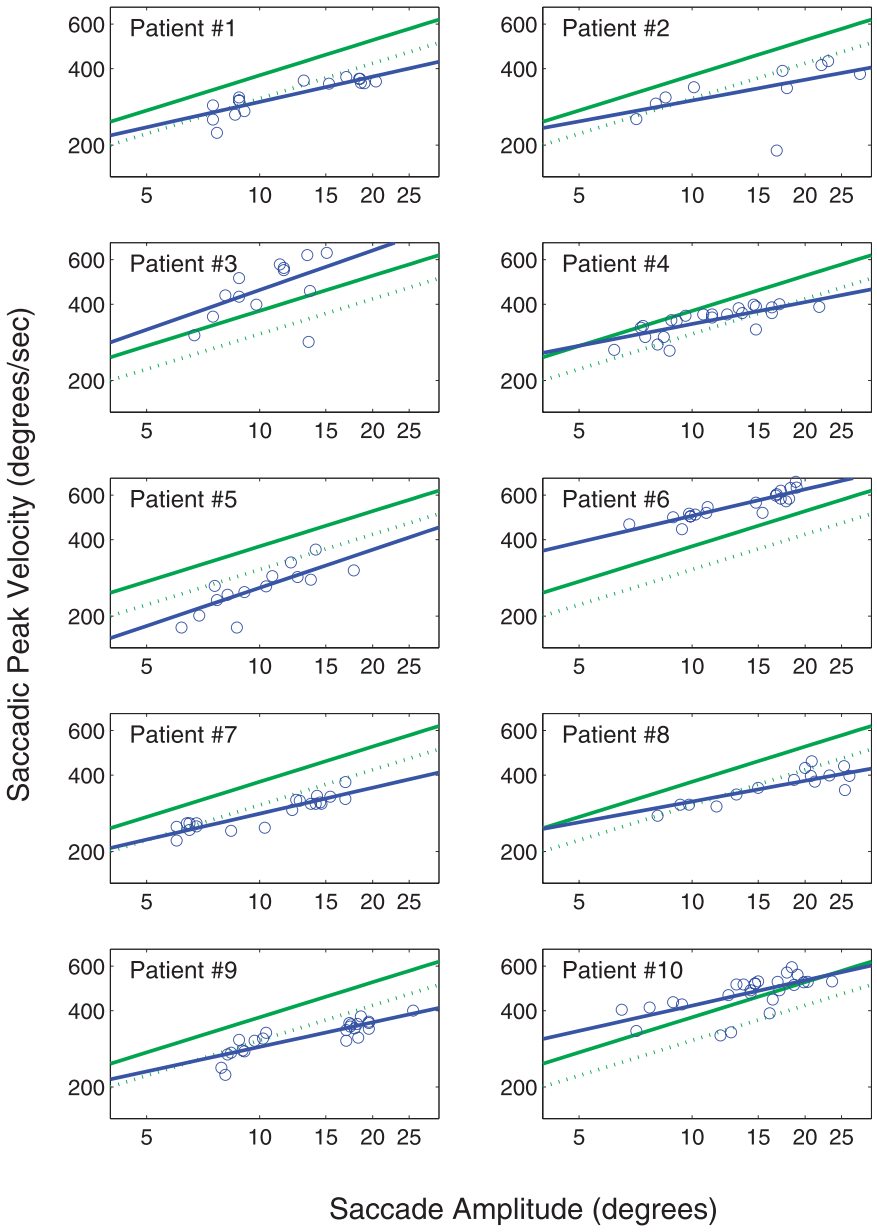

Figure 3. Saccadic main sequence of peak velocity of horizontal saccades as a function of the saccade amplitude for the 10 MJD patients plotted on a log-log scale (following Garbutt et al[26]). The *blue line* is a fit to an exponential function (which is a straight line on a logarithmic scale). The *green solid line* is the main sequence based on the saccades of the healthy controls measured in the current research and the *green dotted line* is the lower range of 2 SD below this mean. The *green lines* are the same in all panels and are given for reference.

propose that MJD patients have a defective velocity feedback, where in some cases the velocity feedback loop may be entirely defective. With this deficit, some of the patients adopt a strategy of low gain, which ensures no overshoot but gives them a slow rise time, while others "choose" a high gain and, in exchange for the fast rise time, are willing to tolerate significant DO. Alternatively, overshoot can exist even with velocity feedback. Canceling the overshoot requires an accurate match between position feedback and velocity feedback. In cases where there isn't a correct match, there can be overshoot and an effect on the response time (Fig. 5B). These patients may have an extant but flawed velocity feedback to which they try to match a position feedback gain. Depending on the gain ratio, they can have a slow rise with no DO or a fast rise time with overshoot.

Velocity Feedback and the Cerebellum

The cerebellum has a pivotal role in the control of multiple types of eye movements. Its better known function is its long-term, adaptive function of keeping ocular motor responses calibrated correctly. Early studies involving cerebellar lesions in primates led to the conclusion that the general function of the cerebellum in saccadic control was repairing dysmetria.[20] Such lesions induce permanent deficits, dramatically affecting the accuracy and consistency of saccades, and impairing the ability of the saccadic system to compensate for changes in the oculomotor plant. However, the cerebellum also has an immediate, on-line function of making each individual movement accurate.[21] Therefore, models of the saccadic system must incorporate a method of how the cerebellum accurately keeps track of how far the eyes have moved since the

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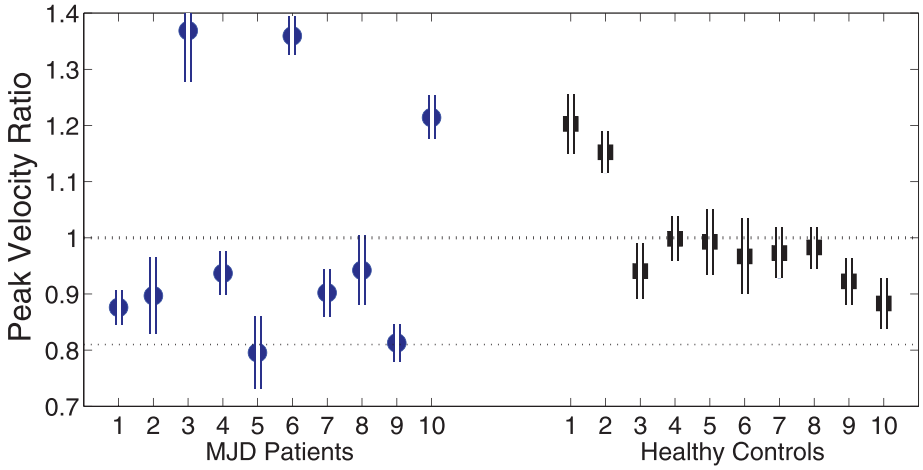

Figure 4. Peak velocity ratio of the 10 MJD patients and the 10 healthy controls. The peak velocity ratio is the measured peak velocity divided by the theoretical peak velocity for a saccade with the same amplitude. The *blue circles* indicate the mean peak velocity for each patient and the *black squares* indicate the mean peak velocity for each healthy subject. The *vertical lines* indicate the confidence interval according to the *t*-test with $P = 0.05$. In cases in which the *vertical error bar* does not touch the *dashed horizontal line* that represents a peak velocity ratio of one, the saccadic velocity is significantly below average. The *lower horizontal line* is at 2 SD below the population mean of the healthy controls. For patients in which the *vertical error bar* touches the 2 SD range, we cannot rule out the possibility that saccades are outside the normal range.

beginning of the saccade. For example, Quaia et al. suggested that the cerebellum derives this information by monitoring the output of the MLBNs, thereby deriving a velocity efference copy or, alternatively, by extracting a velocity signal from the burst-tonic signal provided presumably by the nucleus prepositus hypoglossi to the cerebellum.[22] In these models, the cerebellum uses eye velocity and desired displacement to monitor residual motor error.

The oculomotor vermis (OMV lobules V–VII) and its target in the posterior portion of the underlying fastigial nucleus, the fastigial oculomotor region (FOR), are involved in the control of saccade amplitude and direction. As summarized by Kheradmand and Zee, damage to these regions can cause a variety of saccadic abnormalities.[21] For example, lesions in the OMV cause changes in the accuracy, latency, trajectory, and dynamic properties of saccades. Electrical or magnetic stimulation of Purkinje cells in the OMV can elicit saccades in monkeys and humans. Neurons in the FOR supply a presaccadic burst for contraversive saccades and a "braking" discharge for ipsiversive saccades, such that lesions in the FOR cause ipsiversive saccadic hypermetria and contraversive hypometria. Bilateral FOR lesions cause bilateral hypermetria. The timing for these bursts is adjusted in real-time using information received from the OMV. Thus, the velocity

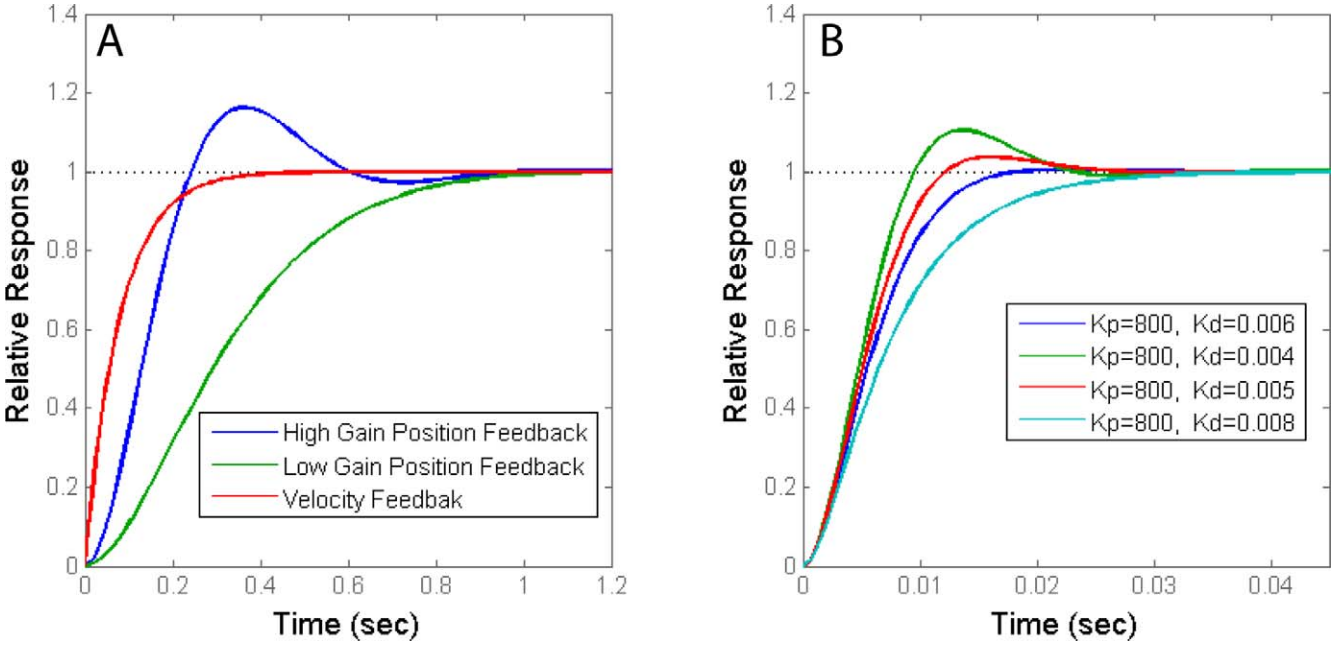

Figure 5. (**A**) Control systems 101. In a linear control system with simple feedback, a low gain produces slow rise time and minimal overshoot (*green line*), while high gain yields a fast rise time and significant overshoot (*blue line*). When a derivative term, that is velocity, is added to the feedback loop, the rise time is faster and dynamic overshoot can be eliminated (*red line*). (**B**) The effect of varying the feed forward and velocity feedback gains. Note that even when there is a velocity feedback term, a mismatch in the gains can result in dynamic overshoot or slowness of response. A fast response with minimal overshoot requires a fine-tuning of the parameters of the control system, in particular the feedback gain.

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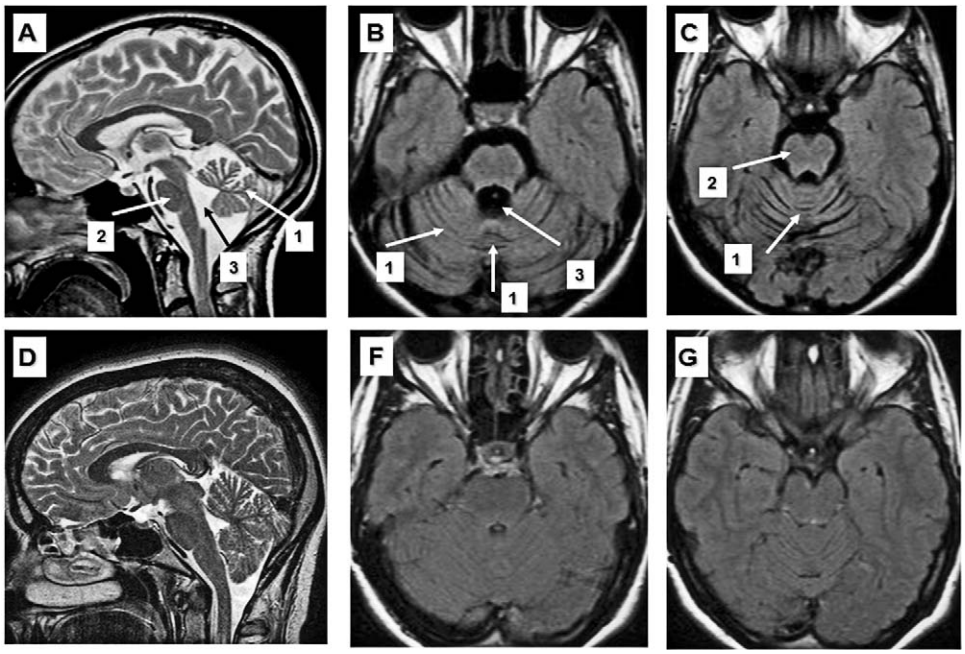

Figure 6. Sagital (**A**, **D**) T2-weighted and axial (**B**, **C**, **F**, **G**) T2-weighted/flair MRI of a patient with SCA-3 (**A**, **B**, **C**), and an aged matched control (**D**, **F**, **G**). *Arrows* indicate cerebellar (1) and brainstem (2) atrophy with marked fourth ventricle (3) enlargement.

feedback is thought to occur in the cerebellum in medial lobules V to VII, and instead of going to a position in the space comparator, for example a true integrator, they go to an integrator that is reset after every saccade.[23] As shown by MRI[2] studies (Fig. 6), patients with SCA-3 have damage to medial lobules V to VII, which we suggest leads to the problems in velocity feedback. However, we did not find any correlation between specific areas of the cerebellum that have degenerated preferentially and either slow saccades or saccadic overshoot.

A recent study of saccades in cerebellar ataxia patients found that patients with SCA-2 have slow but accurate saccades, while patients with late-onset cerebellar ataxia (LOCA) show initial saccades with large errors and, thus, use multiple, mostly hypometric saccades of normal velocity to reach the target.[24,25] These investigators propose that these types of errors correlate with the specific anatomic substrates that are affected by the disease. They suggest that prevalent degeneration of the OMV-cFN region accounts for the fast, but inaccurate, saccades in LOCA, while the degenerative processes affecting the pontine burst generator are behind the slow but accurate saccades seen in SCA-2. In addition, they suggest that SCA-2 patients adopt a strategy using visual feedback to guide the slow saccade to compensate for the neurodegeneration in the cerebellum. Herein, we proposed that SCA-3 patients adopt a strategy of fast saccades with DO to deal with the neurodegenerative control loop.

Previous evidence of velocity feedback was based on monkey data.[1] Here, we offer evidence, albeit indirect, from human data for velocity feedback in saccade control. Absent from the model of Arai et al.[1] are saccades with DO, a phenomenon that can be explained with the assumption of position and velocity feedback in the healthy system. Furthermore, their evidence stems from interrupting saccades mid-flight, an unnatural process. Here, we used evidence obtained from a natural disease process. Thus, a mechanism proposed based on unnatural, nonhuman data seems to be confirmed based on human data from diseased individuals.

Our proposed explanation supports models that include a velocity feedback in the mechanism of saccadic eye movement generation and, in a parsimonious manner, shows that multiple saccadic abnormalities can be attributed to a common mechanism.

Acknowledgments

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