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REVIEW

Ocular Motor System Control Models and the Cerebellum: Hypothetical Mechanisms

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Abstract
To review our studies and "top-down" models of saccadic intrusions and infantile nystagmus syndrome with the aim of hypothesizing areas of cerebellar connections controlling parts of the ocular motor subsystems involved in both types of function and dysfunction. The methods of eye-movement recording and modeling are described in detail in the cited references. Saccadic intrusions, such as square-wave jerks and square-wave oscillations, can be simulated by a single malfunction, whereas staircase saccadic intrusions required two independent malfunctions. The major infantile nystagmus syndrome waveforms are traceable to a failure to calibrate the damping ratio of the smooth pursuit system. The use of a behavioral ocular motor system model demonstrated how putative cerebellar dysfunctions could accurately simulate both the oscillations and the ocular motor responses seen in patients with both saccadic and pursuit disorders.

Keywords Ocular motor system · Cerebellum · Saccadic intrusions/oscillations · Nystagmus

Introduction

The past half-century has produced quantum leaps in our understanding of how the brain controls the ocular motor system (OMS). Much of that progress resulted from electrical and biomedical engineers applying control-systems analysis and computer modeling of the OMS as an adjunct to the more classical approach of neurophysiological studies of specific portions of the brain thought to play a part in OMS control. One feature of "top-down," control-systems models is the absence of anatomical identification of the physiological "black boxes" that make up the model. Each box contains only a mathematical definition of the required input-output relationship which, when properly interconnected to the other boxes, results in a model capable of duplicating both the normal and abnormal physiological OMS behaviors of either experimental animals or humans. Once required neurophysiological functional requirements were defined and introduced into a model, the task of anatomically locating such functional centers became the impetus for further research and "bottom-up" modeling, usually conducted by other, more classically trained, neurophysiologists. Attaching known, or in many instances, presumed anatomy to OMS models simply was unnecessary for understanding neurophysiological mechanisms, although those of us conducting OMS research and modeling remained curious about where our physiological boxes might reside within the brain. Brain sites known to play a part in OMS control are the retina, lateral geniculate nucleus, superior colliculus, visual cortex, cerebellum, and brainstem. In addition, the extraocular muscles and globe also contribute to ocular motor function. David Robinson described the cerebellum as the brain's "repair shop." [1] The cerebellum monitors and makes parametric adjustments to motor subsystems that keeps them in calibration and adjusts for changes due to time, environment, or disease.

In this paper, I will review our studies in two areas of OMS control (saccadic and pursuit) and hypothesize the possible locations of specific neurophysiological functions with the aim of elucidating the role of the cerebellum. However, directly linking lesion sites (whether placed in normal animals or occurring in animal or human patients) with the sites of

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specific neurophysiological function is problematic. The leap of faith between identifying a lesion site as that of the function disturbed by that lesion is both common and also problematic. It is equally possible that the lesion merely interrupted a signal path to or from a distant site that controls the disturbed function. Also, the lesion might affect or interrupt one of the many feedback loops involved in calibration and repair of the disturbed function; because of its role as the brain's repair shop, this is especially likely for cerebellar lesions. These, and other, plausible explanations regarding lesion sites and disturbed physiological function limit the usefulness of lesion-based research.

History

The first, top-down engineering models of OMS control emanated from the work of Larry Young and David Robinson [2–4]. These were models of major portions of the normal OMS, smooth pursuit, and saccades, respectively. Each model postulated the existence of specific, required neurophysiological/mathematical functions residing somewhere within the brain. One function important to all eye movements, the "neural integrator," was hypothesized by Robinson to create a position signal (the "step") from the velocity burst (the "pulse") that generated a saccadic eye movement. Once the need for such an element was established by Robinson's neurophysiological studies, it became part of most top-down models of ocular motor control. However, about two decades would pass before researchers produced evidence that the actual location of the neural integrator was in the cerebellum [5].

In addition to models of the normal OMS, attempts were made to model OMS dysfunction by studying the eye movements of patients with various motility disorders. Study of these "experiments of nature" provided valuable insights into how a predominantly normal OMS responded to the impairment of specific functions within it. The first such attempt was to model "congenital nystagmus" (now referred to as infantile nystagmus syndrome, INS) [6, 7]. Early in that attempt, it became obvious that prior retinal-error-driven models of normal ocular motor function were inadequate for any situation except for eyes that were absolutely still when not responding to target inputs. Such a condition was rarely met in normal subjects and almost never in patients with spontaneous eye movements. A more realistic OMS model had to respond to reconstructed/perceived target position and velocity, not immediately retrievable from oscillatory, often chaotic retinal error signals alone. The INS model was followed by models of adult-onset neurological conditions that produced gaze-evoked nystagmus (GEN) or saccadic dysfunctions (myasthenia gravis, Eaton-Lambert syndrome, or Joubert's syndrome) [8–11]. Each of these models provided additional insights into the structure of the *normal* OMS and the effects of its internal feedback loops on OMS function.

Studies in this Paper

Cerebellar Hypoplasia

In a young boy, the cerebellar lesions associated with cerebellar hypoplasia (Joubert disease) resulted in two independent saccadic disturbances: square-wave jerks (SWJ) and oscillations (SWO), and "staircase" saccadic intrusions (SSI) [11]. Additionally, transient failures in yoking and neural integration were documented. SWJ/SWO are found in normals and in disease affecting the cerebral hemispheres and brain stem. The SSI were a unique finding, never having been seen in hundreds of neurological patients prior to, or subsequent to, the above patient. This paper will concentrate on the saccadic instabilities and the roles played by the cerebellum.

Infantile Nystagmus Syndrome

The data supporting the hypotheses underlying INS come from the eye-movement-based studies of hundreds of patients over a 50-year period [12–28]. They included model studies of both INS and its responses to therapy [6, 25, 29–31]. In its role as the brain's "repair shop," cerebellar circuitry is responsible for the calibration and maintenance of the damping factor of the smooth pursuit subsystem and the Alexander's law relationship.

Materials and Methods

The eye-movement recording techniques used in studying patients with INS or neurologically induced OMS dysfunction are presented in detail in the papers referenced herein. Similarly, the modeling software (MATLAB Simulink) and techniques are also presented in detail in the referenced material. For reasons covered in the "Discussion," this is not a systematic literature review but rather a review of models of subsystem disorders that are contained within a complete behavioral OMS model. However, we have referenced model studies of subsystem components that were used within our behavioral OMS model.

Ocular Motor Findings

Cerebellar Hypoplasia

Fixation on a stationary target was interrupted by SSI (28/min), greater to the right (54%) than to the left (46%). There

was an average of three steps per SSI. Saccades could be unequal (e.g., within each staircase) or disconjugate (e.g., divergent nystagmus). There were also frequent (10/min) SWJ and SWO; occasional bursts of flutter that was disconjugate and of variable interocular phase; centripetal drift of either eye; and variable strabismus.

Smooth pursuit was absent to left and of low gain to the right ($G \leq 0.78$ at 5°/s, 0.62 at 10°/s, 0.47 at 20°/s, and 0.16 at 40°/s). It was also interrupted by the above-described saccadic intrusions; the frequency of saccadic intrusions increased (43/min).

Infantile Nystagmus Syndrome

Fixation on a stationary target occurs during complex oscillations containing "foveation periods" where the retinal image of the target was on or near the fovea with minimal motion. Although the particular waveforms of INS are idiosyncratic, most stem from the primary sinusoidal velocity oscillation of the undamped smooth pursuit system.

Normal smooth pursuit occurs during INS oscillations where the eye position and velocity during foveation periods closely matches the target position and velocity.

Model Results and Hypotheses

Modeling studies of two OMS dysfunctions, saccadic intrusions/oscillations, and INS provided foundations for hypothesizing cerebellar interactions with these respective ocular motor subsystems. The behavioral OMS model into which the subsystem dysfunctions were embedded has evolved over decades of eye-movement-based research into both normal and especially abnormal function. The latter established the need to abandon the retinal error-based approach because the chaotic signals from the retina in subjects with a myriad of oscillatory conditions could not serve as the sole input from which the OMS could make accurate motor responses to specific target inputs. For example, INS patients experience a stable visual world and make normal saccadic and pursuit responses to target motion, i.e., they do not experience the oscillopsia that could result from the chaotic image motion on their retinas. Nor could an OMS model properly extract target motion from such an unmodified retinal error signal. The model must provide a means of reconstructing the sampled target position needed to drive the saccadic subsystem and the continuous target velocity signal needed to drive the pursuit subsystem. Our model does both; retinal error models cannot do either.

Specifically, the internal feedback loop within the pursuit subsystem that normally establishes the damping ratio as underdamped for normal can be adjusted to become undamped for INS. The Alexander's law relationship that uses a tonic imbalance, whose direction depends on gaze angle, is adjustable to simulate different imbalance rates in each direction; their intersection determines the "null" angle in INS. The sampled-data saccadic system relies on a reconstructed target signal that is sampled and used to determine desired saccadic size. These are part of the "repair-shop" duties of the cerebellum required to maintain OMS calibration and modulate slow-phase velocities as a function of gaze angle or, in certain types of nystagmus, fixating eye. I am not aware of any published models that contain this level of complexity or ability to duplicate the normal function in the presence of ocular motor oscillations that individuals with these dysfunctions are capable of.

Cerebellar Hypoplasia

Hypothesis 1 SWJ/SWO were released by transient changes in the internally reconstructed target-position signal.

Hypothesis 2 SSI required two independent ocular motor deficits in the model: loss of retinal position information plus a change in the internal, sampled, reconstructed retinal error signal.

Role of Efference Copy in the Internal Monitor

The relevant portion of the OMS model is shown darkened in Fig. 1 where operations contained within the internal monitor are exploded out for easier inspection; the full details of the functions in the internal monitor may be found in prior publications [30, 32] or down loaded from our website, www.omlab.org. In the OMS model, actual target position (T) is approximated by reconstructed target position (T') by adding efference copy of presumed eye position (E') to retinal error (e). That is, perceived target position, $T' = e + E'$, where e is determined optically at the retina as $T - E$. T' is then sampled, producing T'^*. Note that in the presence of nystagmus (see "Infantile Nystagmus Syndrome" section below), E contains the nystagmus signal, N (i.e., it is the actual eye position signal, E plus the nystagmus signal, N) Thus, e also contains N, albeit as $-N$. Retinal error is approximated internally by sampled, reconstructed retinal error (e'^*), calculated as $e'^* = T'^* - E' = (e + E')^* - E' = e^*$, and the saccadic motor command (smc) is produced from smc $= e'^* + N'$, where N' is reconstructed nystagmus needed to cancel the N signal contained in e'^*. It is smc that drives the pulse generator to make an appropriate saccade to the target, thereby eliminating errors due to any internal ocular motor oscillation (saccadic or nystagmus). Figure 2 illustrates the sites of OMS dysfunction in the model that provided simulations of SSI and the other eye-movement abnormalities exhibited.

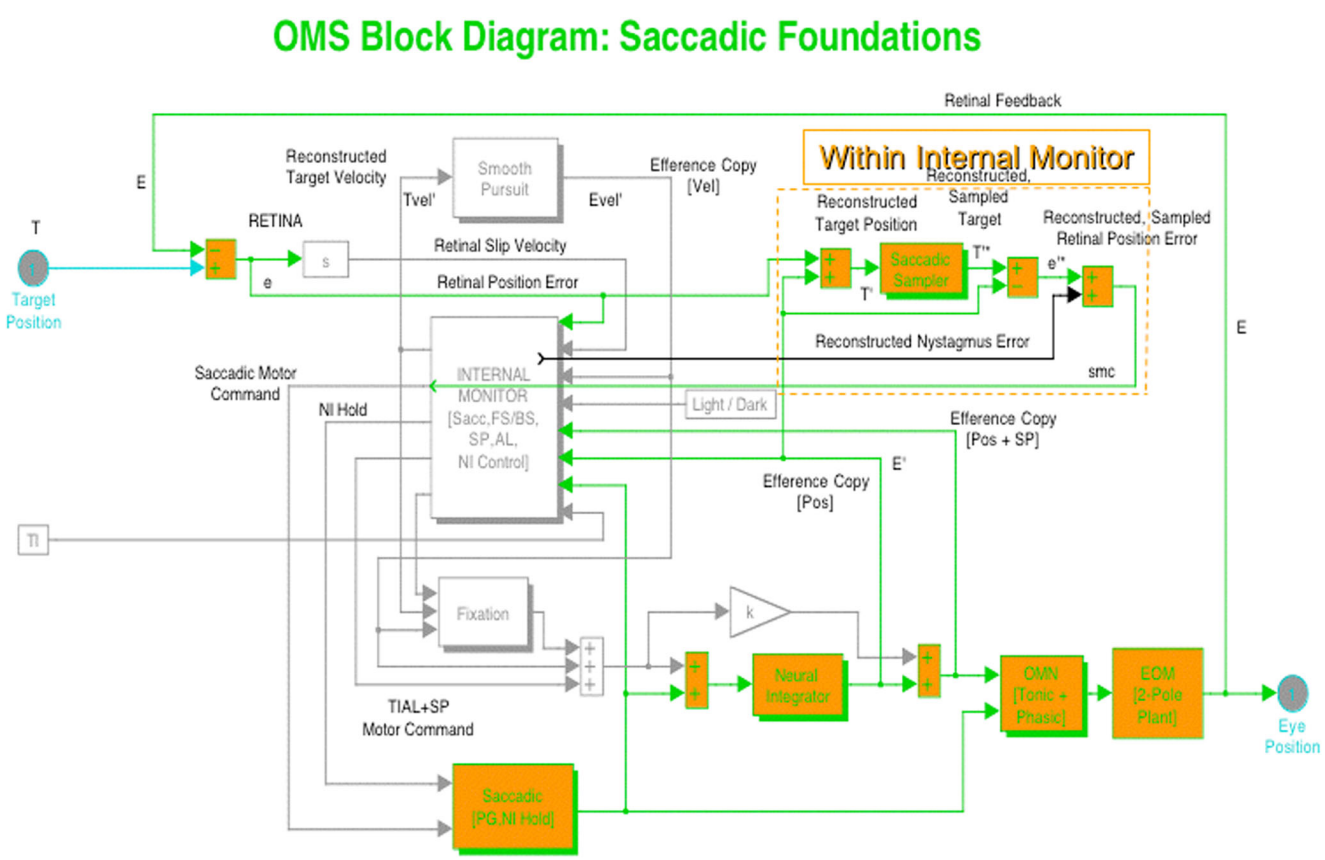

Fig. 1 Ocular motor system (OMS) model with an expanded view (dark lines) of the portion of the relevant functional circuitry within the internal monitor that is responsible for target reconstruction from retina error and efference copy of eye position, reconstructed sampled target position (i.e., perceived target position), reconstruction of retinal position error (sampled), and generation of the saccadic motor command after accounting for internally generated eye movement (e.g., nystagmus). The major subsystems and functional blocks of this behavioral model are shown with their interconnections (from Rucker et al. 2006)

Staircase Saccadic Intrusions (SSI)

Our initial attempt to simulate SSI was to transiently disable the efference copy signal, thereby inducing a constant retinal error signal similar to that caused by the use of external feedback in normals. However, the resulting staircase has intersaccadic intervals of 125 ms, the latency of internally generated corrective saccades—loss of efference copy alone does not simulate the SSI seen in our patient. Simulating SSI correctly, with 250-ms intersaccadic intervals, required two conditions be met: (1) transient loss of retinal position information, e and (2) a transient change in sampled, reconstructed retinal error, e'^{*}.

Square-Wave Jerks/Oscillations (SWJ/SWO)

Because SWJ and SWO were exhibited in isolation and in conjunction with the SSI, we also simulated these conditions. A transient change in reconstructed target-position signal, T' (caused by noise or spurious signal) produced either a SWJ or SWO, depending on the duration of the noise. In Fig. 3, these individual intrusions and oscillations are combined in different ways to simulate the complex behavior of our patient. In the top left panel, the equal-step-size SSI are preceded and followed by a SWJ. When the disturbance causing the SSI was removed, the model accurately made a saccade to the stationary target. In the top right panel, the equal-step-size SSI were followed by SWO. In the bottom left panel, the SSI are preceded by a SWJ and followed by SWO and in the bottom right panel, the SSI are followed by SWO. Note that when SWJ and SSI occurred simultaneously (bottom left and bottom right), SSI with unequal step sizes resulted, an *emergent property* of the model that duplicated those recorded in our patient.

Infantile Nystagmus Syndrome

Hypothesis 1 The underlying pendular velocity oscillation of the smooth pursuit system is released when the cerebellar control fails to maintain the normal underdamped condition, resulting in the system becoming undamped.

Hypothesis 2 The Alexander's law relationship that increases the slow-phase velocity of the nystagmus

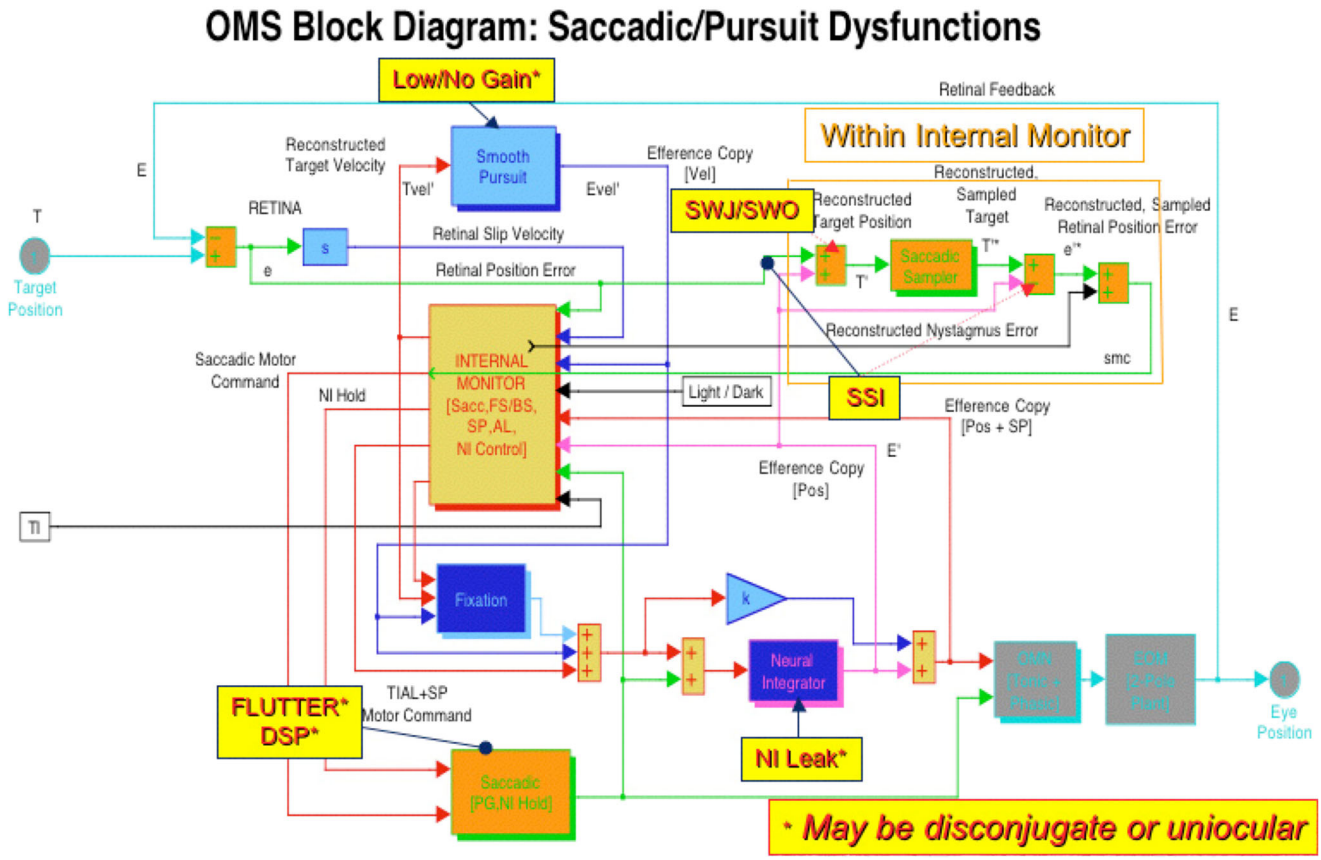

Fig. 2 Ocular motor system (OMS) model with sites of dysfunction producing square-wave jerks/oscillations (SWJ/SWO), staircase saccadic intrusions (SSI), flutter (FLUT), double saccadic pulses (DSP), neural integrator leak (NI), or low/no-gain smooth pursuit (from Rucker et al. 2006)

resulting from vestibular imbalance determines both the position of the INS null and its severity.

The updated model shown in Fig. 4 contains a resettable slow NI that eliminates problems caused by oscillations with non-zero DC values. In previous research, we hypothesized that although the slow NI does not integrate the saccadic pulse signals, it could use signals derived from saccadic pulses to regulate its output. When the input has a DC value, the saccadic signals reset the slow NI output, similar to what saccadic pulses do automatically to the fast NI.

The model modifications allowed accurate and behaviorally correct simulations of unidirectional jerk waveforms. Some fixation simulations are displayed in Fig. 5 (left). The three traces are all fixation at 0°; jerk-right with extended foveation and jerk-left with extended foveation waveforms are plotted at different locations for clarity. The pseudopendular with foveating saccade simulation is shown for comparison. The dot-dashed lines are indication of the ± 0.5° fovea. In all three waveforms, although there were slight differences between the sizes of each saccade (as commonly seen in human data), the final target-image position always remained within the ± 0.5° foveal area (which allows the best visual acuity). Like most pendular INS waveforms recorded in humans, the foveation periods generated by the model extend up to 50 ms. The jerk waveforms simulated here have a much longer and flatter foveation period right on target (up to 300 ms), suggesting good visual function. Inspection of the foveation periods of each of the waveforms reveals how accurately the model achieves and maintains target foveation (i.e., remains within the ± 0.5° by ± 4.0°/s foveation window) but does so with slightly different position and velocity errors from cycle to cycle. This major *emergent property* of the model mimics the variations exhibited by patients with INS. Altering the fast-phase scale (e.g., an inaccurate estimation of required fast-phase size) transitions the waveform from jerk to pseudocycloid, as shown in Fig. 5 (right). This interesting *emergent property* of the model, producing the pseudocycloid waveform (common in INS), requires no additional functional ocular motor blocks and further supports the hypothesis that most of the jerk INS waveforms, although having different apparent morphology, originate from the *same* underlying pendular oscillation.

The model also accurately simulated responses to large and small step changes in target position in both directions and smoothly transitioned to another type of waveform depending

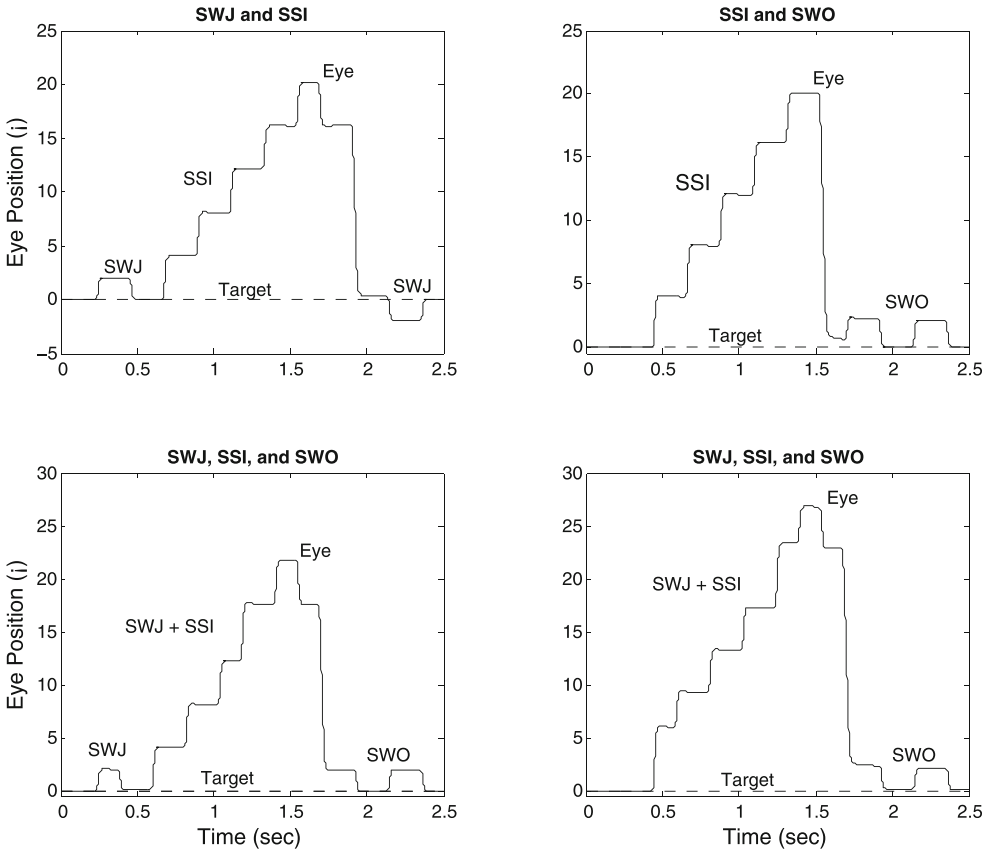

Fig. 3 OMS model simulations of the types of saccadic intrusions and oscillations found in our subject by different combinations of their individual components. (Top left) SWJ before and after a rightward, equal-step SSI, and refixation during attempted fixation. (Top right) SWO after a rightward, equal-step SSI and refixation during attempted fixation. (Bottom left) Simulation of a rightward, unequal-step SSI during fixation proceeded by a SWJ and followed by a SWO. (Bottom right) Simulation of a rightward, unequal-step SSI during fixation, followed by a SWO (from Rucker et al. 2006)

on eye position (Fig. 6). In this figure, the neutral zone of the "simulated subject" is set to be ± 5° around the primary-position null; as long as the intended eye position is in this range, pendular waveforms will result. Right lateral gaze beyond that zone results in transition to jerk-right waveforms and left lateral gaze transitions to jerk-left waveforms; in both, the slow phases accelerate toward the neutral zone, duplicating the INS in patients. Also note that the size of the jerk nystagmus grows as the eye goes more laterally; this represents a "medium" null broadness setting so the gaze-angle

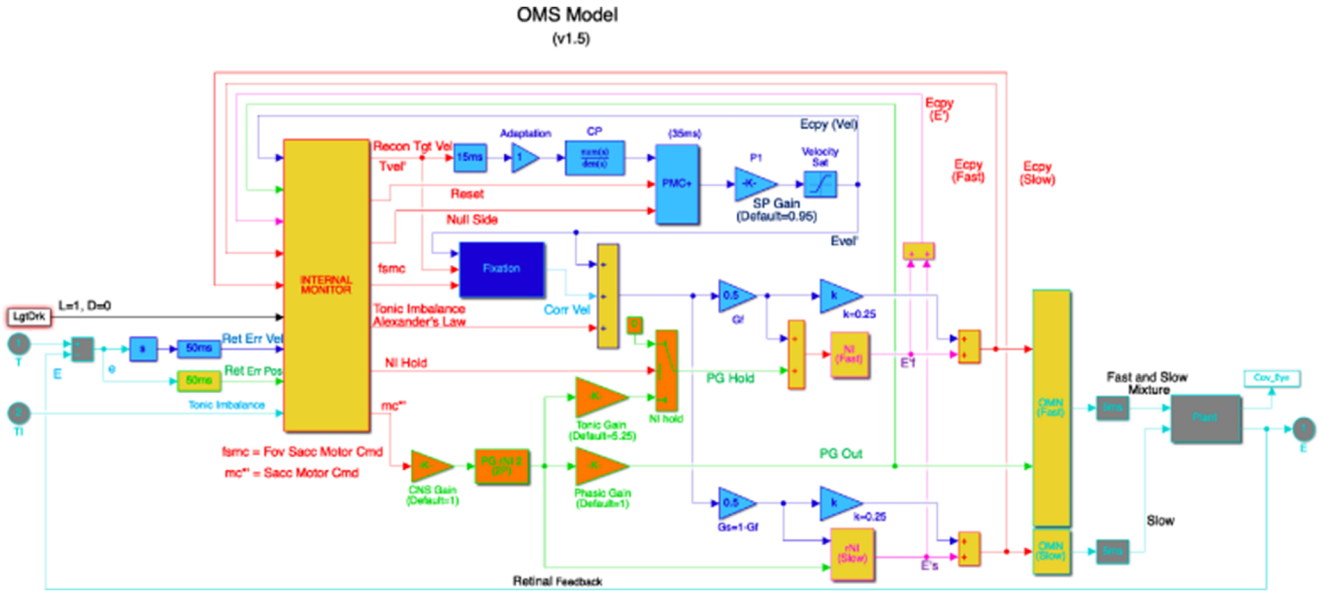

Fig. 4 OMS model that simulates pendular and jerk INS waveforms. Compared to earlier versions of the model, changes were made within the INTERNAL MONITOR (Alexander's Law), the PMC+ blocks, and the signals to the PMC+ block. Also, the two final common integrators "NI (fast)" and "NI (slow)" now simulate their respective neural populations (from Wang and Dell'Osso, 2011)

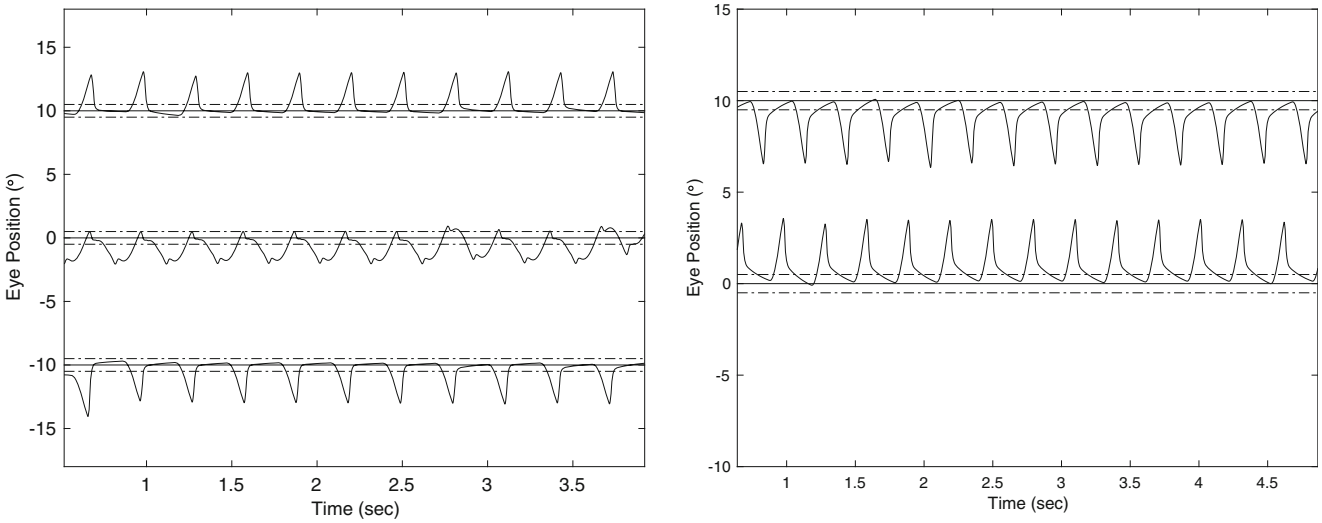

Fig. 5 (Left) OMS model simulations of 0° fixation comparing jerk and pendular waveforms; jerk right and jerk left waveforms are plotted at different locations (10° and − 10°, respectively) for clarity. (Right) OMS model simulations of 0° fixation during pseudocycloid waveforms in either direction; right pseudocycloid waveforms are plotted at a different location (10°) for clarity. Note the accurate target foveations despite differences in INS waveforms and the longer foveation periods common in jerk with extended foveation waveforms. The dot-dashed lines are an indication of the ± 0.5° fovea (from Wang and Dell'Osso, 2011)

amplitude variation is moderate. In all simulations, the voluntary and intrinsic saccades work in concert to acquire and foveate the target. For large target steps, it took a greater than normal amount of time for the eye to arrive on target, also consistent with our findings in patients' target acquisition time [33]. Finally, note the spontaneous changes in the bias of the pseudo-pendular with foveating saccades waveforms at the different gaze angles. This was the first *emergent property* of the model and duplicated the spontaneous changes in side of the waveform that contained the foveation periods.

Discussion

Unlike networks analysis, which provides unique solutions, networks synthesis results in an infinite number of solutions, all of which may satisfy the stated input/output criteria. One way to evaluate such solutions is to embed them in a larger OMS model and test that normal patient responses to known target inputs (e.g., step, pulse, ramp, and their combinations) are duplicated with only the superimposition of the oscillatory disorder. This "top-down" approach has guided our lab and is

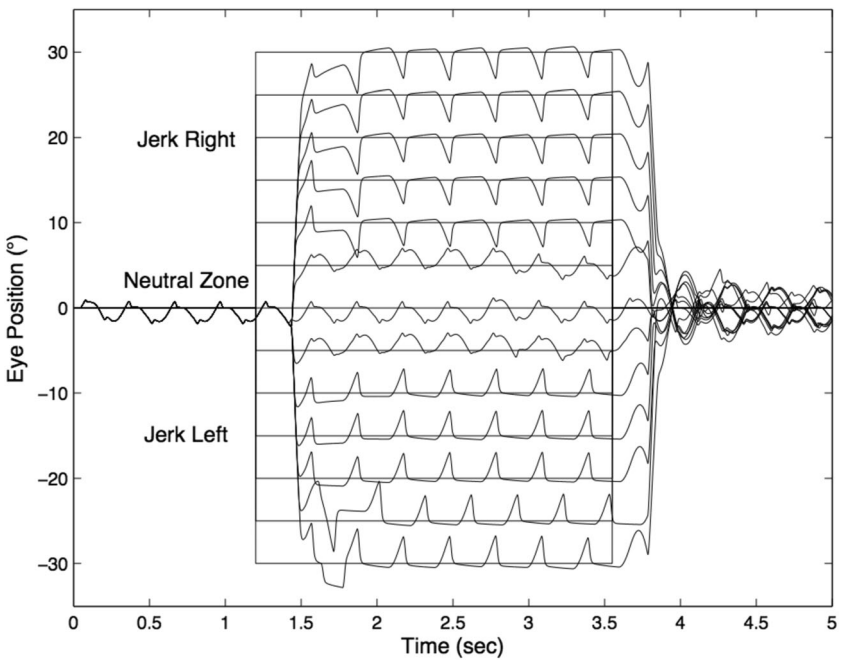

Fig. 6 OMS Model simulation of an INS subject with a ± 5°, primary-position neutral zone, and a medium null broadness; jerk right waveforms occur spontaneously in right lateral gaze, jerk left in left lateral gaze. Note the accurate target foveations at all gaze angles (despite differences in INS amplitudes, waveforms, and occasional bias shifts) and the longer foveation periods common in jerk with extended foveation waveforms (from Wang and Dell'Osso, 2011)

reflected the citations included herein. Although there have been other putative "bottom-up" saccadic and pursuit subsystem models, I am unaware of their testing within a behavioral OMS model and it is far beyond this limited review to conduct such tests, each of which would be a major undertaking.

Cerebellar Hypoplasia

The classic ocular motor abnormality in Joubert syndrome is ocular motor apraxia, which differs from congenital ocular motor apraxia in that both horizontal and vertical volitional saccades are affected in Joubert syndrome [34]. Other identified ocular motor abnormalities in Joubert syndrome include impaired smooth pursuit with decreased gain and pendular nystagmus; our patient demonstrated the former, but not the latter.

The ocular motor abnormalities consistent with cerebellar dysfunction demonstrated by our patient, included prominent and frequent SWJ, SWO, saccadic intrusions, ocular flutter, and impaired smooth pursuit (previously described in the "Model Results and Hypotheses" section). In addition, eye drifts toward primary position from eccentric gaze suggested a neural integrator leak. The neuroanatomic correlate of a neural integrator leak is a lesion of either the nucleus prepositus hypoglossi or the vestibular nuclei in the caudal brainstem, although dysfunction of the midline cerebellum may also result in a leaky neural integrator [35]. Either scenario is possible in Joubert syndrome, as neuropathologic findings show not only severe hypoplasia of the cerebellar vermis but also neuronal reduction and malformation in multiple brainstem structures [36].

Ocular Motor System Model and Simulations

Possible Cerebellar Mechanisms

> Hypothesis 1 SWJ/SWO were released by transient changes in the internally reconstructed target-position signal.

System noise in one ocular motor function, internal reconstruction of the target-position signal, may produce SWJ/SWO in normals and more so in neurological disease.

> Hypothesis 2 SSI required two independent ocular motor deficits in the model: loss of retinal position information plus a change in the internal, sampled, reconstructed retinal error signal.

Creating SSI in normals can be accomplished by externally adding the eye-position signal to the target signal. In neurological disease, it may result from simultaneous dysfunctions: (1) transient loss of accurate retinal-error information and/or sampled, reconstructed error and (2) a constant sampled, reconstructed retinal error that drives saccades. Since duplicating that internally in the model required two independent deficits that helps explain why SSI is so rare.

Each of the above hypotheses was expressed in the form of one or two simple deficits in an OMS model that accurately simulates the behavior of normal humans when responding to common target inputs. SWJ/SWO were simulated by transient changes in the internally reconstructed target-position signal, T' (possibly caused by noise or a spurious signal). They are found in normals and in disease affecting the cerebral hemispheres and brain stem. SSI, on the other hand, required abnormalities in two separate ocular motor functions, loss of retinal position information and a change in the internal sampled, reconstructed retinal error signal. This may result from transient loss of accurate retinal-error information (e), and/or sampled, reconstructed error (e'^*), plus a constant sampled, reconstructed retinal error ($e_k'^*$) that drives saccades. The OMS behavioral model demonstrated that SSI could *not* be simulated solely by the transient loss of accurate reconstructed eye-position information (E'), a demonstration that more limited, partial saccadic models would be incapable of.

The SSI in our patient were associated with dysfunction in the superior cerebellum and vermis. This is the first occurrence of SSI that we are aware of; given the many neurological patients that have been recorded in many labs worldwide, we conclude SSI is a very rare disorder. It is not surprising that the more common SWJ could be simulated by a hypothetical noise signal in one ocular motor function, internal reconstruction of the target-position signal, whereas SSI required a more unlikely double dysfunction. Although both functions may occur in neighboring anatomical sites, they are probably not located at the same site or SSI would be more common. The ability of a normal behavioral OMS model to accurately simulate complex ocular motor dysfunctions of specific patients (when "lesioned" by an hypothetical malfunction) without introducing other, unobserved behavior provides strong support for the hypothetical mechanisms used in the model.

Infantile Nystagmus Syndrome

The easy transition from an underdamped to an undamped smooth pursuit system produces the underlying pendular oscillation of INS. The normal saccadic and foveation systems then modify the oscillations to produce the diverse complex waveforms of INS that, due to Alexander's law, vary in amplitude as gaze is directed lateral to the idiosyncratic "null" position.

Ocular Motor System Model and Simulations

Possible Cerebellar Mechanisms Not only did the model containing each of these diverse deficits reproduce the OMS

behavior recorded from patients but also it also exhibited emergent behavior not specifically modeled.

> Hypothesis 1 The underlying pendular velocity oscillation of the smooth pursuit system is released when the cerebellar control fails to maintain the normal underdamped condition, resulting in the system becoming undamped.

Maintaining an underdamped system is problematic as it can easily become undamped. This explains why INS is so common when associated with many unrelated visual system dysfunctions and also occurs in the absence of any visual system dysfunction.

> Hypothesis 2 The Alexander's law relationship that increases the slow-phase velocity of the nystagmus resulting from vestibular imbalance determines both the position of the INS null and its severity.

The worsening of many types of nystagmus with gaze angle in the direction of the fast phases (Alexander's law) is a well-documented phenomenon. It is therefore not surprising that INS also exhibits an increased intensity as gaze is directed away from an idiosyncratic "null" position.

Conclusion

Through the use of a behavioral OMS model, specific lesion sites (i.e., model "lesions") were demonstrated to reproduce both saccadic and slow-eye-movement disorders and allowed hypothetical anatomical cerebellar sites to be suggested for those disorders. These hypothetical lesions were strengthened by their inclusion in a behavioral OMS model that demonstrated the same normal transient responses to target inputs exhibited by patients afflicted with these disorders.

Compliance with Ethical Standards

Conflicts of Interest The authors declare that there is no conflict of interest.

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