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Saccade and vestibular ocular motor adaptation

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Abstract

Purpose—This paper focuses on motor learning within the saccadic and vestibulo-ocular reflex (VOR) oculomotor systems, vital for our understanding how the brain keeps these subsystems calibrated in the presence of disease, trauma, and the changes that invariably accompany normal development and aging. We will concentrate on new information related to multiple time scales of saccade motor learning, adaptation of the VOR during high-velocity impulses, and the role of saccades in VOR adaptation. The role of the cerebellum in both systems is considered.

Methods—Review of data involving saccade and VOR motor learning.

Results—Data supports learning within the saccadic and VOR oculomotor systems is influenced by 1). Multiple time scales, with different rates of both learning and forgetting (seconds, minutes, hours, days, and months). In the case of forgetting, relearning on a similar task may be faster. 2). Pattern of training, learning and forgetting are not similarly achieved. Different contexts require different motor behaviors and rest periods between training sessions can be important for memory consolidation.

Conclusions—The central nervous system has the difficult task of determining where blame resides when motor performance is impaired (the credit assignment problem). Saccade and VOR motor learning takes place at multiple levels within the nervous system, from alterations in ion channel and membrane properties on single neurons, to more complex changes in neural circuit behavior and higher-level cognitive processes including prediction.

1. Introduction

The ocular motor system is ideal to study the control of movement including the adaptive mechanisms by which the brain maintains the precise calibration necessary for optimal motor performance. With eye movements, it is easy to measure and quantify the motor output and to manipulate the sensory input (e.g., movement of the head or movement of objects in the visual scene). The anatomical and neurophysiological bases of eye movements are well understood, and a computational approach is easily applied to eye movements to develop analytical models of normal and abnormal ocular motor control. Here we will concentrate on two ocular motor subsystems, saccades and the vestibulo-ocular reflex (VOR). We will focus on recent advances in understanding the vital mechanisms by which the brain keeps these systems calibrated in the presence of disease, trauma and the changes that invariably accompany normal

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development and aging. For saccades, we will concentrate in new information related to multiple time scales of motor learning. For the VOR, we will focus on new information related to adaptation of the VOR during the high-velocity impulses and the role of saccades in VOR adaptation. For both we will consider the role for the cerebellum. Finally, we will look for ways in which we can apply what we learn about adaptation to better diagnosis and treatment. Concerning this last point, it is important to remember that there are constraints on adaptive capabilities that help diagnosis but may hinder rehabilitation. This is especially so for saccades and the VOR as they must operate 'open-loop' to ensure rapid stabilization of gaze on objects of importance in the environment. Because 'immediacy' is essential for survival in natural behavior, neither saccades nor the VOR have the luxury of using visual information to update their motor response before the important part of the movement is over. They must rely on other mechanisms, including internal feedback, prediction and recalibration, in order to optimize performance.

Any understanding of the mechanisms underlying adaptation of saccades or the VOR must consider following complexities: 1) There are *multiple time scales* of learning, with different rates of both learning and forgetting (seconds, minutes, hours, days, and months), and once forgotten, relearning on a similar task may be faster (recall). 2) The *pattern of training* influences learning and forgetting, and rest periods between training sessions influence the retention of learning (consolidation). 3) Different *contexts* require different motor behaviors; depending on environmental circumstances (e.g., am I tilted or am I upright) different learned behaviors must be gated in or out. 4) Deciding where blame resides when motor performance is impaired is difficult (the credit assignment problem) For example, am I the problem? Is my motor system at fault? Are my eye muscles weak? Or has there been a change in the environment or how I perceive it? E.g., have I lost calibration because I am wearing corrective spectacles? 5) Learning takes place at multiple levels within the nervous system, from alterations in ion channel and membrane properties on single neurons, to more complex changes in neural circuit behavior, to higher-level cognitive processes including prediction and development of purposeful strategies to optimize motor performance.

2. Saccade adaptation

Since saccades are so fast, usually complete in less than 60 ms or so, there is no time for immediate visual feedback to correct for errors in performance. Hence, the brain must recognize when saccade performance is imperfect and recalibrate premotor commands to restore accuracy. What the error signals are that stimulate adaptive recalibration and how such motor learning is implemented have been investigated since the landmark study of McLaughlin (1967) (see also comprehensive reviews by Hopps and Fuchs, 2004 and Shelhamer et al., 2003). McLaughlin used a double target step paradigm in which he imposed a persistent retinal error after every primary saccade by jumping the target as soon as the saccade toward the first target began. The first saccade becomes inaccurate requiring a second, corrective saccade to reach the new target location. Within a relatively small number of trials premotor commands gradually change so that the initial saccade grows bigger or smaller (depending upon whether the second target moves farther from or closer to the starting position of the eye). The adapted saccades persist even when training stops and their return to the pre-training state is gradual, not abrupt, suggesting that this is a true form of adaptive plasticity rather than a high-level cognitive strategy.

Variations of this relatively simple double-step paradigm have been used for decades and considerable knowledge has emerged, not only about how rich and flexible, but also how complex saccade adaptation can be. Still uncertain are the nature of the error signal(s) that drive saccade adaptation (visual errors or the motor responses that correct them), the mechanisms that underlie saccade adaptation occurring on different time scales and within

different contexts, and the differences between mechanisms that acquire and those that retain motor learning.

There also is an important caveat when inferring underlying mechanisms from results in the double-step paradigm. The double-step paradigm presents an error signal that is on the 'afferent' side of neural processing for saccades, e.g., as if there has been a 'change' in the world or in how visual information is processed. Saccade adaptation is also called for when there is a change on the efferent side, e.g., in response to muscle weakness. Indeed, how the brain deciphers the cause of dysmetria is a nagging unknown. One possibility is ocular proprioception, which can signal whether or not there is a mismatch between afference (position of the eye in the orbit) and efference (premotor command), which would be the case if there were a true muscle weakness.

3. Cross-axis adaptation

Recently, Chen-Harris et al used a short-term (minutes), double-step paradigm (cross-axis) to elicit saccade adaptation in intact humans (Chen Harris et al., 2008). By having the second target jump orthogonal (vertical) to the first (horizontal) subjects learned to develop oblique saccades in response to horizontal target displacement. Furthermore, the adapted saccades were curved, moving more rapidly toward the second (vertical) target as the saccade neared its end. This curvature allowed us to dissect learning into *two processes with different time scales*: a faster process (sec to min) that primarily occurred late in the saccade, leading to saccade curvature and a slower process (tens of min) that occurred early in the saccade and altered its initial direction. The fast and slow mechanisms were evident in both the acquisition and retention of the novel motor behavior. Thus, the *signature* of this two-stage process in saccade learning and forgetting is the way adapted saccades acquire and lose *curvature*.

One may ask if the fast component of the adaptive response reflects an anticipatory, *predictive*, vertical response based on the subject's expectation of the final location of the target. If true, the curvature would arise from a cognitive strategy to produce the vertical component, rather than a lower level, plastic change in motor innervation. Prior evidence indicates some of the change in saccade amplitude during on-axis adaptation is lost immediately when the adaptive stimulus disappears, suggesting some role for an anticipatory strategy rather than more enduring synaptic plasticity (Straube et al., 2001). We would suggest, however, during cross-axis adaptation the curvature arises from the action of a 'forward model' that normally monitors efference copy and, in the case of a discrepancy in what is expected for accurate saccades, corrects movements as they occur online (Chen Harris et al., 2008; Optican, 2005).

Regardless of the mechanism for the fast time scale adaptation, its prompt acquisition and relatively quick forgetting (or dismissal if this response is a higher-level cognitive strategy) gives the brain flexibility and time to determine if there is true dysmetria, and if so, what its cause might be. Is inaccurate performance merely due to random and transient fluctuations in neural activity or is there a problem requiring a more enduring repair? This conundrum is the earliest part of the credit assignment problem. Is the dysmetria due to natural and benign fluctuations in neural activity, changes that are more enduring in the *external* sensory environment, in the *internal circuitry* of the brain that processes sensory information and issues motor commands, or in the *motor effectors* themselves?

4. On axis adaptation: New findings

Ethier et al recently reinvestigated on-axis double step (gain-increase and gain-decrease) saccade adaptation asking if there were also two time scales in this type of learning (Ethier et al., 2008a). They dissected the multiple time scales of learning and forgetting by using a

deadaptation block after a sustained period of training, in which the direction of the adaptive stimulus reversed to baseline. Then, in the post-training period, 'error-clamp trials' were introduced. In an error-clamp trial, a saccade is made to a visual target that is extinguished when the eye begins to move toward the target. After the initial saccade, the subject remains in darkness for 500–800 ms after which the target reappears and is placed on the fovea. In this way, there is no error signal and the brain 'infers' that the saccade is accurate and there is no need to change motor performance. The rate of forgetting of both the fast and slow time scale learning can be revealed using error clamp trials that are unencumbered by error signals that would promote a return to the pretraining state. Ethier et al. found that after the adaptation and deadaptation blocks, the initially learned gain change reappeared albeit with a reduced magnitude. This result showed longer time scale learning was slowly decaying though still present during the reversed training, and that the two adaptive processes were occurring simultaneously. These findings support the fast and slow time scale model of short-term saccade adaptation.

5. Changes in the dynamic properties of adapted saccades

Ethier et al also readdressed the long-standing issue of what happens to the dynamic properties of saccades. i.e., to their peak velocity – amplitude relationships, or 'main sequence', when they undergo adaptation (Ethier et al 2008b). One problem when addressing this issue is that there are changes in saccade dynamics simply due to the repetitive nature of the task (Golla et al., 2008). Saccades slow down in response to a pattern of identically repeating saccades to the same target positions though they remain accurate in normal subjects. Ethier et al used a novel control paradigm in which the saccade pattern during adaptation was mimicked in the same subject on another day but without any error signals to drive adaptation. Then they compared any changes in the dynamics of saccades during adaptation with those associated only with repetition. Ethier et al found that gain-decrease but not gain-increase adaptation led to differences in the dynamic properties (main sequence) of saccades. Using optimal control theory, they evaluated the 'costs' (time to reach target and accuracy) of a change in saccade dynamics. Their analysis suggested that it was optimal for the brain to choose a target remapping strategy with gain-up adaptation and a modification of an internal forward model with gain-down adaptation. Presumably long-term adaptation mechanisms eventually restore saccade dynamics, i.e., their main sequence relationships, back to their original pattern, but how this is accomplished and when this happens is unknown.

5.1. A role for forward models in the control of saccades

As alluded to above, under the credit assignment problem, the brain must face the inevitable variability in premotor saccade commands from one movement to the next. This variability has many sources including internal noise and the vagaries in motor commands related to the degree of attention and the value attached to the intended visual target. Nevertheless, saccades remain remarkably accurate in the face of fluctuating premotor commands. Internal feedback is a proposed solution, and the cerebellum has been implicated in this process (Golla et al., 2008). In this scenario, the cerebellum monitors the progress of the saccade toward its goal. Should there be a deviation in amplitude or direction from what is needed to complete the movement accurately, the cerebellum corrects the trajectory and steers the eye to the target (Optican, 2005). Presumably, the cerebellum uses an efference copy of the on-going position of the eye during the saccade and compares it with a *forward model* that allows it to predict where the eye will end up. Based on this immediate information about saccade trajectory, the cerebellum can make any necessary corrections promptly online and ensure that the saccade is accurate. Our own findings are compatible with this formulation; the major adjustment to the saccade trajectory during repetition fatigue was a delay and a diminution in the later, deceleration phase of the saccade (Xu, Zee, Shadmehr, unpublished observations).

We can apply a similar logic should there be a persistent end-point error, i.e., a consistent pattern of dysmetria. The cerebellum would detect this and then implement a more sustained change in the saccade premotor command to restore the correct calibration for optimal motor performance. Here, however, there must be more than just an adjustment toward the end of the saccade. The initiation of the saccade must also be modified. Indeed firm physiological evidence based on single unit recordings from the fastigial nucleus points to a role for the cerebellum in supervising not only the ending of saccades but also their beginning (Robinson and Fuchs, 2001). The effect of the fastigial nucleus and the corresponding dorsal vermis above it is to modulate activity that a) drives the beginning of contralateral saccades and b) helps to end ipsilateral saccades. Our studies in normal humans suggest an early (near the beginning of the saccade) and a late (toward the end of the saccade) component to saccade adaptation (Chen Harris et al., 2008). Certainly, there is a persuasive rationale and substantial evidence for this formulation, which puts the cerebellum in a central position both to compensate for online variability in saccade commands and to maintain saccade accuracy in the long-term. Even so, exactly how the cerebellum implements such compensation and learning is unknown (see below).

5.2 Behavioral deficits in saccade adaptation with cerebellar lesions

Studies in humans and monkeys with cerebellar lesions have shown deficits in saccade adaptation. Experimental lesions of the dorsal vermis in the monkey impair short-term adaptation in response to a double-step paradigm (Takagi et al., 1998; Barash et al., 1999). Patients with diffuse cerebellar degeneration show deficits in the same type of paradigm (Straube et al., 2001; Golla et al., 2008). Long-term adaptation, in response to an ocular muscle weakness for example, is also impaired in monkeys with cerebellar lesions (Optican and Robinson, 1980). Lesions in thalamic relay neurons (presumably from the cerebellum to cerebral cortex) interfere with saccade adaptation (Gaymard et al., 2001). Studies in patients with focal structural lesions in the lateral cerebellar hemispheres also show defects saccade adaptation (Choi et al., 2008); this suggests that another cerebellar locus, apart from the vermis and fastigial nucleus, also contributes to saccade adaptation. Finally, the effects of cerebellar lesions upon visually guided, ‘reactive’ saccades and upon scanning voluntary saccades appear to be spatially independent (Alahyane et al., 2008). A lesion in the midline vermis affected adaptation of reactive saccades while a lesion in the lateral hemisphere affected adaptation of scanning voluntary saccades. Taken together these results suggest a specific role of the cerebellum in saccade adaptation and that different parts of the cerebellum play different roles in different types of saccade adaptation.

Golla et al recently showed that cerebellar patients are deficient both in feedback control of saccade duration during repetitive saccades to the same target, and in the adaptive process in response to a double-target jump stimulus (Golla et al., 2008). We have also found that the adaptation deficit in cerebellar patients was greater for the faster learning process. These data suggest an overarching *hypothesis about cerebellar function: the cerebellum prevents saccadic dysmetria by playing a key role both in compensation for the inherent internal variability in generating saccade commands and in adapting to persistent end-point errors*. A corollary hypothesis is that the same cerebellar mechanism is involved in the faster time scale learning and in the compensation for internal variability of saccade commands. Implementation of this mechanism could be via a *forward model* of the expectation of the brain of the outcome on performance of any given premotor command.

6. Vestibulo-Ocular Reflex (VOR) adaptation

As for saccades, the VOR operates open loop; its latency (7–10 ms) is too brief for immediate visual feedback to correct for errors performance. Accordingly the brain must identify defective performance and then restore steady gaze so vision is preserved during and just after

movements, the *raison d' être* of the VOR. If the deficit is not too severe, the brain can augment the amplitude of an inadequate slow phase of the VOR. If the deficit is profound, the brain must enlist surrogate eye movements such as saccades to substitute for or augment the inadequate slow-phase response.

Gain (ratio of eye velocity to head velocity) is the usual quantitative measure of performance of the VOR. Experimental studies typically couple head motion with an unnatural pattern of target motion to elicit VOR adaptation. Image motion on the retina during head motion – retinal slip – is the primary error signal that drives adaptation of the VOR, and the adaptive response to this stimulus is robust (e.g., Gauthier and Robinson, 1975; Gonshor and Jones, 1976). Depending on the direction of the motion of the target relative to the motion of the head, the amplitude of the VOR will increase or decrease. The duration of exposure is also important for the consolidation of new learned behaviors, perhaps enabling new protein synthesis for long-term memory construction (Mzcgaugh and Roosendaal, 2002; Barzilai et al., 1989). As an example, exposure to artificial retinal slip during rotation of the head for minutes to hours will increase the VOR gain from 10%–35% of that requested depending of the individual and the specific pattern of stimulation (Tilikete et al., 1993; Tilikete et al., 1994; Shelhamer et al., 1994; Yakushin et al., 2003; Schubert et al., 2008a). In contrast, exposure to an adaptation stimulus lasting hours to days produces gain changes of 60% to 100% of the adaptive demand (Melvill Jones et al., 1988; Istl-Lenz et al., 1985; Miles and Eighmy, 1980; Miles and Braitman, 1980; Clendaniel et al., 2001; Kuki et al., 2004). Recent findings comparing short and long-term gain training show differences that may have important implications for clinical rehabilitation. Longer duration training of the VOR results in a larger in VOR gain compared with shorter exposure times. This learned memory, however, is forgotten more quickly. Interestingly, learned low gains are more resilient; they required hours of up training for restoration, to baseline. Learned high gains, however decay spontaneously, only requiring minutes of down training to return to baseline (Boyden and Raymond, 2003; Kuki et al., 2004). These data suggest the VOR has two time scales for learning and reversal, in part, depending in whether the adaptive change is up or down (Boyden and Raymond, 2003).

Adaptive changes in the VOR gain to retinal slip are greater when the error signal is gradually incremented than presented in its entirety (Schubert et al., 2008a). Using an incremental velocity error in normal subjects, the VOR increased by a mean 17% during active head impulses with head velocities greater than 130 deg/sec. This adaptation also transferred to passive head impulses in most subjects. In patients with unilateral vestibular hypofunction, exposure to the graded incremental retinal slip also increased the VOR during active head impulses by mean 18% better than the −6% that occurred with abrupt learning. Some of the patients also showed VOR gain adapt for passive head impulses. With this paradigm, corrective or 'compensatory' saccades (CS), in the same direction as the inadequate slow phases were recruited during training.

7. VOR adaptation induced by position and alternate error signals

Although retinal slip is probably the most effective means to stimulate VOR adaptation, other error signals may also contribute. These include position error signals (Eggers et al., 2003), imagined motion of the target (Jones et al., 1984), strobe light (Mellvill Jones and Mandl, 1979) and tracking of images stabilized on the retina (flashed after images) (Shelhamer et.al., 1995). Exposure to persistent optokinetic stimulation without concurrent head rotation may also drive VOR adaptation (Tilikete et.al., 1994).

Eggers et al. asked normal subjects to view a stationary target that changed its position at the onset of an unpredictable whole-body rotation (position error signal). With this position-error stimulus, subjects increased the gain of the slow phase of the VOR by 5%–16%, depending on

the individual. Interestingly, subjects also recruited saccades to augment the slow-phase response, which, in the same individuals did not happen during VOR adaptation using retinal slip signals (Eggers et al., 2003). Recently, we investigated the use of an incremental position error signal to adapt the VOR during high-velocity, activated head impulses (Scherer and Schubert, 2009). Subjects made active head impulses while viewing a target that moved with a progressively increasing position error (target was off during head rotation then flashed on in a new target direction opposite of the head position). In a separate experiment, the position error was always 5% of the change in head position. Both paradigms were designed to increase VOR gain. VOR increased with a range of 6 to 15% during active head impulses, and depending on the subject, as much as 7% when tested with passive head impulses. Interestingly, the largest amount of gain change occurred only for the paradigm with the smallest increment in error signals (constant 5%). These findings suggest that position error signals, like velocity errors drive adaptation that can occur in a context different from the adapting stimulus (active and passive) and occurs best when the error signals are small. The position error paradigm also recruited compensatory saccades to augment the VOR.

7.1. Compensatory saccades as an adaptation to abnormal peripheral VOR function

Patients with peripheral vestibular deficits show impaired gaze stabilization and consequently their visual acuity degrades during head rotation (Herdman et al., 1998; Schubert et al., 2002a). When the deficit is marked, patients substitute other types of eye movements to augment the diminished slow-phase component of the VOR. These include CS (Kasai and Zee, 1978; Bloomberg et al., 1991; Maurer et al., 1998; Tian et al., 2000; Della Santina et al., 2002; Schubert et al., 2002b; Schubert et al., 2008b; Weber et al., 2008; Weber et al., 2009). Patients with vestibular hypofunction naturally adopt CS as a strategy to assist gaze stabilization, whether or not patients can be trained to use them is unknown.

Recently, Weber et al quantified VOR deficits in patients with vestibular hypofunction using head acceleration ranges from 750 to 6000°/sec (Weber et al., 2008). They describe ‘covert’ or occult saccades, similar to CS, which occur during the head rotations, making them difficult to observe clinically. The frequency and amplitude of covert saccades increased as head velocity increased. Interestingly, the occurrence of the covert saccades was related to severity of vestibular hypofunction: Patients with partial vestibular function due to intratympanic gentamycin injection generated about three times as many covert saccades as normals, but only half as many as patients with unilateral vestibular deafferentation.

Covert and CS appear to be similar. Their latencies are similar to ‘express’ saccades (~100 ms) and much less than volitional saccades (~200 ms). This unique saccade is present during both predictable and unpredictable head rotations (Della Santina et al., 2002; Fischer et al., 1984; Baloh et al., 1975). CS occur at latencies suggesting they could be triggered from neck proprioception or from changes in activity on intact, contralateral vestibular afferents in the case of unilateral vestibular hypofunction. They may also be pre-programmed (or predictive), for example, if the head movement is active or if the head movement is passive but also predictable. CS can reduce gaze error sizably, e.g., 28–59% for ipsilesional head rotations (Segal and Katsarkas, 1988; Tian et al., 2001). We extended these findings by studying patients with unilateral vestibular hypofunction (UVH) and bilateral vestibular hypofunction (BVH) and comparing the difference in gaze stability when CS occurred during a predictable versus unpredictable head impulse. In UVH subjects during active head impulses (predictable), gaze position error was reduced by 63%, while during unpredictable passive impulses, by only 35%. For BVH subjects, we found that each active head impulse included a CS; for passive head impulses, gaze position error reduced 54% (Schubert, 2002b). These data suggest that when the patient is aware (active or predictable) of the intended head rotation, the brain recruits a compensatory saccade more often.

The translational VOR (tVOR, otolith-mediated) also benefits from the symbiotic relationships between the VOR and saccades. Shelhamer et al. adaptively increased the gain of the tVOR in normal human subjects by exposing them to lateral sinusoidal translations and out of phase target motion for 20 minutes (Shelhamer et al., 2000). Subjects learned to make saccades in response to translation of the head in the direction of the slow eye movements. These CS accounted for 32% of the tVOR after adaptation. Therefore, both the semicircular canal and otolith-mediated VOR can use compensatory saccades to help stabilize gaze during motion of the head.

CS are also modifiable with training. We measured eye rotations during a functional gaze stability task (dynamic visual acuity) in which normal subjects were asked to identify letters that flashed on a monitor during active head rotations with velocities exceeding 120 deg/sec. There was a trend toward a direct relationship between the frequency of compensatory saccades and the demand of the visual acuity task. Subjects made more CS during active head rotations when letters flashed compared to when no letter flashed. We also examined the effects of an exercise program designed to improve gaze stability during active head movements in patients with chronic UVH (Schubert et al., 2008b). There was a combined 40% ± 13% increase in the number of CS used during the acuity task. The slow-phase gain of the VOR also increased on average 35% during the acuity task. In the same patients, the VOR gain did not change during passive head impulses, suggesting the salutary effect with active rotations of the head was from the exercise program and not natural recovery. These findings support the notion that CS become part of an adaptive strategy for vestibular loss that can be recruited with rehabilitation exercises. In contrast, one patient with UVH who showed partial recovery of labyrinthine function (VOR gain with passive head impulses improved over time) had a 47% *reduction* in the frequency of CS during visual acuity testing with ipsilesional head rotations (Schubert, 2006). This suggests an inverse relationship between the recruitment and amplitude of CS and the VOR gain for passive head rotations.

To epitomize, these data suggest that the brain uses whatever error signals available to optimize gaze stability during and after head motion, even if they are self-created error signals using one's imagination. The data also support the idea that the brain creates a new internal model of the perceived relationship of its head and eyes to the external environment, and then uses error signals based on that model to drive adaptive processes. In a sense, this is similar to the idea proposed about optimization of saccades, in which an internal forward model of what should happen is compared with what is actually happening.

7.2. Physiological correlates of saccade and VOR adaptation

In experimental animal, many neurons in the brain change their activity in relation to behavioral changes associated with saccade and VOR adaptation. With saccade adaptation, there are changes in neurons in the brainstem, superior colliculus, cerebellar vermis and fastigial nuclei (Desmurget et al., 2000; Fujita et al., 2002; Scudder and McGee, 2003; Hopp and Fuchs, 2005; Takeichi et al., 2005; Robinson et al., 2006 Takeichi et al., 2007; Kojima et al., 2007; Kojima et al., 2008; Soetedjo et al., 2008; Catz et al., 2008; Golla et al., 2008; Medina and Lisberger, 2008). Lesions in the cerebellum also interfere with saccade adaptation. Likewise, experimental animals undergoing VOR adaptation show changes in neural activity in the vestibulocerebellum and in the portions of the vestibular nuclei that receive projections from the Purkinje cells (Miles et al., 1980; Miles and Lisberger, 1981; Lisberger et al., 1994; Partsalis et al., 1995; Blasquez et al., 2000; Hirata and Highstein., 2001; Blazquez et al., 2006). Furthermore, lesions in the cerebellar flocculus impair adaptation of the gain and the direction of the VOR (Schultheis and Robinson, 1981; Zee et al., 1981; Lisberger et al., 1984; Rambold et al., 2002; Kassardjian et al., 2005).

We do not know how these physiological findings relate to the different time scales of motor learning and the associated issue of the segregation of the substrates for the acquisition and the retention of motor learning. For the vestibuloocular and optokinetic reflexes, physiological studies in experimental animals including those with genetically engineered mutations in the cerebellum support a functional and anatomical dichotomy for different time scales of motor learning (Nagao, 1992; Raymond and Lisberger, 1998; van Alphen et al., 2001; Titley et al., 2007; Broussard and Kassardjian, 2004). Whether or not we can translate these data to the simple hypothesis that the Purkinje cells in the cerebellar cortex are critical for acquisition and short-term learning and the deep nuclei for maintenance and long-term learning is unknown. Any theory of motor learning by the cerebellum must take into account the multiple cell types in the cerebellar cortex, many of which could play a role in synaptic plasticity. Furthermore, changes in activity during motor learning in the fastigial nuclei for saccades or in the cerebellar recipient portions of the vestibular nuclei for the VOR might not only mirror changes in Purkinje cell activity but also reflect direct synaptic plasticity driven by collaterals from axons that are destined for Purkinje cells. These complexities and unknowns make it still difficult to ascribe a specific functional role for the cerebellum in motor learning.

8. Implications for physical rehabilitation

The saccade and vestibular ocular motor systems show a remarkable degree of adaptive flexibility. When the VOR is inadequate, saccades and any residual vestibular generated eye movements work together for gaze stability. Data from animal studies suggest that exposure to retinal slip during head rotation are necessary to increase the gain, and any new memory due to such combined visual-vestibular stimulation only persists with continued exposure. Likewise short-term enhancement of the gain of the VOR when there is vestibular hypofunction is well established, yet how long this learned behavior can be retained without additional training is unknown. To increase an abnormally low VOR gain, training with progressively increasing small retinal slip errors is more effective than with sudden, large errors.

In the case of vestibular hypofunction, the capability of both the saccadic and vestibular systems to undergo modification provides a platform for rehabilitation. The challenge is to design a physical therapy program, that incorporates and optimizes both adaptive strategies

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References

Alahyane N, Fonteille V, Urquizar C, Salemme R, Nighoghossian N, Pelisson D, Tilikete C. Separate Neural Substrates in the Human Cerebellum for Sensory-motor Adaptation of Reactive and of Scanning Voluntary Saccades. Cerebellum 2008;7(4):595–601. [PubMed: 19009327]

Baloh RW, Sills AW, Kumely WE, et al. Quantitative measurement of saccade amplitude, duration, and velocity. Neurol 1975;25:1065–1070.

Barash S, Melikyan A, Sivakov A, Zhang M, Glickstein M, Thier P. Saccadic dysmetria and adaptation after lesions of the cerebellar cortex. J Neurosci 1999 Dec 15;19(24):10931–10939. [PubMed: 10594074]

Barzilai A, Kennedy TE, Sweat JD, Kandel ER. 5-HT modulates protein synthesis and the expression of specific proteins during long-term facilitation in Aplysia sensory neurons. Neuron 1989;2:1577–1586. [PubMed: 2627380]

Blazquez P, Partsalis A, Gerrits NM, Highstein SM. Input of anterior and posterior semicircular canal interneurons encoding head-velocity to the dorsal Y group of the vestibular nuclei. J Neurophys 2000 May;83(5):2891–2904.

Blazquez PM, Hirata Y, Highstein SM. Chronic changes in inputs to dorsal Y neurons accompany VOR motor learning. J Neurophys 2006 Mar;95(3):1812–1825.

Bloomberg J, Melvill Jones G, Segal B. Adaptive plasticity in the gaze stabilizing synergy of slow and saccadic eye movements. Exp Brain Res 1991;84:35–46. [PubMed: 1855563]

Broussard DM, Kassardjian CD. Learning in a simple motor system. Learn Mem 2004 Mar–Apr;11(2): 127–136. Review. [PubMed: 15054127]

Catz N, Dicke PW, Thier P. Cerebellar-dependent motor learning is based on pruning a Purkinje cell population response. Proc Natl Acad Sci USA 2008 May 20;105(20):7309–7314. Epub 2008 May 13. [PubMed: 18477700]

Chen-Harris H, Joiner WM, Ethier V, Zee DS, Shadmehr R. Adaptive control of saccades via internal feedback. J Neurosci 2008 Mar 12;28(11):2804–2813. [PubMed: 18337410]

Clendaniel RA, Lasker DM, Minor LB. Horizontal vestibuloocular reflex evoked by high-acceleration rotations in the squirrel monkey. IV. Responses after spectacle-induced adaptation. J Neurophys 2001 Oct;86(4):1594–1611.

Choi KD, Kim HJ, Cho BM, Kim JS. Saccadic adaptation in lateral medullary and cerebellar infarction. Exp Brain Res 2008 Jul;188(3):475–482. [PubMed: 18421449]

Della Santina CC, Cremer PD, Carey JP, Minor LB. Comparison of head thrust test with head autorotation test reveals that the vestibulo-ocular reflex is enhanced during voluntary head movements. Arch Otolaryngol Head Neck Surg 2002 Sep;128(9):1044–1054. [PubMed: 12220209]

Desmurget M, Pélisson D, Grethe JS, Alexander GE, Urquizar C, Prablanc C, Grafton ST. Functional adaptation of reactive saccades in humans: a PET study. Exp Brain Res 2000;132:243–259. [PubMed: 10853949]

Eggers SD, Pennington N, Walker MF, Shelhamer M, Zee DS. Short Term Adaptation of the VOR: Non-Retinal Slip Error Signals and Saccade Substitution. Ann N.Y. Acad Sci 2003;1004:94–110. [PubMed: 14662451]

Ethier V, Zee DS, Shadmehr R. Spontaneous recovery of motor memory during saccade adaptation. J Neurophysiol 2008a May;99(5):2577–2583. Epub 2008 Mar 19. [PubMed: 18353917]

Ethier V, Zee DS, Shadmehr R. Changes in control of saccades during gain adaptation. J Neurosci 2008b Dec 17;28(51):13929–13937. [PubMed: 19091981]

Fetter M, Zee DS, Proctor LR. Effect of lack of vision and of occipital lobectomy upon recovery from unilateral labyrinthectomy in rhesus monkey. J Neurophys 1988 Feb;59(2):394–407.

Fischer B, Ramsperger E. Human express saccades: extremely short reaction times of goal directed eye movements. Exp Brain Res 1984;57:191–195. [PubMed: 6519226]

Fujita M, Amagai A, Minakawa F, Aoki M. Selective and delay adaptation of human saccades. Brain Res Cogn Brain Res 2002 Feb;13(1):41–52. [PubMed: 11867249]

Gauthier GM, Robinson DA. Adaptation of the human vestibuloocular reflex to magnifying lenses. Brain Res 1975 Jul 11;92(2):331–335. [PubMed: 1080685]

Gaymard B, Rivaud-Péchoux S, Yelnik J, Pidoux B, Ploner CJ. Involvement of the cerebellar thalamus in human saccade adaptation. Eur J Neurosci 2001 Aug;14(3):554–560. [PubMed: 11553305]

Golla H, Tziridis K, Haarmeier T, Catz N, Barash S, Their P. Reduced saccadic resilience and impaired saccadic adaptation due to cerebellar disease. Eur J Neurosci 2008 Jan;27(1):132–144. [PubMed: 18184318]

Gonshor A, Jones GM. Extreme vestibulo-ocular adaptation indueed by prolonged optical reversal of vision. J Physiol (London) 1976;256:381–414. [PubMed: 16992508]

Hirata Y, Highstein SM. Acute adaptation of the vestibuloocular reflex: signal processing by floccular and ventral parafloccular Purkinje cells. J Neurophys 2001 May;85(5):2267–2288.

Hopp JJ, Fuchs AF. The characteristics and neuronal substrate of saccadic eye movement plasticity. Prog Neurobiol 2004 Jan;72(1):27–53. Review. [PubMed: 15019175]

Istl-Lenz Y, Hyden D, Schwarz DW. Response of the human vestibulo-ocular reflex following long-term 2× magnified visual input. Exp Brain Res 1985;57(3):448–455. [PubMed: 3872228]

Jones GM, Mandl G. Effects of strobe light on adaptation of vestibulo-ocular reflex (VOR) to vision reversal. Brain Res 1979 Mar 23;164:300–303. [PubMed: 311671]

Kassardjian CD, Tan TF, Chung JY, Heskin R, Peterson MJ, Broussard DM. The site of a motor memory shifts with consolidation. J Neurosci 2005 Aug 31;25(35):7979–7985. [PubMed: 16135754]

Kasai T, Zee DS. Eye-head coordination in labyrinthine-defective human beings. Brain Res 1978;144:123–141. [PubMed: 638756]

Kojima Y, Yoshida K, Iwamoto Y. Microstimulation of the midbrain tegmentum creates learning signals for saccade adaptation. J Neurosci 2007 Apr 4;27(14):3759–3767. [PubMed: 17409240]

Kojima Y, Iwamoto Y, Robinson FR, Noto CT, Yoshida K. Premotor inhibitory neurons carry signals related to saccade adaptation in the monkey. J Neurophys 2008;99:220–230.

Lisberger SG, Miles FA, Zee DS. Signals used to compute errors in monkey vestibuloocular reflex: possible role of flocculus. J Neurophys 1984 Dec;52(6):1140–1153.

Lisberger SG, Miles FA, Zee DS. Signals used to compute errors in monkey vestibuloocular reflex: possible role of flocculus. J Neurophys 1984 Dec;52(6):1140–1153.

Lisberger SG, Pavelko TA, Broussard DM. Neural basis for motor learning in the vestibuloocular reflex of primates. I Changes in the responses of brain stem neurons. J Neurophys 1994 Aug;72(2):928–953.

Maurer C, Mergner T, Becker, et al. Eye-head coordination in labyrinthine-defective humans. Exp Brain Res 1998;122:260–274. [PubMed: 9808299]

McGaugh JL, Roosendaal B. Role of adrenal stress hormones in forming lasting memories in the brain. Curr Opin Neurobiol 2002;12:205–210. [PubMed: 12015238]

Medina JF, Lisberger SG. Links from complex spikes to local plasticity and motor learning in the cerebellum of awake-behaving monkeys. Nat Neurosci 2008 Oct;11(10):1185–1192. [PubMed: 18806784]

Melvill Jones G, Guitton D, Berthoz A. Changing patterns of eye-head coordination during 6 h of optically reversed vision. Exp Brain Res 1988;69(3):531–544. [PubMed: 3371436]

Miles FA, Braitman DJ. Long-term adaptive changes in primate vestibuloocular reflex. II Electrophysiological observations on semicircular canal primary afferents. J Neurophys 1980 May; 43(5):1426–1436.

Miles FA, Eighmy BB. Long-term adaptive changes in primate vestibuloocular reflex. I. Behavioral observations. J Neurophys 1980 May;43(5):1406–1425.

Miles FA, Fuller JH, Braitman DJ, Dow BM. Long-term adaptive changes in primate vestibuloocular reflex. III. Electrophysiological observations in flocculus of normal monkeys. J Neurophys 1980 May;43(5):1437–1476.

Miles FA, Lisberger SG. The “error” signals subserving adaptive gain control in the primate vestibulo-ocular reflex. Ann N Y Acad Sci 1981;374:513–525. [PubMed: 6803645]

Nagao S. Different roles of flocculus and ventral paraflocculus for oculomotor control in the primate. Neuroreport 1992 Jan;3(1):13–16. [PubMed: 1611029]

Optican LM. Sensorimotor transformation for visually guided saccades. Ann N Y Acad Sci 2005 Apr; 1039:132–148. [PubMed: 15826968]

Optican LM, Robinson DA. Cerebellar-dependent adaptive control of primate saccadic system. J Neurophys 1980 Dec;44(6):1058–1076.

Partsalis AM, Zhang Y, Highstein SM. Dorsal Y group in the squirrel monkey. I. Neuronal responses during rapid and long-term modifications of the vertical VOR. J Neurophys 1995 Feb;73(2):615–631.

Rambold HA, Churchland Y, Selig L, Jasmin, Lisberger SG. Partial ablations of the flocculus and ventral paraflocculus in monkeys cause linked deficits in smooth pursuit eye movements and adaptive modification of the VOR. J Neurophys 2002;87:912–924.

Raymond JL, Lisberger SG. Neural learning rules for the vestibulo-ocular reflex. J Neurosci 1998 Nov 1;18(21):9112–9129. [PubMed: 9787014]

Robinson FR, Soetedjo R, Noto C. Distinct short-term and long-term adaptation to reduce saccade size in monkey. J Neurophys 2006;96:1030–1041.

Schubert MC, Herdman SJ, Tusa RJ. Vertical dynamic visual acuity in normal subjects and subjects with vestibular hypofunction. Otology & Neurotology 2002a;23:372–377. [PubMed: 11981398]

Schubert, MC.; Das, VE.; Tusa, RJ.; Herdman, SJ. Gaze stability during predictable and unpredictable head thrusts. Program No 266.1. Washington, DC: Society for Neuroscience; 2002b. CD ROM

Schubert MC, Della Santina CC, Shelhamer M. Incremental angular vestibulo-ocular reflex adaptation to active head rotation. Exp Brain Res 2008a Dec;191(4):435–446. [PubMed: 18712370]

Schubert MC, Migliaccio AA, Clendaniel RA, Carey JP. Mechanism of dynamic visual acuity recovery with vestibular rehabilitation. Arch Phys Med Rehabil 2008b;89:500–507. [PubMed: 18295629]

Schubert MC, Migliaccio AA, Della Santina CC. Modification of compensatory saccades after a VOR gain recovery. J of Vestib Res 2006;16:1–7. [PubMed: 16917164]

Scherer, MR.; Schubert, MC. Assoc. Res. Otolaryngol. Baltimore MD: 2009. Effects of Constant and Incremental Position Error Signals on a VOR Gain Adaptation.

Schultheis LW, Robinson DA. Directional plasticity of the vestibuloocular reflex in the cat. Ann N Y Acad Sci 1981;374:504–512. [PubMed: 6951449]

Scudder CA, McGee DM. Adaptive modification of saccade size produces correlated changes in the discharges of fastigial nucleus neurons. J Neurophys 2003 Aug;90(2):1011–1026.

Segal BN, Katsarkas A. Long-term deficits of goal directed vestibulo-ocular function following total unilateral loss of peripheral vestibular function. Acta Otolaryngol (Stockh) 1998a;106:102–110. [PubMed: 3262262]

Shelhamer M, Tiliket C, Roberts D, Kramer PD, Zee DS. Short-term vestibulo-ocular reflex adaptation in humans. II. Error signals. Exp Brain Res 1994;100(2):328–336. [PubMed: 7813669]

Shelhamer M, Ramat S, Zee DS. Context-specific adaptation and its significance for neurovestibular problems of space flight. J Vestib Res 2003;13:345–362. [PubMed: 15096677]

Soetedjo R, Kojima Y, Fuchs A. Complex spike activity signals the direction and size of dysmetric saccade errors. Prog Brain Res 2008;171:153–159. [PubMed: 18718294]

Straube A, Deubel H, Ditterich J, Eggert T. Cerebellar lesions impair rapid saccade amplitude adaptation. Neurol 2001 Dec 11;57(11):2105–2108.

Takagi M, Zee DS, Tamargo RJ. Effects of lesions of the oculomotor vermis on eye movements in primate: saccades. J Neurophys 1998 Oct;80(4):1911–1931.

Takeichi N, Kaneko CR, Fuchs AF. Activity changes in monkey superior colliculus during saccade adaption. J Neurophys 2007;97:4096–4107.

Takeichi N, Kaneko CRS, Fuchs AF. Discharge of monkey nucleus reticularis tegmenti pontis (NRTP) neurons changes during saccade adaptation. J Neurophys 2005a;94:1938–1951.

Tian J, Crane BT, Demer JL. Vestibular catch-up saccades in labyrinthine deficiency. Exp Brain Res 2000 Apr;131(4):448–457. [PubMed: 10803413]

Tiliket C, Shelhamer M, Roberts D, Zee DS. Short-term vestibulo-ocular reflex adaptation in humans. I. Effect on the ocular motor velocity-to-position neural integrator. Exp Brain Res 1994;100(2):316–327. [PubMed: 7813668]

Tiliket C, Shelhamer M, Tan HS, Zee DS. Adaptation of the vestibulo-ocular reflex with the head in different orientations and positions relative to the axis of body rotation. J Vestib Res 1993;3(2):181–195. [PubMed: 8275253]

Titley HK, Heskin-Sweezie R, Chung JY, Kassardijan CD, Razik F, Broussard DM. Rapid consolidation of motor memory in the vestibuloocular reflex. J Neurophys 2007 Dec;98(6):3809–3812. Epub 2007 Oct 31.

van Alphen AM, Stahl JS, De Zeeuw CI. The dynamic characteristics of the mouse horizontal vestibulo-ocular and optokinetic response. Brain Res 2001 Feb 2;890(2):296–305. [PubMed: 11164796]

Weber KP, Aw ST, Todd MJ, McGarvie LA, Curthoys IS, Halmagyi GM. Head impulse test in unilateral vestibular loss: vestibulo-ocular reflex and catch-up saccades. Neurol 2008 Feb 5;70(6):454–463.

Weber KP, Aw ST, Todd MJ, McGarvie LA, Curthoys IS, Halmagyi GM. Horizontal head impulse test detects gentamicin vestibulotoxicity. Neurol. 2009 In Press.

Yakushin SB, Palla A, Haslwanter T, Bockisch CJ, Straumann D. Dependence of adaptation of the human vertical angular vestibulo-ocular reflex on gravity. Exp Brain Res 2003 Sep;152(1):137–142. Epub 2003 Jul 17. [PubMed: 12879171]

Zee DS, Yamazaki A, Butler PH, Gücer G. Effects of ablation of flocculus and paraflocculus of eye movements in primate. J Neurophys 1981 Oct;46(4):878–899.